Chapter 722

Group-Sequential Superiority by a Margin Analysis for Two Hazard Rates

Note: The corresponding sample size procedure, found in PASS Sample Size software, is Group-Sequential Superiority by a Margin Tests for Two Hazard Rates (Simulation).

Introduction

This procedure is used to test superiority by a margin for the difference of two hazard rates in stages (sometimes called looks or interim analyses) using group-sequential methods. This methodology assumes an underlying Exponential model. Unless the stage boundaries are entered directly, the stage boundaries are defined using a specified spending function. Futility boundaries can be binding or non-binding. Futility boundaries are specified through a beta-spending function.

Sample size re-estimation, based on current-stage sample sizes and parameter estimates, may also be obtained in this procedure.

The spending functions available in this procedure are the O’Brien-Fleming analog, the Pocock analog, the Hwang-Shih-DeCani gamma family, and the power family.

At each stage, the current and future boundaries are calculated based on the accumulated information proportion. Conditional and predictive power for future stages is also given.

A group-sequential boundary and analysis graph is produced in this procedure.
At each stage, stage-adjusted difference estimates, confidence intervals, and p-values are available. The probabilities of crossing future boundaries may also be assessed, using simulation. The format of the data for use in this procedure is three columns: one column for the response values, one column defining the two groups, and a third column defining the stage.

### Outline of a Group-Sequential Study

There are three basic phases of a group-sequential (interim analysis) study:

- Design
- Group-Sequential Analysis
- Reporting

### Design Phase – Determine the Number of Subjects

To begin the group-sequential testing process, an initial calculation should be made to determine the sample size and target information if the final stage is reached (maximum information). The sample size calculation requires the specification of the following:

- Alpha
- Power
- Test Direction
- Types of boundaries (efficacy, binding futility, non-binding futility)
- Maximum number of stages
- Proportion of maximum information at each stage
- Spending functions
- Assumed survival rates

The design phase calculation may be done in the PASS sample size software program. PASS software permits the user to easily try a range of hazard rate differences, as these values are typically not known in advance.

The resulting sample size of the sample size calculation also permits the calculation of the maximum information, which is the total information of the study if the final stage is reached (for calculation details, see the Information section later in this chapter).

Based on the maximum information, the target information and target sample size of each stage may be calculated. In particular, this permits the user to have a target sample size for the first stage.

Although it is likely to change over the course of the group-sequential analysis, a design group-sequential boundary plot can be a useful visual representation of the design:
Group-Sequential Analysis Phase

A group sequential analysis consists of a series of stages where a decision to stop or continue is made at each stage.

First Interim Stage

The design phase gives the target number of subjects for the first stage, based on the time of the first stage and the accrual specification. The study begins, and response data is collected for subjects, moving toward the first-stage target number of subjects, until a decision to perform an analysis on the existing data is made. The analysis at this point is called the first stage.

Unless the number of subjects at the first stage matches the design target for the first stage, the calculated information at the first stage will not exactly match the design information for the first stage. Generally, the calculated information will not differ too greatly from the design information, but regardless, spending function group-sequential analysis is well-suited to make appropriate adjustments for any differences.

The first stage information is divided by the maximum information to obtain the stage one information proportion (or information fraction). This information proportion is used in conjunction with the spending function(s) to determine the alpha and/or beta spent at that stage. In turn, stage one boundaries, corresponding to the information proportion, are calculated.

A z-statistic is calculated from the raw hazard rate difference, or other logrank-type method. The stage one z-statistic is compared to each of the stage one boundaries. Typically, if one of the boundaries is crossed, the study is stopped (non-binding futility boundaries may be an exception).
If none of the boundaries are crossed the study continues to the next stage.

If none of the boundaries are crossed it may also be useful to examine the conditional power or stopping probabilities of future stages. Conditional power and stopping probabilities are based on the user-specified supposed true difference.
Second and other interim stages (if reached)

If the first stage time proportion is not equal to the design time proportion, a designation must be made at this point as to the target time of the second stage. Two options are available in this procedure.

One option is to target the information proportion of the original design. For example, if the original design proportions of a four-stage design are 0.25, 0.50, 0.75, 1.0, and the stage one observed proportion is 0.22, the researcher might still opt to target 0.50 for the second stage, even though that now requires an additional information accumulation of 0.28 (proportion). The third and fourth stage targets would also remain 0.75 and 1.0.

A second option is to adjust the target information proportionally to the remaining proportions. For this option, if the design proportions are 0.25, 0.50, 0.75, 1.0, and 0.22 is observed, the remaining 0.78 is distributed proportionally to the remaining stages. In this example, the remaining target proportions become 0.48, 0.74, 1.0.

For either option, once the target information is determined for the next stage, revised target sample sizes are given, and the study continues until the decision is made to perform the next interim analysis on the cumulative response data. In the same manner as the first stage, the current stage information proportion is used with the spending function to determine alpha and/or beta spent at the current stage. The current stage boundaries are then computed. The $z$-statistic is calculated and compared to the boundaries, and a decision is made to stop or continue. If a boundary is crossed, the study is typically stopped.
If none of the boundaries are crossed the study continues to the next stage.

Once again, if no boundary is crossed, conditional power and stopping probabilities may be considered based on a choice of a supposed true difference.

The study continues from stage to stage until the study is stopped for the crossing of a boundary, or until the final stage is reached.

**Final Stage (if reached)**

The final stage (if reached) is similar to all the interim stages, with a couple of exceptions. For all interim analyses the decision is made whether to stop for the crossing of a boundary, or to continue to the next stage. At the final stage, only the decision of efficacy or futility can be made.

Another intricacy of the final stage that does not apply to the interim stages is the calculation of the maximum information. At the final stage, the current information must become the maximum information, since the spending functions require that the proportion of information at the final look must be 1.0. If the current information at the final stage is less than the design maximum information, the scenario is sometimes described as *under-running*. Similarly, if the current information at the final stage is greater than the design maximum information, the result may be termed *over-running*.

For both under-running and over-running, the mechanism for adjustment is the same, and is described in the Technical Details section, under Information and Total Information.

Aside from these two exceptions, the final stage analysis is made in the same way that interim analyses were made. The remaining alpha and beta to be spent are used to calculate the final stage boundaries. If the test is a one-sided test, then the final stage boundary is a single value. The final stage $z$-statistic is computed from the sample hazard rates of the complete data from each group. The $z$-statistic is compared to the boundary and a decision of efficacy or futility is made.
Reporting Phase

Once a group-sequential boundary is crossed and the decision is made to stop, there remains the need to properly summarize and communicate the study results. Some or all of the following may be reported:

- Boundary plot showing the crossed boundary
- Adjusted confidence interval and estimate of the hazard rate difference
- Sample size used

Boundary plot showing the crossed boundary

The boundary plot gives an appropriate visual summary of the process leading to the reported decision of the study.

Adjusted confidence interval and estimate of the hazard rate difference

Due to the bias that is introduced in the group-sequential analysis process, the raw data confidence interval of the difference in hazard rates should not be used. An adjusted confidence interval should be used instead. See the Adjusted Confidence Interval topic of the Technical Details section for details. The mid-point of the adjusted confidence interval may be useful as a point estimate of the difference in hazard rates. Further, the confidence level at which the adjusted confidence interval limit is zero gives a rough adjusted p-value.

Sample size used

The sample size at the point the study was stopped should be reported in addition to the sample size that would have been used had the final stage been reached.
Technical Details

Many articles and texts have been written about group sequential analysis. Details of many of the relevant topics are discussed below, but this is not intended to be a comprehensive review of group-sequential methods. One of the more influential works in the area of group-sequential analysis is Jennison and Turnbull (2000).

Null and Alternative Hypotheses

For superiority by a margin tests of two hazard rates, the appropriate null and alternative hypotheses depend on whether higher hazard rates are better or higher hazard rates are worse.

Case 1: Low Hazard Rates Good

In this case, lower hazard rates are better. The hypotheses are arranged so that rejecting the null hypothesis implies that the treatment hazard rate is less than the reference hazard rate by at least the margin of superiority. The value of $\delta$ at which power is calculated must be less than $-|M_S|$. The null and alternative hypotheses with $\delta_0 = -|M_S|$ are

\[
H_0: h_1(T) \geq h_2(T) - |M_S| \quad \text{versus} \quad H_1: h_1(T) < h_2(T) - |M_S|
\]

\[
H_0: h_1(T) - h_2(T) \geq -|M_S| \quad \text{versus} \quad H_1: h_1(T) - h_2(T) < -|M_S|
\]

\[
H_0: \delta \geq -|M_S| \quad \text{versus} \quad H_1: \delta < -|M_S|
\]

Case 2: High Hazard Rates Good

In this case, higher hazard rates are better. The hypotheses are arranged so that rejecting the null hypothesis implies that the treatment hazard rate is greater than the reference hazard rate by at least the margin of superiority. The value of $\delta$ at which power is calculated must be greater than $|M_S|$. The null and alternative hypotheses with $\delta_0 = |M_S|$ are

\[
H_0: h_1(T) \leq h_2(T) + |M_S| \quad \text{versus} \quad H_1: h_1(T) > h_2(T) + |M_S|
\]

\[
H_0: h_1(T) - h_2(T) \leq |M_S| \quad \text{versus} \quad H_1: h_1(T) - h_2(T) > |M_S|
\]

\[
H_0: \delta \leq |M_S| \quad \text{versus} \quad H_1: \delta > |M_S|
\]

Stages in Group-Sequential Testing

The potential to obtain the benefit from a group-sequential design and analysis occurs when the response data are collected over a period of weeks, months, or years rather than all at once. A typical example is the case where patients are enrolled in a study as they become available, as in many types of clinical trials.

A group-sequential testing stage is a point in the accumulation of the data where an interim analysis occurs, either by design or by necessity. At each stage, a test statistic is computed with all the accumulated data, and it is determined whether a boundary (efficacy or futility) is crossed. When an efficacy (or futility) boundary is crossed, the study is usually concluded, and inference is made. If the final stage is reached, the group-sequential design forces a decision of efficacy or futility at this stage.

For the discussions below, a non-specific interim analysis stage is referenced as $k$, and the final stage is $K$. 

Test Statistic (MLE)

The $z$-statistic from MLE estimates for any stage $k$ is obtained from all the accumulated data up to and including that stage.

The general form of the test statistic is, when lower hazard rates are better:

$$
z_k = \frac{\hat{h}_{1k} - \hat{h}_{2k} - (-|SM|)}{\sqrt{\hat{\sigma}_k^2(\hat{h}_{1k}) + \hat{\sigma}_k^2(\hat{h}_{2k})}} = \frac{\hat{h}_{1k} - \hat{h}_{2k} + |SM|}{\sqrt{\hat{\sigma}_k^2(\hat{h}_{1k}) + \hat{\sigma}_k^2(\hat{h}_{2k})}}$$

and, when higher hazard rates are better:

$$
z_k = \frac{\hat{h}_{1k} - \hat{h}_{2k} - |SM|}{\sqrt{\hat{\sigma}_k^2(\hat{h}_{1k}) + \hat{\sigma}_k^2(\hat{h}_{2k})}}$$

with

$$\hat{h}_{ik} = \frac{\sum_{j=1}^{n_{ik}} c_{ijk}}{\sum_{j=1}^{n_{ik}} x_{ijk}}$$

$$\hat{\sigma}_k^2(\hat{h}_{ik}) = \frac{\sum_{j=1}^{n_{ik}} c_{ijk}^2}{\left(\sum_{j=1}^{n_{ik}} x_{ijk}\right)^2} = \frac{\hat{h}_{ik}^2}{\sum_{j=1}^{n_{ik}} x_{ijk}}$$

where

- $i = 1, 2$ for the two groups
- $\hat{h}_{ik}$ is the estimated group hazard rate at stage $k$
- $\hat{\sigma}_k^2(\hat{h}_{ik})$ is the variance of the hazard rate estimator
- $c_{ijk}$ is an indicator of censoring
- $x_{ijk}$ is the elapsed time

Group-Sequential Design Phase

In most group-sequential studies there is a design or planning phase prior to beginning response collection. In this phase, researchers specify the anticipated number and spacing of stages, the types of boundaries that will be used, the desired alpha and power levels, the spending functions, and the anticipated hazard rates with the corresponding estimate of the true difference in hazard rates.

Based on these input parameters, an initial set of boundaries is produced, an estimate of the total number of needed subjects is determined, and the anticipated total information at the final stage is calculated. The appropriate procedure in PASS (sample size software) can be used to make these planning phase sample size estimation calculations.
Information and Total Information

In the group-sequential design phase, the final stage ($K$) or total (design) information is calculated from the specified rates and the final sample sizes, as

\[
I_K = \frac{1}{\sigma_K^2(h_1, l_1, p_1) + \sigma_K^2(h_2, l_2, p_2)} \frac{n_1K}{n_2K}
\]

where

\[
i = 1,2 \text{ for the two groups}
\]

\[
\sigma_K^2(h_i, l_i, p_i) \text{ is the variance of the hazard rate estimator}
\]

\[
h_i \text{ is the group hazard rate}
\]

\[
l_i \text{ is the group loss hazard rate}
\]

\[
p_i \text{ is the group patient entry parameter}
\]

and

\[
\sigma_K^2(h_i, l_i, p_i) = h_i^2 \left( \frac{h_i}{h_i + l_i} + \frac{h_i p_i e^{-(h_i + l_i)T}(1 - e^{-(h_i + l_i)(h_i + l_i - p_i)})}{(1 - e^{-p_i T_0})(h_i + l_i)(h_i + l_i - p_i)} \right)^{-1}
\]

for $i = 1,2$,

where

\[
T_0 \text{ is the accrual time}
\]

\[
T \text{ is the total time}
\]

If patient entry is uniform, the group variance is (Lachin and Foulkes, 1986):

\[
\sigma_K^2(h_i, l_i, p_i) = h_i^2 \left( \frac{h_i}{h_i + l_i} + \frac{1 - e^{-(T - T_0)(h_i + l_i) - e^{-T_0(h_i + l_i)}}}{T_0(h_i + l_i)} \right)^{-1}
\]

The information at any data stage $k$ may be calculated from the specified rates and the sample sizes, as

\[
l_k = \frac{1}{\sigma_K^2(h_{1k}) + \sigma_K^2(h_{2k})}
\]

with variance estimates as defined in the Test Statistic (MLE) section.

The proportion of the total information (or information fraction) at any stage is

\[
p_k = \frac{l_k}{l_K}
\]

The information fractions are used in conjunction with the spending function(s) to define the alpha and/or beta to be spent at each stage.

To properly use the spending function at the final stage, it is required that $p_K = 1$. However, if the final stage is reached, we see that

\[
l_K = \frac{1}{\sigma_K^2(h_{1K}) + \sigma_K^2(h_{2K})} \neq l_K^* = \frac{1}{\sigma_K^2(h_1, l_1, p_1) + \sigma_K^2(h_2, l_2, p_2)} \frac{n_1K}{n_2K}
\]
so that

\[ p_K = \frac{I_K}{I_K^*} \neq 1 \]

When \( I_K > I_K^* \), it is called over-running. When \( I_K < I_K^* \), it is called under-running. In either case, the spending function is adjusted to accommodate the inequality, by redefining

\[ I_K^* = I_K \]

See the discussion in Wassmer and Brannath (2016), pages 78-79, or Jennison and Turnbull (2000), pages 153-154, 162.

**Types of Boundaries**

A variety of boundary designs are available to reflect the needs of the study design.

**Efficacy Only**

The simplest group-sequential test involves a single set of stage boundaries with early stopping for efficacy.
**Efficacy and Binding Futility**

This design allows early stopping for either efficacy or futility. For binding futility designs, the Type I error protection (alpha) is only maintained if the study is strictly required to stop if either boundary is crossed.

**Efficacy and Non-Binding Futility**

This design also allows early stopping for either efficacy or futility. For non-binding futility designs, the Type I error protection (alpha) is maintained, regardless of whether the study continues after crossing a futility boundary. However, the effect is to make the test conservative (alpha is lower than the stated alpha and power is lower than the stated power).
**Futility Only**
In this design, the interim analyses are used only for futility. Please be aware that, due to computational complexity, these boundaries may take several minutes to compute, particularly when some stages are skipped.

**Boundary Calculations**
The foundation of the spending function approach used in this procedure is given in Lan & DeMets (1983). This procedure implements the methods given in Reboussin, DeMets, Kim, & Lan (1992) to calculate the boundaries and stopping probabilities of the various group sequential designs. Some adjustments are made to these methods to facilitate the calculation of futility boundaries.

**Binding vs. Non-Binding Futility Boundaries**
Futility boundaries are used to facilitate the early stopping of studies when early evidence leans to lack of efficacy. When binding futility boundaries are to be used, the calculation of the futility and efficacy boundaries assumes that the study will be strictly stopped at any stage where a futility or efficacy boundary is crossed. If strict adherence is not maintained, then the Type I and Type II error probabilities associated with the boundaries are no longer valid. One (perhaps undesirable) effect of using binding futility boundaries is that the resulting final stage boundary may be lower than the boundary given in the corresponding fixed-sample design.

When non-binding futility boundaries are calculated, the efficacy boundaries are first calculated ignoring futility boundaries completely. This is done so that alpha may be maintained whether or not a study continues after crossing a futility boundary. One (perhaps undesirable) effect of using non-binding futility boundaries is that the overall group-sequential test becomes conservative (alpha is lower than the stated alpha and power is lower than the stated power).
Spending Functions

Spending functions are used to distribute portions of alpha (or beta) to the stages according to the proportion of accumulated information at each look.

Spending Function Characteristics

- Spending functions give a value of zero when the proportion of accumulated information is zero.

  \[
  \alpha(0) = 0 \text{ (for alpha-spending)} \\
  \beta(0) = 0 \text{ (for beta-spending)}
  \]

- Spending functions are increasing functions.

- Spending functions give a value of alpha (or beta) when the proportion of accumulated information is one.

  \[
  \alpha(1) = \alpha \text{ (for alpha-spending)} \\
  \beta(1) = \beta \text{ (for beta-spending)}
  \]

Using spending functions in group-sequential analyses is very flexible in that neither the information proportions nor the number of stages need be specified in advance to maintain Type I and Type II error protection.

Spending Functions Available in this Procedure

The following spending functions are shown as alpha-spending functions. The corresponding beta-spending function is given by replacing \( \alpha \) with \( \beta \).

O’Brien-Fleming Analog

The O’Brien Fleming Analog (Lan & DeMets, 1983) roughly mimics the O’Brien-Fleming (non-spending function) design, with the key attribute that only a small proportion of alpha is spent early. Its popularity comes from it proportioning enough alpha to the final stage that the final stage boundary is not too different from the fixed-sample (non-group-sequential) boundary.

\[
\alpha(0) = 0 \\
\alpha(p_k) = 2 - 2\Phi\left(\frac{Z_{1-\alpha/2}}{\sqrt{p_k}}\right) \\
\alpha(1) = \alpha
\]
Pocock Analog

The Pocock Analog (Lan & DeMets, 1983) roughly mimics the Pocock (non-spending function) design, with the key attribute that alpha is spent roughly equally across all stages.

\[
\alpha(0) = 0
\]

\[
\alpha(p_k) = \alpha \ln(1 + (e - 1)p_k)
\]

\[
\alpha(1) = \alpha
\]
Power Family
The power family of spending functions has a $\rho$ parameter that gives flexibility in the spending function shape.

\[
\begin{align*}
\alpha(0) &= 0 \\
\alpha(p_k) &= p_k^\rho, \quad \rho > 0 \\
\alpha(1) &= \alpha
\end{align*}
\]

A power family spending function with a $\rho$ of 1 is similar to a Pocock design, while a power family spending function with a $\rho$ of 3 is more similar to an O’Brien-Fleming design.

$\rho = 1$

\[\text{Group-Sequential Plot}\]

$\rho = 2$

\[\text{Group-Sequential Plot}\]
\[ \rho = 3 \]
Hwang-Shih-DeCani (Gamma Family)

The Hwang-Shih-DeCani gamma family of spending function has a $\gamma$ parameter that allows for a variety of spending functions.

\[ \alpha(0) = 0 \]
\[ \alpha(p_k) = \alpha \left( \frac{1 - e^{-\gamma p_k}}{1 - e^{-\gamma}} \right), \quad \gamma \neq 0 \]
\[ \alpha(p_k) = \alpha p_k, \quad \gamma = 0 \]
\[ \alpha(1) = \alpha \]

$\gamma = -3$

$\gamma = -1$
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\[ \gamma = 1 \]

\[ \gamma = 3 \]
Adjusted Confidence Intervals

Except at the first stage, the raw (naïve) estimates of the confidence interval limits are inherently biased in the group-sequential analysis setting. The method given in Reboussin, DeMets, Kim, & Lan (1992) is used to calculate appropriately adjusted confidence limits and is based on Kim and DeMets (1987). This stage-wise ordering method is recommended by Jennison and Turnbull (2000) as “the only method available for use with unpredictable information sequences.”

The methods used for the calculation of these confidence limits are based on the assumption that the current stage is the stopping stage of the study (typically from the crossing of a boundary).

As the methods in Reboussin et al. (1992) give only efficacy boundary results, the calculation adjustments are based only on the efficacy boundaries. The futility boundaries are not used in these calculations, except as they affect the efficacy boundaries.

Adjusted ‘p-values’

As the raw (naïve) p-value is inherently biased in the group-sequential analysis setting, a sequential-test adjusted p-value should be used instead. Rather than giving a p-value in this procedure, a search is used to determine the adjusted confidence interval level at which an interval limit equals zero. As such, the methods used for this calculation are also based on the assumptions that the current stage is the stopping stage of the study. Again, only efficacy bounds are used.

Adjusted Hazard Rate Difference

The adjusted hazard rate difference is rough estimate of the difference calculated simply as the midpoint of the adjusted confidence interval limits.

Conditional Power

From Jennison and Turnbull (2000) pages 205 to 208, the general upper one-sided conditional power at stage $k$ for rejecting a null hypothesis about a parameter $\theta$ at the end of the study, given the observed test statistic, $Z_k$, is computed as

$$ P_{uk}(\theta) = \Phi \left( \frac{Z_k \sqrt{I_k} - z_{1-\alpha} \sqrt{I_k} + \theta(I_k - I_k)}{\sqrt{I_k} - I_k} \right), $$

the general lower one-sided conditional power at stage $k$ is computed as

$$ P_{lk}(\theta) = \Phi \left( \frac{-Z_k \sqrt{I_k} - z_{1-\alpha} \sqrt{I_k} - \theta(I_k - I_k)}{\sqrt{I_k} - I_k} \right), $$

and the general two-sided conditional power at stage $k$ is computed as

$$ P_k(\theta) = \Phi \left( \frac{Z_k \sqrt{I_k} - z_{1-\alpha/2} \sqrt{I_k} + \theta(I_k - I_k)}{\sqrt{I_k} - I_k} \right) + \Phi \left( \frac{-Z_k \sqrt{I_k} - z_{1-\alpha/2} \sqrt{I_k} - \theta(I_k - I_k)}{\sqrt{I_k} - I_k} \right), $$

where

$\theta =$ the parameter being tested by the hypothesis

$k =$ an interim stage at which the conditional power is computed ($k = 1, \ldots, K - 1$)

$K =$ the stage at which the study is terminated, and the final test computed
\( Z_k \) = the test statistic calculated from the observed data that has been collected up to stage \( k \)

\( I_k \) = the information level at stage \( k \)

\( I_K \) = the information level at the end of the study

\( z_{1-\alpha} \) = the standard normal value for the test with a type I error rate of \( \alpha \).

**Predictive Power**

*Predictive power* (a Bayesian concept) is the result of averaging the conditional power over the posterior distribution of effect size. From Jennison and Turnbull (2000) pages 210 to 213, the general upper one-sided predictive power at stage \( k \) is given by

\[
P_{uk} = \Phi \left( \frac{Z_k \sqrt{I_K} - z_{1-\alpha} \sqrt{I_k}}{\sqrt{I_K - I_k}} \right)
\]

the general lower one-sided predictive power at stage \( k \) is given by

\[
P_{lk} = \Phi \left( -\frac{Z_k \sqrt{I_K} - z_{1-\alpha} \sqrt{I_k}}{\sqrt{I_K - I_k}} \right)
\]

the general two-sided predictive power at stage \( k \) is given by

\[
P_k = \Phi \left( \frac{Z_k \sqrt{I_K} - z_{1-\alpha/2} \sqrt{I_k}}{\sqrt{I_K - I_k}} \right) + \Phi \left( -\frac{Z_k \sqrt{I_K} - z_{1-\alpha/2} \sqrt{I_k}}{\sqrt{I_K - I_k}} \right)
\]

with all terms defined as in the equations for conditional power.

**Using Simulation to obtain Future Boundary Crossing Probabilities**

It can be useful to researchers to know the probability of crossing future group-sequential boundaries, given the data already obtained, and given specified assumed values for the hazard rates. The following steps are used to estimate these probabilities using simulation:

1. From the data obtained to the current stage, obtain a current estimate of the information.
2. Determine the target (cumulative) sample sizes and numbers of events for each future stage, including the final stage. Fractional sample sizes are rounded up to the next integer.
3. For each simulation, append simulated values to the current sample data to obtain a data set with the final stage sample sizes. Simulated values correspond to assumed hazard rates.
4. For each data set, determine which boundary or boundaries were crossed first (except in the case of non-binding futility boundaries). The proportion of simulations crossing each boundary (first) provides an estimate of the probability of crossing each boundary, given the specified assumed hazard rates.

**Non-binding Futility Boundaries**

When non-binding futility boundaries are used, the study may continue when a futility boundary is crossed. The simulation proportions will have a slightly different interpretation when this is the case.
Data Structure

The data for this procedure is entered in four columns, with an additional column to identify the stage times. Two columns give the individual start and end times. A censor column identifies whether the end time is due to an event or to censoring. Another column identifies the group of the patient, individual, or experimental unit.

These five columns are assigned on the Variables tab of the procedure. Groups 1 and 2 are also assigned on the Variables tab.

The current stage is also identified directly on the Variables tab.

For this data set, start dates and end dates are converted to start and end times through a transformation. The transformation for converting to year times, is

\[
Time = \frac{StartDate - Time0DateValue}{365}
\]
For this dataset, the study began on January 1, 2017. The corresponding day value for January 1, 2017 is 42736. This value is found by entering the date in an empty column, changing the Data Type to Date & Time, and then changing the Data Type back to General. Thus, the formula is

\[ \text{Start Time} = \frac{\text{StartDate} - 42736}{365} \]

and

\[ \text{End Time} = \frac{\text{EndDate} - 42736}{365} \]

The units for the Start, End, and StageTimes columns are years. Any units may be used, but the units must be consistent throughout the use of the procedure. For example, if years are the units, then hazard rates must be yearly hazard rates. Conversions may be accomplished through the Survival Parameter Conversion Tool, which is available through the Tools menu.

If an individual has not had an event at the time of the stage analysis, but is still in the study, the end time should be left blank, as in

<table>
<thead>
<tr>
<th>StartDate</th>
<th>EndDate</th>
<th>Censor</th>
<th>Group</th>
<th>Start</th>
<th>End</th>
<th>StageTimes</th>
<th>C8</th>
<th>C9</th>
<th>C10</th>
</tr>
</thead>
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<td>496</td>
<td>6/3/2019</td>
<td>0</td>
<td>Trt</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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</table>
Procedure Options

This section describes the options available in this procedure. To find out more about using a procedure in general, go to the Procedures chapter.

Variables Tab

Variables

Start Time Variable
Specify the column containing the start times for each individual. Each individual is a member of each stage for which the start time is less than the stage time. Any row without a start time will be omitted from the analysis.

<table>
<thead>
<tr>
<th>Start</th>
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<th>Cnsr</th>
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</table>

A variable containing dates should not be used here. Start times and end times may be computed from dates using a transformation or the Time Calculator tool.

End Time Variable
Specify the column containing the end times for each individual. If an end time has not been reached for an individual, the cell for the end time should be left blank.

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</table>

A variable containing dates should not be used here. Start times and end times may be computed from dates using a transformation or the Time Calculator tool.
Censor Indicator Variable
Specify the column containing the censor values for each individual. The censor values are defined in the Censored and Not Censored boxes. An individual is Censored if the end time reflects exit from the study without an event. An individual is Not Censored if the end time reflects an event, or if the individual is still in the study without an event (i.e., the End Time value is blank). Any row without a censor value will be omitted from the analysis.

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Censored Value
Specify the value of the Censor Indicator Variable that corresponds to an end time that is censored. An individual is Censored if the end time reflects exit from the study without an event. An individual is Not Censored if the end time reflects an event, or if the individual is still in the study without an event (i.e., the End Time value is blank).

Not Censored Value
Specify the value of the Censor Indicator Variable that corresponds to an un-censored individual response. An individual is Not Censored if the end time reflects an event, or if the individual is still in the study without an event (i.e., the End Time value is blank). An individual is Censored if the end time reflects exit from the study without an event.

Group Variable
Specify the column defining the grouping of the response data. The Group Variable values are assigned to Group 1 and Group 2 using the Group 1 Value and Group 2 Value entries.

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</table>

Group 1 Value
Enter the value of the Group Variable column that designates Group 1. For example, if the Group Variable column is filled with Trt and Cntrl, enter Trt as the Group 1 Value to designate all Trt rows as Group 1. Do not put quotes around the Group 1 Value.

Group 2 Value
Enter the value of the Group Variable column that designates Group 2. For example, if the Group Variable column is filled with Trt and Cntrl, enter Cntrl as the Group 2 Value to designate all Cntrl rows as Group 2. Do not put quotes around the Group 2 Value.
Stage Times Variable

Specify the column containing the stage times up to the current stage. The values in this column must begin in row 1, must be increasing, and the final row number must be the same as the number given for Current Stage (k). Each individual is a member of each stage for which the start time is less than the stage time.

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Current Stage

Current Stage (k)

Enter the number of the current stage. Corresponding stage times should be entered in the column of the Stage Times Variable.

Design

Test Type

Specify the hypothesis test Z statistic that will be calculated for comparison to boundaries and in the simulations. The most common test for comparing two survival curves is the Logrank test. Regardless of the test chosen here, the MLE estimation methods with corresponding Exponential model assumptions will be used to determine the information at each stage, as well as sample size re-estimation calculations. MLE estimation methods will also be used in the calculation of hazard rate estimates, differences, and confidence intervals.

Maximum Number of Stages (K)

Enter an integer value indicating the number of stages in the planning design if the final stage is reached.

Time Proportion at each Stage

Specify whether stages are intended to reflect evenly spaced increments in time, or whether custom spacing is to be used.

- Equally incremented
  For this selection, the increment in time at each stage is the same for all stages. For example, if the maximum number of stages is 4, the time proportion at each stage is planned to be 0.25, 0.50, 0.75, 1.00.

- Custom (Enter cumulative time proportions)
  Select this option to enter specific cumulative time proportions for each stage. The values entered should be between 0 and 1, increasing in value, and the final value should be 1. The number of proportions entered should equal the Maximum Number of Stages.

Cumulative Time Proportions

When Time Proportion at each Stage is set to Custom, this option appears to allow the user to enter specific cumulative time proportions for each stage. The values entered should be between 0 and 1, increasing in value, and the final value should be 1. The number of proportions should equal the Maximum Number of Stages. The values may be separated by spaces or commas.
N's if Final Stage Reached
Enter the sample sizes N1 and N2 corresponding to the planned group-sequential analysis study if the final stage is reached. For example, these values might be obtained through the PASS sample size software. These values are also used in the calculation of the maximum information.

Hazard Rates ($\delta = h_1 - h_2$): ($h_1$ and $h_2$)
Enter the planning design hazard rates upon which the power and sample size calculations were based. These hazard rates will be used in calculations of maximum information, conditional power, predictive power, future stage stopping probabilities, and future stage estimates of needed sample size.

Design – Accrual

T0 (Accrual or Recruitment Time)
The accrual or recruitment time, T0, is the intended (planned) length of time during which subjects can enter the study. That is, subjects are accrued, according to the accrual specifications, until time T0. T0 must be greater than 0. If all patients will enter the study at the same time (at the beginning of the study), enter a very small value, such as 0.001, for T0. T0 should also be greater than the latest start time. T0 is part of the total time.

Accrual Parameter Entry
Specify whether the accrual parameter will be specified directly, or through a calculation based on a percentage.

Percent of T0 Until 50% are Accrued
This option controls the pattern of patient entry by specifying the percentage of the accrual time needed to enroll 50% of the patients. Values between 1 and 97 may be entered. If you expect uniform patient entry, enter 50. 50 is also a reasonable middle-ground entry if the accrual pattern is unknown. If you expect more patients to enter during the early part of the accrual period, enter an amount less than 50 such as 30 or 40. A 30 here means that 50% of the patients will have been enrolled when 30% of the accrual time has elapsed. If you expect more patients to enter during the later part of the accrual period, enter an amount greater than 50 such as 60 or 70. A 70 here means that 50% of the patients will have been enrolled when 70% of the accrual time has elapsed. NCSS assumes that patient entry times follow the truncated exponential distribution. NCSS uses this entry to calculate the corresponding truncated exponential distribution parameter.

Accrual Parameter
Enter the value for the truncated exponential distribution parameter that defines the accrual pattern. This parameter controls the shape and scale of that distribution. When this parameter is 0, the result is uniform patient entry. 0 is a reasonable middle-ground entry if the accrual pattern is unknown. When this parameter is less than zero, this implies slower patient entry at the beginning of the accrual period, and faster patient entry later. When this parameter is greater than zero, patients enter more quickly early on.

T (Total Time)
Enter the (planned) total time of the study. The accrual time is part of the total time. For example, if a 5-year study is anticipated, with the first 2 years of the 5 for accrual, 5 would be entered here, and 2 would be entered for T0.
Superiority Margin

SM (Superiority Margin)
Enter the value for the superiority margin. The sign of the superiority margin is determined by the direction of the alternative hypothesis:

- **Ha: h1 - h2 < -|SM|** (Lower hazard rates are better)
  In this case, rejecting the null hypothesis implies that the treatment hazard rate is less than the reference/control/standard hazard rate by at least the margin of superiority.

- **Ha: h1 - h2 > |SM|** (Higher hazard rates are better)
  In this case, rejecting the null hypothesis implies that the treatment hazard rate is greater than the reference/control/standard hazard rate by at least the margin of superiority.

Design – Loss Hazard Rates

L1 (Loss Hazard Rate of Group 1)
This is the loss hazard rate for losses to follow-up and dropout in group 1. This rate assumes that loss to follow-up follows an Exponential distribution. This value is the reciprocal of the average number lost per unit of time (months, years, etc.). If instead you have the proportion lost to follow-up, use the Survival Parameter Conversion Tool to translate this proportion to the corresponding hazard rate.

L2 (Loss Hazard Rate of Group 2)
This is the loss hazard rate for losses to follow-up and dropout in group 3. This rate assumes that loss to follow-up follows an Exponential distribution. This value is the reciprocal of the average number lost per unit of time (months, years, etc.). If instead you have the proportion lost to follow-up, use the Survival Parameter Conversion Tool to translate this proportion to the corresponding hazard rate.

Future Stage Times

Future Stage Time Adjustment
At each stage, the actual stage time may not match the original design time. The Future Stage Time Adjustment specifies how future stage time proportions will be determined.

- **Adjust time proportions proportional to original design**
  For this selection, the target time proportion for each future stage is calculated proportionally to the remaining proportions. For this option, if the design proportions are 0.25, 0.50, 0.75, 1.0, and 0.22 is observed, the remaining 0.78 is distributed proportionally to the remaining stages. In this example, the remaining target proportions become 0.48, 0.74, 1.0.

- **Keep original design time proportions exactly**
  For this choice, the target time proportion for each future stage is left as that specified by the original design. For example, if the original design proportions of a four-stage design are 0.25, 0.50, 0.75, 1.0, and the stage one observed proportion is 0.22, the selection would target 0.50 for the second stage, even though that now requires an additional time accumulation of 0.28 (proportion). The third and fourth stage targets would also remain 0.75 and 1.0. If the next time proportion is less than the current stage time proportion, the software will automatically switch to adjusting the time proportions proportional to the original design.

Boundaries
This section is used to specify the details of the types of boundaries, the direction of the alternative hypothesis, and alpha and beta spending.
Boundaries – Boundary Structure

Boundaries Used
Use this option to determine whether boundaries are for efficacy only, futility only, or both. To see example images of each of the boundary types, see the Type of Boundaries section of the documentation.

- **Efficacy Only**
  The simplest group-sequential test involves a single set of stage boundaries with early stopping for efficacy (Rejecting H0).

- **Efficacy with Futility**
  This design allows early stopping for either efficacy (Reject H0) or futility (Accept H0). The final stage boundary is equal for the two sets of boundaries.

- **Futility Only**
  In this one-sided design, the interim analyses are used only for futility. Please be aware that these boundaries may take several minutes to compute, particularly when one or more stages are skipped.

Hypothesis Direction
Specify the direction of the alternative hypothesis. This procedure is set up to assume that group 1 is the treatment/new method group, and group 2 is the reference/control/standard group.

- **Ha: h1 - h2 < -|SM|** (Lower hazard rates are better)
  In this case, rejecting the null hypothesis implies that the treatment hazard rate is less than the reference/control/standard hazard rate by at least the margin of superiority.

- **Ha: h1 - h2 > |SM|** (Higher hazard rates are better)
  In this case, rejecting the null hypothesis implies that the treatment hazard rate is greater than the reference/control/standard hazard rate by at least the margin of superiority.

Boundary Specification
Specify whether the boundaries are calculated based on spending functions or input directly.

- **Spending Function Calculation**
  Spending function methods are now mainstream methods since they are flexible to the proportion of information at each stage, and there is a wide variety of spending functions available.

- **Enter Boundaries Directly**
  In some cases, it may be useful to enter specific Z-value boundaries. This selection provides that option.

Alpha
Alpha is the significance level used in the hypothesis tests. It is the overall probability of a Type I error. Alpha is divided among the stages of the study according the spending function. A value of 0.05 is most commonly used for two-sided tests, and 0.025 is commonly used for one-sided tests, but 0.01, 0.1, and other values are sometimes used.

Beta
Beta is the probability of a Type II error during the course of the study. Power is one minus beta. Beta is divided among the stages of the study according the selected spending function. Beta values of 0.2 and 0.1 are common, but any value between 0 and 1 is eligible.
Spending Function (Alpha or Beta)
The alpha- and beta-spending functions determine how alpha and/or beta are distributed across the stages. See the Spending Function section of the documentation for more details.

- Hwang-Shih-Decani (Gamma Family)
The Hwang-Shih-Decani gamma family of spending function has a $\gamma$ parameter that allows for a variety of spending functions. The $\gamma$ parameter can be positive, negative, or 0.

- O’Brien-Fleming Analog
The O’Brien Fleming Analog (Lan & DeMets, 1983) roughly mimics the O’Brien-Fleming (non-spending function) design, with the key attribute that only a small proportion of alpha or beta is spent early. Its popularity comes from it proportioning enough alpha (or beta) to the final stage that the final stage boundary is not too different from the fixed-sample (non-group-sequential) boundary.

- Pocock Analog
The Pocock Analog (Lan & DeMets, 1983) roughly mimics the Pocock (non-spending function) design, with the key attribute that alpha and/or beta are spent roughly equally across all stages.

- Power Family
The power family of spending functions has a $\rho$ parameter that gives flexibility in the spending function shape. The $\rho$ parameter must be greater than 0. A power family spending function with a $\rho$ of 1 is similar to a Pocock design, while a power family spending function with a $\rho$ of 3 is more similar to an O’Brien-Fleming design.

- Custom
Select this option to enter specific cumulative alpha (or beta) values for each stage. The values entered should be between 0 and alpha (or half alpha for two-sided tests) or beta, increasing in value, and the final value should be alpha (or half alpha) or beta. The number of custom cumulative alpha (or beta) spent values should equal the Maximum Number of Stages.

γ (Gamma)
$\gamma$ is used to define the Hwang-Shih-Decani ($\gamma$) spending function. Negative values of $\gamma$ spend more of alpha or beta at later looks, values near 0 spend alpha or beta evenly, and positive values of $\gamma$ spend more of alpha or beta at earlier looks.

$\rho$
$\rho$ is used to define the power family spending function. Only positive values for $\rho$ are permitted. Values of $\rho$ near zero spend more of alpha or beta at earlier looks, values near 1 spend alpha or beta evenly, and larger values of $\rho$ spend more of alpha or beta at later looks. A power family spending function with a $\rho$ of 1 is similar to a Pocock design, while a power family spending function with a $\rho$ of 3 is more similar to an O’Brien-Fleming design.

Custom Cumulative Alpha or Beta Spent
Enter a series of cumulative alpha or beta values, separated by spaces. The number of values should equal the Maximum Number of Stages. As cumulative values, the values must be increasing. The final value could be set to equal alpha or beta. Otherwise, the values will be scaled so that the final value is equal to alpha or beta.

Boundary Z Values (Entered Directly)
Enter a Z value for each stage of this boundary, separated by spaces or commas. The number of Z values entered should match the Maximum Number of Stages (K).
Skipped Stages
Specify the stages that will be skipped, if any, for this boundary. The final stage cannot be skipped. The stage numbers should be separated by spaces or commas. For example, if the maximum number of stages is 5, but a boundary analysis at stages 2 and 4 is to be skipped, 2 4 may be entered here. The spending function accounts for the amount of alpha or beta that should be spent at a stage following a skipped stage.

Binding or Non-Binding Futility
This option specifies whether the futility boundaries are binding or non-binding.

- Binding
  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.

- Non-Binding
  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. One effect of using non-binding futility boundaries is that the overall group-sequential test becomes conservative (alpha is lower than the stated alpha and power is lower than the stated power).

Reports Tab
The options on this panel specify which reports will be included in the output.

Reports for Current Stage

Summary using Z Scale
This report gives the Z-Test statistics and corresponding decision, as well as the boundary values, and the information proportion at each stage.

Summary using P-Value Scale
This report gives the Z-Test p-values and corresponding decision, as well as the boundary p-values, and the information proportion at each stage.

Current Stage Results Adjusted for Sequential Analysis
This section provides the raw hazard rate difference, the group-sequential adjusted confidence interval and difference, and the confidence level at which the adjusted confidence interval boundary is zero. These group-sequential adjusted results are based on the assumption that a stopping decision has been made. See more details near the end of the Technical Details section of the documentation.

Confidence Level
This is the confidence level used in the group-sequential adjusted confidence interval of the difference.

Descriptive Statistics
This section provides the sample sizes, raw sample hazard rates, and sample hazard rate differences at each stage. The data used at each stage is the cumulative data.

Information Report
The Information Report gives the target and achieved information, and target and achieved information proportions. Projected informations and sample sizes are given for future stages.
**Alpha Spending**

This report shows the amount and percentage of alpha spent at each stage, both individually and cumulatively. Projected values are given for future stages. The report is blank if boundaries are input directly.

**Beta Spending**

This report shows the amount and percentage of beta spent at each stage, both individually and cumulatively. Projected values are given for future stages. The report is blank if there are no futility boundaries or if boundaries are input directly.

**Conditional and Predictive Power**

This report gives the predictive power and conditional power based on the current $z$-statistic and the proportion of the information to the maximum information. The conditional power is based on the specified differences, while the predictive power is not.

**Future Boundary Crossing Probabilities using Simulation**

This report gives the various probabilities of crossing all future boundaries. These probabilities are calculated as proportions of a large number of simulated data sets. For two-sided boundary scenarios, such as ‘Two-sided Efficacy with Futility (Asymmetric)’, the comparisons of the simulation $Z$-statistics to the two (upper and lower) sides are made independently. For more details, see the description at the end of the Technical Details section of the documentation.

**Number of Simulations**

Increasing the number of simulations improves the accuracy of the estimated probabilities of boundary crossing, but it also increases the computation time. One suggestion is to first run the procedure with a small number of simulations, such as 1,000 or 10,000. The simulation time can then be estimated and a reasonable increase in simulations can be made before a second run. A decent lower number of simulations is 100,000, but more is better when feasible.

**After Boundary Crossing**

This option specifies whether simulation $Z$-values are ‘held out’ after crossing a boundary, or whether simulation $Z$-values are compared to boundaries at all future stages, regardless of whether a boundary was crossed at a previous stage. For two-sided boundary scenarios, such as ‘Two-sided Efficacy with Futility (Asymmetric)’, the comparisons of the simulation $Z$-statistics to the two (upper and lower) sides are made independently.

- **Hold out**
  
  For this selection, once a simulation $Z$-statistic crosses an efficacy boundary or a binding futility boundary, it is removed from consideration for future stages. For non-binding futility boundaries, simulation $Z$-statistics remain in the simulation for future stages, regardless of whether ‘After Boundary Crossing’ is set to ‘Hold out’ or ‘Leave in’.

- **Leave In**

  For this choice, simulation $Z$-statistics at all future stages are compared to the boundary values, regardless of whether a boundary was crossed at a previous stage.
Reports for Current Stage – Conditional and Predictive Power and Boundary Crossing Probability Parameters

Design Hazard Rates ($\delta = h_1 - h_2$)

The design difference in hazard rates is typically the difference upon which the sample size calculation is based. The design hazard rates are specified in the Design section of the Variables tab. The difference in design hazard rates is used for conditional power. For future boundary crossing probability simulations, values are simulated from Exponential distributions with these hazard rates.

Data Hazard Rates ($\delta = \text{Sample } h_1 - \text{Sample } h_2$)

The data difference in hazard rates is the difference in sample hazard rates at the current stage. The difference in data hazard rates is used for conditional power. For future boundary crossing probability simulations, values are simulated from Exponential distributions with these hazard rates.

Custom Hazard Rates ($\delta = h_1 - h_2$)

Custom differences in hazard rates, by specifying custom $h_1$ and $h_2$, may be used to determine their effect on conditional power or future boundary crossing probabilities. For future boundary crossing probability simulations, values are simulated from Exponential distributions with these hazard rates. Multiple values may be separated by spaces or commas. A separate report will be generated for each hazard rate combination.

Custom $h_1$ and $h_2$

Enter one or more values for $h_1$ and $h_2$. The difference in hazard rates is used for conditional power. For future boundary crossing probability simulations, values are simulated from Exponential distributions with these hazard rates. When more than one value is entered, a separate analysis is made for each combination of $h_1$ and $h_2$.

Planning Stage (Stage 0) Reports

Various Reports

Check the box to include this planning stage report. The reports are the same as those of the current stage reports, except that no stage results are given.

Past Reports for Previous Stages

Various Reports

Check the box to include this previous stage report. These reports are the same as those of the current stage reports, except that the results are given for each previous stage.

Report Options Tab

The options on this panel control the label and decimal options of the reports.

Report Options

Variable Names

This option lets you select whether to display only variable names, variable labels, or both.

Value Labels

This option applies to the Group Variable. It lets you select whether to display data values, value labels, or both. Use this option if you want the output to automatically attach labels to the values (like 1=Yes, 2=No, etc.). See the section on specifying Value Labels elsewhere in this manual.
Decimal Places

Decimals
This option allows the user to specify the number of decimal places directly or based on the significant digits (auto).

If one of the auto options is used, the ending zero digits are not shown. For example, if ‘Auto (Up to 7)’ is chosen, 0.0500 is displayed as 0.05

1.314583689 is displayed as 1.314584

The output formatting system is not designed to accommodate ‘Auto (Up to 13)’, and if chosen, this will likely lead to lines that run on to a second line. This option is included, however, for the rare case when a very large number of decimals is needed. Sometimes Auto (Up to 7) doesn’t show well and causes formatting problems as well.

Plots Tab

The options on this panel control the inclusion and appearance of the plots. The set of available plots depends upon the choice of ‘Boundaries Used’.

Group-Sequential Boundary Plots

Z-Statistic vs Information / Time / Stage / N
Check the boxes to display the plot. Click the plot format button to change the plot settings. To edit the plot with live data, check the box in the top-right corner before running the procedure.

Use care when adding Stage Notes (notes for each stage just above the X-axis). These notes should only be added with live data, as their position is based on the X-axis values.
**Example 1 – Group-Sequential Analysis**

A colorectal cancer study is to be conducted to determine whether a new treatment following tumor excision will result in a tumor recurrence time that is lower than that of the current standard treatment by at least 0.2. Thus, the desired margin of superiority is 0.2. The response for each patient is time, in years, before recurrence. A one-sided test with alpha equal to 0.025 is used. The MLE Z-Test for comparing two hazard rates will be used.

The new treatment is assigned to Group 1, and the standard is assigned to Group 2, so that the null and alternative hypotheses are

\[ H_0: h_1 - h_2 = -0.2 \quad (H_0: h_{\text{New}} = h_{\text{Std}} - 0.2) \]

versus

\[ H_a: h_1 - h_2 < -0.2 \quad (H_a: h_{\text{New}} < h_{\text{Std}} - 0.2) \]

The design calls for five stages of one year each, if the final stage is reached. The current stage is the 3rd stage. In the design phase, a needed power of 0.90 called for 490 patients per group if the final stage is reached, based on assumed hazard rates of 0.85 and 1.3 for the new and standard treatments, respectively. Both efficacy and non-binding futility boundaries are implemented. The efficacy (alpha-spending) spending function used is the O’Brien-Fleming analog. The Hwang-Shih-DeCani (Gamma) beta-spending function with gamma parameter 1.5 is used for futility. Accrual is intended to be steady over the 5-year period of the study. Loss hazard rates of 0.03 for both groups are anticipated.

The boundary plot for stage 2 appeared as

resulting in continuance of the study to stage 3.
You may follow along here by making the appropriate entries or load the completed template Example 1 by clicking on Open Example Template from the File menu of the procedure window.

1 Open the GS Survival SM dataset.
   - From the File menu of the NCSS Data window, select Open Example Data.
   - Click on the file GS Survival SM.NCSS.
   - Click Open.

2 Open the procedure window.
   - Using the Analysis menu or the Procedure Navigator, find and select this procedure.
   - On the menus, select File, then New Template. This will fill the procedure with the default template.

3 Specify the variables.
   - Select the Variables tab.
   - Click the small Column Selection button to the right of Start Time Variable. Select Start and click Ok. The column name ‘Start’ will appear in the Start Time Variable box.
   - Click the small Column Selection button to the right of End Time Variable. Select End and click Ok. The column name ‘End’ will appear in the End Time Variable box.
   - Click the small Column Selection button to the right of Censor Indicator Variable. Select Censor and click Ok. The column name ‘Censor’ will appear in the Censor Indicator Variable box.
   - For Censored, enter 1.
   - For Not Censored, enter 0.
   - Click the small Column Selection button to the right of Group Variable. Select Group and click Ok. The column name ‘Group’ will appear in the Group Variable box.
   - For Group 1 Value, enter Trt.
   - For Group 2 Value, enter Ctrl.
   - Click the small Column Selection button to the right of Stage Times Variable. Select StageTimes and click Ok. The column name ‘StageTimes’ will appear in the Stage Times Variable box.

4 Specify the current stage.
   - Set Current Stage (k) to 3.

5 Specify the design.
   - Set Maximum Number of Stages (K) to 5.
   - Set Time Proportion at each Stage to Equally incremented.
   - Enter 490 and 490 for N1 and N2.
   - Enter 0.85 and 1.3 for h1 and h2.
   - Set T0 (Accrual or Recruitment Time) to 5.
   - Set Accrual Parameter Entry to Enter Accrual Parameter Directly.
   - Set Accrual Parameter to 0.
   - Set T (Total Time) to 5.
   - Set L1 and L2 to 0.03.
   - Set Superiority Margin to 0.2.

6 Specify the time adjustment for future stages.
   - Set Future Stage Time Adjustment to Keep original design time proportions exactly.

7 Specify the boundaries.
   - Set Boundaries Used to Efficacy with Futility.
   - Set Hypothesis Direction to Ha: h1 – h2 < |NIM| (Lower hazard rates are better).
   - Set Boundary Specification to Spending Function Calculation.
   - Enter 0.025 for Alpha.
• Set Alpha Spending Function to O’Brien-Fleming Analog.
• Leave Skipped Efficacy Stages empty.
• Enter 0.10 for Beta.
• Set Beta Spending Function to Hwang-Shih-DeCani (γ).
• Enter 1.5 for γ.
• Leave Skipped Futility Stages empty.
• Set Binding or Non-Binding Futility to Non-Binding.

8 Specify the reports.
• Select the Reports tab.
• Check all of the reports under Reports for Current Stage.
• Leave the Confidence Level at 95%.
• For Number of Simulations, enter 2000. This number is fewer than what would normally be used, but a smaller number is used here to keep the run time down.
• Under Conditional and Predictive Power and Boundary Crossing Probability Parameters, check all three checkboxes. For Custom Hazard Rates, enter 1.1 and 1.1 for h1 and h2.
• Under Planning Stage (Stage 0) Reports, check the reports Summary using Z Scale and Plots.
• Leave or uncheck all the remaining checkboxes, including those under Past Reports for Previous Stages.

9 Specify the plots.
• Select the Plots tab.
• Make sure the Z-Statistic vs Information and Z-Statistic vs Time checkboxes are checked.
• The stage number could be added to the plot by clicking the small box on the Plot Format button (under Z-Statistic vs Information and Z-Statistic vs Time). When the procedure is run, select the Stage Notes tab and press the Add Stage Number button.

10 Run the procedure.
• From the Run menu, select Run Procedure. Alternatively, just click the green Run button.

The following reports and charts will be displayed in the Output window.

Run Summary Report
This report can be used to confirm that the input was processed as intended.

<table>
<thead>
<tr>
<th>Item</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Number of Stages (Design):</td>
<td>5</td>
</tr>
<tr>
<td>Current Stage:</td>
<td>3</td>
</tr>
<tr>
<td>Alternative Hypothesis:</td>
<td>h1 - h2 &lt; -</td>
</tr>
<tr>
<td>Superiority Margin (SM):</td>
<td>0.2</td>
</tr>
<tr>
<td>Alpha Spending Function:</td>
<td>O’Brien-Fleming Analog</td>
</tr>
<tr>
<td>Beta Spending Function:</td>
<td>Hwang-Shih-DeCani (γ = 1.5)</td>
</tr>
<tr>
<td>Futility Boundaries:</td>
<td>Non-Binding</td>
</tr>
<tr>
<td>Alpha:</td>
<td>0.0250</td>
</tr>
<tr>
<td>Maximum Information:</td>
<td>163.3840</td>
</tr>
<tr>
<td>Z Statistic:</td>
<td>MLE</td>
</tr>
</tbody>
</table>
Z-Values and Boundaries at Stage 3

This section gives the Z-test values and boundaries, numerically. These values are reflected in the group-sequential boundary plot. The Decision column indicates whether a boundary was crossed at each stage.

Maximum Information: 163.3840  
Alternative Hypothesis: \( h_1 - h_2 < -|SM| \)  
Superiority Margin (SM): 0.2  
Futility Boundaries: Non-Binding  
Z Statistic: MLE

<table>
<thead>
<tr>
<th>Stage</th>
<th>Z-Test Value</th>
<th>Efficacy</th>
<th>Futility</th>
<th>Time</th>
<th>Information Proportion</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-1.3832</td>
<td>-6.5464</td>
<td>0.8096</td>
<td>1.0</td>
<td>0.1116</td>
<td>Continue</td>
</tr>
<tr>
<td>2</td>
<td>-2.2761</td>
<td>-3.5232</td>
<td>-0.5204</td>
<td>2.0</td>
<td>0.3664</td>
<td>Continue</td>
</tr>
<tr>
<td>3</td>
<td>-3.7574</td>
<td>-2.6445</td>
<td>-1.2038</td>
<td>3.0</td>
<td>0.6118</td>
<td>Crossed Effic</td>
</tr>
<tr>
<td>4</td>
<td>-2.3780</td>
<td>-1.4633</td>
<td>4.0</td>
<td>0.7565</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>-2.0183</td>
<td>-2.0183</td>
<td>5.0</td>
<td>1.0000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Group-Sequential Boundary Plot at Stage 3

This plot shows the Z-test values and boundaries. The efficacy boundary is crossed at Stage 3.
P-Values and Boundaries at Stage 3

This section reflects the conversion of the Z-test values and boundaries to the corresponding P-values and P-value boundaries.

Maximum Information: 163.3840  
Alternative Hypothesis: h1 - h2 < -|SM|  
Superiority Margin (SM): 0.2  
Futility Boundaries: Non-Binding  
Z Statistic: MLE  
P-values and P-value boundaries are one-sided values.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Z-Test P-Value</th>
<th>Efficacy</th>
<th>Futility</th>
<th>Time</th>
<th>Information Proportion</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.08330</td>
<td>0.00000</td>
<td>0.79091</td>
<td>1.0</td>
<td>0.1116</td>
<td>Continue</td>
</tr>
<tr>
<td>2</td>
<td>0.01142</td>
<td>0.00021</td>
<td>0.30139</td>
<td>2.0</td>
<td>0.3664</td>
<td>Continue</td>
</tr>
<tr>
<td>3</td>
<td>0.00009</td>
<td>0.00409</td>
<td>0.11434</td>
<td>3.0</td>
<td>0.6118</td>
<td>Crossed Efficacy</td>
</tr>
<tr>
<td>4</td>
<td>0.00870</td>
<td>0.07170</td>
<td>0.7565</td>
<td>4.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.02178</td>
<td>0.02178</td>
<td></td>
<td>5.0</td>
<td>1.0000</td>
<td></td>
</tr>
</tbody>
</table>
Current Stage Results Adjusted for Sequential Analysis (Stage 3)

This section gives appropriate adjustments to the raw results to reflect the group-sequential nature of the analysis. Additional explanation is given in early sections of this chapter: Adjusted Confidence Intervals, Adjusted p-values, and Adjusted Hazard Rate Difference.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Actual Difference</th>
<th>Group Sequential Adjusted Difference</th>
<th>Conf. Level Where Upper Boundary Is Zero</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>h1 - h2 + SM</td>
<td>95.0% C.I. of Diff.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>-0.37581</td>
<td>-0.72589</td>
<td>-0.21214</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-0.47201</td>
<td></td>
</tr>
</tbody>
</table>

The adjustments are based only on the efficacy boundaries. The futility boundaries are not used in these calculations.

Descriptive Statistics up to Stage 3

This section gives the raw sample statistics for the cumulative data at each stage.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Sample Size</th>
<th>Event Count</th>
<th>Sample Haz. Rates</th>
<th>Difference</th>
<th>SE(Diff)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N1 107</td>
<td>E1 28</td>
<td>h1 0.68176</td>
<td>-0.52397</td>
<td>0.23422</td>
</tr>
<tr>
<td></td>
<td>N2 92</td>
<td>E2 38</td>
<td>h2 1.20573</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>N1 209</td>
<td>E1 96</td>
<td>h1 0.68007</td>
<td>-0.49418</td>
<td>0.12526</td>
</tr>
<tr>
<td></td>
<td>N2 195</td>
<td>E2 116</td>
<td>h2 1.17425</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>N1 318</td>
<td>E1 177</td>
<td>h1 0.67756</td>
<td>-0.57581</td>
<td>0.10002</td>
</tr>
<tr>
<td></td>
<td>N2 293</td>
<td>E2 212</td>
<td>h2 1.25338</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Information Report at Stage 3

This section gives the target and achieved statistics for each stage, as well as the sample sizes and hazard rates used to calculate those informations.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Target Information Proportion</th>
<th>Achieved Information Proportion</th>
<th>Target Information Proportion</th>
<th>Achieved Information Proportion</th>
<th>N1</th>
<th>N2</th>
<th>h1</th>
<th>h2</th>
</tr>
</thead>
<tbody>
<tr>
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<td>48.1453</td>
<td>59.8641</td>
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<td>195.00</td>
<td>0.68007</td>
<td>1.17425</td>
</tr>
<tr>
<td>3</td>
<td>0.5220</td>
<td>0.6118</td>
<td>85.2925</td>
<td>99.9612</td>
<td>318.00</td>
<td>212.00</td>
<td>0.67756</td>
<td>1.25338</td>
</tr>
<tr>
<td>4</td>
<td>0.7594</td>
<td>*0.7565</td>
<td>124.0695</td>
<td>*123.6070</td>
<td>*335.35</td>
<td>*335.35</td>
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<td>*1.0000</td>
<td>163.3840</td>
<td>*163.3840</td>
<td>*419.19</td>
<td>*419.19</td>
<td>*0.67756</td>
<td>*1.25338</td>
</tr>
</tbody>
</table>

* Projected value.
Alpha Spending at Stage 3

This section shows how alpha was spent (or is anticipated to be spent) across the stages.

Target Final Stage Alpha: 0.0250
Spending Function: O'Brien-Fleming Analog

<table>
<thead>
<tr>
<th>Stage</th>
<th>Information Proportion</th>
<th>Alpha Spent this Stage</th>
<th>Cumulative Alpha Spent</th>
<th>Nominal (Boundary) Alpha</th>
<th>Percentage Alpha Spent this Stage</th>
<th>Cumulative Percentage Alpha Spent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1116</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.000000</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>2</td>
<td>0.3664</td>
<td>0.0002</td>
<td>0.0002</td>
<td>0.000213</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>3</td>
<td>0.6118</td>
<td>0.0039</td>
<td>0.0042</td>
<td>0.004091</td>
<td>15.8</td>
<td>16.7</td>
</tr>
<tr>
<td>4 *</td>
<td>0.7565</td>
<td>0.0058</td>
<td>0.0100</td>
<td>0.008703</td>
<td>23.2</td>
<td>39.9</td>
</tr>
<tr>
<td>5 *</td>
<td>1.0000</td>
<td>0.0150</td>
<td>0.0260</td>
<td>0.021780</td>
<td>60.1</td>
<td>100.0</td>
</tr>
</tbody>
</table>

* projected

Beta Spending for Futility at Stage 3

This section shows how beta was spent (or is anticipated to be spent) across the stages.

Target Final Stage Beta: 0.1000
Spending Function for Futility: Hwang-Shih-DeCani ($\gamma = 1.5$)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Information Proportion</th>
<th>Beta Spent this Stage</th>
<th>Cumulative Beta Spent</th>
<th>Nominal (Boundary) Beta</th>
<th>Percentage Beta Spent this Stage</th>
<th>Cumulative Percentage Beta Spent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1116</td>
<td>0.0198</td>
<td>0.0198</td>
<td>0.790913</td>
<td>19.8</td>
<td>19.8</td>
</tr>
<tr>
<td>2</td>
<td>0.3664</td>
<td>0.0346</td>
<td>0.0544</td>
<td>0.301391</td>
<td>34.6</td>
<td>54.4</td>
</tr>
<tr>
<td>3</td>
<td>0.6118</td>
<td>0.0229</td>
<td>0.0773</td>
<td>0.114336</td>
<td>22.9</td>
<td>77.3</td>
</tr>
<tr>
<td>4 *</td>
<td>0.7565</td>
<td>0.0100</td>
<td>0.0873</td>
<td>0.071699</td>
<td>10.0</td>
<td>87.3</td>
</tr>
<tr>
<td>5 *</td>
<td>1.0000</td>
<td>0.0127</td>
<td>0.1000</td>
<td>0.021780</td>
<td>12.7</td>
<td>100.0</td>
</tr>
</tbody>
</table>

* projected

Conditional and Predictive Power Report at Stage 3

This section gives the conditional power for the various differences assumed. It also gives the predictive power.

Maximum Information: 163.3840
Information this Stage: 99.9612
Proportion of Maximum Information: 0.6118
Predictive Power: 0.9998

<table>
<thead>
<tr>
<th>$\delta$ Name</th>
<th>$\delta$ Value</th>
<th>Conditional Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>-0.4500</td>
<td>0.9998</td>
</tr>
<tr>
<td>Data</td>
<td>-0.5758</td>
<td>1.0000</td>
</tr>
<tr>
<td>$\delta 1$</td>
<td>0.0000</td>
<td>0.4915</td>
</tr>
</tbody>
</table>

The conditional power values are calculated based on Jennison and Tumbull (2000), pages 205 to 208. They do not account for future interim stages, nor futility boundaries, if applicable.
Boundary Probabilities for $\delta = -0.45$

Using simulation based on the specified hazard rates, this section gives the estimated probabilities of crossing each of the future boundaries. Values given here will vary for each simulation.

<table>
<thead>
<tr>
<th>Stage</th>
<th>N1</th>
<th>N2</th>
<th>Z-Test Value</th>
<th>Efficacy Boundary</th>
<th>Probability</th>
<th>Futility Boundary</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>107.00</td>
<td>92.00</td>
<td>-1.3832</td>
<td>-6.5464</td>
<td>0.8096</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>209.00</td>
<td>195.00</td>
<td>-2.2761</td>
<td>-3.5232</td>
<td>-0.5204</td>
<td></td>
<td>-1.2038</td>
</tr>
<tr>
<td>3</td>
<td>318.00</td>
<td>293.00</td>
<td>-3.7574</td>
<td>-2.6445</td>
<td>-1.4633</td>
<td>0.0000</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>*335.35</td>
<td>*335.35</td>
<td>-2.3780</td>
<td>0.9990</td>
<td>0.0000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>*419.19</td>
<td>*419.19</td>
<td>-2.0183</td>
<td>0.0010</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Simulation sample size (Non-integer sample sizes were rounded to the next highest integer.)

Event Summary for $\delta = -0.45$

Using simulation based on the specified hazard rates, this section gives the estimated number of events at each future stage. Values given here will vary for each simulation.

<table>
<thead>
<tr>
<th>Stage</th>
<th>N1</th>
<th>N2</th>
<th>Z-Test Value</th>
<th>Average Cumulative Number of Events</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>107</td>
<td>92</td>
<td>-1.3832</td>
<td>E1 28 E2 38</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>209</td>
<td>195</td>
<td>-2.2761</td>
<td>E1 96 E2 116</td>
<td>2.00</td>
</tr>
<tr>
<td>3</td>
<td>318</td>
<td>293</td>
<td>-3.7574</td>
<td>E1 177 E2 212</td>
<td>3.00</td>
</tr>
<tr>
<td>4</td>
<td>*335.35</td>
<td>*335.35</td>
<td>**269.03 **293.82</td>
<td>**4.00</td>
<td>*5.00</td>
</tr>
<tr>
<td>5</td>
<td>*419.19</td>
<td>*419.19</td>
<td>**335.98 **361.01</td>
<td>**4.00</td>
<td>*5.00</td>
</tr>
</tbody>
</table>

* Simulation sample size (Non-integer sample sizes were rounded to the next highest integer.)
** Simulation average
### Boundary Probabilities for $\delta = -0.5758126$

Number of Simulations: 2000  
Futility Boundaries: Non-Binding  
After Efficacy Boundary Crossing: Hold Out  
After Non-Binding Futility Boundary Crossing: Leave In  
Alternative Hypothesis: $h_1 - h_2 < -|SM|$  
Superiority Margin (SM): 0.2  
Z Statistic: MLE  
h1: 0.6775628  
h2: 1.253375  
$\delta$: -0.5758126

<table>
<thead>
<tr>
<th>Stage</th>
<th>N1</th>
<th>N2</th>
<th>Z-Test Value</th>
<th>Z-Test Boundary Probability</th>
<th>Efficacy Boundary Probability</th>
<th>Futility Boundary Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>107</td>
<td>92</td>
<td>-1.3832</td>
<td>-6.5464</td>
<td>-0.8096</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>209</td>
<td>195</td>
<td>-2.2761</td>
<td>-3.5232</td>
<td>-0.5204</td>
<td>-1.2038</td>
</tr>
<tr>
<td>3</td>
<td>318</td>
<td>293</td>
<td>-3.7574</td>
<td>-2.6445</td>
<td>1.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>4</td>
<td>*335.35</td>
<td>*335.35</td>
<td>**256.00</td>
<td>**292.36</td>
<td>*4.00</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>*419.19</td>
<td>*419.19</td>
<td>**319.39</td>
<td>**359.04</td>
<td>*5.00</td>
<td></td>
</tr>
</tbody>
</table>

* Simulation sample size (Non-integer sample sizes were rounded to the next highest integer.)

### Event Summary for $\delta = -0.5758126$

Number of Simulations: 2000  
h1: 0.6775628  
h2: 1.253375  
$\delta$: -0.5758126

<table>
<thead>
<tr>
<th>Stage</th>
<th>N1</th>
<th>N2</th>
<th>Z-Test Value</th>
<th>Average Cumulative Number of Events</th>
<th>E1</th>
<th>E2</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>107</td>
<td>92</td>
<td>-1.3832</td>
<td>28</td>
<td>38</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>209</td>
<td>195</td>
<td>-2.2761</td>
<td>96</td>
<td>116</td>
<td>2.00</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>318</td>
<td>293</td>
<td>-3.7574</td>
<td>177</td>
<td>212</td>
<td>3.00</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>*335.35</td>
<td>*335.35</td>
<td>**256.00</td>
<td>**292.36</td>
<td>*4.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>*419.19</td>
<td>*419.19</td>
<td>**319.39</td>
<td>**359.04</td>
<td>*5.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Simulation sample size (Non-integer sample sizes were rounded to the next highest integer.)

** Simulation average

### Boundary Probabilities for $\delta = 0$

Number of Simulations: 2000  
Futility Boundaries: Non-Binding  
After Efficacy Boundary Crossing: Hold Out  
After Non-Binding Futility Boundary Crossing: Leave In  
Alternative Hypothesis: $h_1 - h_2 < -|SM|$  
Superiority Margin (SM): 0.2  
Z Statistic: MLE  
h1: 1.1  
h2: 1.1  
$\delta$: 0

<table>
<thead>
<tr>
<th>Stage</th>
<th>N1</th>
<th>N2</th>
<th>Z-Test Value</th>
<th>Efficacy Boundary Probability</th>
<th>Futility Boundary Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>107</td>
<td>92</td>
<td>-1.3832</td>
<td>-6.5464</td>
<td>0.8096</td>
</tr>
<tr>
<td>2</td>
<td>209</td>
<td>195</td>
<td>-2.2761</td>
<td>-3.5232</td>
<td>-0.5204</td>
</tr>
<tr>
<td>3</td>
<td>318</td>
<td>293</td>
<td>-3.7574</td>
<td>-2.6445</td>
<td>-1.2038</td>
</tr>
<tr>
<td>4</td>
<td>*335.35</td>
<td>*335.35</td>
<td>-2.3780</td>
<td>0.6330</td>
<td>-1.4633</td>
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<tr>
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<td>*419.19</td>
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<td>0.0485</td>
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</tbody>
</table>

* Simulation sample size (Non-integer sample sizes were rounded to the next highest integer.)
Event Summary for $\delta = 0$

Number of Simulations: 2000  
$h1$: 1.1  
$h2$: 1.1  
$\delta$: 0

<table>
<thead>
<tr>
<th>Stage</th>
<th>N1</th>
<th>N2</th>
<th>Z-Test Value</th>
<th>Average Cumulative Number of Events</th>
<th>Stage N1</th>
<th>N2</th>
<th>Value</th>
<th>E1</th>
<th>E2</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>107</td>
<td>92</td>
<td>-1.3832</td>
<td>28 38 1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>209</td>
<td>195</td>
<td>-2.2761</td>
<td>96 116 2.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>318</td>
<td>293</td>
<td>-3.7574</td>
<td>177 212 3.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>*335.35</td>
<td>*335.35</td>
<td>**285.30</td>
<td>**286.33</td>
<td>*4.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>*419.19</td>
<td>*419.19</td>
<td>**354.03</td>
<td>**352.13</td>
<td>*5.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Simulation sample size (Non-integer sample sizes were rounded to the next highest integer.)  
** Simulation average

Z-Values and Boundaries at Stage 0

This section gives the boundaries that were initially projected at the planning stage.

Maximum Information: 163.3840  
Alternative Hypothesis: $h1 - h2 < -|SM|$  
Superiority Margin (SM): 0.2  
Futility Boundaries: Non-Binding  
Z Statistic: MLE

<table>
<thead>
<tr>
<th>Stage</th>
<th>Z-Test Value</th>
<th>Efficacy</th>
<th>Futility</th>
<th>Time</th>
<th>Information Proportion</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>-0.9347</td>
<td>1.0</td>
<td>0.0983</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-2.8930</td>
<td>-0.9507</td>
<td>3.0</td>
<td>0.5220</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>-2.3456</td>
<td>-1.5189</td>
<td>4.0</td>
<td>0.7594</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>-2.0170</td>
<td>-2.0170</td>
<td>5.0</td>
<td>1.0000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Group-Sequential Boundary Plot at Planning Stage (Stage 0)

This plot shows the projected boundaries at the planning stage.
Kaplan-Meier Survival Plot

In order to obtain a Kaplan-Meier survival curve plot, the data must be converted into a form that can be used in the Kaplan-Meier Curves (Logrank Tests) procedure:

1. Rows with blank end times should be identified as censored.
2. Blank end times must be filled in with the current stage time.
3. An Elapsed Time column should be created by subtracting start times from end times.

When these steps are taken, the GS Survival NI dataset becomes the GS Survival NI B dataset.

You may follow along here by making the appropriate entries or load the completed template Example GS by clicking on Open Example Template from the File menu of the Kaplan-Meier Curves (Logrank Tests) procedure window.

1. **Open the GS Survival SM B dataset.**
   - From the File menu of the NCSS Data window, select Open Example Data.
   - Click on the file GS Survival SM B.NCSS.
   - Click Open.

2. **Open the Kaplan-Meier Curves (Logrank Tests) window.**
   - Using the Analysis menu or the Procedure Navigator, find and select the Kaplan-Meier Curves (Logrank Tests) procedure.
   - On the menus, select File, then New Template. This will fill the procedure with the default template.

3. **Specify the variables.**
   - Select the Variables tab.
   - Click the small Column Selection button to the right of (Elapsed) Time Variable. Select Elapsed and click Ok. The column name ‘Elapsed’ will appear in the (Elapsed) Time Variable box.
   - Click the small Column Selection button to the right of Censor Variable. Select Censor and click Ok. The column name ‘Censor’ will appear in the Censor Variable box.
   - For Failed, enter 0.
   - For Censored, enter 1.
   - Click the small Column Selection button to the right of Group Variable. Select Group and click Ok. The column name ‘Group’ will appear in the Group Variable box.

4. **Specify the reports.**
   - Select the Reports tab.
   - Uncheck all reports except Data Summary. (Any desired reports can be checked.)

5. **Specify the plots.**
   - Select the Plots tab.
   - Leave the box checked next to Kaplan-Meier Survival/Reliability Plot.
   - Uncheck the box next to Individual-Group Plots.
   - Make sure the box is checked next to Combined Plots(s).
   - Click on the large Plot Format button under Kaplan-Meier Survival/Reliability Plot. Check Confidence Limits and corresponding Fill.

6. **Run the procedure.**
   - From the Run menu, select Run Procedure. Alternatively, just click the green Run button.
Kaplan-Meier Survival Curve(s)

This plot shows the survival curves for the two groups.
Example 2 – Skipping Stage Boundaries

Suppose that the setup is the same as in Example 1, except that the first two futility boundaries are skipped.

You may follow along here by making the appropriate entries or load the completed template Example 2 by clicking on Open Example Template from the File menu of the procedure window.

1 Specify the boundaries.
   • Enter 1 2 for Skipped Futility Stages.

2 Run the procedure.
   • From the Run menu, select Run Procedure. Alternatively, just click the green Run button.

The following reports and charts will be displayed in the Output window.

Run Summary Report

The skipped futility stages are now reported.

<table>
<thead>
<tr>
<th>Item</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Number of Stages (Design):</td>
<td>5</td>
</tr>
<tr>
<td>Skipped Futility Stage(s):</td>
<td>1 2</td>
</tr>
<tr>
<td>Current Stage:</td>
<td>3</td>
</tr>
<tr>
<td>Alternative Hypothesis:</td>
<td>h1 - h2 &lt; -</td>
</tr>
<tr>
<td>Superiority Margin (SM):</td>
<td>0.2</td>
</tr>
<tr>
<td>Alpha Spending Function:</td>
<td>O'Brien-Fleming Analog</td>
</tr>
<tr>
<td>Beta Spending Function:</td>
<td>Hwang-Shih-DeCani (γ = 1.5)</td>
</tr>
<tr>
<td>Futility Boundaries:</td>
<td>Non-Binding</td>
</tr>
<tr>
<td>Alpha:</td>
<td>0.0250</td>
</tr>
<tr>
<td>Maximum Information:</td>
<td>163.3840</td>
</tr>
<tr>
<td>Z Statistic:</td>
<td>MLE</td>
</tr>
</tbody>
</table>

Z-Values and Boundaries at Stage 3

The futility boundaries change slightly from those where no boundaries are skipped.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Z-Test Value</th>
<th>Efficacy</th>
<th>Futility</th>
<th>Time</th>
<th>Information Proportion</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-1.3832</td>
<td></td>
<td></td>
<td>1.0</td>
<td>0.1116</td>
<td>Continue</td>
</tr>
<tr>
<td>2</td>
<td>-2.2761</td>
<td>-6.5464</td>
<td></td>
<td>2.0</td>
<td>0.3664</td>
<td>Continue</td>
</tr>
<tr>
<td>3</td>
<td>-3.7574</td>
<td>-2.6445</td>
<td>-1.4412</td>
<td>3.0</td>
<td>0.6118</td>
<td>Crossed Efficacy</td>
</tr>
<tr>
<td>4</td>
<td>-2.3780</td>
<td>-2.3780</td>
<td>-1.5233</td>
<td>4.0</td>
<td>0.7565</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>-2.0183</td>
<td>-2.0183</td>
<td>-2.0183</td>
<td>5.0</td>
<td>1.0000</td>
<td></td>
</tr>
</tbody>
</table>
Group-Sequential Boundary Plot at Stage 3

The plot now has two futility boundaries skipped.
Example 3 – Sample Size Re-estimation and Boundary Probabilities

Suppose that the setup is the same as in Example 1, except that only the data up through Stage 2 has been collected.

You may follow along here by making the appropriate entries or load the completed template Example 3 by clicking on Open Example Template from the File menu of the procedure window.

1. Open the GS Survival NI 2 Stages dataset.
   - From the File menu of the NCSS Data window, select Open Example Data.
   - Click on the file GS Survival NI 2 Stages.NCSS.
   - Click Open.

2. Select the Current Stage.
   - Set Current Stage (k) to 2.

3. Run the procedure.
   - From the Run menu, select Run Procedure. Alternatively, just click the green Run button.

The following reports and charts will be displayed in the Output window.

Run Summary Report

This report can be used to confirm that the input was processed as intended.

<table>
<thead>
<tr>
<th>Item</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Number of Stages (Design):</td>
<td>5</td>
</tr>
<tr>
<td>Current Stage:</td>
<td>2</td>
</tr>
<tr>
<td>Alternative Hypothesis:</td>
<td>h1 - h2 &lt; -</td>
</tr>
<tr>
<td>Superiority Margin (SM):</td>
<td>0.2</td>
</tr>
<tr>
<td>Alpha Spending Function:</td>
<td>O'Brien-Fleming Analog</td>
</tr>
<tr>
<td>Beta Spending Function:</td>
<td>Hwang-Shih-DeCani (γ = 1.5)</td>
</tr>
<tr>
<td>Futility Boundaries:</td>
<td>Non-Binding</td>
</tr>
<tr>
<td>Alpha:</td>
<td>0.0250</td>
</tr>
<tr>
<td>Maximum Information:</td>
<td>163.3840</td>
</tr>
<tr>
<td>Z Statistic:</td>
<td>MLE</td>
</tr>
</tbody>
</table>

Z-Values and Boundaries at Stage 2

Examining the Z-Test values, the boundaries, and the decisions, no boundary has been crossed at this stage.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Z-Test Value</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Z-Test Value</td>
<td>Efficacy</td>
<td>Futility</td>
<td>Time</td>
<td>Information Proportion</td>
</tr>
<tr>
<td>1</td>
<td>-1.3832</td>
<td>-6.5464</td>
<td>0.8114</td>
<td>1.0</td>
<td>0.1116</td>
</tr>
<tr>
<td>2</td>
<td>-2.2761</td>
<td>3.5232</td>
<td>-0.5170</td>
<td>2.0</td>
<td>0.3664</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>3.0</td>
<td>0.5132</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td>4.0</td>
<td>0.7541</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td>5.0</td>
<td>1.0000</td>
</tr>
</tbody>
</table>
Group-Sequential Boundary Plot at Stage 2

This plot shows the Z-test values in the vicinity of the efficacy boundary side.
### Descriptive Statistics up to Stage 2

<table>
<thead>
<tr>
<th>Stage</th>
<th>Sample Size</th>
<th>Event Count</th>
<th>Sample Haz. Rates</th>
<th>Difference</th>
<th>SE(Diff)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N1</td>
<td>N2</td>
<td>E1</td>
<td>h1</td>
<td>h2</td>
</tr>
<tr>
<td>1</td>
<td>107</td>
<td>28</td>
<td>0.68176</td>
<td>-0.52397</td>
<td>0.23422</td>
</tr>
<tr>
<td>2</td>
<td>209</td>
<td>38</td>
<td>0.68007</td>
<td>-0.49418</td>
<td>0.12925</td>
</tr>
</tbody>
</table>

### Information Report at Stage 2 (Gives Sample Size Re-estimation)

This section shows that the target sample size for the next stage should be 232 per group.

<table>
<thead>
<tr>
<th>Maximum Information: 163.3840</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative Hypothesis: h1 - h2 &lt; -</td>
</tr>
<tr>
<td>Superiority Margin (SM): 0.2</td>
</tr>
<tr>
<td>Alpha: 0.0250</td>
</tr>
</tbody>
</table>

#### Alpha Spending at Stage 2

This section shows how alpha was spent (or is anticipated to be spent) across the stages.

<table>
<thead>
<tr>
<th>Target Final Stage Alpha: 0.0250</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spending Function: O'Brien-Fleming Analog</td>
</tr>
</tbody>
</table>

### Alpha Spending at Stage 2

<table>
<thead>
<tr>
<th>Stage</th>
<th>Information Proportion</th>
<th>Alpha Spent this Stage</th>
<th>Cumulative Alpha Spent</th>
<th>Nominal (Boundary) Alpha</th>
<th>Percentage Alpha Spent this Stage</th>
<th>Cumulative Percentage Alpha Spent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1116</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.000000</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>2</td>
<td>0.3664</td>
<td>0.0002</td>
<td>0.0002</td>
<td>0.000213</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>3</td>
<td>0.5132</td>
<td>0.0015</td>
<td>0.0018</td>
<td>0.001685</td>
<td>6.2</td>
<td>7.0</td>
</tr>
<tr>
<td>4</td>
<td>0.7541</td>
<td>0.0081</td>
<td>0.0099</td>
<td>0.009280</td>
<td>32.4</td>
<td>39.4</td>
</tr>
<tr>
<td>5</td>
<td>1.0000</td>
<td>0.0151</td>
<td>0.0250</td>
<td>0.021924</td>
<td>60.6</td>
<td>100.0</td>
</tr>
</tbody>
</table>

* projected
Beta Spending for Futility at Stage 2

This section shows how beta was spent (or is anticipated to be spent) across the stages.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Information Proportion</th>
<th>Beta Spent this Stage</th>
<th>Cumulative Beta Spent</th>
<th>Nominal (Boundary) Beta</th>
<th>Percentage Beta Spent this Stage</th>
<th>Cumulative Percentage Beta Spent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1116</td>
<td>0.0198</td>
<td>0.0198</td>
<td>0.791446</td>
<td>19.8</td>
<td>19.8</td>
</tr>
<tr>
<td>2</td>
<td>0.3664</td>
<td>0.0346</td>
<td>0.0594</td>
<td>0.302563</td>
<td>34.6</td>
<td>54.4</td>
</tr>
<tr>
<td>3 *</td>
<td>0.5132</td>
<td>0.0147</td>
<td>0.0871</td>
<td>0.191765</td>
<td>14.7</td>
<td>69.1</td>
</tr>
<tr>
<td>4 *</td>
<td>0.7541</td>
<td>0.0181</td>
<td>0.0872</td>
<td>0.066163</td>
<td>18.1</td>
<td>87.2</td>
</tr>
<tr>
<td>5 *</td>
<td>1.0000</td>
<td>0.0128</td>
<td>0.1000</td>
<td>0.021924</td>
<td>12.8</td>
<td>100.0</td>
</tr>
</tbody>
</table>

* projected

Conditional and Predictive Power Report at Stage 2

Conditional power and predictive power are described earlier in the Technical details section. The predictive power does not depend on an assumed difference, as does the conditional power.

<table>
<thead>
<tr>
<th>Name</th>
<th>δ Value</th>
<th>Conditional Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>-0.4500</td>
<td>0.9650</td>
</tr>
<tr>
<td>Data</td>
<td>-0.4942</td>
<td>0.9881</td>
</tr>
<tr>
<td>δ1</td>
<td>0.0000</td>
<td>0.0028</td>
</tr>
</tbody>
</table>

The conditional power values are calculated based on Jennison and Turnbull (2000), pages 205 to 208. They do not account for future interim stages, nor futility boundaries, if applicable.

Boundary Probabilities for δ = -0.45

Given the data that have already accumulated in the first two stages, and assuming hazard rates of 0.85 and 1.3 going forward, this report gives the simulation probabilities of crossing each of the future boundaries. The sum of the efficacy boundary probabilities is another estimate of the conditional power.

<table>
<thead>
<tr>
<th>Stage</th>
<th>N1</th>
<th>N2</th>
<th>Z-Test Value</th>
<th>Efficacy Boundary Probability</th>
<th>Futility Boundary Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>107.00</td>
<td>92.00</td>
<td>-1.3832</td>
<td>-6.5464</td>
<td>0.8114</td>
</tr>
<tr>
<td>2</td>
<td>209.00</td>
<td>195.00</td>
<td>-2.2761</td>
<td>-3.5232</td>
<td>-0.5170</td>
</tr>
<tr>
<td>3 *</td>
<td>231.32</td>
<td>231.32</td>
<td>-2.9318</td>
<td>0.3090</td>
<td>-0.8714</td>
</tr>
<tr>
<td>4 *</td>
<td>308.42</td>
<td>308.42</td>
<td>-2.3543</td>
<td>0.5035</td>
<td>-1.5050</td>
</tr>
<tr>
<td>5 *</td>
<td>385.53</td>
<td>385.53</td>
<td>-2.0155</td>
<td>0.1385</td>
<td>-2.0155</td>
</tr>
</tbody>
</table>

* Simulation sample size (Non-integer sample sizes were rounded to the next highest integer.)
Event Summary for $\delta = -0.45$

Using simulation based on the specified hazard rates, this section gives the estimated number of events at each future stage. Values given here will vary for each simulation.

<table>
<thead>
<tr>
<th>Stage</th>
<th>N1</th>
<th>N2</th>
<th>Z-Test Value</th>
<th>Average Cumulative Number of Events</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>107</td>
<td>92</td>
<td>-1.3832</td>
<td>E1 28  E2 38</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>209</td>
<td>195</td>
<td>-2.2761</td>
<td>96 116</td>
<td>2.00</td>
</tr>
<tr>
<td>3</td>
<td><em>231.32</em></td>
<td><em>231.32</em></td>
<td><strong>177.68</strong></td>
<td><strong>197.57</strong></td>
<td><em>3.00</em></td>
</tr>
<tr>
<td>4</td>
<td><strong>308.42</strong></td>
<td><strong>308.42</strong></td>
<td><strong>245.00</strong></td>
<td><strong>265.02</strong></td>
<td><em>4.00</em></td>
</tr>
<tr>
<td>5</td>
<td><em>385.53</em></td>
<td><em>385.53</em></td>
<td><strong>306.14</strong></td>
<td><strong>328.72</strong></td>
<td><em>5.00</em></td>
</tr>
</tbody>
</table>

* Simulation sample size (Non-integer sample sizes were rounded to the next highest integer.)
** Simulation average

Boundary Probabilities for $\delta = -0.4941798$

Given the data that have already accumulated in the first two stages, and assuming hazard rates of 0.6800724 and 1.174252 going forward, this report gives the simulation probabilities of crossing each of the future boundaries.

<table>
<thead>
<tr>
<th>Stage</th>
<th>N1</th>
<th>N2</th>
<th>Z-Test Value</th>
<th>Efficacy Boundary Probability</th>
<th>Futility Boundary Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>107.00</td>
<td>92.00</td>
<td>-1.3832</td>
<td>-6.5464 0.8114</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>209.00</td>
<td>195.00</td>
<td>-2.2761</td>
<td>-3.5232 0.0605</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td><em>231.32</em></td>
<td><em>231.32</em></td>
<td><strong>2.9318</strong></td>
<td>0.5245 -0.8714 0.0005</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><strong>308.42</strong></td>
<td><strong>308.42</strong></td>
<td><strong>2.3543</strong></td>
<td>0.8050 -1.5050 0.0050</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><em>385.53</em></td>
<td><em>385.53</em></td>
<td><strong>2.0155</strong></td>
<td>0.0605 -2.0155 0.0095</td>
<td></td>
</tr>
</tbody>
</table>

* Simulation sample size (Non-integer sample sizes were rounded to the next highest integer.)
# Event Summary for $\delta = -0.4941798$

Number of Simulations: 2000
h1: 0.6800724
h2: 1.174252
$\delta$: -0.4941798

<table>
<thead>
<tr>
<th>Stage</th>
<th>N1</th>
<th>N2</th>
<th>Z-Test Value</th>
<th>E1</th>
<th>E2</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>107</td>
<td>92</td>
<td>-1.3832</td>
<td>28</td>
<td>38</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>209</td>
<td>195</td>
<td>-2.2761</td>
<td>96</td>
<td>116</td>
<td>2.00</td>
</tr>
<tr>
<td>3</td>
<td>*231.32</td>
<td>*231.32</td>
<td>**166.09</td>
<td>**193.04</td>
<td>*3.00</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>*308.42</td>
<td>*308.42</td>
<td>**229.55</td>
<td>**259.58</td>
<td>*4.00</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>*385.53</td>
<td>*385.53</td>
<td>**289.40</td>
<td>**323.10</td>
<td>*5.00</td>
<td></td>
</tr>
</tbody>
</table>

* Simulation sample size (Non-integer sample sizes were rounded to the next highest integer.)
** Simulation average

# Boundary Probabilities for $\delta = 0$

Given the data that have already accumulated in the first two stages, and assuming hazard rates of 1.1 and 1.1 going forward, this report gives the simulation probabilities of crossing each of the future boundaries.

Number of Simulations: 2000
Futility Boundaries: Non-Binding
After Efficacy Boundary Crossing: Hold Out
After Non-Binding Futility Boundary Crossing: Leave In
Alternative Hypothesis: $h_1 - h_2 < -|SM|
Superiority Margin (SM): 0.2
Z Statistic: MLE

<table>
<thead>
<tr>
<th>Stage</th>
<th>N1</th>
<th>N2</th>
<th>Z-Test Value</th>
<th>Efficacy Boundary</th>
<th>Futility Boundary</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>107</td>
<td>92</td>
<td>-1.3832</td>
<td>-6.5464</td>
<td>0.8114</td>
</tr>
<tr>
<td>2</td>
<td>209</td>
<td>195</td>
<td>-2.2761</td>
<td>-3.5232</td>
<td>-0.5170</td>
</tr>
<tr>
<td>3</td>
<td>*231.32</td>
<td>*231.32</td>
<td>**229.55</td>
<td>**193.04</td>
<td>0.0010</td>
</tr>
<tr>
<td>4</td>
<td>*308.42</td>
<td>*308.42</td>
<td>**229.55</td>
<td>**259.58</td>
<td>0.0025</td>
</tr>
<tr>
<td>5</td>
<td>*385.53</td>
<td>*385.53</td>
<td>**229.55</td>
<td>**323.10</td>
<td>0.0025</td>
</tr>
</tbody>
</table>

* Simulation sample size (Non-integer sample sizes were rounded to the next highest integer.)

# Event Summary for $\delta = 0$

Number of Simulations: 2000
h1: 1.1
h2: 1.1
$\delta$: 0

<table>
<thead>
<tr>
<th>Stage</th>
<th>N1</th>
<th>N2</th>
<th>Z-Test Value</th>
<th>Average Cumulative Number of Events</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>107</td>
<td>92</td>
<td>-1.3832</td>
<td>E1: 28 E2: 38</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>209</td>
<td>195</td>
<td>-2.2761</td>
<td>96 116</td>
<td>2.00</td>
</tr>
<tr>
<td>3</td>
<td>*231.32</td>
<td>*231.32</td>
<td>**192.26</td>
<td>**190.29</td>
<td>*3.00</td>
</tr>
<tr>
<td>4</td>
<td>*308.42</td>
<td>*308.42</td>
<td>**262.24</td>
<td>**256.39</td>
<td>*4.00</td>
</tr>
<tr>
<td>5</td>
<td>*385.53</td>
<td>*385.53</td>
<td>**323.55</td>
<td>**319.49</td>
<td>*5.00</td>
</tr>
</tbody>
</table>

* Simulation sample size (Non-integer sample sizes were rounded to the next highest integer.)
** Simulation average