

## Chapter 781

# Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

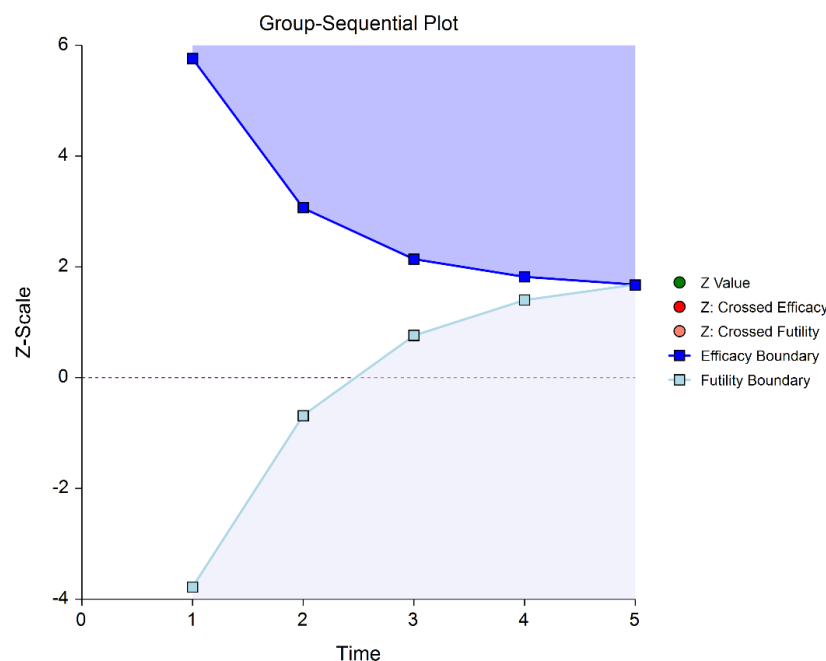
Note: The corresponding analysis and sample size re-estimation procedure, found in NCSS Analysis and Graphics software, is *Group-Sequential Non-Inferiority Analysis for Two Hazard Rates*.

## Introduction

This procedure can be used to determine power, sample size and/or boundaries for group-sequential Z-tests comparing the survival curves of two groups, with a non-inferiority margin. This methodology assumes an underlying Exponential model. For one- and two-sided tests, efficacy and/or futility boundaries can be generated. The spacing of the stages can be equal or custom specified. Individual stages may also be skipped. Boundaries can be computed based on popular alpha- and beta-spending functions (O'Brien-Fleming Analog, Pocock Analog, Hwang-Shih-DeCani Gamma family, linear) or custom spending functions, or boundaries may be input directly, if desired. Futility boundaries can be binding or non-binding. Corresponding P-Value boundaries are given for each boundary statistic. Alpha and/or beta spent at each stage is reported. Plots of boundaries are also produced.

This procedure is used as the planning tool for determining sample size and initial boundaries. Stage data, as it is obtained, can be evaluated using the companion procedure *Group-Sequential Non-Inferiority Analysis for Two Hazard Rates*. The companion procedure also gives the option for sample-size re-estimation and updated boundaries for current-stage information. In that procedure, simulation can be used to evaluate boundary-crossing probabilities given the current stage results.

An example of a group-sequential boundary plot produced in this procedure is shown below.



---

## 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 (two-sided or one-sided 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
- Non-inferiority margin

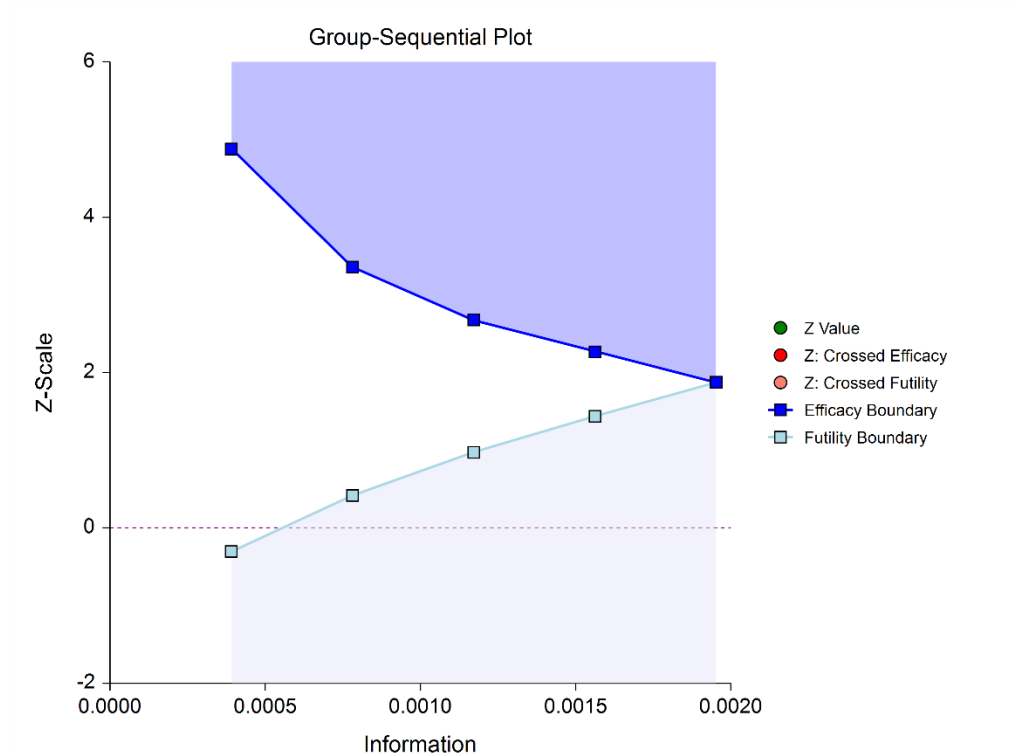
The design phase calculation is performed in this procedure. **PASS** software permits the user to easily try a range of survival rate differences, as these values are typically not known in advance.

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 Non-Inferiority Tests for Two Hazard Rates (Simulation)



## 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. This analysis can be performed using the companion (analysis) procedure to this sample size procedure in **NCSS**.

### First Interim Stage

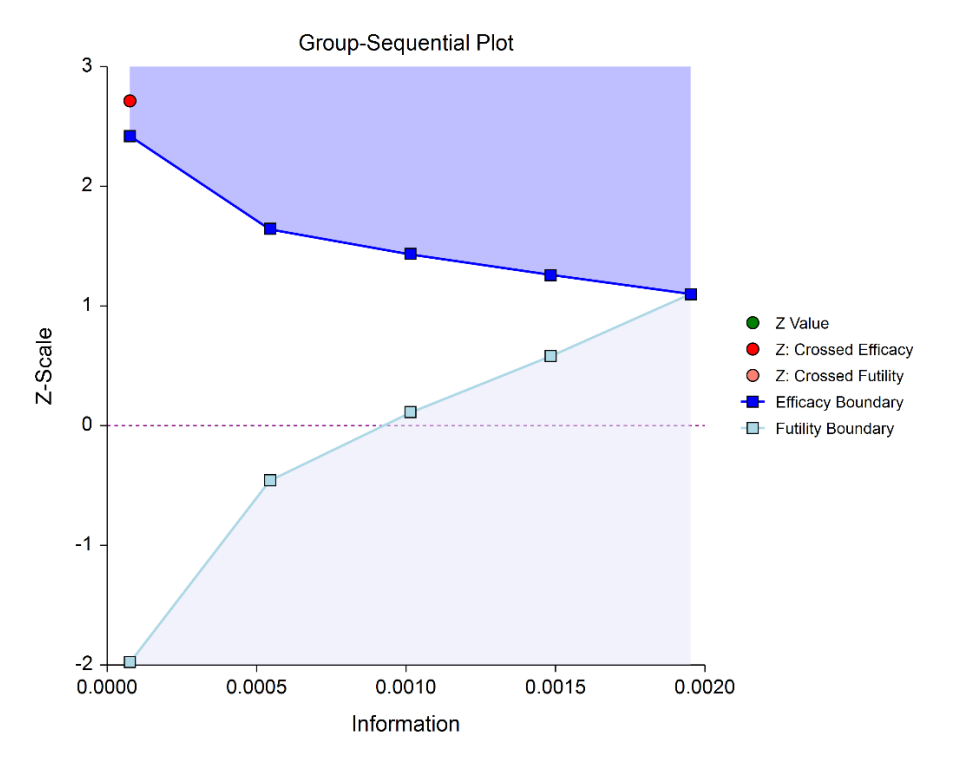
The design phase gives the target number of subjects for the first stage, based on the time of the first stage and the accrual specification. The study begins, and response data is collected for subjects, moving toward the first-stage target number of subjects, until a decision to perform an analysis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

Unless the number of subjects and time 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.

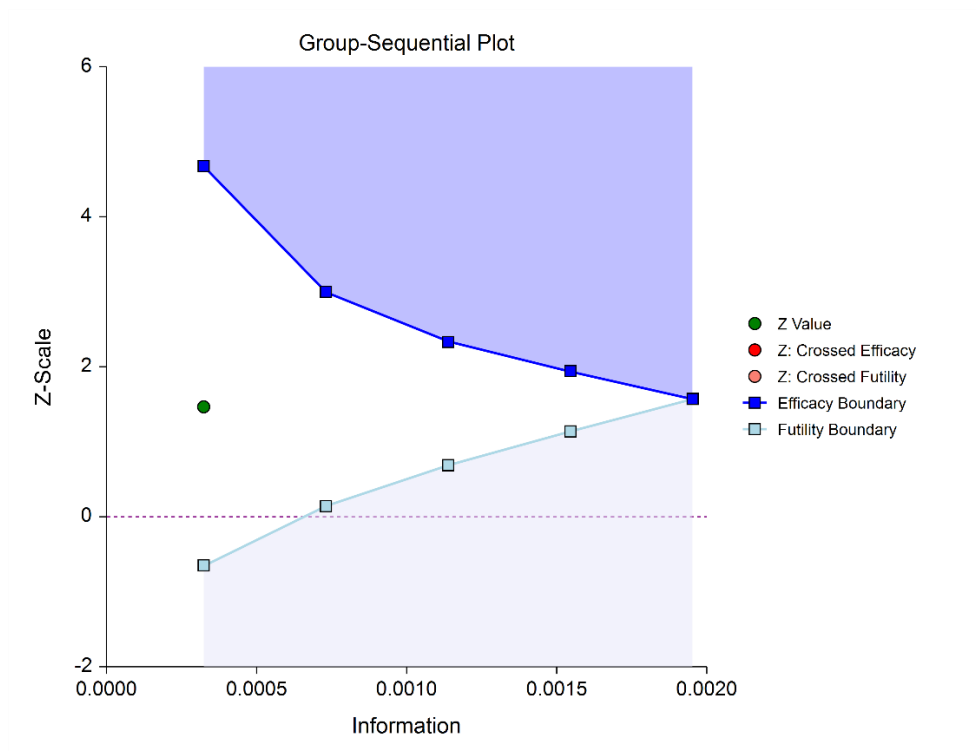
The first stage information is divided by the maximum information to obtain the stage one information proportion (or information fraction). This information proportion is used in conjunction with the spending function(s) to determine the alpha and/or beta spent at that stage. In turn, stage one boundaries,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

## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)



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, using the **NCSS** procedure. Conditional power and stopping probabilities are based on the user-specified supposed true difference.

## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

## Second and other interim stages (if reached)

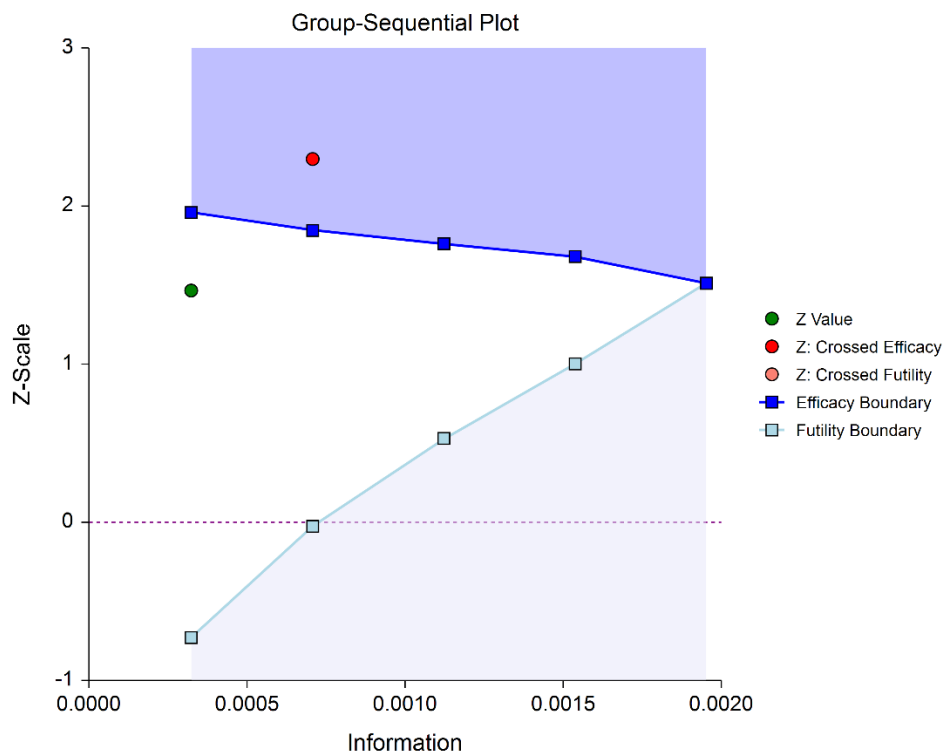
If the first stage time proportion is not equal to the design time proportion, a designation must be made at this point as to the target time of the second stage. Two options are available in the **NCSS** procedure.

One option is to target the time 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 time 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 time 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.

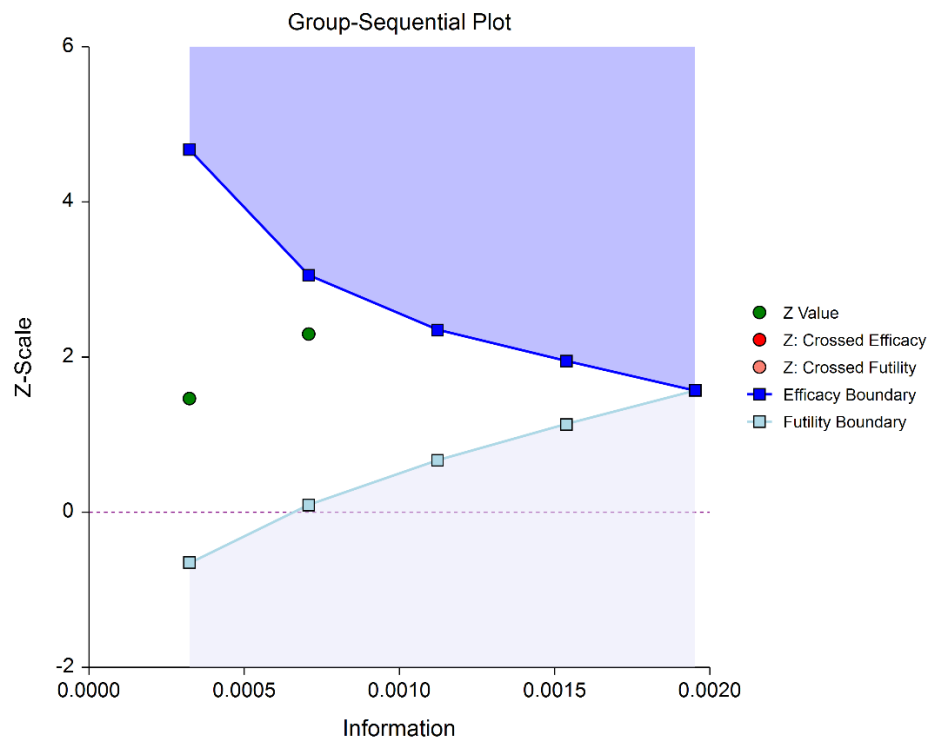
For either option, once the target time is determined for the next stage, revised target sample sizes are given (in the **NCSS** procedure), and the study continues until the decision is made to perform the next interim analysis on the cumulative response data. In the same manner as the first stage, 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.



## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

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.

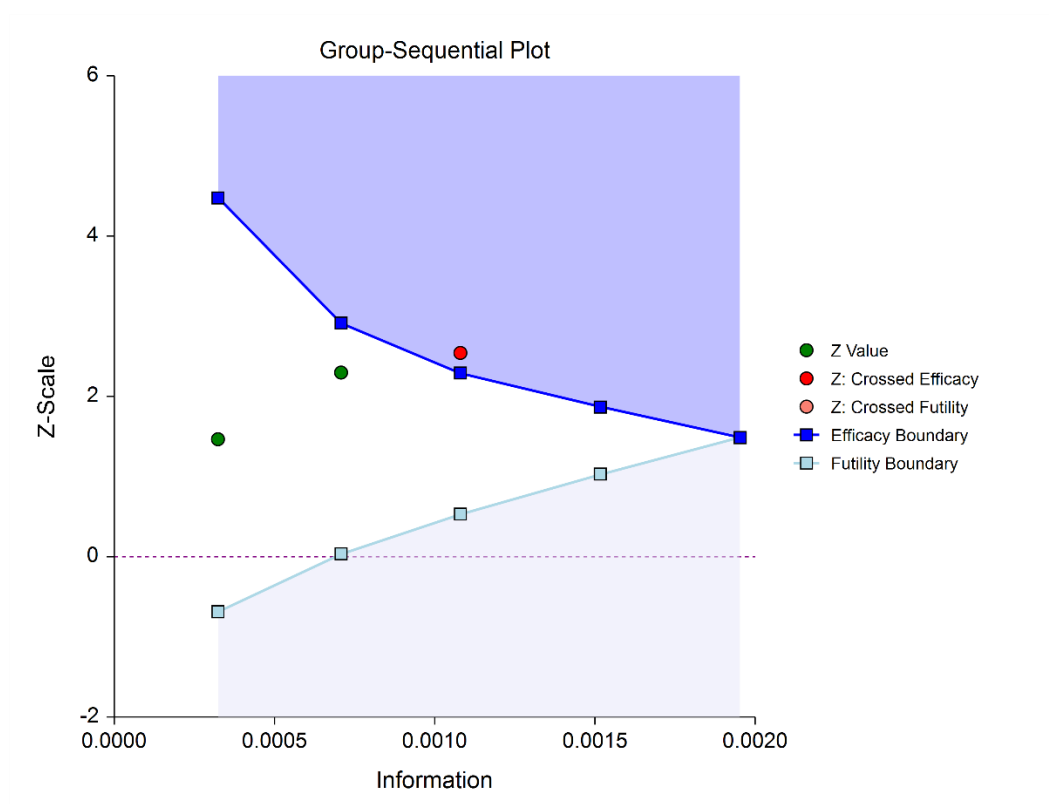
## Reporting Phase

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.

### 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 non-inferiority 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 no more than a small amount above the reference hazard rate. The value of  $\delta$  at which power is calculated is often set to zero. The null and alternative hypotheses, with non-inferiority margin  $M_{NI}$ , are

$$H_0: h_1(T) \geq h_2(T) + |M_{NI}| \quad \text{versus} \quad H_1: h_1(T) < h_2(T) + |M_{NI}|$$

$$H_0: h_1(T) - h_2(T) \geq |M_{NI}| \quad \text{versus} \quad H_1: h_1(T) - h_2(T) < |M_{NI}|$$

$$H_0: \delta \geq |M_{NI}| \quad \text{versus} \quad H_1: \delta < |M_{NI}|$$

#### 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 (1) is no less than a small amount below the reference hazard rate (2). The value of  $\delta$  at which power is calculated is often set to zero. The null and alternative hypotheses, with non-inferiority margin  $M_{NI}$ , are

$$H_0: h_1(T) \leq h_2(T) - |M_{NI}| \quad \text{versus} \quad H_1: h_1(T) > h_2(T) - |M_{NI}|$$

$$H_0: h_1(T) - h_2(T) \leq -|M_{NI}| \quad \text{versus} \quad H_1: h_1(T) - h_2(T) > -|M_{NI}|$$

$$H_0: \delta \leq -|M_{NI}| \quad \text{versus} \quad H_1: \delta > -|M_{NI}|$$

### 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:

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

and, when higher hazard rates are better:

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

with

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

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

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. This procedure 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

$$I_K^* = \frac{1}{\frac{\sigma_K^2(h_1, l_1, p_1)}{n_{1K}} + \frac{\sigma_K^2(h_2, l_2, p_2)}{n_{2K}}}$$

where

$i = 1, 2$  for the two groups

$\sigma_K^2(h_i, l_i, p_i)$  is the variance of the hazard rate estimator

$h_i$  is the group hazard rate

$l_i$  is the group loss hazard rate

$p_i$  is the group patient entry parameter

and

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

for  $i = 1, 2$ ,

where

$T_0$  is the accrual time

$T$  is the total time

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

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

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

$$I_k = \frac{1}{\hat{\sigma}_k^2(\hat{h}_{1k}) + \hat{\sigma}_k^2(\hat{h}_{2k})}$$

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

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

$$p_k = \frac{I_k}{I_K^*}$$

## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

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

$$I_K = \frac{1}{\hat{\sigma}_K^2(\hat{h}_{1K}) + \hat{\sigma}_K^2(\hat{h}_{2K})} \neq I_K^* = \frac{1}{\frac{\sigma_K^2(h_1, l_1, p_1)}{n_{1K}} + \frac{\sigma_K^2(h_2, l_2, p_2)}{n_{2K}}}$$

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

$$I_K^* = I_K$$

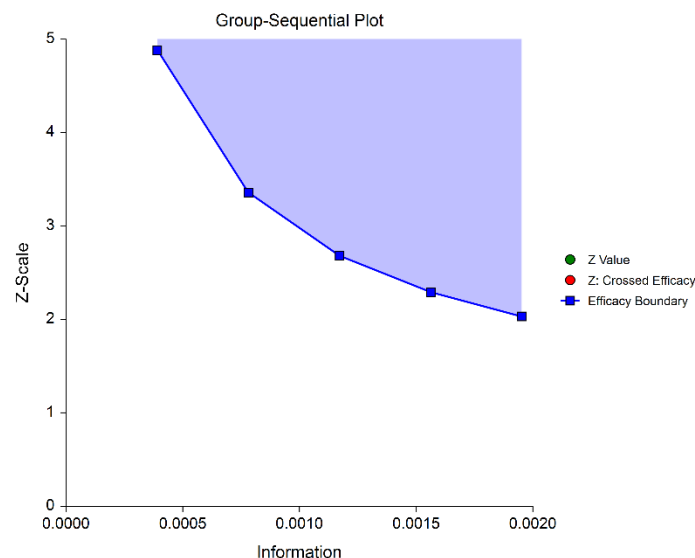
See the discussion in Wassmer and Brannath (2016), pages 78-79, or Jennison and Turnbull (2000), pages 153-154, 162.

## Types of Boundaries

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

### Efficacy Only

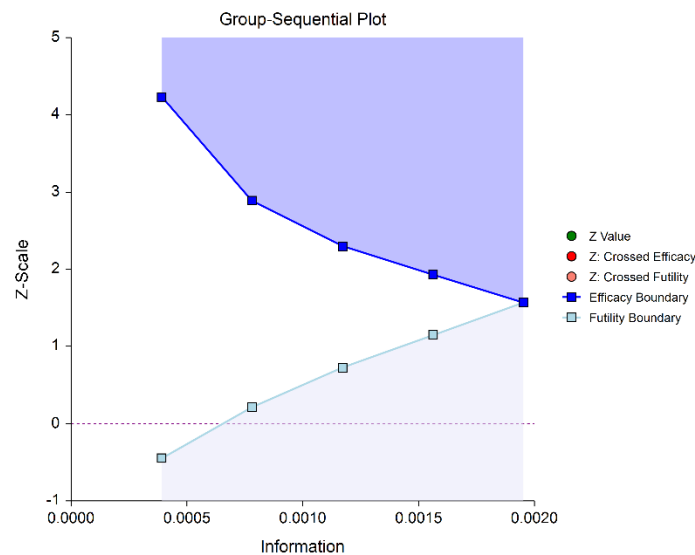
The simplest group-sequential test involves a single set of stage boundaries with early stopping for efficacy.



## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

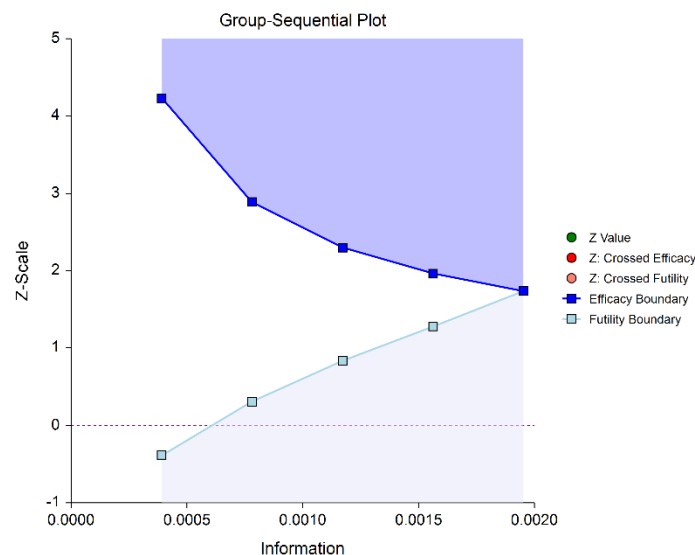
## Efficacy and Binding Futility

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

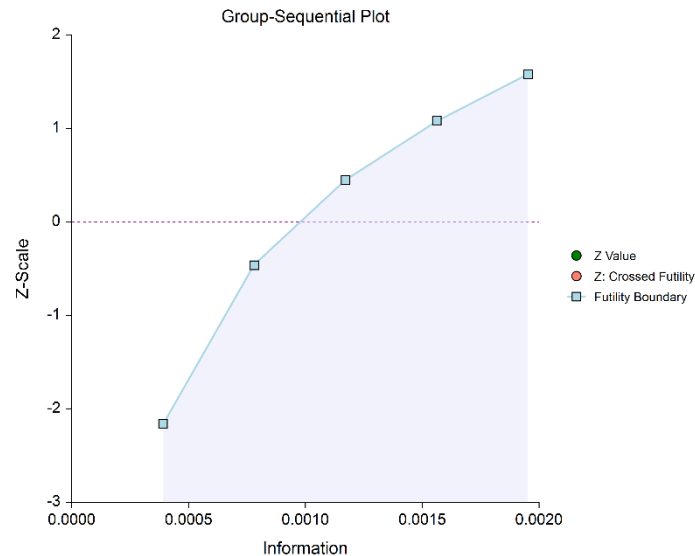
This design also allows early stopping for either efficacy or futility. For non-binding futility designs, the Type I error protection ( $\alpha$ ) is maintained, regardless of whether the study continues after crossing a futility boundary. However, the effect is to make the test conservative ( $\alpha$  is lower than the stated  $\alpha$  and power is lower than the stated power).



## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

## 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  $\beta$ .

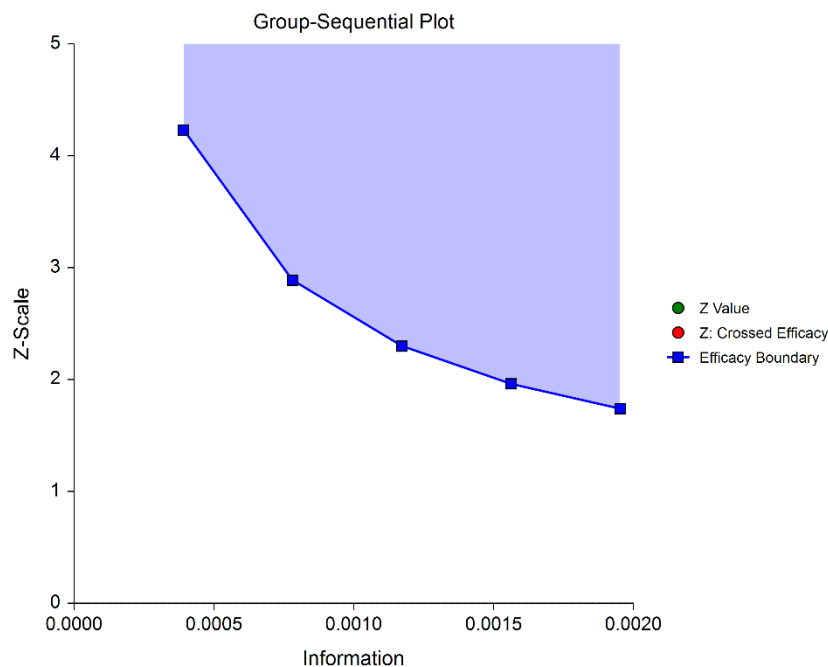
### O'Brien-Fleming Analog

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.

$$\alpha(0) = 0$$

$$\alpha(p_k) = 2 - 2\Phi\left(\frac{Z_{1-\alpha/2}}{\sqrt{p_k}}\right)$$

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



## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

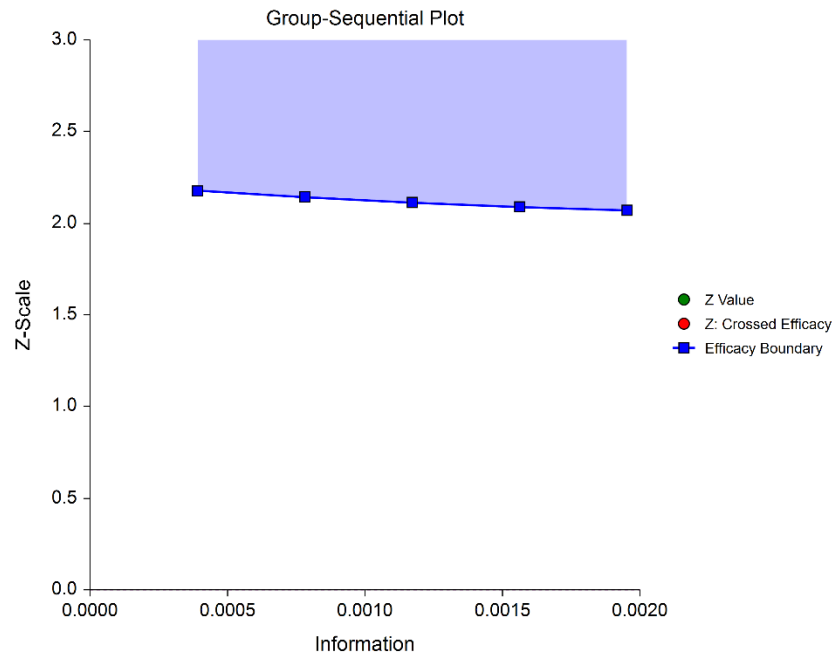
**Pocock Analog**

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.

$$\alpha(0) = 0$$

$$\alpha(p_k) = \alpha \ln(1 + (e - 1)p_k)$$

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



## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

**Power Family**

The power family of spending functions has a  $\rho$  parameter that gives flexibility in the spending function shape.

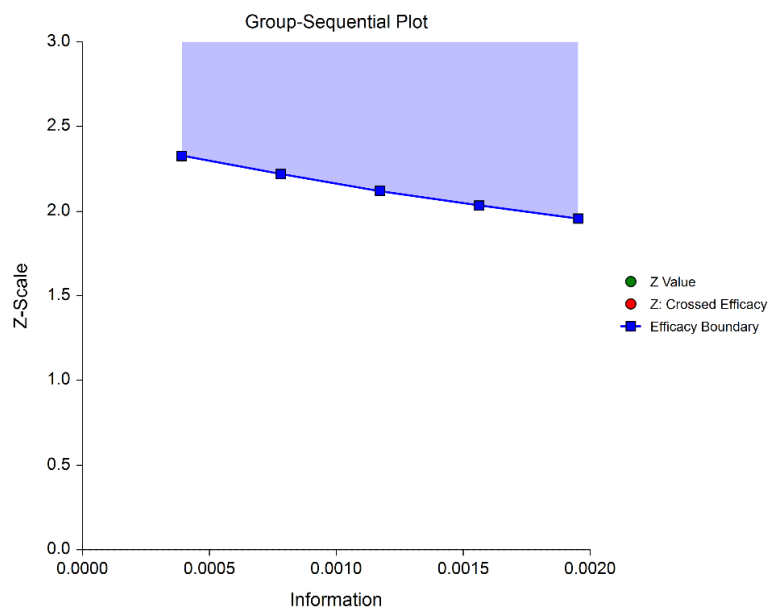
$$\alpha(0) = 0$$

$$\alpha(p_k) = p_k^\rho, \quad \rho > 0$$

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

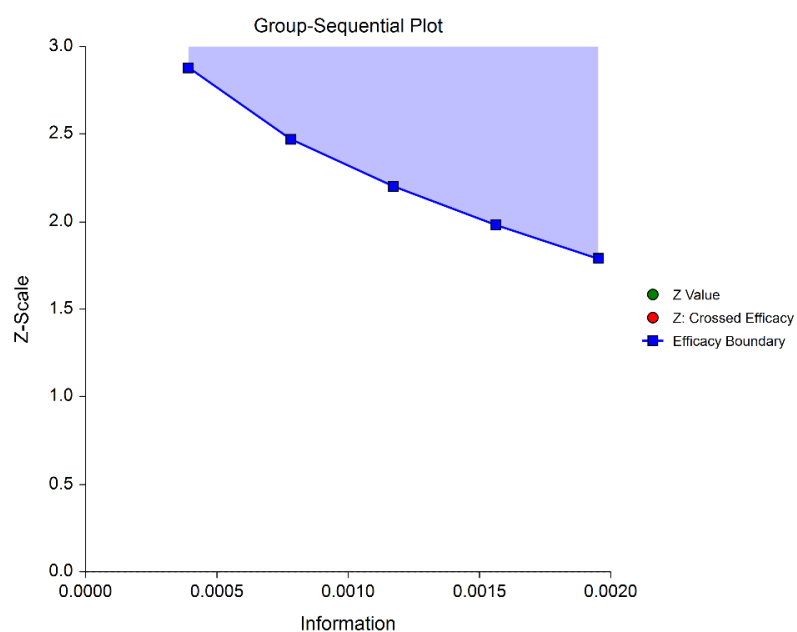
A power family spending function with a  $\rho$  of 1 is similar to a Pocock design, while a power family spending function with a  $\rho$  of 3 is more similar to an O'Brien-Fleming design.

$$\rho = 1$$

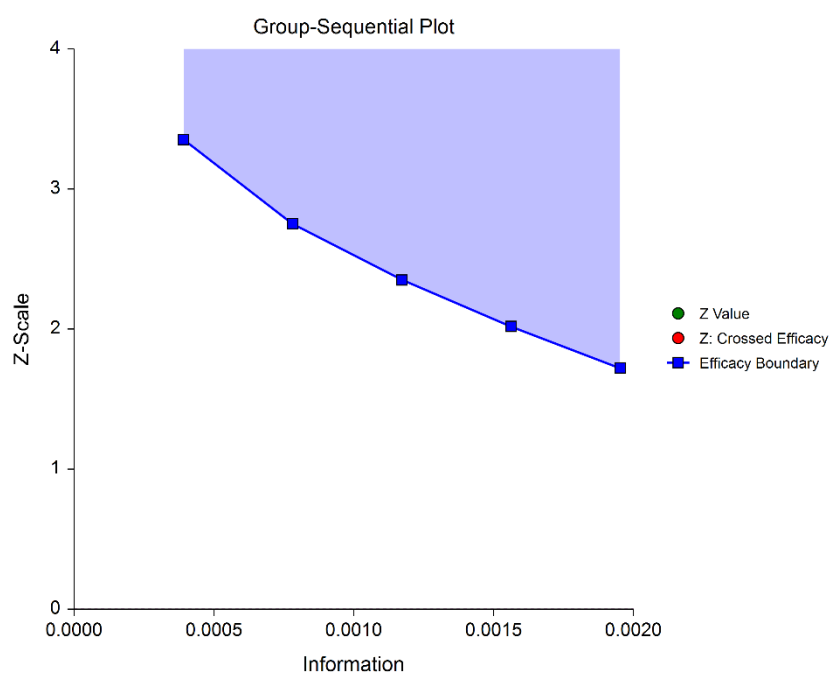


## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

$$\rho = 2$$



$$\rho = 3$$



## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

## 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.

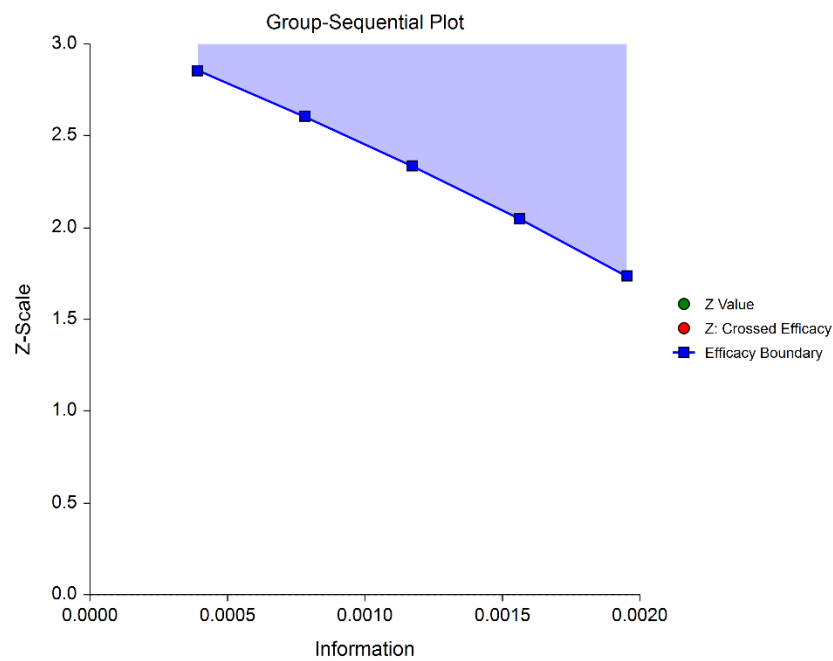
$$\alpha(0) = 0$$

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

$$\alpha(p_k) = \alpha p_k, \quad \gamma = 0$$

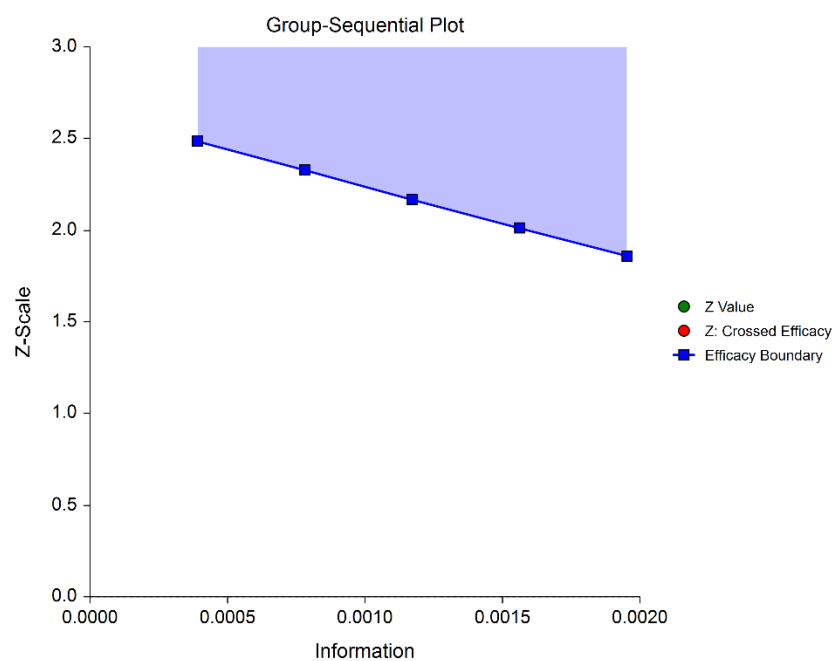
$$\alpha(1) = \alpha$$

$$\gamma = -3$$

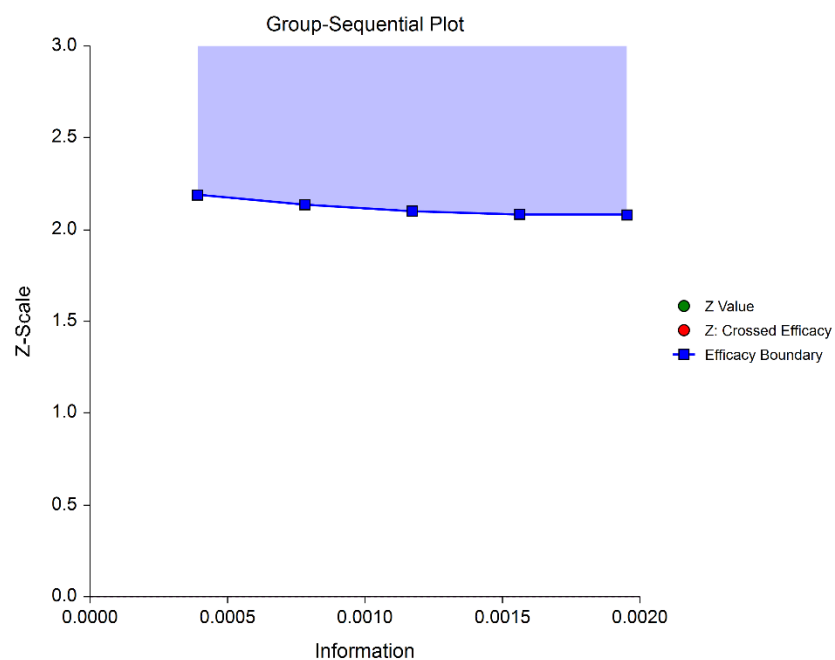


## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

$$\gamma = -1$$

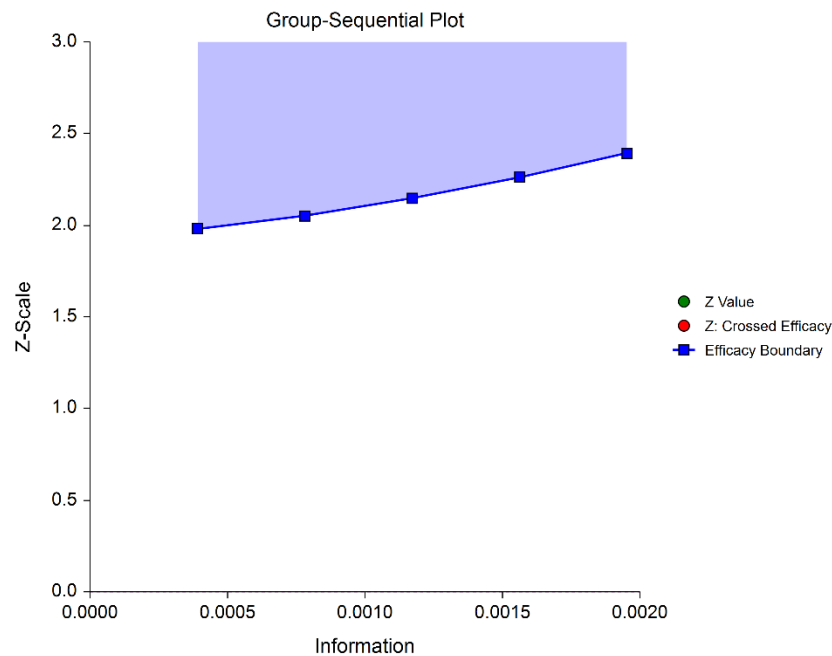


$$\gamma = 1$$



## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

$$\gamma = 3$$



## Using Simulation to obtain Boundary Crossing Probabilities

In addition to providing an overall estimate of power, it can be useful to researchers to know the probability of crossing each of the group-sequential boundaries, given a specified assumed value for the hazard rates. The following steps are used to estimate these probabilities using simulation:

1. Determine the target (cumulative) sample sizes and times for each stage, including the final stage. Fractional sample sizes are rounded up to the next integer.
2. For each simulation, obtain a simulated data set with the final stage sample sizes. Simulated values are generated from Exponential distributions with user-specified hazard rates.
3. Determine whether simulation Z-values are 'held out' after crossing a boundary, or whether simulation Z-values are 'left in' (compared to boundaries at all future stages, regardless of whether a boundary was crossed at a previous stage).
  - a. If simulation Z-values are 'held out' after crossing a boundary, it is determined for each simulation which boundary was crossed first (except in the case of non-binding futility boundaries).
  - b. If simulation Z-values are 'left in' after crossing a boundary, it is determined for each simulation all the boundaries where the Z-value is across the boundary.
4. The proportion of simulations crossing each boundary provides an estimate of the probability of crossing each boundary, given the specified assumed hazard rates.

## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

5. Overall power and alpha calculations are also based on the specification of 'held out' or 'left in'.
  - a. When Hold Out is selected, power and alpha are calculated as the sum of all efficacy boundary proportions.
  - b. When Leave In is selected, power and alpha are calculated as the efficacy boundary proportion of the final stage.

**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.

## Example 1 – Sample Size and Initial Boundaries for a Group-Sequential Test

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 no higher than that of the current standard treatment. The desired margin of non-inferiority is 0.25. 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

$$H_0: h_1 - h_2 = 0.25 \quad (H_0: h_{New} = h_{Std} + 0.25)$$

versus

$$H_a: h_1 - h_2 < 0.25 \quad (H_a: h_{New} < h_{Std} + 0.25)$$

The design calls for five stages of one year each, if the final stage is reached. It is anticipated that the patients will be accrued as they come, for all 5 years of the study. Accrual is expected to occur at an even rate. The loss hazard rate for both groups is assumed to be 0.03. A power of 0.90 is needed. The assumed hazard rate for the standard approach is 0.7. Researchers wish to examine the sample sizes needed for new approach hazard rates of 0.5, 0.6, and 0.7. Both efficacy and non-binding futility boundaries are intended. 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.

### Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 1** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

#### Design Tab

Solve For .....	<b>Sample Size</b>
Power.....	<b>0.90</b>
Alpha.....	<b>0.025</b>
Group Allocation .....	<b>Equal (N1 = N2)</b>
L1 (Loss Hazard Rate of Group 1) .....	<b>0.03</b>
L2 (Loss Hazard Rate of Group 2) .....	<b>0.03</b>
T0 (Accrual or Recruitment Time).....	<b>5</b>
Accrual Parameter Entry.....	<b>Calculate Accrual Parameter</b>
Percent of T0 Until 50% are Accrued.....	<b>50</b>
T (Total Time) .....	<b>5</b>
h1 (Hazard Rate of Group 1) .....	<b>0.5 0.6 0.7</b>
h2 (Hazard Rate of Group 2) .....	<b>0.7</b>
NIM (Non-Inferiority Margin) .....	<b>0.25</b>
Maximum Number of Stages (K).....	<b>5</b>
Time Proportion at each Stage .....	<b>Equally incremented</b>

## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

Boundaries Used ..... **Efficacy with Futility**  
 Hypothesis Direction ..... **Ha:  $h_1 - h_2 < |NIM|$  (Lower hazard rates are better)**  
 Boundary Specification ..... **Spending Function Calculation**  
 Alpha Spending Function ..... **O'Brien-Fleming Analog**  
 Skipped Efficacy Stages ..... **<Empty>**  
 Design Beta ..... **0.10**  
 Beta Spending Function ..... **Hwang-Shih-DeCani ( $\gamma$ )**  
 $\gamma$  ..... **1.5**  
 Skipped Futility Stages ..... **<Empty>**  
 Binding or Non-Binding Futility ..... **Non-Binding**

## Options Tab

Number of Simulations ..... **10000** (set for the sake of time, 100,000 or more are recommended)  
 Random Seed ..... **2231554** (for Reproducibility)  
 After Boundary Crossing ..... **Hold out**

## Boundary Reports Tab

All Reports ..... **Checked**

## Boundary Plots Tab

Z-Statistic vs Information ..... **Checked**  
 Z-Statistic vs Time ..... **Checked**  
 Z-Statistic vs Stage ..... **Checked**  
 Z-Statistic vs N ..... **Checked**

## Summary Reports Tab

All Reports ..... **Checked**

## Summary Plots Tab

All plots ..... **Checked** (only 2D will be used)

## Output

Click the Calculate button to perform the calculations and generate the following output. Due to simulation time, this run will take a few minutes. The simulation results will differ slightly for each separate run.

### Run Summary Report – Scenario 1

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

#### Run Summary Report - Scenario 1

Item	Value
Solve For	Sample Size
Maximum Number of Stages (Design)	5
Current Stage	0
Alternative Hypothesis	$h_1 - h_2 <  NIM $
Non-Inferiority Margin (NIM)	0.25
Alpha Spending Function	O'Brien-Fleming Analog
Beta Spending Function	Hwang-Shih-DeCani ( $\gamma = 1.5$ )
Futility Boundaries	Non-Binding
Target Alpha	0.025
Alpha (from simulations)	0.023
Hazard Rate of Group 1	0.5
Hazard Rate of Group 2	0.7
Loss Hazard Rate of Group 1	0.03
Loss Hazard Rate of Group 2	0.03
T0 (Accrual Time)	5
% of T0 Until 50% Accrual	50
Accrual Parameter	0
Total Time	5
N1 (if final stage reached)	59
N2 (if final stage reached)	59
Target Power	0.9
Power (from simulations)	0.9117
Maximum Information	53.3877

## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

## Z-Value Boundaries

This section gives the planning stage Z-statistic boundaries, numerically. These values are reflected in the group-sequential boundary plot. Because the stage one information proportion is so low, and the O'Brien-Fleming Analog Alpha spending function is used, the stage one boundary was too extreme to calculate.

## Z-Value Boundaries

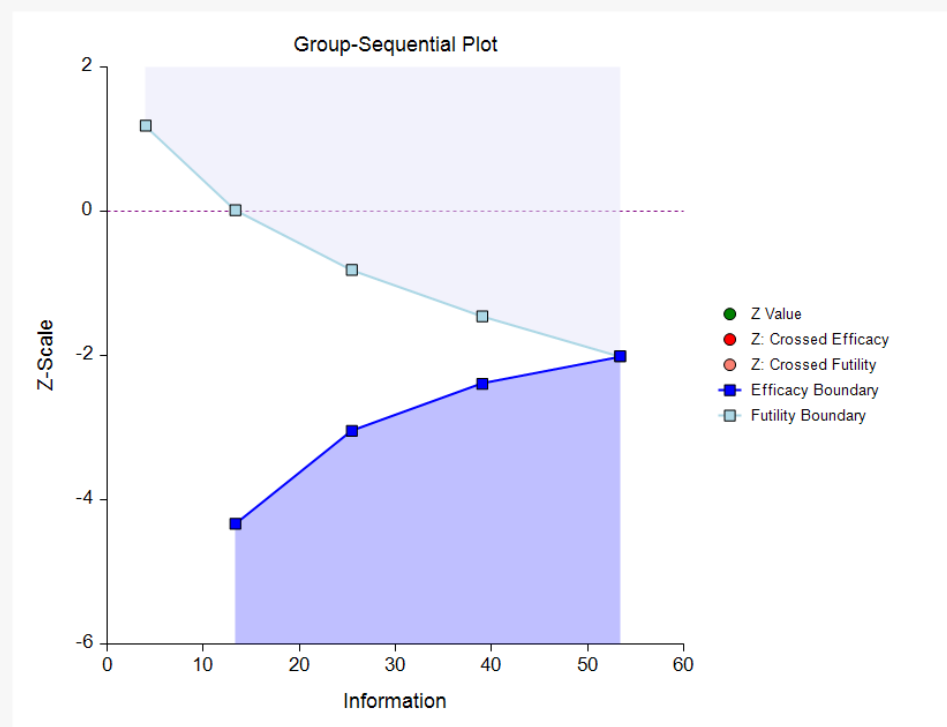
Maximum Information: 53.3877  
 Alternative Hypothesis:  $h_1 - h_2 < |NIM|$   
 Futility Boundaries: Non-Binding

Stage	Boundaries		Time Proportion	Time	Information Proportion
	Efficacy	Futility			
1		1.1876	0.2	1	0.0751
2	-4.3323	0.0161	0.4	2	0.2499
3	-3.0434	-0.8117	0.6	3	0.4769
4	-2.3916	-1.4553	0.8	4	0.7313
5	-2.0089	-2.0089	1.0	5	1.0000

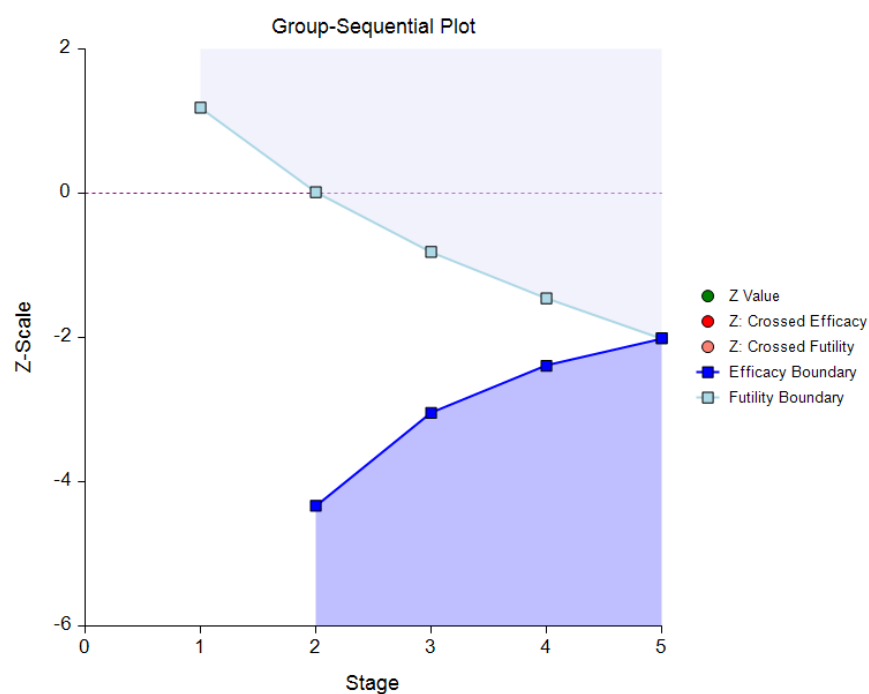
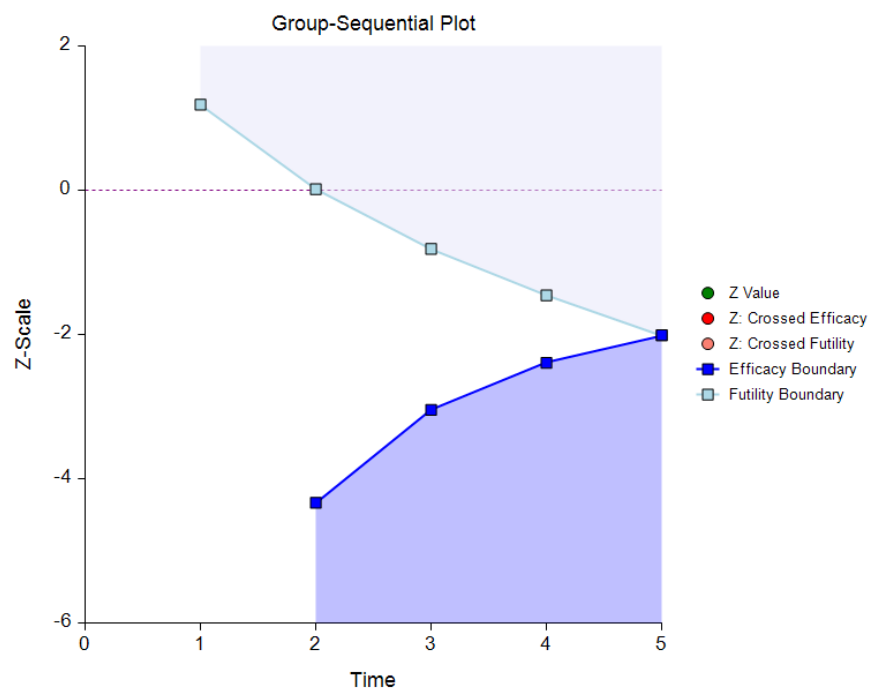
## Boundary Plot(s)

These plots show the efficacy and futility Z-statistic planning boundaries. It is anticipated that these boundaries will adjust to the actual information proportions as the data for each stage is realized. Because the stage one information proportion is so low, and the O'Brien-Fleming Analog Alpha spending function is used, the stage one boundary was too extreme to calculate.

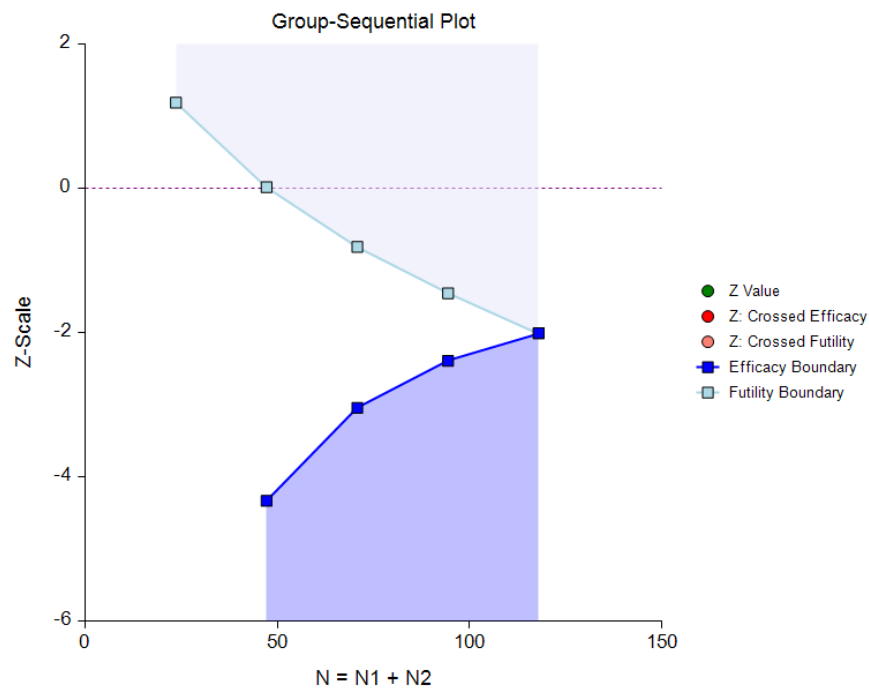
## Boundary Plot(s)



## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)



## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)



## P-Value Boundaries

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

## P-Value Boundaries

Maximum Information: 53.3877  
 Alternative Hypothesis:  $h_1 - h_2 < |NIM|$   
 Futility Boundaries: Non-Binding  
 P-value boundaries are one-sided values.

Stage	Boundaries		Time Proportion	Time	Information Proportion
	Efficacy	Futility			
1		0.88251	0.2	1	0.0751
2	0.00001	0.50642	0.4	2	0.2499
3	0.00117	0.20848	0.6	3	0.4769
4	0.00839	0.07280	0.8	4	0.7313
5	0.02228	0.02228	1.0	5	1.0000

## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

## Information Report

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

## Information Report

Maximum Information: 53.3877  
 Alternative Hypothesis:  $h_1 - h_2 < |NIM|$   
 Alpha: 0.025

Stage	Target Time Proportion	Target Time	Target Information Proportion	Target Information	Target Sample Size		h1	h2
					N1	N2		
1	0.2	1	0.0751	4.0075	11.8	11.8	0.5	0.7
2	0.4	2	0.2499	13.3420	23.6	23.6	0.5	0.7
3	0.6	3	0.4769	25.4623	35.4	35.4	0.5	0.7
4	0.8	4	0.7313	39.0417	47.2	47.2	0.5	0.7
5	1.0	5	1.0000	53.3877	59.0	59.0	0.5	0.7

## Alpha Spending

This section shows how alpha is anticipated to be spent across the stages.

## Alpha Spending

Target Final Stage Alpha: 0.025  
 Spending Function: O'Brien-Fleming Analog

Stage	Information Proportion	Alpha Spent this Stage	Cumulative Alpha Spent	Nominal (Boundary) Alpha	Percentage Alpha Spent this Stage	Cumulative Percentage Alpha Spent
1 *	0.0751	0.0000	0.0000	0.000000	0.0	0.0
2 *	0.2499	0.0000	0.0000	0.000007	0.0	0.0
3 *	0.4769	0.0012	0.0012	0.001170	4.7	4.7
4 *	0.7313	0.0076	0.0088	0.008387	30.4	35.1
5 *	1.0000	0.0162	0.0250	0.022275	64.9	100.0

\* projected

## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

## Beta Spending for Futility

This section shows how beta is anticipated to be spent across the stages.

**Beta Spending for Futility**

Target Cumulative Beta at Final Stage: 0.1  
 Spending Function for Futility: Hwang-Shih-DeCani ( $\gamma = 1.5$ )

Stage	Information Proportion	Beta Spent this Stage	Cumulative Beta Spent	Nominal (Boundary) Beta	Percentage Beta Spent this Stage	Cumulative Percentage Beta Spent
1 *	0.0751	0.0137	0.0137	0.882513	13.7	13.7
2 *	0.2499	0.0265	0.0402	0.506418	26.5	40.2
3 *	0.4769	0.0255	0.0658	0.208481	25.5	65.8
4 *	0.7313	0.0200	0.0857	0.072797	20.0	85.7
5 *	1.0000	0.0143	0.1000	0.022275	14.3	100.0

\* projected

Boundary Probabilities for  $\delta = -0.2$ 

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

**Boundary Probabilities for  $\delta = -0.2$** 

Number of Simulations: 10000  
 Random Seed: 2231554 (User-Entered)  
 Warning: Some simulation results had zero variance due to no events.  
 These Z values were set to 0.  
 Number Set to 0: Stage 1: 24, Stage 2: 0, Stage 3: 0, Stage 4: 0, Stage 5: 0  
 Futility Boundaries: Non-Binding  
 After Efficacy Boundary Crossing: Hold Out  
 After Non-Binding Futility Boundary Crossing: Leave In  
 Alternative Hypothesis:  $h_1 - h_2 < |NIM|$   
 Non-Inferiority Margin (NIM): 0.25  
 Z Statistic: MLE  
 h1: 0.5  
 h2: 0.7  
 $\delta$ : -0.2

Stage			Efficacy		Futility	
	N1	N2	Boundary	Probability	Boundary	Probability
1	*11.8	*11.8		0.0000	1.1876	0.0186
2	*23.6	*23.6	-4.3323	0.0006	0.0161	0.0515
3	*35.4	*35.4	-3.0434	0.2034	-0.8117	0.0739
4	*47.2	*47.2	-2.3916	0.4716	-1.4553	0.0863
5	*59.0	*59.0	-2.0089	0.2361	-2.0089	0.0919

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

## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

Event Summary for  $\delta = -0.2$ 

From the simulations corresponding to the specified hazard rates, this section gives the estimated cumulative number of events at each stage.

**Event Summary for  $\delta = -0.2$** 

Number of Simulations: 10000  
 Random Seed: 2231554 (User-Entered)  
 Warning: Some simulation results had zero variance due to no events. These Z values were set to 0.  
 Number Set to 0: Stage 1: 24, Stage 2: 0, Stage 3: 0, Stage 4: 0, Stage 5: 0  
 h1: 0.5  
 h2: 0.7  
 $\delta$ : -0.2

Stage	Average Cumulative Number of Events	
	E1	E2
1	2.48	3.32
2	8.52	10.77
3	16.63	20.18
4	26.04	30.63
5	36.10	41.51

Boundary Probabilities for  $\delta = |\text{NIM}|$  (Alpha)

This section estimates the probabilities of crossing each boundary if the hazard rate difference is assumed to be the non-inferiority margin.

**Boundary Probabilities for  $\delta = |\text{NIM}|$  (Alpha)**

Number of Simulations: 10000  
 Warning: Some simulation results had zero variance due to no events. These Z values were set to 0.  
 Number Set to 0: Stage 1: 3, Stage 2: 0, Stage 3: 0, Stage 4: 0, Stage 5: 0  
 Futility Boundaries: Non-Binding  
 After Efficacy Boundary Crossing: Hold Out  
 After Non-Binding Futility Boundary Crossing: Leave In  
 Alternative Hypothesis:  $h1 - h2 < |\text{NIM}|$   
 Non-Inferiority Margin (NIM): 0.25  
 Z Statistic: MLE  
 h1:  $0.7 + |\text{NIM}| = 0.7 + 0.25 = 0.95$   
 h2: 0.7  
 $\delta$ :  $|\text{NIM}| = 0.25$

Stage	N1	N2	Efficacy		Futility	
			Boundary	Probability	Boundary	Probability
1	*11.8	*11.8		0.0000	1.1876	0.1105
2	*23.6	*23.6	-4.3323	0.0000	0.0161	0.4970
3	*35.4	*35.4	-3.0434	0.0004	-0.8117	0.7841
4	*47.2	*47.2	-2.3916	0.0079	-1.4553	0.9269
5	*59.0	*59.0	-2.0089	0.0147	-2.0089	0.9795

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

## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

Event Summary for  $\delta = |\text{NIM}|$  (Alpha)

This section gives the estimated cumulative number of events at each stage when the hazard rate difference is assumed to be the non-inferiority margin.

**Event Summary for  $\delta = |\text{NIM}|$  (Alpha)**


---

Number of Simulations: 10000  
 Random Seed: 2231554 (User-Entered)  
 Warning: Some simulation results had zero variance due to no events. These Z values were set to 0.  
 Number Set to 0: Stage 1: 3, Stage 2: 0, Stage 3: 0, Stage 4: 0, Stage 5: 0  
 h1:  $0.7 + |\text{NIM}| = 0.7 + 0.25 = 0.95$   
 h2: 0.7  
 $\delta$ :  $|\text{NIM}| = 0.25$

---

Stage	Average Cumulative Number of Events	
	E1	E2
1	4.18	3.27
2	12.91	10.67
3	23.29	20.14
4	34.35	30.59
5	45.62	41.54

---

## Scenario 2

All of the same boundary reports are given for Scenario 2, corresponding to an h1 value of 0.6.

## Scenario 3

All of the same boundary reports are given for Scenario 3, corresponding to an h1 value of 0.7.

## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

## Power and Sample Size Summary

## Power and Sample Size Summary

Solve For:	Sample Size
Maximum Number of Stages:	5
Alternative Hypothesis:	$h_1 - h_2 <  NIM $
Alpha Spending Function:	O'Brien-Fleming Analog
Beta Spending Function:	Hwang-Shih-DeCani ( $\gamma = 1.5$ )
Number of Simulations:	10000
Random Seed:	2231554 (User-Entered)

Target Power	Sim Power	N1	N2	N	h1	h2	NIM	Target Alpha	Sim Alpha
0.9	0.9117	59	59	118	0.5	0.7	0.25	0.025	0.0230
0.9	0.9025	111	111	222	0.6	0.7	0.25	0.025	0.0249
0.9	0.9062	246	246	492	0.7	0.7	0.25	0.025	0.0243

Target Power	The desired power value (or values) entered in the procedure.
Sim Power	The proportion of simulation z-values that cross an efficacy boundary. Because "After Boundary Crossing" is set to "Hold out," it is the sum of the individual boundary crossing proportions.
N1 and N2	The anticipated number of individuals in each group if the final stage is reached.
N	The total sample size if the final stage is reached. $N = N1 + N2$ .
h1	The assumed hazard rate of population 1 for power calculation simulations.
h2	The assumed hazard rate of population 2 for power calculation simulations. $h_2 \pm  NIM $ is the assumed hazard rate of population 1 for alpha calculation simulations.
NIM	The non-inferiority margin.
Target Alpha	The alpha used in the computation of the boundaries. The desired overall probability of a Type 1 error.
Sim Alpha	The proportion of null simulation z-values that cross an efficacy boundary. Because "After Boundary Crossing" is set to "Hold out," it is the sum of the individual boundary crossing proportions.

## Summary Statements

A parallel, two-group, group-sequential design with a maximum of 5 stages (where lower hazard rates are considered better) will be used to test whether the Group 1 (treatment) hazard rate is non-inferior to the Group 2 (control) hazard rate, with a non-inferiority margin of 0.25 ( $H_0: h_1 - h_2 \geq 0.25$  versus  $H_1: h_1 - h_2 < 0.25$ ). The comparison will be made at each stage using a two-sample MLE hazard rate difference Z-test, with efficacy and utility boundary values calculated from the designated spending functions. The target cumulative Type I error rate ( $\alpha$ ) at the final stage is 0.025. The accrual time of the study will be 5 and the total time will be 5. The group loss hazard rates will be 0.03 for Group 1 and 0.03 for Group 2. To detect a Group 1 hazard rate of 0.5 and a Group 2 hazard rate of 0.7 (difference of -0.2), with 90% power, the number of needed subjects at the final stage will be 59 in Group 1 and 59 in Group 2.

## References

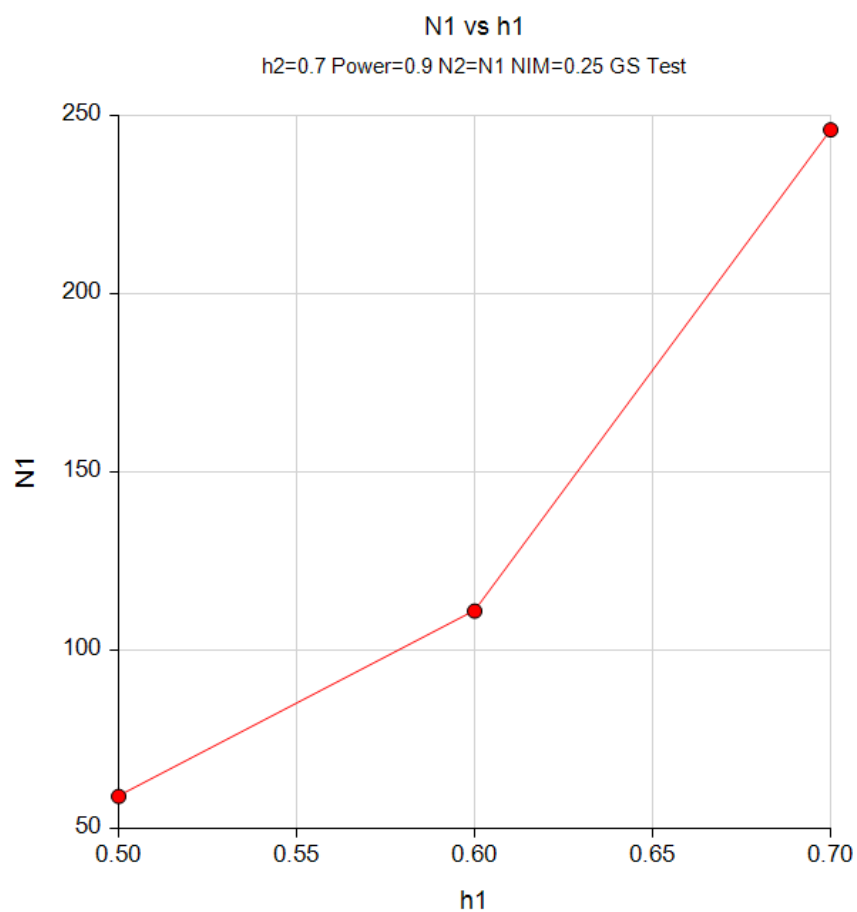
- Jennison, C. and Turnbull, B.W. 2000. Group Sequential Methods with Applications to Clinical Trials. Chapman and Hall/CRC. Boca Raton.
- Lan, K.K.G. and DeMets, D.L. 1983. 'Discrete sequential boundaries for clinical trials.' Biometrika, 70, pages 659-663.
- Reboussin, D.M., DeMets, D.L., Kim, K., and Lan, K.K.G. 1992. 'Programs for computing group sequential boundaries using the Lan-DeMets Method.' Technical Report 60, Department of Biostatistics, University of Wisconsin-Madison.

This report shows the values of each of the parameters, one scenario per row. The values may vary slightly due to the variation in simulations. The details for each of the rows of this report are given in the earlier boundary reports.

The values from this table are exhibited in the plot below.

## Plots Section for Power and Sample Size Summary

## Plots



## Example 2 – Skipping Stage Boundaries

Suppose that the scenario is exactly as in Example 1, except that the first two futility boundaries are to be skipped.

### Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 2** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

#### Design Tab

Solve For .....	<b>Sample Size</b>
Power.....	<b>0.90</b>
Alpha.....	<b>0.025</b>
Group Allocation .....	<b>Equal (N1 = N2)</b>
L1 (Loss Hazard Rate of Group 1) .....	<b>0.03</b>
L2 (Loss Hazard Rate of Group 2) .....	<b>0.03</b>
T0 (Accrual or Recruitment Time) .....	<b>5</b>
Accrual Parameter Entry.....	<b>Calculate Accrual Parameter</b>
Percent of T0 Until 50% are Accrued.....	<b>50</b>
T (Total Time) .....	<b>5</b>
h1 (Hazard Rate of Group 1) .....	<b>0.5 0.6 0.7</b>
h2 (Hazard Rate of Group 2) .....	<b>0.7</b>
NIM (Non-Inferiority Margin) .....	<b>0.25</b>
Maximum Number of Stages (K).....	<b>5</b>
Time Proportion at each Stage .....	<b>Equally incremented</b>
Boundaries Used .....	<b>Efficacy with Futility</b>
Hypothesis Direction .....	<b>Ha: <math>h_1 - h_2 &lt;  NIM </math> (Lower hazard rates are better)</b>
Boundary Specification .....	<b>Spending Function Calculation</b>
Alpha Spending Function.....	<b>O'Brien-Fleming Analog</b>
Skipped Efficacy Stages .....	<b>&lt;Empty&gt;</b>
Design Beta .....	<b>0.10</b>
Beta Spending Function.....	<b>Hwang-Shih-DeCani (<math>\gamma</math>)</b>
$\gamma$ .....	<b>1.5</b>
<b>Skipped Futility Stages</b> .....	<b>1 2</b>
Binding or Non-Binding Futility.....	<b>Non-Binding</b>

#### Options Tab

Number of Simulations.....	<b>10000</b> (set for the sake of time, 100,000 or more are recommended)
Random Seed .....	<b>2311884</b> (for Reproducibility)
After Boundary Crossing.....	<b>Hold out</b>

#### Boundary Reports Tab

All Reports .....	<b>Checked</b>
-------------------	----------------

## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

## Boundary Plots Tab

Z-Statistic vs Information ..... **Checked**  
 Z-Statistic vs Time ..... **Checked**  
 Z-Statistic vs Stage ..... **Checked**  
 Z-Statistic vs N ..... **Checked**

## Summary Reports Tab

All Reports ..... **Checked**

## Summary Plots Tab

All plots ..... **Checked** (only 2D will be used)

## Output

Click the Calculate button to perform the calculations and generate the following output. The simulation results will differ slightly for each separate run.

## Run Summary Report

### Run Summary Report - Scenario 1

Item	Value
Solve For	Sample Size
Maximum Number of Stages (Design)	5
Skipped Futility Stage(s)	1 2
Current Stage	0
Alternative Hypothesis	$h_1 - h_2 <  NIM $
Non-Inferiority Margin (NIM)	0.25
Alpha Spending Function	O'Brien-Fleming Analog
Beta Spending Function	Hwang-Shih-DeCani ( $\gamma = 1.5$ )
Futility Boundaries	Non-Binding
Target Alpha	0.025
Alpha (from simulations)	0.0271
Hazard Rate of Group 1	0.5
Hazard Rate of Group 2	0.7
Loss Hazard Rate of Group 1	0.03
Loss Hazard Rate of Group 2	0.03
T0 (Accrual Time)	5
% of T0 Until 50% Accrual	50
Accrual Parameter	0
Total Time	5
N1 (if final stage reached)	57
N2 (if final stage reached)	57
Target Power	0.9
Power (from simulations)	0.9034
Maximum Information	51.5779

## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

## Z-Value Boundaries

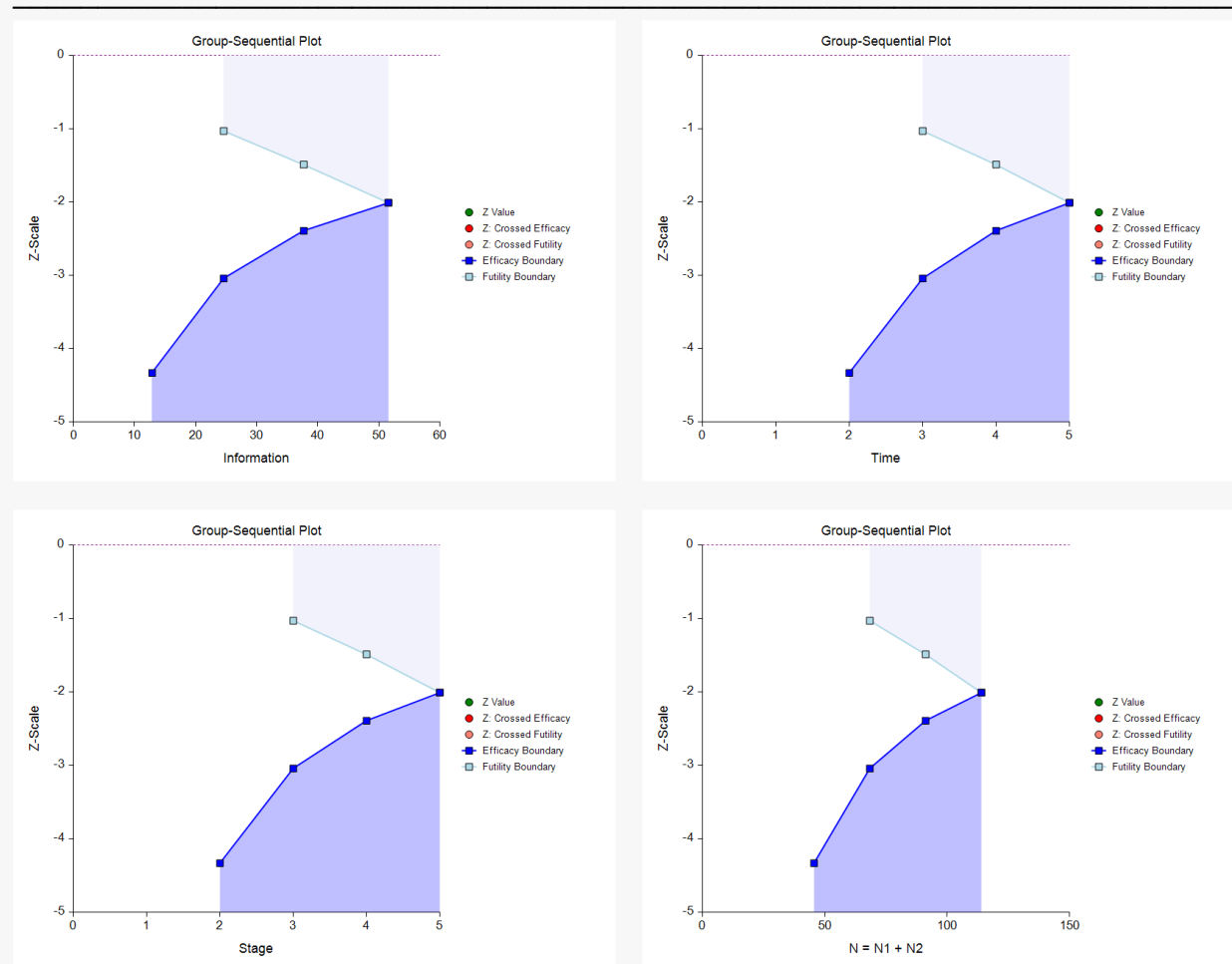
## Z-Value Boundaries

Maximum Information: 51.5779  
 Alternative Hypothesis:  $h_1 - h_2 < |NIM|$   
 Futility Boundaries: Non-Binding

Stage	Boundaries		Time Proportion	Time	Information Proportion
	Efficacy	Futility			
1			0.2	1	0.0751
2	-4.3323		0.4	2	0.2499
3	-3.0434	-1.0298	0.6	3	0.4769
4	-2.3916	-1.4873	0.8	4	0.7313
5	-2.0089	-2.0089	1.0	5	1.0000

## Boundary Plot(s)

## Boundary Plot(s)



## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

## P-Value Boundaries

## P-Value Boundaries

Maximum Information: 51.5779  
 Alternative Hypothesis:  $h_1 - h_2 < |NIM|$   
 Futility Boundaries: Non-Binding  
 P-value boundaries are one-sided values.

Stage	Boundaries		Time		Information Proportion
	Efficacy	Futility	Proportion	Time	
1			0.2	1	0.0751
2	0.00001		0.4	2	0.2499
3	0.00117	0.15154	0.6	3	0.4769
4	0.00839	0.06847	0.8	4	0.7313
5	0.02228	0.02228	1.0	5	1.0000

## Information Report

## Information Report

Maximum Information: 51.5779  
 Alternative Hypothesis:  $h_1 - h_2 < |NIM|$   
 Alpha: 0.025

Stage	Target Time Proportion	Target Time	Target Information Proportion	Target Information	Target Sample Size		h1	h2
					N1	N2		
1	0.2	1	0.0751	3.8716	11.4	11.4	0.5	0.7
2	0.4	2	0.2499	12.8897	22.8	22.8	0.5	0.7
3	0.6	3	0.4769	24.5992	34.2	34.2	0.5	0.7
4	0.8	4	0.7313	37.7182	45.6	45.6	0.5	0.7
5	1.0	5	1.0000	51.5779	57.0	57.0	0.5	0.7

## Alpha Spending

## Alpha Spending

Target Final Stage Alpha: 0.025  
 Spending Function: O'Brien-Fleming Analog

Stage	Information Proportion	Alpha Spent this Stage	Cumulative Alpha Spent	Nominal (Boundary) Alpha	Percentage Alpha Spent this Stage	Cumulative Percentage Alpha Spent
1 *	0.0751	0.0000	0.0000	0.000000	0.0	0.0
2 *	0.2499	0.0000	0.0000	0.000007	0.0	0.0
3 *	0.4769	0.0012	0.0012	0.001170	4.7	4.7
4 *	0.7313	0.0076	0.0088	0.008387	30.4	35.1
5 *	1.0000	0.0162	0.0250	0.022275	64.9	100.0

\* projected

## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

## Beta Spending for Futility

## Beta Spending for Futility

Target Cumulative Beta at Final Stage: 0.1  
 Spending Function for Futility: Hwang-Shih-DeCani ( $\gamma = 1.5$ )

Stage	Information Proportion	Beta Spent this Stage	Cumulative Beta Spent	Nominal (Boundary) Beta	Percentage Beta Spent this Stage	Cumulative Percentage Beta Spent
1 *	0.0751	0.0000	0.0000	1.000000	0.0	0.0
2 *	0.2499	0.0000	0.0000	1.000000	0.0	0.0
3 *	0.4769	0.0658	0.0658	0.151542	65.8	65.8
4 *	0.7313	0.0200	0.0857	0.068472	20.0	85.7
5 *	1.0000	0.0143	0.1000	0.022275	14.3	100.0

\* projected

Boundary Probabilities for  $\delta = -0.2$ Boundary Probabilities for  $\delta = -0.2$ 

Number of Simulations: 10000  
 Random Seed: 2311884 (User-Entered)  
 Warning: Some simulation results had zero variance due to no events.  
 These Z values were set to 0.  
 Number Set to 0: Stage 1: 35, Stage 2: 0, Stage 3: 0, Stage 4: 0, Stage 5: 0  
 Futility Boundaries: Non-Binding  
 After Efficacy Boundary Crossing: Hold Out  
 After Non-Binding Futility Boundary Crossing: Leave In  
 Alternative Hypothesis:  $h_1 - h_2 < |NIM|$   
 Non-Inferiority Margin (NIM): 0.25  
 Z Statistic: MLE  
 $h_1$ : 0.5  
 $h_2$ : 0.7  
 $\delta$ : -0.2

Stage	N1	N2	Efficacy		Futility	
			Boundary	Probability	Boundary	Probability
1	*11.4	*11.4		0.0000		0.0000
2	*22.8	*22.8	-4.3323	0.0000		0.0000
3	*34.2	*34.2	-3.0434	0.1854	-1.0298	0.1125
4	*45.6	*45.6	-2.3916	0.4718	-1.4873	0.0960
5	*57.0	*57.0	-2.0089	0.2462	-2.0089	0.1002

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

## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

Event Summary for  $\delta = -0.2$ Event Summary for  $\delta = -0.2$ 

Number of Simulations: 10000  
 Random Seed: 2311884 (User-Entered)  
 Warning: Some simulation results had zero variance due to no events. These Z values were set to 0.  
 Number Set to 0: Stage 1: 35, Stage 2: 0, Stage 3: 0, Stage 4: 0, Stage 5: 0  
 h1: 0.5  
 h2: 0.7  
 $\delta$ : -0.2

Stage	Average Cumulative Number of Events	
	E1	E2
1	2.41	3.14
2	8.24	10.37
3	16.09	19.49
4	25.14	29.52
5	34.93	40.05

Boundary Probabilities for  $\delta = |\text{NIM}|$  (Alpha)Boundary Probabilities for  $\delta = |\text{NIM}|$  (Alpha)

Number of Simulations: 10000  
 Random Seed: 2311884 (User-Entered)  
 Warning: Some simulation results had zero variance due to no events. These Z values were set to 0.  
 Number Set to 0: Stage 1: 4, Stage 2: 0, Stage 3: 0, Stage 4: 0, Stage 5: 0  
 Futility Boundaries: Non-Binding  
 After Efficacy Boundary Crossing: Hold Out  
 After Non-Binding Futility Boundary Crossing: Leave In  
 Alternative Hypothesis:  $h1 - h2 < |\text{NIM}|$   
 Non-Inferiority Margin (NIM): 0.25  
 Z Statistic: MLE  
 h1:  $0.7 + |\text{NIM}| = 0.7 + 0.25 = 0.95$   
 h2: 0.7  
 $\delta$ :  $|\text{NIM}| = 0.25$

Stage	N1	N2	Efficacy		Futility	
			Boundary	Probability	Boundary	Probability
1	*11.4	*11.4		0.0000		0.0000
2	*22.8	*22.8	-4.3323	0.0000		0.0000
3	*34.2	*34.2	-3.0434	0.0008	-1.0298	0.8405
4	*45.6	*45.6	-2.3916	0.0083	-1.4873	0.9267
5	*57.0	*57.0	-2.0089	0.0180	-2.0089	0.9757

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

## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

Event Summary for  $\delta = |\text{NIM}|$  (Alpha)**Event Summary for  $\delta = |\text{NIM}|$  (Alpha)**


---

Number of Simulations: 10000  
 Random Seed: 2311884 (User-Entered)  
 Warning: Some simulation results had zero variance due to no events. These Z values were set to 0.  
 Number Set to 0: Stage 1: 4, Stage 2: 0, Stage 3: 0, Stage 4: 0, Stage 5: 0  
 $h_1$ :  $0.7 + |\text{NIM}| = 0.7 + 0.25 = 0.95$   
 $h_2$ : 0.7  
 $\delta$ :  $|\text{NIM}| = 0.25$

---

Stage	Average Cumulative Number of Events	
	E1	E2
1	4.02	3.16
2	12.45	10.34
3	22.52	19.51
4	33.20	29.56
5	44.11	40.05

---

## Scenario 2

All of the same boundary reports are given for Scenario 2, corresponding to an  $h_1$  value of 0.6.

## Scenario 3

All of the same boundary reports are given for Scenario 3, corresponding to an  $h_1$  value of 0.7.

## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

## Power and Sample Size Summary

## Power and Sample Size Summary

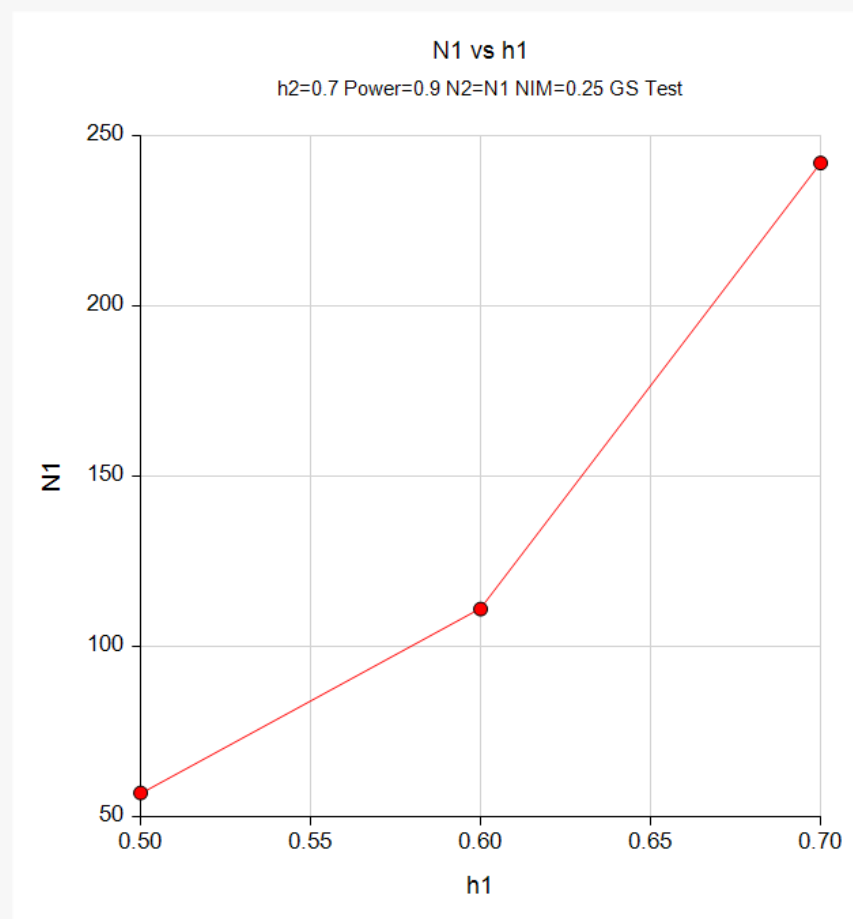
Solve For: Sample Size  
 Maximum Number of Stages: 5  
 Skipped Futility Stage(s): 1 2  
 Alternative Hypothesis:  $h_1 - h_2 < |NIM|$   
 Alpha Spending Function: O'Brien-Fleming Analog  
 Beta Spending Function: Hwang-Shih-DeCani ( $\gamma = 1.5$ )  
 Number of Simulations: 10000  
 Random Seed: 2311884 (User-Entered)

Target Power	Sim Power	N1	N2	N	h1	h2	NIM	Target Alpha	Sim Alpha
0.9	0.9034	57	57	114	0.5	0.7	0.25	0.025	0.0271
0.9	0.9046	111	111	222	0.6	0.7	0.25	0.025	0.0235
0.9	0.9020	242	242	484	0.7	0.7	0.25	0.025	0.0268

This report shows no noteworthy change in overall sample size.

## Plots Section for Power and Sample Size Summary

## Plots



## Example 3 – Finding Power

Suppose that the scenario is similar to the setup of Example 1, except that now we will solve for power for various sample sizes of 20 to 200 per group.

### Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 3** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

#### Design Tab

Solve For ..... **Power**  
 Alpha..... **0.025**  
 Group Allocation ..... **Equal (N1 = N2)**  
 Sample Size Per Group ..... **20 to 200 by 20**  
 L1 (Loss Hazard Rate of Group 1) ..... **0.03**  
 L2 (Loss Hazard Rate of Group 2) ..... **0.03**  
 T0 (Accrual or Recruitment Time)..... **5**  
 Accrual Parameter Entry..... **Calculate Accrual Parameter**  
 Percent of T0 Until 50% are Accrued..... **50**  
 T (Total Time) ..... **5**  
 h1 (Hazard Rate of Group 1) ..... **0.5 0.6 0.7**  
 h2 (Hazard Rate of Group 2) ..... **0.7**  
 NIM (Non-Inferiority Margin) ..... **0.25**  
 Maximum Number of Stages (K)..... **5**  
 Time Proportion at each Stage ..... **Equally incremented**  
 Boundaries Used ..... **Efficacy with Futility**  
 Hypothesis Direction ..... **Ha:  $h_1 - h_2 < |NIM|$  (Lower hazard rates are better)**  
 Boundary Specification ..... **Spending Function Calculation**  
 Alpha Spending Function..... **O'Brien-Fleming Analog**  
 Skipped Efficacy Stages ..... **<Empty>**  
 Design Beta ..... **0.10**  
 Beta Spending Function..... **Hwang-Shih-DeCani ( $\gamma$ )**  
 $\gamma$  ..... **1.5**  
 Skipped Futility Stages ..... **<Empty>**  
 Binding or Non-Binding Futility..... **Non-Binding**

#### Options Tab

Number of Simulations..... **10000** (set for the sake of time, 100,000 or more are recommended)  
 Random Seed ..... **3019843** (for Reproducibility)  
 After Boundary Crossing..... **Hold out**

#### Boundary Reports Tab

All Reports ..... **Checked**

## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

## Boundary Plots Tab

Z-Statistic vs Information .....	<b>Checked</b>
Z-Statistic vs Time .....	<b>Checked</b>
Z-Statistic vs Stage .....	<b>Checked</b>
Z-Statistic vs N .....	<b>Checked</b>

## Summary Reports Tab

All Reports .....	<b>Checked</b>
-------------------	----------------

## Summary Plots Tab

All plots .....	<b>Checked</b>
-----------------	----------------

---

## Output

Click the Calculate button to perform the calculations and generate the following output. The simulation results will differ slightly for each separate run.

## Scenario Reports

All of the scenario reports for each of the 30 scenarios are generated in the output, but they are not shown here.

## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

## Power and Sample Size Summary

## Power and Sample Size Summary

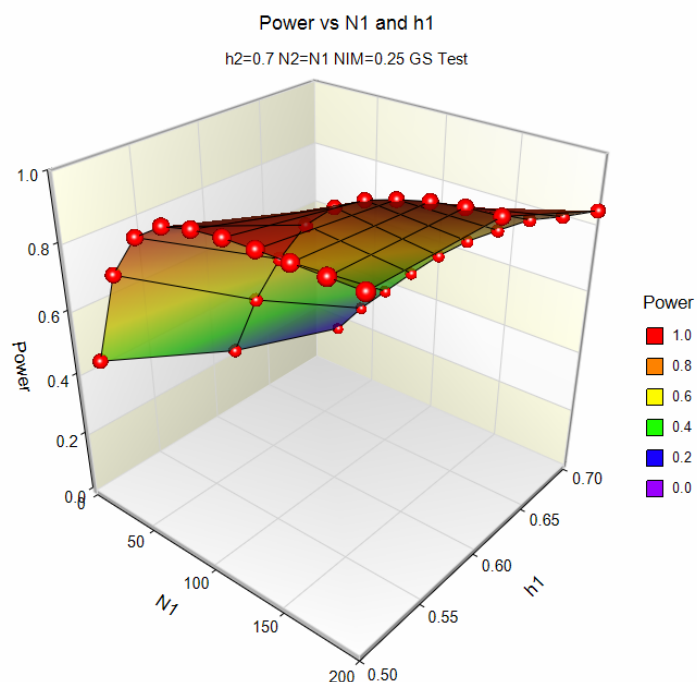
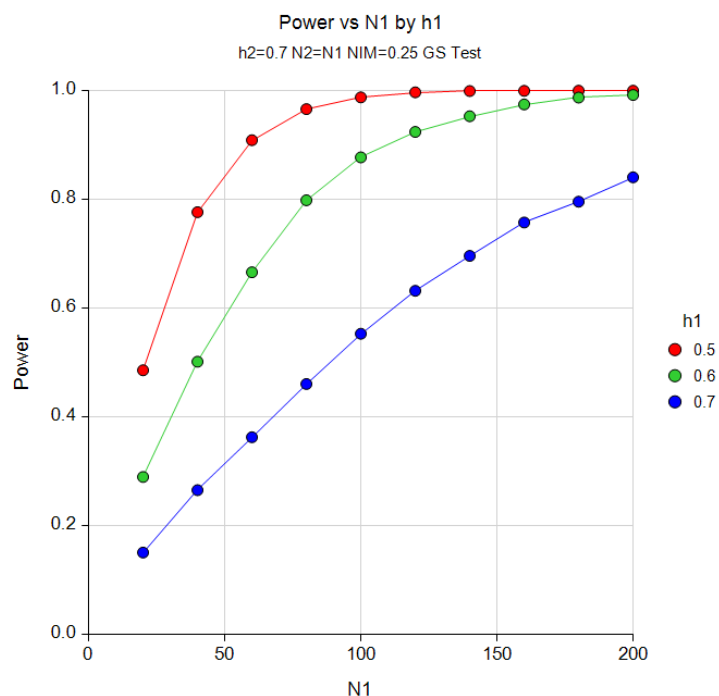
Solve For: Power  
 Maximum Number of Stages: 5  
 Alternative Hypothesis:  $h_1 - h_2 < |NIM|$   
 Alpha Spending Function: O'Brien-Fleming Analog  
 Beta Spending Function: Hwang-Shih-DeCani ( $\gamma = 1.5$ )  
 Number of Simulations: 10000  
 Random Seed: 3019843 (User-Entered)

Sim Power	N1	N2	N	h1	h2	NIM	Target Alpha	Sim Alpha
0.4858	20	20	40	0.5	0.7	0.25	0.025	0.0277
0.7766	40	40	80	0.5	0.7	0.25	0.025	0.0282
0.9089	60	60	120	0.5	0.7	0.25	0.025	0.0269
0.9661	80	80	160	0.5	0.7	0.25	0.025	0.0254
0.9877	100	100	200	0.5	0.7	0.25	0.025	0.0282
0.9969	120	120	240	0.5	0.7	0.25	0.025	0.0248
0.9993	140	140	280	0.5	0.7	0.25	0.025	0.0263
0.9997	160	160	320	0.5	0.7	0.25	0.025	0.0264
0.9999	180	180	360	0.5	0.7	0.25	0.025	0.0251
0.9999	200	200	400	0.5	0.7	0.25	0.025	0.0267
0.2896	20	20	40	0.6	0.7	0.25	0.025	0.0287
0.5015	40	40	80	0.6	0.7	0.25	0.025	0.0253
0.6660	60	60	120	0.6	0.7	0.25	0.025	0.0267
0.7984	80	80	160	0.6	0.7	0.25	0.025	0.0251
0.8773	100	100	200	0.6	0.7	0.25	0.025	0.0269
0.9242	120	120	240	0.6	0.7	0.25	0.025	0.0276
0.9529	140	140	280	0.6	0.7	0.25	0.025	0.0267
0.9747	160	160	320	0.6	0.7	0.25	0.025	0.0248
0.9873	180	180	360	0.6	0.7	0.25	0.025	0.0221
0.9920	200	200	400	0.6	0.7	0.25	0.025	0.0224
0.1505	20	20	40	0.7	0.7	0.25	0.025	0.0295
0.2653	40	40	80	0.7	0.7	0.25	0.025	0.0272
0.3627	60	60	120	0.7	0.7	0.25	0.025	0.0241
0.4605	80	80	160	0.7	0.7	0.25	0.025	0.0262
0.5529	100	100	200	0.7	0.7	0.25	0.025	0.0280
0.6319	120	120	240	0.7	0.7	0.25	0.025	0.0254
0.6962	140	140	280	0.7	0.7	0.25	0.025	0.0265
0.7576	160	160	320	0.7	0.7	0.25	0.025	0.0245
0.7958	180	180	360	0.7	0.7	0.25	0.025	0.0296
0.8407	200	200	400	0.7	0.7	0.25	0.025	0.0243

## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

## Plots Section for Power and Sample Size Summary

## Plots



The power curve plot shows the effect of sample size and hazard rate difference on the power for each scenario.

## Example 4 – Finding Power with Binding Futility Boundaries

Following the setup of Example 3, we wish to see the effect on power of changing from non-binding futility boundaries to binding futility boundaries.

### Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 4** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

#### Design Tab

Solve For .....	<b>Power</b>
Alpha.....	<b>0.025</b>
Group Allocation .....	<b>Equal (N1 = N2)</b>
Sample Size Per Group .....	<b>20 to 200 by 20</b>
L1 (Loss Hazard Rate of Group 1) .....	<b>0.03</b>
L2 (Loss Hazard Rate of Group 2) .....	<b>0.03</b>
T0 (Accrual or Recruitment Time) .....	<b>5</b>
Accrual Parameter Entry .....	<b>Calculate Accrual Parameter</b>
Percent of T0 Until 50% are Accrued .....	<b>50</b>
T (Total Time) .....	<b>5</b>
h1 (Hazard Rate of Group 1) .....	<b>0.5 0.6 0.7</b>
h2 (Hazard Rate of Group 2) .....	<b>0.7</b>
NIM (Non-Inferiority Margin) .....	<b>0.25</b>
Maximum Number of Stages (K) .....	<b>5</b>
Time Proportion at each Stage .....	<b>Equally incremented</b>
Boundaries Used .....	<b>Efficacy with Futility</b>
Hypothesis Direction .....	<b>Ha: h1 - h2 &lt;  NIM  (Lower hazard rates are better)</b>
Boundary Specification .....	<b>Spending Function Calculation</b>
Alpha Spending Function .....	<b>O'Brien-Fleming Analog</b>
Skipped Efficacy Stages .....	<b>&lt;Empty&gt;</b>
Design Beta .....	<b>0.10</b>
Beta Spending Function .....	<b>Hwang-Shih-DeCani (<math>\gamma</math>)</b>
$\gamma$ .....	<b>1.5</b>
Skipped Futility Stages .....	<b>&lt;Empty&gt;</b>
<b>Binding or Non-Binding Futility</b> .....	<b>Binding</b>

#### Options Tab

Number of Simulations .....	<b>10000</b> (set for the sake of time, 100,000 or more are recommended)
Random Seed .....	<b>3913155</b> (for Reproducibility)
After Boundary Crossing .....	<b>Hold out</b>

## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

## Boundary Reports Tab

---

All Reports ..... **Checked**

## Boundary Plots Tab

---

Z-Statistic vs Information ..... **Checked**Z-Statistic vs Time ..... **Checked**Z-Statistic vs Stage ..... **Checked**Z-Statistic vs N..... **Checked**

## Summary Reports Tab

---

All Reports ..... **Checked**

## Summary Plots Tab

---

All plots ..... **Checked**

---

## Output

Click the Calculate button to perform the calculations and generate the following output. The simulation results will differ slightly for each separate run.

## Scenario Reports

All the scenario reports for each of the 30 scenarios are generated in the output, but they are not shown here.

## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

## Power and Sample Size Summary

## Power and Sample Size Summary

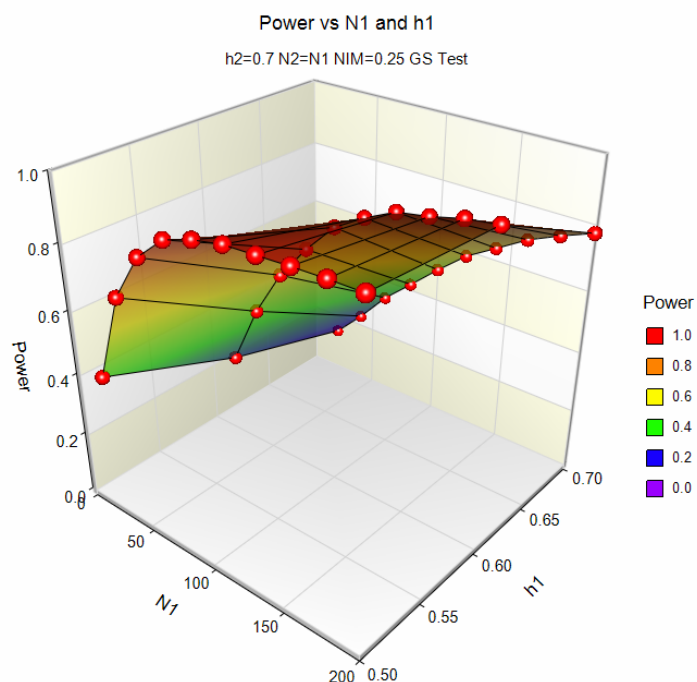
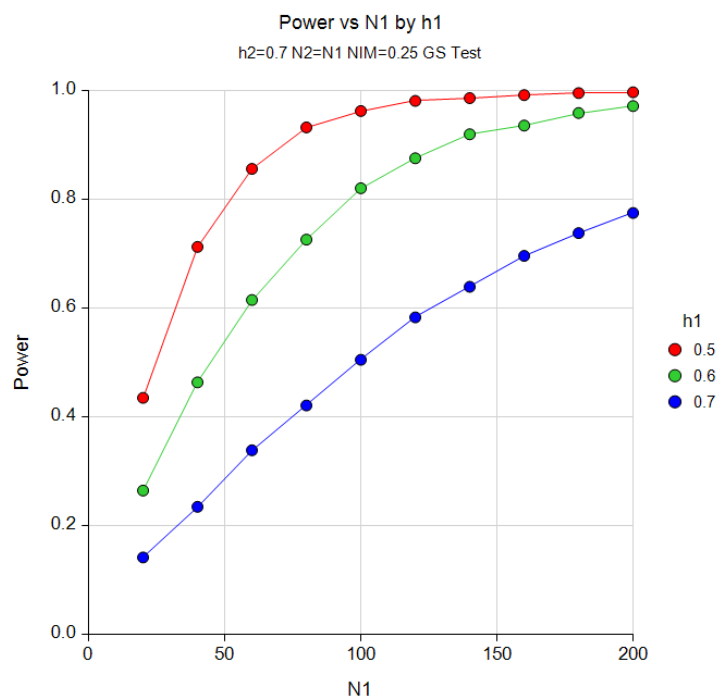
Solve For: Power  
 Maximum Number of Stages: 5  
 Alternative Hypothesis:  $h1 - h2 < |NIM|$   
 Alpha Spending Function: O'Brien-Fleming Analog  
 Beta Spending Function: Hwang-Shih-DeCani ( $\gamma = 1.5$ )  
 Number of Simulations: 10000  
 Random Seed: 3913155 (User-Entered)

Sim Power	N1	N2	N	h1	h2	NIM	Target Alpha	Sim Alpha
0.4350	20	20	40	0.5	0.7	0.25	0.025	0.0303
0.7127	40	40	80	0.5	0.7	0.25	0.025	0.0232
0.8562	60	60	120	0.5	0.7	0.25	0.025	0.0242
0.9324	80	80	160	0.5	0.7	0.25	0.025	0.0243
0.9626	100	100	200	0.5	0.7	0.25	0.025	0.0211
0.9812	120	120	240	0.5	0.7	0.25	0.025	0.0285
0.9863	140	140	280	0.5	0.7	0.25	0.025	0.0253
0.9918	160	160	320	0.5	0.7	0.25	0.025	0.0291
0.9956	180	180	360	0.5	0.7	0.25	0.025	0.0257
0.9970	200	200	400	0.5	0.7	0.25	0.025	0.0248
0.2645	20	20	40	0.6	0.7	0.25	0.025	0.0317
0.4636	40	40	80	0.6	0.7	0.25	0.025	0.0245
0.6150	60	60	120	0.6	0.7	0.25	0.025	0.0282
0.7261	80	80	160	0.6	0.7	0.25	0.025	0.0271
0.8205	100	100	200	0.6	0.7	0.25	0.025	0.0251
0.8757	120	120	240	0.6	0.7	0.25	0.025	0.0251
0.9198	140	140	280	0.6	0.7	0.25	0.025	0.0268
0.9358	160	160	320	0.6	0.7	0.25	0.025	0.0250
0.9589	180	180	360	0.6	0.7	0.25	0.025	0.0257
0.9717	200	200	400	0.6	0.7	0.25	0.025	0.0241
0.1416	20	20	40	0.7	0.7	0.25	0.025	0.0302
0.2347	40	40	80	0.7	0.7	0.25	0.025	0.0217
0.3387	60	60	120	0.7	0.7	0.25	0.025	0.0234
0.4211	80	80	160	0.7	0.7	0.25	0.025	0.0238
0.5051	100	100	200	0.7	0.7	0.25	0.025	0.0292
0.5831	120	120	240	0.7	0.7	0.25	0.025	0.0266
0.6393	140	140	280	0.7	0.7	0.25	0.025	0.0290
0.6962	160	160	320	0.7	0.7	0.25	0.025	0.0260
0.7380	180	180	360	0.7	0.7	0.25	0.025	0.0259
0.7751	200	200	400	0.7	0.7	0.25	0.025	0.0234

## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

## Plots Section for Power and Sample Size Summary

## Plots



If the power results are compared to those with non-binding futility boundaries in Example 3, it is seen that the power for binding futility boundaries is several percent lower. Higher numbers of simulations might be used to fine-tune these differences.

## Example 5 – Comparing Numbers of Stages

Following the setup of Example 3, we wish to see the effect on power of changing the number of stages. This requires multiple runs with different numbers of stages. The numbers of stages examined here are 2, 3, 4, 5, 10 and 20. A hazard rate for Group 1 of 0.7 and a sample size of 100 per group will be considered. More simulations will be used in this example.

### Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 5** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

#### Design Tab

Solve For .....	<b>Power</b>
Alpha.....	<b>0.025</b>
Group Allocation .....	<b>Equal (N1 = N2)</b>
Sample Size Per Group .....	<b>100</b>
L1 (Loss Hazard Rate of Group 1).....	<b>0.03</b>
L2 (Loss Hazard Rate of Group 2).....	<b>0.03</b>
T0 (Accrual or Recruitment Time).....	<b>5</b>
Accrual Parameter Entry.....	<b>Calculate Accrual Parameter</b>
Percent of T0 Until 50% are Accrued.....	<b>50</b>
T (Total Time) .....	<b>5</b>
h1 (Hazard Rate of Group 1) .....	<b>0.7</b>
h2 (Hazard Rate of Group 2) .....	<b>0.7</b>
NIM (Non-Inferiority Margin) .....	<b>0.25</b>
Maximum Number of Stages (K).....	<b>2 (Also run with 3, 4, 5, 10, and 20)</b>
Time Proportion at each Stage .....	<b>Equally incremented</b>
Boundaries Used .....	<b>Efficacy with Futility</b>
Hypothesis Direction .....	<b>Ha: h1 - h2 &lt;  NIM  (Lower hazard rates are better)</b>
Boundary Specification .....	<b>Spending Function Calculation</b>
Alpha Spending Function.....	<b>O'Brien-Fleming Analog</b>
Skipped Efficacy Stages .....	<b>&lt;Empty&gt;</b>
Design Beta .....	<b>0.10</b>
Beta Spending Function.....	<b>Hwang-Shih-DeCani (γ)</b>
γ .....	<b>1.5</b>
Skipped Futility Stages .....	<b>&lt;Empty&gt;</b>
Binding or Non-Binding Futility.....	<b>Non-Binding</b>

#### Options Tab

Number of Simulations.....	<b>100000</b>
Random Seed .....	<b>Random</b>
After Boundary Crossing.....	<b>Hold out</b>

## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

## Boundary Reports Tab

All Reports ..... **Checked**

## Boundary Plots Tab

Z-Statistic vs Information ..... **Checked**Z-Statistic vs Time ..... **Checked**Z-Statistic vs Stage ..... **Checked**Z-Statistic vs N ..... **Checked**

## Summary Reports Tab

All Reports ..... **Checked**

## Summary Plots Tab

All plots ..... **Checked** (only 2D will be used)

## Output

Click the Calculate button to perform the calculations and generate the following output. The simulation results will differ slightly for each separate run.

## Scenario Reports

All the scenario reports for each of the 6 scenarios are generated in the output, but they are not shown here.

## Power and Sample Size Summary

### Power and Sample Size Summary

Solve For: [Power](#)  
 Maximum Number of Stages: 2 3 4 5 10 20 (separate runs)  
 Alternative Hypothesis:  $h_1 - h_2 < |NIM|$   
 Alpha Spending Function: O'Brien-Fleming Analog  
 Beta Spending Function: Hwang-Shih-DeCani ( $\gamma = 1.5$ )  
 Number of Simulations: 100000

Sim Power	N1	N2	N	h1	h2	NIM	Target Alpha	Sim Alpha	Number of Stages
0.56271	100	100	200	0.7	0.7	0.25	0.025	0.0268	2
0.55783	100	100	200	0.7	0.7	0.25	0.025	0.0255	3
0.55428	100	100	200	0.7	0.7	0.25	0.025	0.0264	4
0.55332	100	100	200	0.7	0.7	0.25	0.025	0.0251	5
0.55158	100	100	200	0.7	0.7	0.25	0.025	0.0261	10
0.54329	100	100	200	0.7	0.7	0.25	0.025	0.0289	20

It is seen that the impact of the number of stages on the overall power is very minor.

## Example 6 – Validation Using Simulation

A run is performed that is similar to Example 3, but with a design beta of 0.2, a sample size of 100 per group, hazard rates of 0.563 and 0.7, a non-inferiority margin of 0.2, binding futility boundaries, and 100,000 simulations. The alpha-spending and beta-spending will be compared to the results of the simulated boundary crossings.

### Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 6** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

#### Design Tab

Solve For .....	<b>Power</b>
Alpha.....	<b>0.025</b>
Group Allocation .....	<b>Equal (N1 = N2)</b>
Sample Size Per Group .....	<b>100</b>
L1 (Loss Hazard Rate of Group 1).....	<b>0.03</b>
L2 (Loss Hazard Rate of Group 2).....	<b>0.03</b>
T0 (Accrual or Recruitment Time).....	<b>5</b>
Accrual Parameter Entry.....	<b>Calculate Accrual Parameter</b>
Percent of T0 Until 50% are Accrued.....	<b>50</b>
T (Total Time) .....	<b>5</b>
h1 (Hazard Rate of Group 1) .....	<b>0.563</b>
h2 (Hazard Rate of Group 2) .....	<b>0.7</b>
NIM (Non-Inferiority Margin) .....	<b>0.2</b>
Maximum Number of Stages (K).....	<b>5</b>
Time Proportion at each Stage .....	<b>Equally incremented</b>
Boundaries Used .....	<b>Efficacy with Futility</b>
Hypothesis Direction .....	<b>Ha: h1 - h2 &lt;  NIM  (Lower hazard rates are better)</b>
Boundary Specification .....	<b>Spending Function Calculation</b>
Alpha Spending Function.....	<b>O'Brien-Fleming Analog</b>
Skipped Efficacy Stages .....	<b>&lt;Empty&gt;</b>
Design Beta .....	<b>0.20</b>
Beta Spending Function.....	<b>Hwang-Shih-DeCani (γ)</b>
γ .....	<b>1.5</b>
Skipped Futility Stages .....	<b>&lt;Empty&gt;</b>
Binding or Non-Binding Futility.....	<b>Binding</b>

#### Options Tab

Number of Simulations.....	<b>100000</b>
Random Seed .....	<b>20720202</b> (for Reproducibility)
After Boundary Crossing.....	<b>Hold out</b>

## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

## Boundary Reports Tab

All Reports ..... **Checked**

## Boundary Plots Tab

Z-Statistic vs Information ..... **Checked**Z-Statistic vs Time ..... **Checked**Z-Statistic vs Stage ..... **Checked**Z-Statistic vs N ..... **Checked**

## Summary Reports Tab

All Reports ..... **Checked**

## Summary Plots Tab

All plots ..... **Checked** (only 2D will be used)

## Output

Click the Calculate button to perform the calculations and generate the following output. The simulation results will differ slightly for each separate run.

## Run Summary Report

### Run Summary Report

Item	Value
Solve For	Power
Maximum Number of Stages (Design)	5
Current Stage	0
Alternative Hypothesis	$h_1 - h_2 <  NIM $
Non-Inferiority Margin (NIM)	0.2
Alpha Spending Function	O'Brien-Fleming Analog
Beta Spending Function	Hwang-Shih-DeCani ( $\gamma = 1.5$ )
Futility Boundaries	Binding
Target Alpha	0.025
Alpha (from simulations)	0.02527
Hazard Rate of Group 1	0.563
Hazard Rate of Group 2	0.7
Loss Hazard Rate of Group 1	0.03
Loss Hazard Rate of Group 2	0.03
T0 (Accrual Time)	5
% of T0 Until 50% Accrual	50
Accrual Parameter	0
Total Time	5
N1 (if final stage reached)	100
N2 (if final stage reached)	100
Power (from simulations)	0.79998
Maximum Information	84.1839

## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

## Z-Value Boundaries

## Z-Value Boundaries

Maximum Information: 84.1839  
 Alternative Hypothesis:  $h_1 - h_2 < |NIM|$   
 Futility Boundaries: Binding

Stage	Boundaries		Time Proportion	Time	Information Proportion
	Efficacy	Futility			
1		1.0609	0.2	1	0.0762
2	-4.3104	-0.0301	0.4	2	0.2523
3	-3.0325	-0.7843	0.6	3	0.4796
4	-2.3670	-1.3563	0.8	4	0.7331
5	-1.8289	-1.8289	1.0	5	1.0000

## Information Report

## Information Report

Maximum Information: 84.1839  
 Alternative Hypothesis:  $h_1 - h_2 < |NIM|$   
 Alpha: 0.025

Stage	Target Time Proportion	Target Time	Target Information Proportion	Target Information	Target Sample Size		h1	h2
					N1	N2		
1	0.2	1	0.0762	6.4114	20	20	0.563	0.7
2	0.4	2	0.2523	21.2375	40	40	0.563	0.7
3	0.6	3	0.4796	40.3711	60	60	0.563	0.7
4	0.8	4	0.7331	61.7113	80	80	0.563	0.7
5	1.0	5	1.0000	84.1839	100	100	0.563	0.7

## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

## Alpha Spending

## Alpha Spending

Target Final Stage Alpha: 0.025  
 Spending Function: O'Brien-Fleming Analog

Stage	Information Proportion	Alpha Spent this Stage	Cumulative Alpha Spent	Nominal (Boundary) Alpha	Percentage Alpha Spent this Stage	Cumulative Percentage Alpha Spent
1 *	0.0762	0.0000	0.0000	0.000000	0.0	0.0
2 *	0.2523	0.0000	0.0000	0.000008	0.0	0.0
3 *	0.4796	0.0012	0.0012	0.001213	4.8	4.8
4 *	0.7331	0.0076	0.0088	0.008967	30.6	35.4
5 *	1.0000	0.0162	0.0250	0.033710	64.6	100.0

\* projected

The Alpha Spent this Stage is compared to the results of the simulations, found in the section Boundary Probabilities for  $\delta = |\text{NIM}|$  (Alpha).

Boundary Probabilities for  $\delta = |\text{NIM}|$  (Alpha)Boundary Probabilities for  $\delta = |\text{NIM}|$  (Alpha)

Number of Simulations: 100000  
 Random Seed: 20720202 (User-Entered)  
 Futility Boundaries: Binding  
 After Efficacy Boundary Crossing: Hold Out  
 After Binding Futility Boundary Crossing: Hold Out  
 Alternative Hypothesis:  $h_1 - h_2 < |\text{NIM}|$   
 Non-Inferiority Margin (NIM): 0.2  
 Z Statistic: MLE  
 $h_1$ :  $0.7 + |\text{NIM}| = 0.7 + 0.2 = 0.9$   
 $h_2$ : 0.7  
 $\delta$ :  $|\text{NIM}| = 0.2$

Stage	N1	N2	Efficacy		Futility	
			Boundary	Probability	Boundary	Probability
1	*20	*20		0.0000	1.0609	0.1427
2	*40	*40	-4.3104	0.0000	-0.0301	0.3950
3	*60	*60	-3.0325	0.0010	-0.7843	0.2762
4	*80	*80	-2.3670	0.0078	-1.3563	0.1186
5	*100	*100	-1.8289	0.0165	-1.8289	0.0423

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

The Efficacy Probabilities are very similar to Alpha Spent this Stage, indicating agreement.

## Group-Sequential Non-Inferiority Tests for Two Hazard Rates (Simulation)

## Beta Spending for Futility

## Beta Spending for Futility

Target Cumulative Beta at Final Stage: 0.2  
 Spending Function for Futility: Hwang-Shih-DeCani ( $\gamma = 1.5$ )

Stage	Information Proportion	Beta Spent this Stage	Cumulative Beta Spent	Nominal (Boundary) Beta	Percentage Beta Spent this Stage	Cumulative Percentage Beta Spent
1 *	0.0762	0.0278	0.0278	0.855624	13.9	13.9
2 *	0.2523	0.0533	0.0811	0.487986	26.7	40.6
3 *	0.4796	0.0509	0.1320	0.216444	25.5	66.0
4 *	0.7331	0.0397	0.1717	0.087503	19.8	85.9
5 *	1.0000	0.0283	0.2000	0.033710	14.1	100.0

\* projected

Similarly, the Beta Spent this Stage is compared to the results of the simulations, found in the section Boundary Probabilities for  $\delta = -0.137$ .

Boundary Probabilities for  $\delta = -0.137$ Boundary Probabilities for  $\delta = -0.137$ 

Number of Simulations: 100000  
 Random Seed: 20720202 (User-Entered)  
 Warning: Some simulation results had zero variance due to no events. These Z values were set to 0.  
 Number Set to 0: Stage 1: 4, Stage 2: 0, Stage 3: 0, Stage 4: 0, Stage 5: 0  
 Futility Boundaries: Binding  
 After Efficacy Boundary Crossing: Hold Out  
 After Binding Futility Boundary Crossing: Hold Out  
 Alternative Hypothesis:  $h_1 - h_2 < |NIM|$   
 Non-Inferiority Margin (NIM): 0.2  
 Z Statistic: MLE  
 h1: 0.563  
 h2: 0.7  
 $\delta$ : -0.137

Stage	N1	N2	Efficacy		Futility	
			Boundary	Probability	Boundary	Probability
1	*20	*20		0.0000	1.0609	0.0270
2	*40	*40	-4.3104	0.0007	-0.0301	0.0551
3	*60	*60	-3.0325	0.1740	-0.7843	0.0507
4	*80	*80	-2.3670	0.4212	-1.3563	0.0398
5	*100	*100	-1.8289	0.2042	-1.8289	0.0274

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

The Futility Probabilities are very similar to Beta Spent this Stage, also showing that the simulated results are in agreement with the spending function boundary calculations.