

## Chapter 711

# Group-Sequential Logrank Tests (Simulation)

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### 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.

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### 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.

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### 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.

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## 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).

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## 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.

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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<sup>th</sup> (20 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  $N_1 = N_2 = 60$  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.

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## 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.

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## 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.

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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.

<b><u>Test</u></b>	<b><u>Weight</u></b>	<b><u>Comments</u></b>
Logrank	1	This is the most commonly used test and the one we recommend. Equal weights across all times. This test has optimum power when the hazard rates of the $K$ populations are proportional to each other.
Gehan	$Y_i$	Places very heavy weight on hazards at the beginning of the study.
Tarone-Ware	$\sqrt{Y_i}$	Places heavy weight on hazards at the beginning of the study.
Peto-Peto	$\tilde{S}(t_i)$	Places a little more weight on hazards at the beginning of the study.
Modified Peto-Peto	$\tilde{S}(t_i) Y_i / (Y_i + 1)$	Places a little more weight on hazards at the beginning of the study.
Fleming-Harrington (0,0)	$1 - \hat{S}(t_{i-1})$	Places heavy weight on hazards at the end of the study.
Fleming-Harrington (1,0)	$\hat{S}(t_{i-1})$	Places almost equal weight at all times.

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Fleming-Harrington (1,1)	$\hat{S}(t_{i-1})(1 - \hat{S}(t_{i-1}))$	Places heavy weight on hazards at the end of the study.
Fleming-Harrington (0.5,0.5)	$\sqrt{\hat{S}(t_{i-1})(1 - \hat{S}(t_{i-1}))}$	Places a little more weight on hazards at the end of the study.
Fleming-Harrington (0.5,2)	$(1 - \hat{S}(t_{i-1}))^2 \sqrt{\hat{S}(t_{i-1})}$	Places very heavy weight on hazards at the end of the study.

This table uses the following definitions.

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

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

## 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

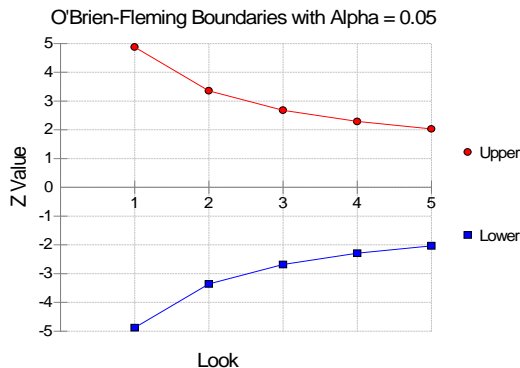
$$\alpha(0) = 0$$

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

The last characteristic guarantees a fixed  $\alpha$  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.

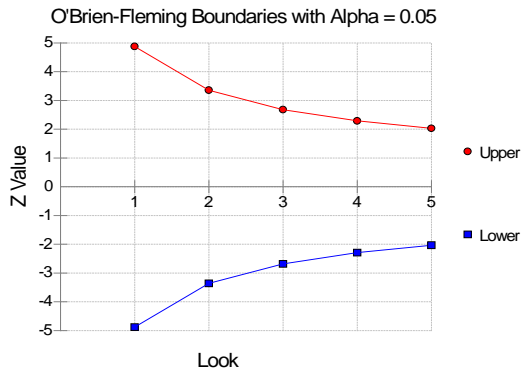
PASS provides several popular spending functions plus the ability to enter and analyze your own percents of alpha or beta spent. These are calculated as follows (beta may be substituted for alpha for beta-spending functions):

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

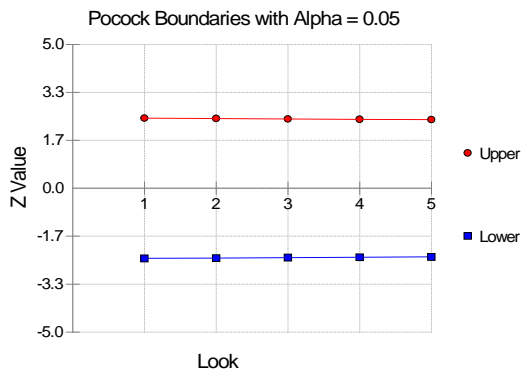


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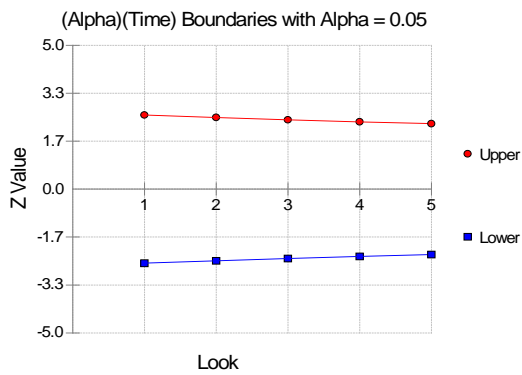
2. O'Brien-Fleming Analog  $2 - 2\Phi\left(\frac{Z_{\alpha/2}}{\sqrt{t}}\right)$



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

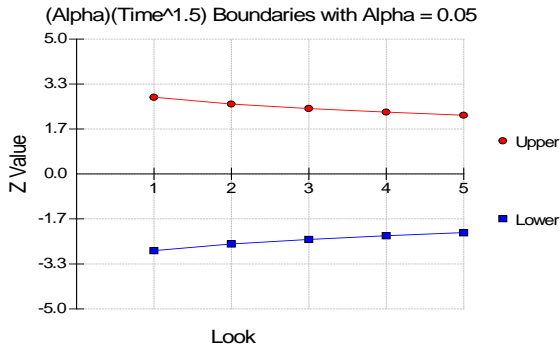


4. Alpha \* time  $\alpha \cdot t$

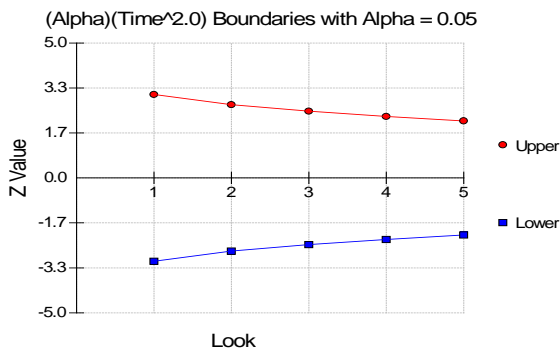


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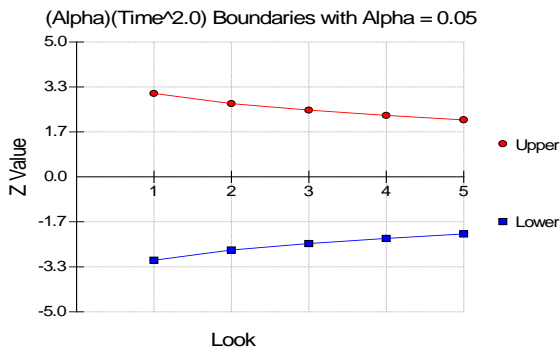
5. Alpha \* time<sup>1.5</sup>  $\alpha \cdot t^{3/2}$



6. Alpha \* time<sup>2</sup>  $\alpha \cdot t^2$



7. Alpha \* time<sup>C</sup>  $\alpha \cdot t^C$



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<sup>C</sup>) 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.

## Group-Sequential Logrank Tests (Simulation)

### Procedure Options

This section describes the options that are specific to this procedure. These are located on the Design, Looks & Boundaries, and Options tabs. For more information about the options of other tabs, go to the Procedure Window chapter.

### Design Tabs

The Design tabs contain most of the parameters and options for the general setup of the procedure.

### Solve For

#### Solve For

Solve for either power, sample size, or enter the boundaries directly and solve for power and alpha. When solving for power or sample size, the look and boundary details are specified on the “Looks & Boundaries” tab and the “Enter Boundaries” tab is ignored. When entering the boundaries directly and solving for power and alpha, the boundaries are input on the “Enter Boundaries” tab and the “Looks & Boundaries” tab is ignored.

When solving for power or N1, the early-stopping boundaries are also calculated. High accuracy for early-stopping boundaries requires a very large number of simulations (Recommended 100,000 to 10,000,000).

The parameter selected here is the parameter displayed on the vertical axis of the plot.

Because this is a simulation based procedure, the search for the sample size may take several minutes or hours to complete. You may find it quicker and more informative to solve for Power for a range of sample sizes.

### Test and Simulations

#### Test Type

Specify the hypothesis test that will be calculated in the simulations. Details for the tests are given in the Test Statistics section above.

The most common test for comparing hazard rates is the logrank test.

#### Alternative Hypothesis

Specify the direction of the alternative hypothesis for the comparison of hazard rates. For one-sided tests, the direction should be consistent with the direction specified under the Effect Size.

#### Simulations

Specify the number of Monte Carlo iterations, M.

The following table gives an estimate of the precision that is achieved for various simulation sizes when the power is near 0.50 and 0.95. The values in the table are the “Precision” amounts that are added and subtracted to form a 95% confidence interval.

<b>Simulation Size M</b>	<b>Precision when Power = 0.50</b>	<b>Precision when Power = 0.95</b>
100	0.100	0.044
500	0.045	0.019
1000	0.032	0.014
2000	0.022	0.010
5000	0.014	0.006
10000	0.010	0.004
50000	0.004	0.002
100000	0.003	0.001



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However, when solving for Power or  $N1$ , the simulations are used to calculate the look boundaries. To obtain precise boundary estimates, the number of simulations needs to be high. However, this consideration competes with the length of time to complete the simulation. When solving for power, a large number of simulations (100,000 or 1,000,000) will finish in several minutes. When solving for  $N1$ , perhaps 10,000 simulations can be run for each iteration. Then, a final run with the resulting  $N1$  solving for power can be run with more simulations.

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### Power and Alpha

#### Power

Power is the probability of rejecting the null hypothesis when it is false. Power is equal to  $1 - \text{Beta}$ , so specifying power implicitly specifies beta.

Beta is the probability obtaining a false negative on the statistical test. That is, it is the probability of accepting a false null hypothesis.

In the context of simulated group sequential trials, the power is the proportion of the alternative hypothesis simulations that cross any one of the significance (efficacy) boundaries.

The valid range is between 0 and 1.

Different disciplines and protocols have different standards for setting power. A common choice is 0.90, but 0.80 is also popular.

You can enter a range of values such as *0.70 0.80 0.90* or *0.70 to 0.90 by 0.1*.

#### Alpha

Alpha is the probability of obtaining a false positive on the statistical test. That is, it is the probability of rejecting a true null hypothesis.

The null hypothesis is usually that the parameters (the means, proportions, etc.) are all equal.

In the context of simulated group sequential trials, alpha is the proportion of the null hypothesis simulations that cross any one of the significance (efficacy) boundaries.

Since Alpha is a probability, it is bounded by 0 and 1. Commonly, it is between 0.001 and 0.250.

Alpha is often set to 0.05 for two-sided tests and to 0.025 for one-sided tests.

You may enter a range of values such as *0.01 0.05 0.10* or *0.01 to 0.10 by 0.01*.

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### Sample Size (When Solving for Sample Size)

#### Group Allocation

Select the option that describes the constraints on  $N1$  or  $N2$  or both.

The options are

- **Equal ( $N1 = N2$ )**

This selection is used when you wish to have equal sample sizes in each group. Since you are solving for both sample sizes at once, no additional sample size parameters need to be entered.

- **Enter  $R = N2/N1$ , solve for  $N1$  and  $N2$**

For this choice, you set a value for the ratio of  $N2$  to  $N1$ , and then PASS determines the needed  $N1$  and  $N2$ , with this ratio, to obtain the desired power. An equivalent representation of the ratio,  $R$ , is

$$N2 = R * N1.$$

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- **Enter percentage in Group 1, solve for N1 and N2**

For this choice, you set a value for the percentage of the total sample size that is in Group 1, and then PASS determines the needed  $N1$  and  $N2$  with this percentage to obtain the desired power.

### R (Group Sample Size Ratio)

*This option is displayed only if Group Allocation = "Enter R = N2/N1, solve for N1 and N2."*

$R$  is the ratio of  $N2$  to  $N1$ . That is,

$$R = N2 / N1.$$

Use this value to fix the ratio of  $N2$  to  $N1$  while solving for  $N1$  and  $N2$ . Only sample size combinations with this ratio are considered.

$N2$  is related to  $N1$  by the formula:

$$N2 = [R \times N1],$$

where the value  $[Y]$  is the next integer  $\geq Y$ .

For example, setting  $R = 2.0$  results in a Group 2 sample size that is double the sample size in Group 1 (e.g.,  $N1 = 10$  and  $N2 = 20$ , or  $N1 = 50$  and  $N2 = 100$ ).

$R$  must be greater than 0. If  $R < 1$ , then  $N2$  will be less than  $N1$ ; if  $R > 1$ , then  $N2$  will be greater than  $N1$ . You can enter a single or a series of values.

### Percent in Group 1

*This option is displayed only if Group Allocation = "Enter percentage in Group 1, solve for N1 and N2."*

Use this value to fix the percentage of the total sample size allocated to Group 1 while solving for  $N1$  and  $N2$ . Only sample size combinations with this Group 1 percentage are considered. Small variations from the specified percentage may occur due to the discrete nature of sample sizes.

The Percent in Group 1 must be greater than 0 and less than 100. You can enter a single or a series of values.

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## Sample Size (When Not Solving for Sample Size)

### Group Allocation

Select the option that describes how individuals in the study will be allocated to Group 1 and to Group 2.

The options are

- **Equal ( $N1 = N2$ )**

This selection is used when you wish to have equal sample sizes in each group. A single per group sample size will be entered.

- **Enter N1 and N2 individually**

This choice permits you to enter different values for  $N1$  and  $N2$ .

- **Enter N1 and R, where  $N2 = R * N1$**

Choose this option to specify a value (or values) for  $N1$ , and obtain  $N2$  as a ratio (multiple) of  $N1$ .

- **Enter total sample size and percentage in Group 1**

Choose this option to specify a value (or values) for the total sample size ( $N$ ), obtain  $N1$  as a percentage of  $N$ , and then  $N2$  as  $N - N1$ .

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### Sample Size Per Group

*This option is displayed only if Group Allocation = "Equal ( $N1 = N2$ )."*

The Sample Size Per Group is the number of items or individuals sampled from each of the Group 1 and Group 2 populations. Since the sample sizes are the same in each group, this value is the value for  $N1$ , and also the value for  $N2$ .

The Sample Size Per Group must be  $\geq 2$ . You can enter a single value or a series of values.

### N1 (Sample Size, Group 1)

*This option is displayed if Group Allocation = "Enter  $N1$  and  $N2$  individually" or "Enter  $N1$  and  $R$ , where  $N2 = R * N1$ ."*

$N1$  is the number of items or individuals sampled from the Group 1 population.

$N1$  must be  $\geq 2$ . You can enter a single value or a series of values.

### N2 (Sample Size, Group 2)

*This option is displayed only if Group Allocation = "Enter  $N1$  and  $N2$  individually."*

$N2$  is the number of items or individuals sampled from the Group 2 population.

$N2$  must be  $\geq 2$ . You can enter a single value or a series of values.

### R (Group Sample Size Ratio)

*This option is displayed only if Group Allocation = "Enter  $N1$  and  $R$ , where  $N2 = R * N1$ ."*

$R$  is the ratio of  $N2$  to  $N1$ . That is,

$$R = N2/N1$$

Use this value to obtain  $N2$  as a multiple (or proportion) of  $N1$ .

$N2$  is calculated from  $N1$  using the formula:

$$N2 = [R \times N1],$$

where the value  $[Y]$  is the next integer  $\geq Y$ .

For example, setting  $R = 2.0$  results in a Group 2 sample size that is double the sample size in Group 1.

$R$  must be greater than 0. If  $R < 1$ , then  $N2$  will be less than  $N1$ ; if  $R > 1$ , then  $N2$  will be greater than  $N1$ . You can enter a single value or a series of values.

### Total Sample Size (N)

*This option is displayed only if Group Allocation = "Enter total sample size and percentage in Group 1."*

This is the total sample size, or the sum of the two group sample sizes. This value, along with the percentage of the total sample size in Group 1, implicitly defines  $N1$  and  $N2$ .

The total sample size must be greater than one, but practically, must be greater than 3, since each group sample size needs to be at least 2.

You can enter a single value or a series of values.

### Percent in Group 1

*This option is displayed only if Group Allocation = "Enter total sample size and percentage in Group 1."*

This value fixes the percentage of the total sample size allocated to Group 1. Small variations from the specified percentage may occur due to the discrete nature of sample sizes.

The Percent in Group 1 must be greater than 0 and less than 100. You can enter a single value or a series of values.

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### Effect Size

#### Input Type

Indicate what type of values to enter to specify the effect size. Regardless of the entry type chosen, the test statistics used in the power and sample size calculations are the same. This option is simply given for convenience in specifying the effect size.

The choices are

- **Hazard Rate**

Enter  $h_1$ , the hazard rate of the control group, and either  $h_2$ , the hazard rate of the treatment group, or  $HR = h_2/h_1$ , the hazard ratio.

- **Median Survival Time**

Enter  $T_1$ , the median survival time of the control group, and either  $T_2$ , the median survival time of the treatment group, or  $HR = T_1/T_2$ , the hazard ratio.

- **Proportion Surviving**

Enter  $S_1$ , the proportion surviving past time  $T_0$  in the control group, and either  $S_2$ , the proportion surviving past time  $T_0$  in the treatment group, or  $HR$ , the hazard ratio.

- **Mortality**

Enter  $M_1$ , the mortality rate through time  $T_0$  in the control group, and either  $M_2$ , the mortality rate through time  $T_0$  in the treatment group, or  $MR = M_2/M_1$ , the mortality ratio.

### Effect Size = Hazard Rate

#### $h_1$ (Hazard rate of Control Group)

Specify one or more values for the hazard rate of the Control group.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric hazard rate values is entered directly, each represents the hazard rate assuming an exponential survival distribution.

Column Entry: Enter columns by beginning the entry with an equals sign (as in “=C1” or “=1 2 3”). Each row of the spreadsheet contains the hazard rate for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under “Total Time”.

For example, if the Total Time is set to “4” and you enter “=1” here, the indicated column could contain:

1.3

1.7

1.9

1.5

If the time is years, the hazard rate for the first year would be 1.3, the hazard rate for the second year would be 1.7, and so on.

Range: Numeric values must be greater than zero. Columns may be specified by name or number, and the values in the columns must be greater than zero.

#### Treatment Group Parameter

Specify whether the hazard rate of the treatment group will be entered directly or based on the Hazard Ratio ( $h_2/h_1$ ).

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### **h2 (Hazard Rate of Treatment Group)**

Specify one or more values for the hazard rate of the Treatment group.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric hazard rate values is entered directly, each represents the hazard rate assuming an exponential survival distribution.

Column Entry: Enter columns by beginning the entry with an equals sign (as in “=C1” or “=1 2 3”). Each row of the spreadsheet contains the hazard rate for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under “Total Time”.

For example, if the Total Time is set to “4” and you enter “=1” here, the indicated column could contain:

1.3

1.7

1.9

1.5

If the time is years, the hazard rate for the first year would be 1.3, the hazard rate for the second year would be 1.7, and so on.

Range: Numeric values must be greater than zero. Columns may be specified by name or number, and the values in the columns must be greater than zero.

### **HR (Hazard Ratio = $h_2/h_1$ )**

Specify one or more values for the hazard ratio of the Treatment group to the Control group.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric hazard ratio values is entered directly, each represents the hazard ratio for a treatment subject at risk to a control subject.

Column Entry: Enter columns by beginning the entry with an equals sign (as in “=C1” or “=1 2 3”). Each row of the spreadsheet contains the hazard ratio for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under “Total Time”.

For example, if the Total Time is set to “4” and you enter “=1” here, the indicated column could contain:

0.9

0.8

0.7

0.8

If the time is years, the hazard ratio for the first year would be 0.9, the hazard ratio for the second year would be 0.8, and so on.

Range: Numeric values must be greater than zero. Columns may be specified by name or number, and the values in the columns must be greater than zero.

**Group-Sequential Logrank Tests (Simulation)****Effect Size = Median Survival Time****T1 (Median Survival Time, Control)**

Specify one or more values for the median survival time of the Control group.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric median survival time values is entered directly, each represents the median time to an event assuming an exponential survival distribution.

Column Entry: Enter columns by beginning the entry with an equals sign (as in “=C1” or “=1 2 3”). Each row of the spreadsheet contains the median survival time for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under “Total Time”.

For example, if the Total Time is set to “4” and you enter “=1” here, the indicated column could contain:

2.3

2.7

2.9

3.5

If the time is years, the median survival time for the first year would be 2.3, the median survival time for the second year would be 2.7, and so on.

Range: Numeric values must be greater than zero. Columns may be specified by name or number, and the values in the columns must be greater than zero.

**Treatment Group Parameter**

Specify whether the median survival time of the treatment group will be entered directly or based on the Hazard Ratio ( $T1/T2 = h2/h1$ ).

**T2 (Median Survival Time, Treatment)**

Specify one or more values for the median survival time of the Treatment group.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric median survival time values is entered directly, each represents the median time to an event assuming an exponential survival distribution.

Column Entry: Enter columns by beginning the entry with an equals sign (as in “=C1” or “=1 2 3”). Each row of the spreadsheet contains the median survival time for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under “Total Time”.

For example, if the Total Time is set to “4” and you enter “=1” here, the indicated column could contain:

2.3

2.7

2.9

3.5

If the time is years, the median survival time for the first year would be 2.3, the median survival time for the second year would be 2.7, and so on.

Range: Numeric values must be greater than zero. Columns may be specified by name or number, and the values in the columns must be greater than zero.

## Group-Sequential Logrank Tests (Simulation)

### HR (Hazard Ratio = $T1/T2 = h2/h1$ )

Specify one or more values for the hazard ratio of the Treatment group to the Control group.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric hazard ratio values is entered directly, each represents the hazard ratio for a treatment subject at risk to a control subject.

Column Entry: Enter columns by beginning the entry with an equals sign (as in “=C1” or “=1 2 3”). Each row of the spreadsheet contains the hazard ratio for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under “Total Time”.

For example, if the Total Time is set to “4” and you enter “=1” here, the indicated column could contain:

0.9

0.8

0.7

0.8

If the time is years, the hazard ratio for the first year would be 0.9, the hazard ratio for the second year would be 0.8, and so on.

Range: Numeric values must be greater than zero. Columns may be specified by name or number, and the values in the columns must be greater than zero.

### Effect Size = Proportion Surviving

#### S1 (Proportion Surviving, Control)

Specify one or more values for the proportion surviving (proportion without events during the corresponding time) of the Control group.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric proportion surviving values is entered directly, each represents the probability that no event occurs for a subject at risk during the time  $T_0$ .

Column Entry: Enter columns by beginning the entry with an equals sign (as in “=C1” or “=1 2 3”). Each row of the spreadsheet contains the proportion surviving for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under “Total Time”.

For example, if the Total Time is set to “4” and you enter “=1” here, the indicated column could contain:

0.89

0.91

0.77

0.85

If the time is years, the proportion surviving for the first year would be 0.89, the proportion surviving for the second year would be 0.91, and so on.

Range: Numeric values must be between zero and one. Columns may be specified by name or number, and the values in the columns must be between zero and one.

#### Treatment Group Parameter

Specify whether the hazard rate of the treatment group will be entered directly or based on the Hazard Ratio ( $h2/h1$ ).

## Group-Sequential Logrank Tests (Simulation)

### S2 (Proportion Surviving, Treatment)

Specify one or more values for the proportion surviving (proportion without events during the corresponding time) of the Treatment group.

Values can be entered by number directly or by spreadsheet column.

**Numeric Entry:** If one or more numeric proportion surviving values is entered directly, each represents the probability that no event occurs for a subject at risk during the time T0.

**Column Entry:** Enter columns by beginning the entry with an equals sign (as in “=C1” or “=1 2 3”). Each row of the spreadsheet contains the proportion surviving for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under “Total Time”.

For example, if the Total Time is set to “4” and you enter “=1” here, the indicated column could contain:

0.89

0.91

0.77

0.85

If the time is years, the proportion surviving for the first year would be 0.89, the proportion surviving for the second year would be 0.91, and so on.

**Range:** Numeric values must be between zero and one. Columns may be specified by name or number, and the values in the columns must be between zero and one.

### HR (Hazard Ratio = $h_2/h_1$ )

Specify one or more values for the hazard ratio of the Treatment group to the Control group.

Values can be entered by number directly or by spreadsheet column.

**Numeric Entry:** If one or more numeric hazard ratio values is entered directly, each represents the hazard ratio for a treatment subject at risk during the time T0 to a control subject during the same period.

**Column Entry:** Enter columns by beginning the entry with an equals sign (as in “=C1” or “=1 2 3”). Each row of the spreadsheet contains the hazard ratio for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under “Total Time”.

For example, if the Total Time is set to “4” and you enter “=1” here, the indicated column could contain:

0.9

0.8

0.7

0.8

If the time is years, the hazard ratio for the first year would be 0.9, the hazard ratio for the second year would be 0.8, and so on.

**Range:** Numeric values must be greater than zero. Columns may be specified by name or number, and the values in the columns must be greater than zero.

### T0 (Proportion Surviving Time)

Specify the time that corresponds to the proportion surviving values S1, S2, NCS1, and NCS2 if they are entered directly. When columns are used, T0 is ignored.



## Group-Sequential Logrank Tests (Simulation)

### Effect Size = Mortality

#### M1 (Mortality of Control Group)

Specify one or more values for the mortality (proportion with events during the corresponding time) of the Control group.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric mortality values is entered directly, each represents the probability that an event occurs for a subject at risk during the time  $T_0$ .

Column Entry: Enter columns by beginning the entry with an equals sign (as in “=C1” or “=1 2 3”). Each row of the spreadsheet contains the mortality for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under “Total Time”.

For example, if the Total Time is set to “4” and you enter “=1” here, the indicated column could contain:

0.11

0.09

0.23

0.15

If the time is years, the mortality for the first year would be 0.11, the mortality for the second year would be 0.09, and so on.

Range: Numeric values must be between zero and one. Columns may be specified by name or number, and the values in the columns must be between zero and one.

#### Treatment Group Parameter

Specify whether the mortality of the treatment group will be entered directly or based on the Mortality Ratio ( $M_2/M_1$ ).

#### M2 (Mortality of Treatment Group)

Specify one or more values for the mortality (proportion with events during the corresponding time) of the Treatment group.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric mortality values is entered directly, each represents the probability that an event occurs for a subject at risk during the time  $T_0$ .

Column Entry: Enter columns by beginning the entry with an equals sign (as in “=C1” or “=1 2 3”). Each row of the spreadsheet contains the mortality for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under “Total Time”.

For example, if the Total Time is set to “4” and you enter “=1” here, the indicated column could contain:

0.11

0.09

0.23

0.15

If the time is years, the mortality for the first year would be 0.11, the mortality for the second year would be 0.09, and so on.

Range: Numeric values must be between zero and one. Columns may be specified by name or number, and the values in the columns must be between zero and one.

## Group-Sequential Logrank Tests (Simulation)

### MR (Mortality Ratio = $M2/M1$ )

Specify one or more values for the mortality ratio of the TREATMENT group to the CONTROL group.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric mortality ratio values is entered directly, each represents the ratio of the mortality for a treatment subject at risk during the time  $T_0$  to a control subject during the same period.

Column Entry: Enter columns by beginning the entry with an equals sign (as in “=C1” or “=1 2 3”). Each row of the spreadsheet contains the mortality ratio for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under “Total Time”.

For example, if the Total Time is set to “4” and you enter “=1” here, the indicated column could contain:

0.9

0.8

0.7

0.8

If the time is years, the mortality ratio for the first year would be 0.9, the mortality ratio for the second year would be 0.8, and so on.

Range: Numeric values must be greater than zero. Columns may be specified by name or number, and the values in the columns must be greater than zero.

### T0 (Mortality Time)

Specify the time that corresponds to the mortality values  $M_1$ ,  $M_2$ ,  $NCM_1$ , and  $NCM_2$  if they are entered directly. When columns are used,  $T_0$  is ignored.

## Proportion Lost (Per Time Period)

### Controls Lost

Specify one or more values for the proportion of Controls that are lost-to-follow-up (right-censored) during each time period of the total time.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric loss values is entered directly, each represents the probability that an at-risk subject will be lost-to-follow-up during each time period of the total time.

Column Entry: Enter columns by beginning the entry with an equals sign (as in “=C1” or “=1 2 3”). Each row of the spreadsheet contains the loss proportion for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under “Total Time”.

For example, if the Total Time is set to “4” and you enter “=1” here, the indicated column could contain:

0.05

0.05

0.10

0.15

If the time is years, the loss proportion for the first year would be 0.05, the loss proportion for the second year would be 0.05, and so on.

Range: Numeric values must be between zero and one. Columns may be specified by name or number, and the values in the columns must be between zero and one.

## Group-Sequential Logrank Tests (Simulation)

### Treatments Lost

Specify one or more values for the proportion of Treatments that are lost-to-follow-up (right-censored) during each time period of the total time.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric loss values is entered directly, each represents the probability that an at-risk subject will be lost-to-follow-up during each time period of the total time.

Column Entry: Enter columns by beginning the entry with an equals sign (as in “=C1” or “=1 2 3”). Each row of the spreadsheet contains the loss proportion for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under “Total Time”.

For example, if the Total Time is set to “4” and you enter “=1” here, the indicated column could contain:

0.05

0.05

0.10

0.15

If the time is years, the loss proportion for the first year would be 0.05, the loss proportion for the second year would be 0.05, and so on.

Range: Numeric values must be between zero and one. Columns may be specified by name or number, and the values in the columns must be between zero and one.

### For Treatments Lost under H0, Use

Specify whether the simulations of the treatment subjects under the Null hypothesis should use the loss values specified under “Controls Lost:” or the values specified under “Treatments Lost:”.

---

## Noncompliance (Per Time Period)

### Noncompliance Proportion (Control)

Specify one or more values for the proportion of Controls that are noncompliant (change treatment structure from that of other controls) during each time period of the total time.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric noncompliance values is entered directly, each represents the probability that an at-risk subject will become noncompliant during each time period of the total time.

Column Entry: Enter columns by beginning the entry with an equals sign (as in “=C1” or “=1 2 3”). Each row of the spreadsheet contains the loss proportion for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under “Total Time”.

For example, if the Total Time is set to “4” and you enter “=1” here, the indicated column could contain:

0.05

0.05

0.10

0.15

If the time is years, the noncompliance proportion for the first year would be 0.05, the noncompliance proportion for the second year would be 0.05, and so on.

Range: Numeric values must be between zero and one. Columns may be specified by name or number, and the values in the columns must be between zero and one.

## Group-Sequential Logrank Tests (Simulation)

### NCM1 (Noncompliance Mortality, Control)

Specify one or more values for the noncompliance mortality (proportion with events during the corresponding time) of the Control group.

Values can be entered by number directly, by spreadsheet column, or by specifying a switch to M2 mortality.

**Numeric Entry:** If one or more numeric noncompliance mortality values is entered directly, each represents the probability that an event occurs for a subject at risk during the time T0.

**Column Entry:** Enter columns by beginning the entry with an equals sign (as in “=C1” or “=1 2 3”). Each row of the spreadsheet contains the mortality for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under “Total Time”.

For example, if the Total Time is set to “4” and you enter “=1” here, the indicated column could contain:

0.11

0.09

0.23

0.15

If the time is years, the noncompliance mortality for the first year would be 0.11, the noncompliance mortality for the second year would be 0.09, and so on.

**M2:** If M2 is entered, the value(s) entered for M2 will be used for the mortality of M1 when noncompliant.

**Range:** Numeric values must be between zero and one. Columns may be specified by name or number, and the values in the columns must be between zero and one.

### At time of noncompliance, start NCM1 at

At the time of noncompliance, the simulated subjects’ mortalities can switch to the beginning of the specified noncompliance mortality or the specified noncompliance mortality at the time of noncompliance.

### Noncompliance Proportion (Treatment)

Specify one or more values for the proportion of Treatments that are noncompliant (change treatment structure from that of other treatment subjects) during each time period of the total time.

Values can be entered by number directly or by spreadsheet column.

**Numeric Entry:** If one or more numeric noncompliance values is entered directly, each represents the probability that an at-risk subject will become noncompliant during each time period of the total time.

**Column Entry:** Enter columns by beginning the entry with an equals sign (as in “=C1” or “=1 2 3”). Each row of the spreadsheet contains the loss proportion for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under “Total Time”.

For example, if the Total Time is set to “4” and you enter “=1” here, the indicated column could contain:

0.05

0.05

0.10

0.15

If the time is years, the noncompliance proportion for the first year would be 0.05, the noncompliance proportion for the second year would be 0.05, and so on.

**Range:** Numeric values must be between zero and one. Columns may be specified by name or number, and the values in the columns must be between zero and one.

## Group-Sequential Logrank Tests (Simulation)

### NCM2 (Noncompliance Mortality, Treatment)

Specify one or more values for the noncompliance mortality (proportion with events during the corresponding time) of the Treatment group.

Values can be entered by number directly, by spreadsheet column, or by specifying a switch to M1 mortality.

**Numeric Entry:** If one or more numeric noncompliance mortality values is entered directly, each represents the probability that an event occurs for a subject at risk during the time  $T_0$ .

**Column Entry:** Enter columns by beginning the entry with an equals sign (as in “=C1” or “=1 2 3”). Each row of the spreadsheet contains the mortality for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under “Total Time”.

For example, if the Total Time is set to “4” and you enter “=1” here, the indicated column could contain:

0.11

0.09

0.23

0.15

If the time is years, the noncompliance mortality for the first year would be 0.11, the noncompliance mortality for the second year would be 0.09, and so on.

**M1:** If M1 is entered, the value(s) entered for M1 will be used for the mortality of M2 when noncompliant.

**Range:** Numeric values must be between zero and one. Columns may be specified by name or number, and the values in the columns must be between zero and one.

#### At time of noncompliance, start NCM2 at

At the time of noncompliance, the simulated subjects’ mortalities can switch to the beginning of the specified noncompliance mortality or the specified noncompliance mortality at the time of noncompliance.

#### For Treatment Noncompliance under $H_0$ , use

Specify whether the simulations of the treatment subjects under the Null hypothesis should use the noncompliance values specified under Control Noncompliance or the values specified under Treatment Noncompliance.

### Duration (Number of Time Periods)

#### Accrual Time (Integers Only)

Enter one or more values for the number of time periods (months, years, etc.) during which subjects are entered into the study.

The total duration of the study is equal to the Accrual Time plus the Follow-Up Time.

These values must be integers.

**Range:** Accrual times can range from 0 to the Total Time. That is, the accrual time must be less than or equal to the Total Time.

Enter “0” when all subjects begin the study together.

#### Accrual Pattern

Specify the type of accrual (patient entry) pattern. Two types of entries are possible:

- **Equal (Uniform)**

If you want to specify a uniform accrual rate for all time periods, enter *Equal* here.

## Group-Sequential Logrank Tests (Simulation)

- **Linear Increasing Probability w/Time**

The probability of accrual increases linearly during the accrual time. This is used to specify slow early enrollment and heavy late enrollment.

- **Linear Decreasing Probability w/Time**

The probability of accrual decreases linearly during the accrual time. This is used to specify heavy early enrollment and slow late enrollment.

- **Non-Uniform (Spreadsheet Entry)**

Use this option when you want to specify one or more accrual patterns with different accrual rates per time period. You will specify the different accrual rates for each time period in the spreadsheet.

### Accrual Values in Columns

Specify the columns of the spreadsheet containing the different accrual (patient entry) rates. One value per row is entered in spreadsheet cells for each time period. Each value is the proportion of the total number of subjects that enroll during the corresponding time period.

#### Syntax

Enter an equals sign followed by a list of columns containing the accrual patterns. For example, if you have entered two sets of accrual patterns in columns 1 and 2, you would enter “=C1 C2.”

#### Standardized

Note that cell values in a column are standardized so they sum to one. Thus, the accrual patterns 2 1 1 and 50 25 25 both result in the same accrual pattern as 0.50 0.25 0.25 .

#### Number of Rows and Columns

The number of rows in each column should equal the Accrual Time. The number of columns is up to you. A separate analysis is conducted for each column.

#### Spreadsheet Cells

In a specified column, the proportion of all subjects that are expected to enroll during the first time period is specified in row one. The proportion of all subjects that are expected during the second time period is specified in row two. And so on.

For example, if you had specified three accrual-time periods and you wanted to specify double the accrual rate in the first period than in the other two, the spreadsheet would appear as

```
C1
2
1
1
```

#### Total Time (Integers Only)

Enter one or more values for the number of time periods (months, years, etc.) in the study.

The follow-up time is equal to the Total Time minus the Accrual Time.

These values must be integers.

Range: Total times must be integers, 1 or greater.

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## Looks & Boundaries Tab when Solving for Power or Sample Size

The Looks & Boundaries tab contains most of the parameters and options for the general setup of the procedure.

---

### Looks and Boundaries

#### Specification of Looks and Boundaries

Choose whether spending functions will be used to divide alpha and beta for each look (Simple Specification), or whether the percents of alpha and beta to be spent at each look will be specified directly (Custom Specification).

Under Simple Specification, the looks are automatically considered to be equally spaced. Under Custom Specification, the looks may be equally spaced or custom defined based on the percent of accumulated information.

---

### Looks and Boundaries – Simple Specification

#### Number of Equally Spaced Looks

Select the total number of looks that will be used if the study is not stopped early for the crossing of a boundary.

#### Alpha Spending Function

Specify the type of alpha spending function to use.

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

#### C (Alpha Spending)

C is used to define the Hwang-Shih-DeCani (C) or (Alpha)(Time<sup>C</sup>) spending functions.

For the Hwang-Shih-DeCani (C) spending function, negative values of C spend more of alpha at later looks, values near 0 spend alpha evenly, and positive values of C spend more of alpha at earlier looks.

For the (Alpha)(Time<sup>C</sup>) spending function, only positive values for C are permitted. Values of C near zero spend more of alpha at earlier looks, values near 1 spend alpha evenly, and larger values of C spend more of alpha at later looks.

#### Type of Futility Boundary

This option determines whether or not futility boundaries will be created, and if so, whether they are binding or non-binding.

Futility boundaries are boundaries such that, if crossed at a given look, stop the study in favor of H<sub>0</sub>.

Binding futility boundaries are computed in concert with significance boundaries. They are called binding because they require the stopping of a trial if they are crossed. If the trial is not stopped, the probability of a false positive will exceed alpha.

When non-binding futility boundaries are computed, the significance boundaries are first computed, ignoring the futility boundaries. The futility boundaries are then computed. These futility boundaries are non-binding because continuing the trial after they are crossed will not affect the overall probability of a false positive declaration.

#### Number of Skipped Futility Looks

In some trials it may be desirable to wait a number of looks before examining the trial for futility. This option allows the beta to begin being spent after a specified number of looks.

The Number of Skipped Futility Looks should be less than the number of looks.

## Group-Sequential Logrank Tests (Simulation)

### Beta Spending Function

Specify the type of beta spending function to use.

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

### C (Beta Spending)

C is used to define the Hwang-Shih-DeCani (C) or (Beta)(Time<sup>C</sup>) spending functions.

For the Hwang-Shih-DeCani (C) spending function, negative values of C spend more of beta at later looks, values near 0 spend beta evenly, and positive values of C spend more of beta at earlier looks.

For the (Beta)(Time<sup>C</sup>) spending function, only positive values for C are permitted. Values of C near zero spend more of beta at earlier looks, values near 1 spend beta evenly, and larger values of C spend more of beta at later looks.

---

## Looks and Boundaries – Custom Specification

### Number of Looks

This is the total number of looks of either type (significance or futility or both).

### Equally Spaced

If this box is checked, the Accumulated Information boxes are ignored and the accumulated information is evenly spaced.

### Type of Futility Boundary

This option determines whether or not futility boundaries will be created, and if so, whether they are binding or non-binding.

Futility boundaries are boundaries such that, if crossed at a given look, stop the study in favor of H<sub>0</sub>.

Binding futility boundaries are computed in concert with significance boundaries. They are called binding because they require the stopping of a trial if they are crossed. If the trial is not stopped, the probability of a false positive will exceed alpha.

When Non-binding futility boundaries are computed, the significance boundaries are first computed, ignoring the futility boundaries. The futility boundaries are then computed. These futility boundaries are non-binding because continuing the trial after they are crossed will not affect the overall probability of a false positive declaration.

### Accumulated Information

The accumulated information at each look defines the proportion or percent of the sample size that is used at that look.

These values are accumulated information values so they must be increasing.

Proportions, percents, or sample sizes may be entered. All proportions, percents, or sample sizes will be divided by the value at the final look to create an accumulated information proportion for each look.

### Percent of Alpha Spent

This is the percent of the total alpha that is spent at the corresponding look. It is not the cumulative value.

Percents, proportions, or alphas may be entered here. Each of the values is divided by the sum of the values to obtain the proportion of alpha that is used at the corresponding look.



## Group-Sequential Logrank Tests (Simulation)

### Percent of Beta Spent

This is the percent of the total beta (1-power) that is spent at the corresponding look. It is not the cumulative value.

Percents, proportions, or betas may be entered here. Each of the values is divided by the sum of the values to obtain the proportion of beta that is used at the corresponding look.

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## Looks & Boundaries Tab when Solving for Alpha and Power

The Looks & Boundaries tab contains settings for the looks and significance boundaries.

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### Looks and Boundaries

#### Number of Looks

This is the total number of looks of either type (significance or futility or both).

#### Equally Spaced

If this box is checked, the Accumulated Information boxes are ignored and the accumulated information is evenly spaced.

#### Types of Boundaries

This option determines whether or not futility boundaries will be entered.

Futility boundaries are boundaries such that, if crossed at a given look, stop the study in favor of  $H_0$ .

#### Accumulated Information

The accumulated information at each look defines the proportion or percent of the sample size that is used at that look.

These values are accumulated information values so they must be increasing.

Proportions, percents, or sample sizes may be entered. All proportions, percents, or sample sizes will be divided by the value at the final look to create an accumulated information proportion for each look.

#### Significance Boundary

Enter the value of the significance boundary corresponding to the chosen test statistic. These are sometimes called efficacy boundaries.

#### Futility Boundary

Enter the value of the futility boundary corresponding to the chosen test statistic.

## Options Tab

The Options tab contains limits on the number of iterations and various options about individual tests.

---

### Maximum Sample Size Searched

#### Maximum N1 Before Search Termination

Specify the maximum N1 before the search for N1 is aborted.

Since simulations for large sample sizes are very computationally intensive and hence time-consuming, this value can be used to stop searches when N1 is larger than reasonable sample sizes for the study.

This applies only when “Find (Solve For)” is set to N1.

The procedure uses a binary search when searching for N1. If a value for N1 is tried that exceeds this value, and the power is not reached, a warning message will be shown on the output indicating the desired power was not reached.

We recommend a value of at least 20000.

---

### Random Numbers

#### Random Number Pool Size

You can speed up the simulation by creating a large pool of random numbers from which random samples are drawn. This is the size of the pool.

If you do not want to draw numbers from a pool, enter “0” here.

If you want to use a pool, the minimum pool size is 10000. Also, the pool size should be at least twice the number of simulations.

---

### Matching Boundaries at Final Look

#### Beta Search Increment

For each simulation, when futility bounds are computed, the appropriate beta is found by searching from 0 to 1 by this increment. Smaller increments are more refined, but the search takes longer.

We recommend 0.001 or 0.0001.

## Group-Sequential Logrank Tests (Simulation)

**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**

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Group-Sequential Logrank Tests (Simulation)** procedure. You may then make the appropriate entries as listed below, or open **Example 1** by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
<b>Design 1 Tab</b>	
Solve For .....	<b>Power</b>
Test Type.....	<b>Logrank</b>
Alternative Hypothesis .....	<b>H1: Hazard1 ≠ Hazard2</b>
Simulations .....	<b>10000</b>
Alpha.....	<b>0.05</b>
Group Allocation .....	<b>Enter total sample size and percentage in Group 1</b>
Total Sample Size (N).....	<b>200</b>
Percent in Group 1.....	<b>50</b>
Input Type.....	<b>Hazard Rate</b>
h1 .....	<b>1.4</b>
Treatment Group Parameter .....	<b>h2 (Hazard Rate)</b>
h2.....	<b>1.0</b>
<b>Design 2 Tab</b>	
Controls Lost.....	<b>0</b>
Treatments Lost.....	<b>0</b>
Noncompliance Proportion (Control) .....	<b>0</b>
Noncompliance Proportion (Treatment) .	<b>0</b>
Accrual Time.....	<b>0</b>
Total Time.....	<b>5</b>
<b>Looks &amp; Boundaries Tab</b>	
Specification of Looks and Boundaries ..	<b>Simple</b>
Number of Equally Spaced Looks .....	<b>5</b>
Alpha Spending Function .....	<b>O'Brien-Fleming Analog</b>

## Group-Sequential Logrank Tests (Simulation)

## Output

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

## Numeric Results and Plots

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

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

## Numeric Summary for Scenario 1

Power			Alpha				Beta
Value	95% LCL	95% UCL	Target	Actual	95% LCL	95% UCL	
0.644	0.635	0.654	0.050	0.052	0.048	0.057	0.356

N1	N2	HR	h1	h2	Accrual Time	Accrual Pattern	Total Time
100	100	0.714	1.400	1.000	0.0	Equal	5.0

Noncompliance					
Loss1	Loss2	Prop 1	h1	Prop 2	h2
0.000	0.000	0.000	1.000	0.000	1.000

## Whole Study Averages

Study Length		Cum. Subject Time			
H0	H1	H0		H1	
		G1	G2	G1	G2
5.0	3.9	71.4	71.3	70.2	95.8

Sample Size				Events			
H0		H1		H0		H1	
G1	G2	G1	G2	G1	G2	G1	G2
100.0	100.0	100.0	100.0	99.9	99.9	98.3	95.7

## 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.

## Report Definitions

Power is 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 are the lower and upper confidence limits for the power estimate. The width of the interval is based on the number of simulations.

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

Actual Alpha is 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 are the lower and upper confidence limits for the actual alpha estimate. The width of the interval is based on the number of simulations.

Beta is 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 Logrank Tests (Simulation)

N1 and N2 are the sample sizes of each group if the study reaches the final look.  
 HR is the hazard ratio  $h_2/h_1$  at which power is computed.  
 $h_1$  is the hazard rate of the control group. It is the hazard rate that is simulated for both groups under  $H_0$ , and for group 1 under  $H_1$ .  
 $h_2$  is the hazard rate of the treatment group. It is the hazard rate that is simulated for group 2 under  $H_1$ .  
 Accrual Time is 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 is the total length of the study. It is the sum of the accrual time and the follow-up time.  
 Loss1 and Loss2 are the loss rates (lost to follow-up and right censored) for the control and treatment groups, respectively.  
 Noncompliance Proportion 1 and Noncompliance Proportion 2 are the proportion noncompliant in each time period for the control and treatment groups, respectively.  
 Noncompliance  $h_1$  and Noncompliance  $h_2$  are the noncompliance hazard rates for the control and treatment groups, respectively.  
 For Whole Study Averages,  $H_0$  and  $H_1$  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 is the average length of the study across all simulations. This length includes accrual time and follow-up time.  
 Cumulative Subject Time is 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 is 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 is 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 0.052 significance level (alpha) using a two-sided Logrank Test.

**Detailed Input**

Time	Accrual	Control Hazard Rate	Trt Hazard Rate	Control Loss	Trt Loss	NComp Prop Control	NComp Hazard Control	NComp Prop Trt	NComp Hazard Trt
Period	Pattern	h1	h2	Ls1	Ls2	NCP1	NCh1	NCP2	NCh2
1	100% Accrual	1.400	1.000	0.000	0.000	0.000	1.000	0.000	1.000
2	100% Accrual	1.400	1.000	0.000	0.000	0.000	1.000	0.000	1.000
3	100% Accrual	1.400	1.000	0.000	0.000	0.000	1.000	0.000	1.000
4	100% Accrual	1.400	1.000	0.000	0.000	0.000	1.000	0.000	1.000
5	100% Accrual	1.400	1.000	0.000	0.000	0.000	1.000	0.000	1.000

**Look Details for Scenario 1**

Look	Time	--- Sample Size ---		----- Events -----				-- Cum. Subject Time --	
		Group 1	Group 2	Group 1	% of S.S.	Group 2	% of S.S.	Group 1	Group 2
1	1.0	100.0	100.0	75.4	75.4	63.2	75.4	53.8	63.2
2	2.0	100.0	100.0	93.9	93.9	86.5	93.9	67.1	86.5
3	3.0	100.0	100.0	98.5	98.5	95.0	98.5	70.4	95.1
4	4.0	100.0	100.0	99.6	99.6	98.2	99.6	71.2	98.3
5	5.0	100.0	100.0	99.9	99.9	99.3	99.9	71.4	99.4

**Look Details Definitions (Averages are across all simulations)**

Look is the number of the look.  
 Time is the Time of the look from the beginning of the study (i.e., the beginning of the accrual period).  
 Sample Size Group 1 is 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 is 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 is the average number of events in the control group up to the corresponding look.  
 % of S.S. is 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 is the average number of events in the treatment group up to the corresponding look.  
 % of S.S. is 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 is 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.

## Group-Sequential Logrank Tests (Simulation)

### Boundaries for Scenario 1

Look	-- Significance Boundary --	
	Z-Value Scale	P-Value Scale
1	+/- 4.101	0.000
2	+/- 3.290	0.001
3	+/- 2.644	0.008
4	+/- 2.245	0.025
5	+/- 1.982	0.047

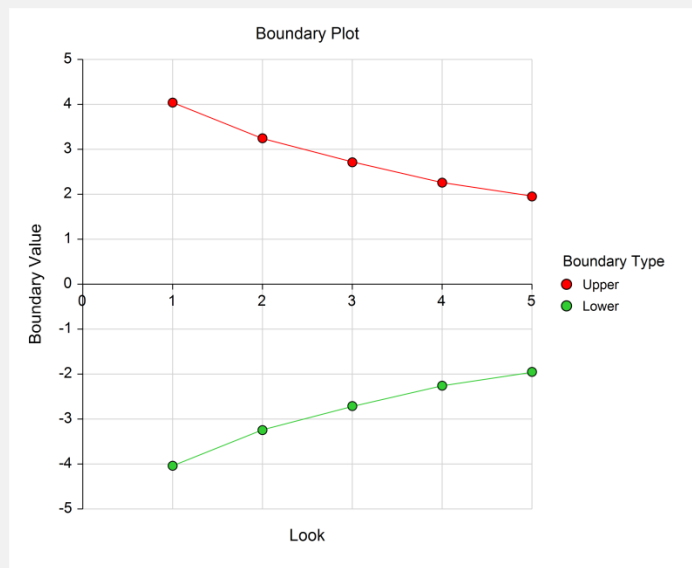
### Boundaries Definitions

Look is the number of the look.

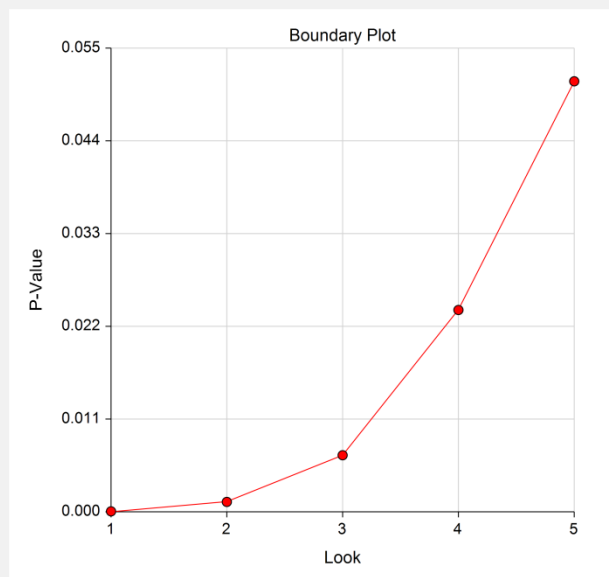
Significance Boundary Z-Value Scale is the value such that statistics outside this boundary at the corresponding look indicate termination of the study and rejection of the null hypothesis. They are sometimes called efficacy boundaries.

Significance Boundary P-Value Scale is 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



### Group-Sequential Logrank Tests (Simulation)

#### 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	+/- 4.101			0.000		
2	+/- 3.290	3.146	3.690	0.001	0.000	0.002
3	+/- 2.644	2.597	2.809	0.008	0.005	0.009
4	+/- 2.245	2.208	2.301	0.025	0.021	0.027
5	+/- 1.982	1.943	2.013	0.047	0.044	0.052

#### Significance Boundary Confidence Limit Definitions

Look is the number of the look.

Z-Value Boundary Value is 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 is 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 are 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	Cum.
	Z-Value Scale	P-Value Scale	Spending Function Alpha	Spending Function Alpha	Alpha Spent	Alpha Spent	H1 Sims Outside Signif. Boundary	H1 Sims Outside Signif. Boundary
1	+/- 4.101	0.000	0.000	0.000	0.000	0.000	0.020	0.020
2	+/- 3.290	0.001	0.001	0.001	0.001	0.001	0.137	0.156
3	+/- 2.644	0.008	0.007	0.008	0.008	0.009	0.217	0.373
4	+/- 2.245	0.025	0.017	0.024	0.017	0.026	0.171	0.544
5	+/- 1.982	0.047	0.026	0.050	0.026	0.052	0.101	0.644

#### Alpha-Spending Details Definitions

Look is the number of the look.

Significance Boundary Z-Value Scale is 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 is 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 is the intended portion of alpha allocated to the particular look based on the alpha-spending function.

Cumulative Spending Function Alpha is 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 is the proportion of the null hypothesis simulations resulting in statistics outside the Significance Boundary at this look.

Cumulative Alpha Spent is 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 is 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 is 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.

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

## Group-Sequential Logrank Tests (Simulation)

**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**

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Group-Sequential Logrank Tests (Simulation)** procedure. You may then make the appropriate entries as listed below, or open **Example 2** by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
<b>Design 1 Tab</b>	
Solve For .....	<b>Power</b>
Test Type .....	<b>Logrank</b>
Alternative Hypothesis .....	<b>H1: Hazard1 &gt; Hazard2</b>
Simulations .....	<b>10000</b>
Alpha .....	<b>0.025</b>
Group Allocation .....	<b>Enter total sample size and percentage in Group 1</b>
Total Sample Size (N) .....	<b>200</b>
Percent in Group 1 .....	<b>50</b>
Input Type .....	<b>Hazard Rate</b>
h1 .....	<b>1.49</b>
Treatment Group Parameter .....	<b>h2 (Hazard Rate)</b>
h2 .....	<b>1.0</b>
<b>Design 2 Tab</b>	
Controls Lost .....	<b>0</b>
Treatments Lost .....	<b>0</b>
Noncompliance Proportion (Control) .....	<b>0</b>
Noncompliance Proportion (Treatment) .....	<b>0</b>
Accrual Time .....	<b>0</b>
Total Time .....	<b>5</b>
<b>Looks &amp; Boundaries Tab</b>	
Specification of Looks and Boundaries ..	<b>Simple</b>
Number of Equally Spaced Looks .....	<b>5</b>
Alpha Spending Function .....	<b>O'Brien-Fleming Analog</b>
Type of Futility Boundary .....	<b>Non-Binding</b>
Number of Skipped Futility Looks .....	<b>0</b>
Beta Spending Function .....	<b>O'Brien-Fleming Analog</b>



Group-Sequential Logrank Tests (Simulation)

Output

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

Numeric Results and Plots

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

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

Numeric Summary for Scenario 1

Power			Alpha				Beta
Value	95% LCL	95% UCL	Target	Actual	95% LCL	95% UCL	
0.779	0.771	0.788	0.025	0.025	0.022	0.028	0.221

N1	N2	HR	h1	h2	Accrual Time	Accrual Pattern	Total Time
100	100	0.671	1.490	1.000	0.0	Equal	5.0

Noncompliance					
Loss1	Loss2	Prop 1	h1	Prop 2	h2
0.000	0.000	0.000	1.000	0.000	1.000

Whole Study Averages

Study Length		Cum. Subject Time			
H0	H1	H0		H1	
G1	G2	G1	G2	G1	G2
1.8	3.1	59.1	59.0	64.6	91.6

Sample Size				Events			
H0		H1		H0		H1	
G1	G2	G1	G2	G1	G2	G1	G2
100.0	100.0	100.0	100.0	88.0	88.0	96.4	91.5

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	1.490	1.000	0.000	0.000	0.000	1.000	0.000	1.000
2	100% Accrual	1.490	1.000	0.000	0.000	0.000	1.000	0.000	1.000
3	100% Accrual	1.490	1.000	0.000	0.000	0.000	1.000	0.000	1.000
4	100% Accrual	1.490	1.000	0.000	0.000	0.000	1.000	0.000	1.000
5	100% Accrual	1.490	1.000	0.000	0.000	0.000	1.000	0.000	1.000

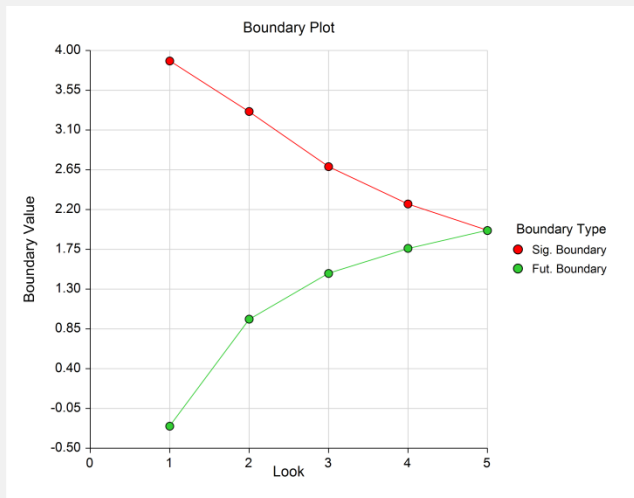
Look Details for Scenario 1

Look	Time	Sample Size		Events				Cum. Subject Time	
		Group 1	Group 2	Group 1 % of S.S.	Group 2 % of S.S.	Group 1	Group 2		
1	1.0	100.0	100.0	77.5	77.5	63.2	77.5	52.0	63.2
2	2.0	100.0	100.0	94.9	94.9	86.4	94.9	63.6	86.5
3	3.0	100.0	100.0	98.9	98.9	95.0	98.9	66.3	95.1
4	4.0	100.0	100.0	99.7	99.7	98.2	99.7	66.9	98.3
5	5.0	100.0	100.0	99.9	99.9	99.3	99.9	67.0	99.4

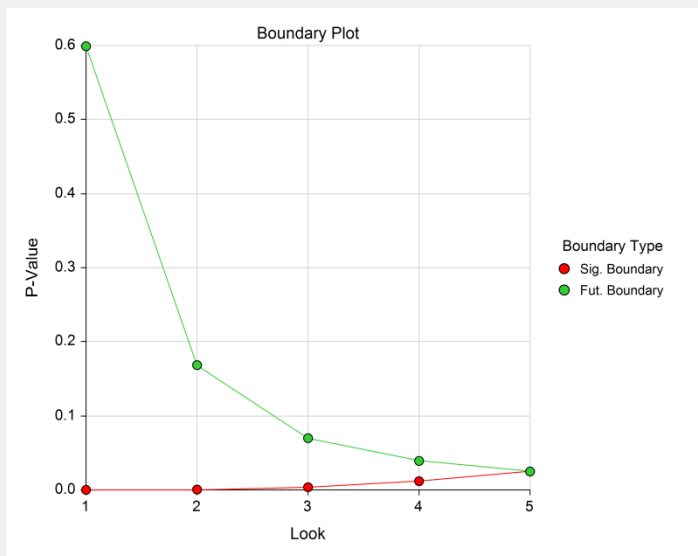
### Group-Sequential Logrank Tests (Simulation)

Look	-- Significance Boundary --		---- Futility Boundary ----	
	Z-Value	P-Value	Z-Value	P-Value
1	3.768	0.000	-0.183	0.573
2	3.318	0.000	1.070	0.142
3	2.757	0.003	1.576	0.058
4	2.268	0.012	1.833	0.033
5	2.008	0.022	2.008	0.022

Boundary Plot



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	3.768			0.000		
2	3.318	3.208	3.649	0.000	0.000	0.001
3	2.757	2.643	2.884	0.003	0.002	0.004
4	2.268	2.236	2.343	0.012	0.010	0.013
5	2.008	1.965	2.051	0.022	0.020	0.025

## Group-Sequential Logrank Tests (Simulation)

## 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	-0.183	-0.254	-0.068	0.573		
2	1.070	1.026	1.108	0.142	0.134	0.152
3	1.576	1.549	1.601	0.058	0.055	0.061
4	1.833	1.820	1.848	0.033	0.032	0.034
5	2.008	2.000	2.021	0.022	0.022	0.023

## Alpha-Spending and Null Hypothesis Simulation Details for Scenario 1

Look	----- Target -----		----- Actual -----		Proportion H0 Sims Outside Futility Boundary	Cum. H0 Sims Outside Futility Boundary
	--- Signif. Boundary---		Cum.			
	Z-Value Scale	P-Value Scale	Spending Function Alpha	Spending Function Alpha		
1	3.768	0.000	0.000	0.000	0.431	0.431
2	3.318	0.000	0.000	0.000	0.428	0.859
3	2.757	0.003	0.003	0.004	0.082	0.941
4	2.268	0.012	0.008	0.012	0.024	0.965
5	2.008	0.022	0.013	0.025	0.010	0.975

## Beta-Spending and Alternative Hypothesis Simulation Details for Scenario 1

Look	----- Target -----		----- Actual -----		Proportion H1 Sims Outside Signif. Boundary	Cum. H1 Sims Outside Signif. Boundary
	-- Futility Boundary--		Cum.			
	Z-Value Scale	P-Value Scale	Spending Function Beta	Spending Function Beta		
1	-0.183	0.573	0.006	0.006	0.083	0.083
2	1.070	0.142	0.047	0.053	0.187	0.270
3	1.576	0.058	0.061	0.114	0.235	0.505
4	1.833	0.033	0.057	0.171	0.191	0.696
5	2.008	0.022	0.050	0.221	0.083	0.779

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

## Group-Sequential Logrank Tests (Simulation)

**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**

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Group-Sequential Logrank Tests (Simulation)** procedure. You may then make the appropriate entries as listed below, or open **Example 3** by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
<b>Design 1 Tab</b>	
Solve For .....	Alpha and Power (Enter Boundaries)
Test Type .....	Logrank
Alternative Hypothesis .....	H1: Hazard1 > Hazard2
Simulations .....	10000
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 .....	1.49
Treatment Group Parameter .....	h2 (Hazard Rate)
h2.....	1.0
<b>Design 2 Tab</b>	
Controls Lost.....	0
Treatments Lost.....	0
Noncompliance Proportion (Control) .....	0
Noncompliance Proportion (Treatment) .	0
Accrual Time.....	0
Total Time.....	5
<b>Looks &amp; Boundaries Tab</b>	
Number of Looks .....	5
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)

Group-Sequential Logrank Tests (Simulation)

Output

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

Numeric Results and Plots

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

Hypotheses: H0: Hazard1 = Hazard2; H1: Hazard1 > Hazard2

Test Statistic: Logrank Test

Type of Boundaries: Significance and Futility Boundaries

Number of Looks: 5

Simulations: 10000

Numeric Summary for Scenario 1

Power			Alpha				Beta
Value	95% LCL	95% UCL	Target	Actual	95% LCL	95% UCL	
0.964	0.960	0.967	0.164	0.157	0.172	0.036	

N1	N2	HR	h1	h2	Accrual Time	Accrual Pattern	Total Time
100	100	0.671	1.490	1.000	0.0	Equal	5.0

Noncompliance					
Loss1	Loss2	Prop 1	h1	Prop 2	h2
0.000	0.000	0.000	1.000	0.000	1.000

Whole Study Averages

Study Length		Cum. Subject Time			
H0	H1	H0		H1	
G1	G2	G1	G2	G1	G2
3.8	3.1	66.0	66.0	62.5	87.6

Sample Size				Events			
H0		H1		H0		H1	
G1	G2	G1	G2	G1	G2	G1	G2
100.0	100.0	100.0	100.0	98.3	98.3	93.2	87.5

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	1.490	1.000	0.000	0.000	0.000	1.000	0.000	1.000
2	100% Accrual	1.490	1.000	0.000	0.000	0.000	1.000	0.000	1.000
3	100% Accrual	1.490	1.000	0.000	0.000	0.000	1.000	0.000	1.000
4	100% Accrual	1.490	1.000	0.000	0.000	0.000	1.000	0.000	1.000
5	100% Accrual	1.490	1.000	0.000	0.000	0.000	1.000	0.000	1.000

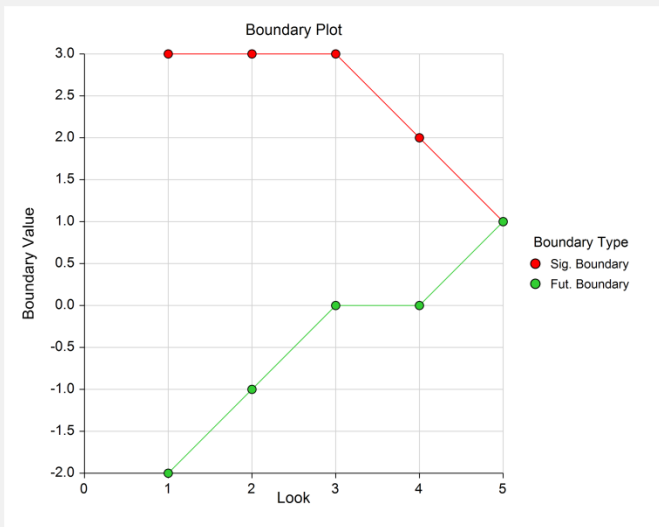
Look Details for Scenario 1

Look	Time	Sample Size		Events				Cum. Subject Time	
		Group 1	Group 2	Group 1	% of S.S.	Group 2	% of S.S.	Group 1	Group 2
1	1.0	100.0	100.0	77.5	77.5	63.2	77.5	51.9	63.2
2	2.0	100.0	100.0	94.9	94.9	86.4	94.9	63.7	86.5
3	3.0	100.0	100.0	98.9	98.9	95.0	98.9	66.3	95.1
4	4.0	100.0	100.0	99.7	99.7	98.2	99.7	66.9	98.3
5	5.0	100.0	100.0	99.9	99.9	99.3	99.9	67.0	99.5

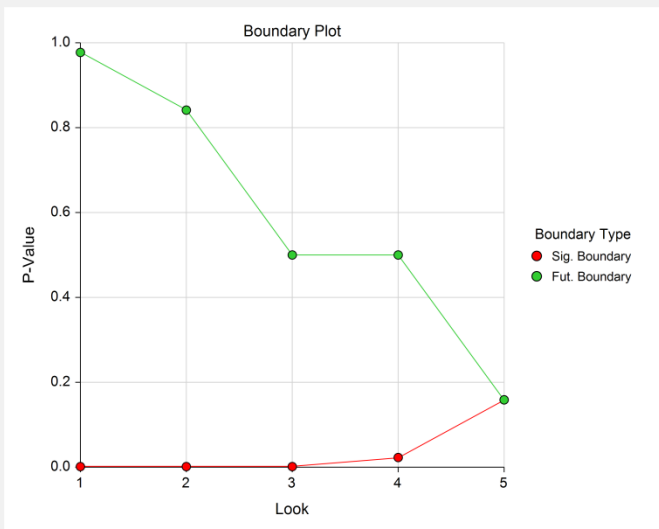
### Group-Sequential Logrank Tests (Simulation)

Look	-- Significance Boundary --		---- Futility Boundary ----	
	Z-Value Scale	P-Value Scale	Z-Value Scale	P-Value Scale
1	3.000	0.001	-2.000	0.977
2	3.000	0.001	-1.000	0.841
3	3.000	0.001	0.000	0.500
4	2.000	0.023	0.000	0.500
5	1.000	0.159	1.000	0.159

**Boundary Plot**



**Boundary Plot - P-Value**



**Group-Sequential Logrank Tests (Simulation)****Alpha-Spending and Null Hypothesis Simulation Details for Scenario 1**

Look	--- Signif. Boundary---		Alpha Spent	Cum. Alpha Spent	Proportion	Cum.
	Z-Value Scale	P-Value Scale			H0 Sims Outside Futility Boundary	H0 Sims Outside Futility Boundary
1	3.000	0.001	0.001	0.001	0.024	0.024
2	3.000	0.001	0.001	0.002	0.133	0.157
3	3.000	0.001	0.001	0.002	0.341	0.498
4	2.000	0.023	0.019	0.022	0.008	0.506
5	1.000	0.159	0.143	0.164	0.329	0.836

**Beta-Spending and Alternative Hypothesis Simulation Details for Scenario 1**

Look	-- Futility Boundary--		Beta Spent	Cum. Beta Spent	Proportion	Cum.
	Z-Value Scale	P-Value Scale			H1 Sims Outside Signif. Boundary	H1 Sims Outside Signif. Boundary
1	-2.000	0.977	0.000	0.000	0.262	0.262
2	-1.000	0.841	0.000	0.000	0.142	0.403
3	0.000	0.500	0.003	0.003	0.042	0.445
4	0.000	0.500	0.000	0.003	0.343	0.788
5	1.000	0.159	0.033	0.036	0.176	0.964

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

## Group-Sequential Logrank Tests (Simulation)

**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**

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Group-Sequential Logrank Tests (Simulation)** procedure. You may then make the appropriate entries as listed below, or open **Example 4** by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
<b>Design 1 Tab</b>	
Solve For .....	Alpha and Power (Enter Boundaries)
Test Type .....	Logrank
Alternative Hypothesis .....	H1: Hazard1 ≠ Hazard2
Simulations .....	10000
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 .....	1.4
Treatment Group Parameter .....	h2 (Hazard Rate)
h2.....	1.0
<b>Design 2 Tab</b>	
Controls Lost.....	0
Treatments Lost.....	0
Noncompliance Proportion (Control) .....	0
Noncompliance Proportion (Treatment) .	0
Accrual Time.....	0
Total Time.....	5
<b>Looks &amp; Boundaries Tab</b>	
Number of Looks .....	5
Types of Boundaries.....	Significance Boundaries
Significance Boundary.....	4.101, 3.290, 2.644, 2.245, 1.982 (looks 1 through 5)



## Group-Sequential Logrank Tests (Simulation)

**Output**

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

**Numeric Results and Plots**

Numeric Summary for Scenario 1							
----- Power -----				----- Alpha -----			
Value	95% LCL	95% UCL	Target	Actual	95% LCL	95% UCL	
0.642	0.633	0.652	0.045	0.041	0.049	0.358	
N1	N2	HR	h1	h2	Accrual Time	Accrual Pattern	Total Time
100	100	0.714	1.400	1.000	0.0	Equal	5.0
----- Noncompliance -----							
Loss1	Loss2	Prop 1	h1	Prop 2	h2		
0.000	0.000	0.000	1.000	0.000	1.000		
Whole Study Averages							
--- Study Length ---		----- Cum. Subject Time -----					
		----- H0 -----		----- H1 -----			
H0	H1	G1	G2	G1	G2		
5.0	3.9	71.3	71.3	70.3	95.8		
----- Sample Size -----				----- Events -----			
----- H0 -----		----- H1 -----		----- H0 -----		----- H1 -----	
G1	G2	G1	G2	G1	G2	G1	G2
100.0	100.0	100.0	100.0	99.9	99.9	98.3	95.8

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.

## Group-Sequential Logrank Tests (Simulation)

**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**

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Group-Sequential Logrank Tests (Simulation)** procedure. You may then make the appropriate entries as listed below, or open **Example 5** by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
<b>Design 1 Tab</b>	
Solve For .....	<b>Power</b>
Test Type .....	<b>Logrank</b>
Alternative Hypothesis .....	<b>H1: Hazard1 &gt; Hazard2</b>
Simulations .....	<b>200000</b>
Alpha .....	<b>0.025</b>
Group Allocation .....	<b>Enter total sample size and percentage in Group 1</b>
Total Sample Size (N) .....	<b>1244</b>
Percent in Group 1 .....	<b>50</b>
Input Type .....	<b>Mortality</b>
M1 .....	<b>=pC</b>
Treatment Group Parameter .....	<b>M2 (Mortality)</b>
M2 .....	<b>=pE</b>
T0 .....	<b>1.0</b>

**Group-Sequential Logrank Tests (Simulation)**

**Design 2 Tab**

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

**Looks & Boundaries Tab**

Specification ..... **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**

**Output**

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

**Numeric Results and Plots**

**Numeric Summary for Scenario 1**

Power				Alpha				Beta
Value	95% LCL	95% UCL	Target	Actual	95% LCL	95% UCL		
0.89508	0.89374	0.89642	0.02500	0.02500	0.02432	0.02568	0.10492	

N1	N2	HR	h1	h2	Accrual Time	Accrual Pattern	Total Time
622	622	Calc.	pC	pE	1.0	24.0	Accrual60.0

Noncompliance						
Loss1	Loss2	Prop 1	h1	Prop 2	h2	
0.00000	0.00000	dropin	h2	NonComp	h1	

**Whole Study Averages**

Study Length		Cum. Subject Time			
H0	H1	H0		H1	
G1	G2	G1	G2	G1	G2
59.6	38.3	16554.6	16554.8	9877.8	10686.6

Sample Size				Events			
H0		H1		H0		H1	
G1	G2	G1	G2	G1	G2	G1	G2
622.0	622.0	621.8	621.8	381.2	381.2	252.2	208.1

### Group-Sequential Logrank Tests (Simulation)

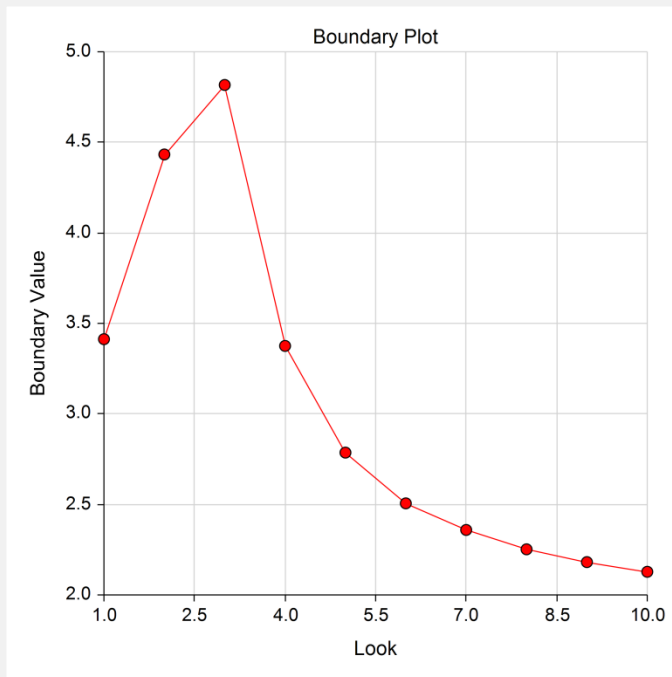
#### Look Details for Scenario 1

Look	Time	--- Sample Size ---		----- Events -----				-- Cum. Subject Time --	
		Group 1	Group 2	Group 1	% of S.S.	Group 2	% of S.S.	Group 1	Group 2
1	6.0	37.0	37.0	3.2	8.7	2.4	8.7	84.4	86.0
2	12.0	159.0	159.0	19.9	12.5	15.1	12.5	574.2	590.3
3	18.0	378.0	378.0	61.7	16.3	47.5	16.3	1918.1	1988.1
4	24.0	622.0	622.0	131.3	21.1	102.5	21.1	4351.3	4548.0
5	30.0	622.0	622.0	197.2	31.7	157.3	31.7	7086.0	7492.5
6	36.0	622.0	622.0	248.6	40.0	202.4	40.0	9475.6	10141.9
7	42.0	622.0	622.0	290.9	46.8	241.1	46.8	11585.2	12540.8
8	48.0	622.0	622.0	326.1	52.4	274.4	52.4	13463.0	14723.9
9	54.0	622.0	622.0	356.2	57.3	303.9	57.3	15146.4	16719.7
10	60.0	622.0	622.0	383.1	61.6	331.1	61.6	16658.9	18545.7

#### Boundaries for Scenario 1

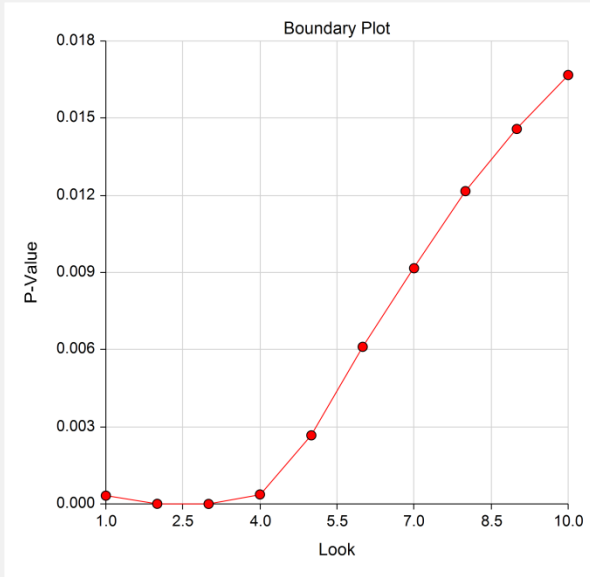
Look	-- Significance Boundary --	
	Z-Value Scale	P-Value Scale
1	3.41264	0.00032
2	4.43292	0.00000
3	4.81688	0.00000
4	3.37535	0.00037
5	2.78612	0.00267
6	2.50579	0.00611
7	2.35888	0.00916
8	2.25193	0.01216
9	2.18130	0.01458
10	2.12776	0.01668

#### Boundary Plot



### Group-Sequential Logrank Tests (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	3.41264			0.00032		
2	4.43292			0.00000		
3	4.81688			0.00000		
4	3.37535	3.28706	3.43887	0.00037	0.00029	0.00051
5	2.78612	2.76076	2.80458	0.00267	0.00252	0.00288
6	2.50579	2.48677	2.52154	0.00611	0.00584	0.00645
7	2.35888	2.34004	2.37485	0.00916	0.00878	0.00964
8	2.25193	2.23824	2.26422	0.01216	0.01178	0.01260
9	2.18130	2.16893	2.19663	0.01458	0.01402	0.01504
10	2.12776	2.11619	2.14044	0.01668	0.01616	0.01716

Alpha-Spending and Null Hypothesis Simulation Details for Scenario 1

Look	----- Target -----		----- Actual -----		Proportion H1 Sims Outside Signif. Boundary	Cum. H1 Sims Outside Signif. Boundary
	--- Signif. Boundary ---		Cum.			
	Z-Value Scale	P-Value Scale	Spending Function Alpha	Spending Function Alpha		
1	3.41264	0.00032	0.00000	0.00000	0.00000	0.00006
2	4.43292	0.00000	0.00000	0.00000	0.00000	0.00012
3	4.81688	0.00000	0.00000	0.00000	0.00000	0.00057
4	3.37535	0.00037	0.00036	0.00036	0.00036	0.11145
5	2.78612	0.00267	0.00248	0.00284	0.00248	0.31104
6	2.50579	0.00611	0.00415	0.00699	0.00415	0.21382
7	2.35888	0.00916	0.00474	0.01173	0.00474	0.11818
8	2.25193	0.01216	0.00465	0.01638	0.00465	0.06987
9	2.18130	0.01458	0.00442	0.02080	0.00442	0.04274
10	2.12776	0.01668	0.00420	0.02500	0.00420	0.02744

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 0.89508, 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.