Chapter 780

Group-Sequential Tests for Two Hazard Rates (Simulation)

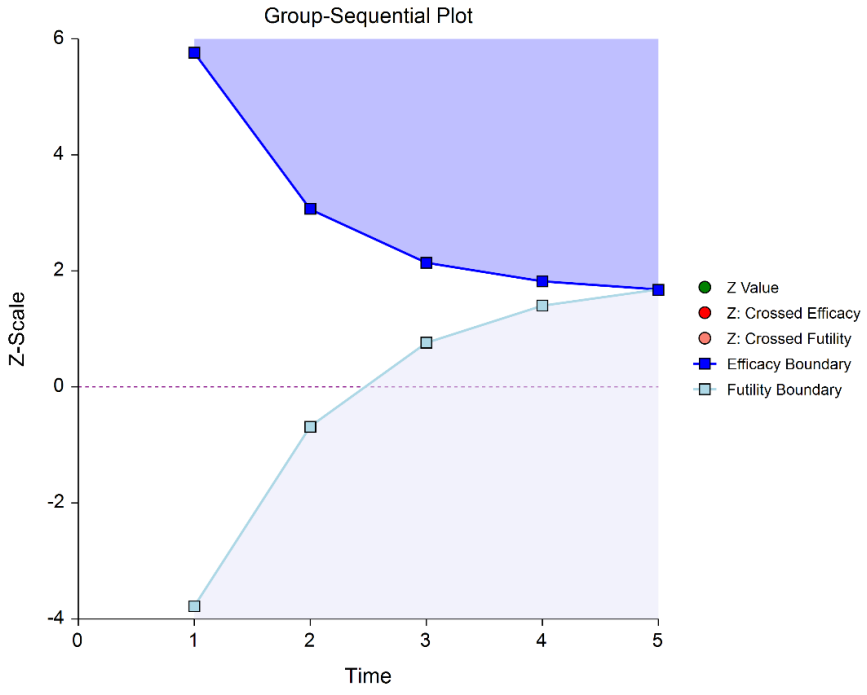
Note: The corresponding analysis and sample size re-estimation procedure, found in NCSS Analysis and Graphics software, is *Group-Sequential Analysis for Two Hazard Rates*.

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. 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 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:

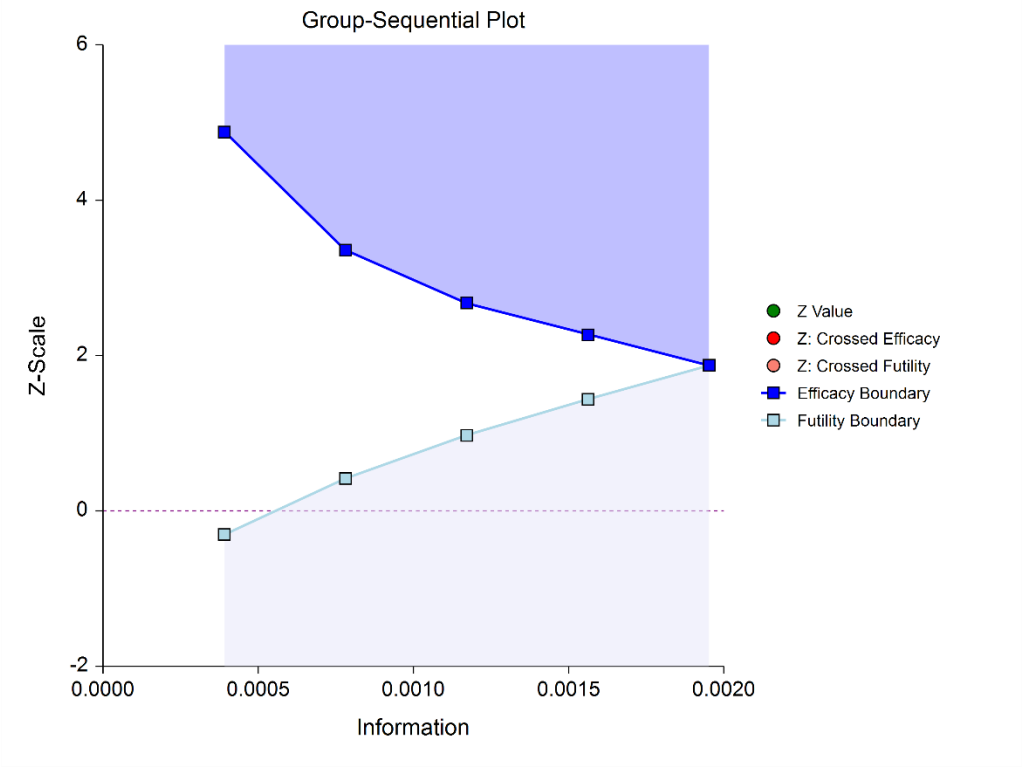
- Alpha
- Power
- Test Direction (two-sided or one-sided direction)
- Types of boundaries (efficacy, binding futility, non-binding futility)
- Maximum number of stages
- Proportion of maximum information at each stage
- Spending functions
- Assumed survival rates

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 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**.

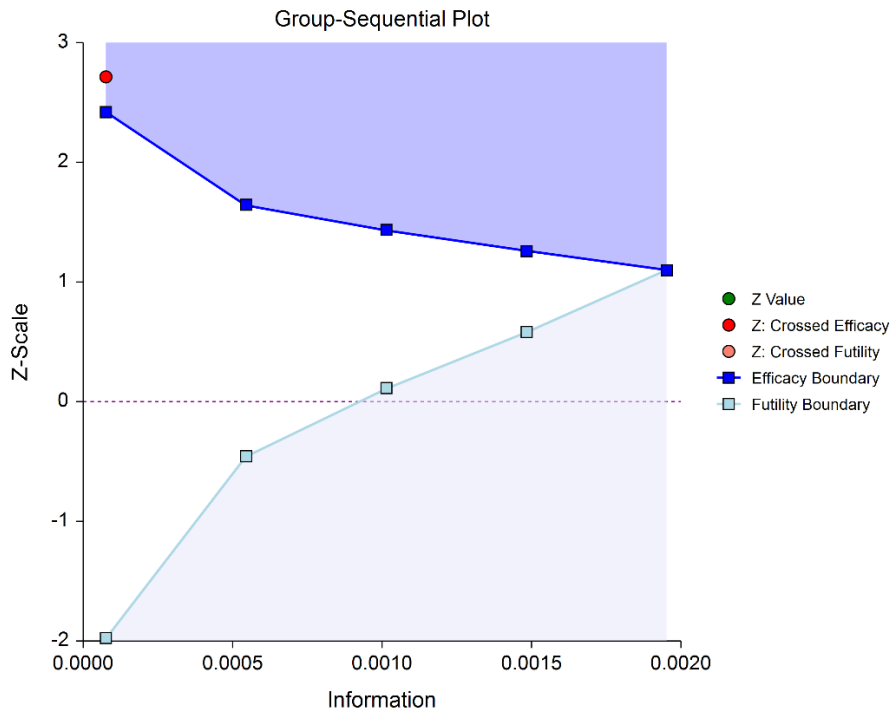
First Interim Stage

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.

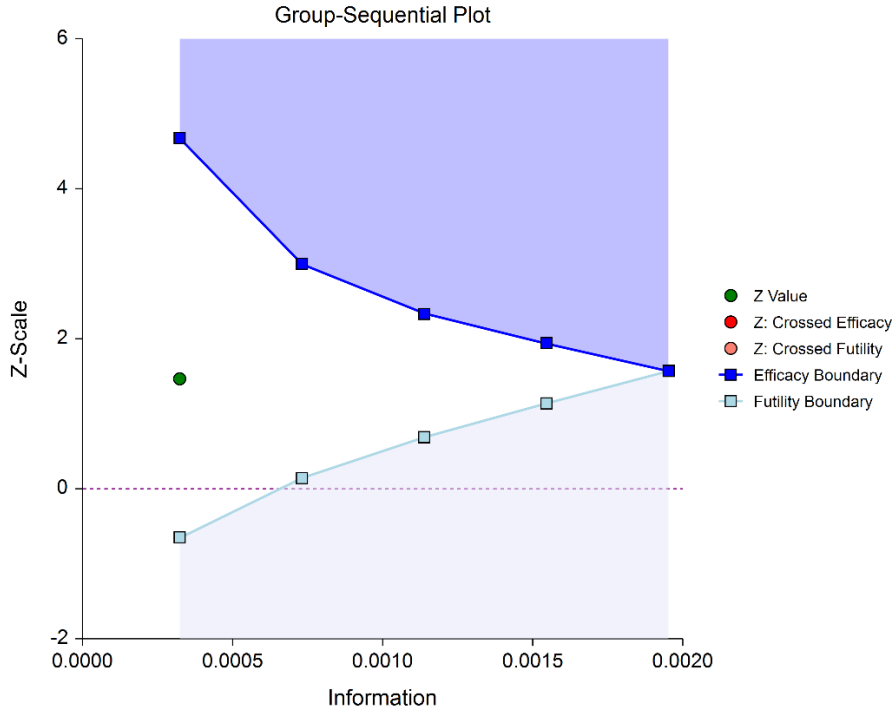
Unless the number of subjects and time at the first stage matches the design target for the first stage, the calculated information at the first stage will not exactly match the design information for the first stage. Generally, the calculated information will not differ too greatly from the design information, 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).



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.

Second and other interim stages (if reached)

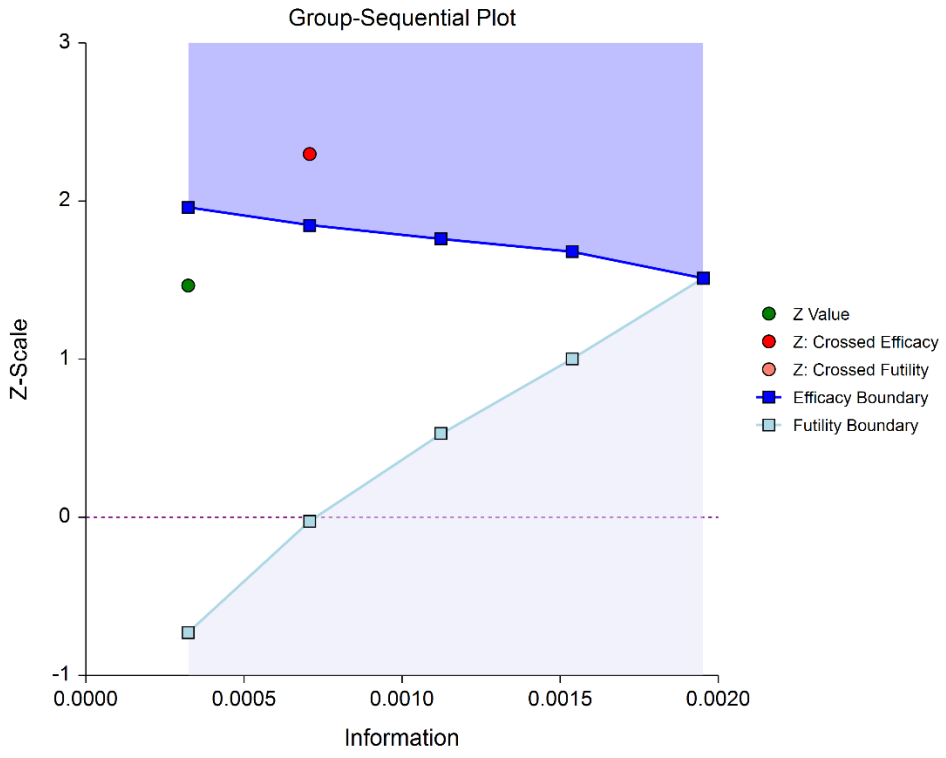
If the first stage time proportion is not equal to the design time proportion, a designation must be made at this point as to the target time of the second stage. Two options are available in the **NCSS** procedure.

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.

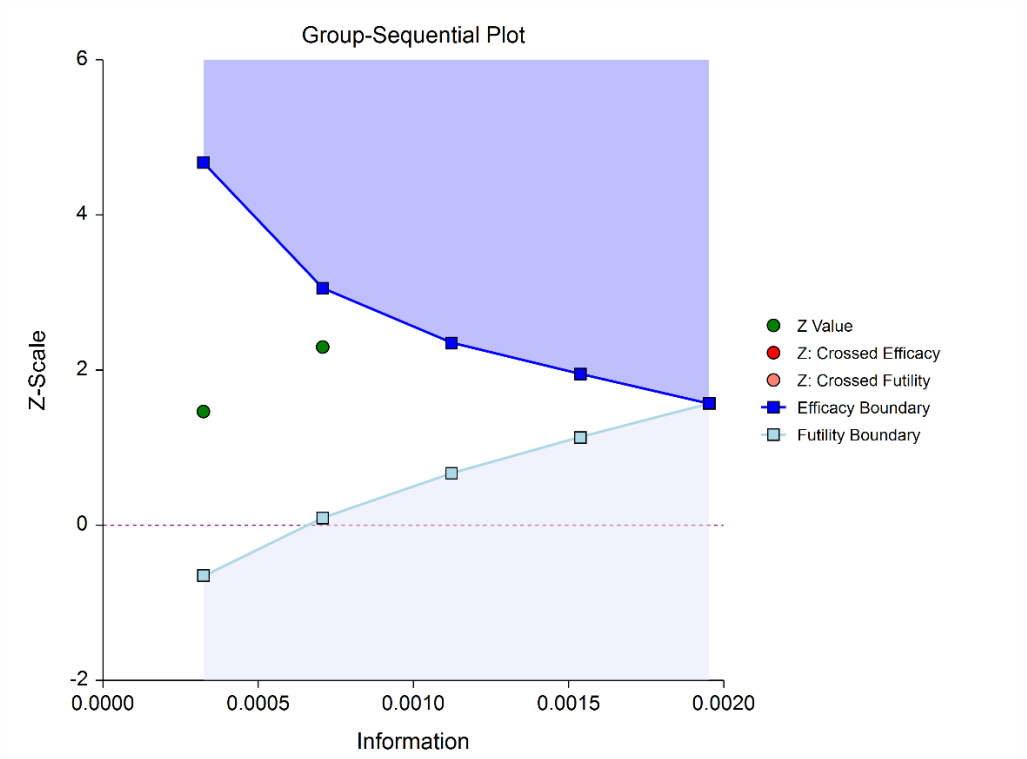
A second option is to adjust the target time proportionally to the remaining proportions. For this option, if the design proportions are 0.25, 0.50, 0.75, 1.0, and 0.22 is observed, the remaining 0.78 is distributed proportionally to the remaining stages. In this example, the remaining target proportions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



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.

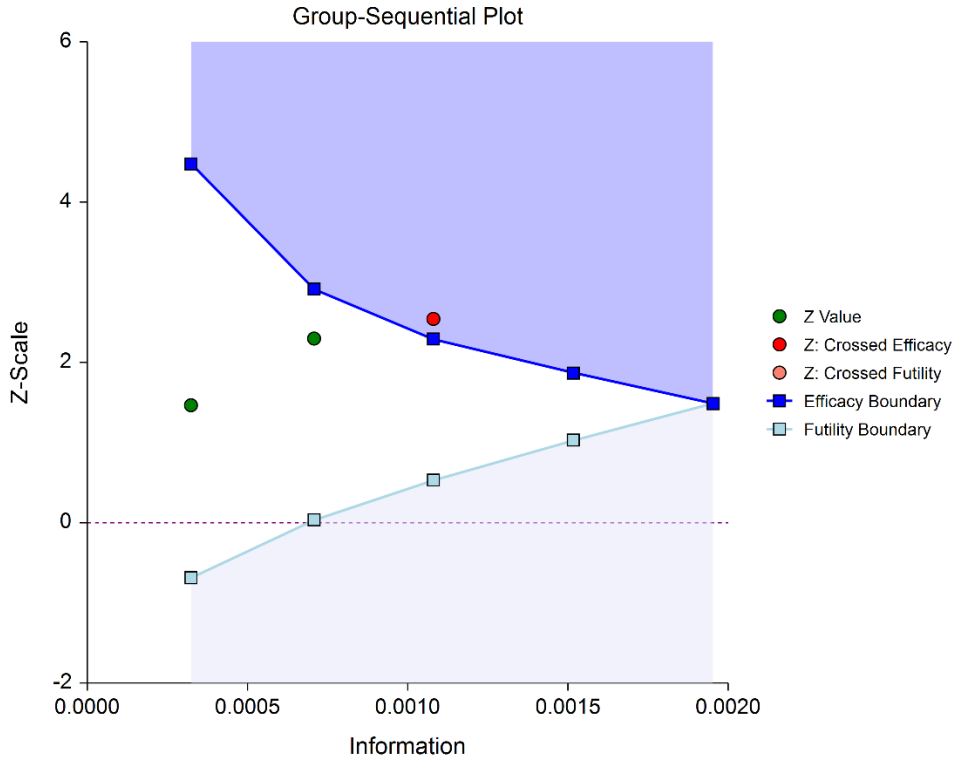
Reporting Phase

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 comparing two hazard rates, the basic null hypothesis is that the hazard rates are equal,

$$H_0: h_1(T) = h_2(T)$$

with three common alternative hypotheses,

$$H_a: h_1(T) \neq h_2(T)\ ,$$

$$H_a: h_1(T) < h_2(T)\ , \text{ or}$$

$$H_a: h_1(T) > h_2(T)\ ,$$

one of which is chosen according to the nature of the experiment or study.

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

These hypotheses may be specified equivalently as

$$H_0: h_1(T) - h_2(T) = 0$$

versus

$$H_a: h_1(T) - h_2(T) \neq 0$$

$$H_a: h_1(T) - h_2(T) < 0$$

$$H_a: h_1(T) - h_2(T) > 0$$

A slightly different set of null and alternative hypotheses are used if the goal of the test is to determine whether $h_1(T)$ or $h_2(T)$ is greater than or less than the other by a given amount.

The null hypothesis then takes on the form

$$H_0: h_1(T) - h_2(T) = \textit{Hypothesized Difference}$$

and the alternative hypotheses,

$$H_a: h_1(T) - h_2(T) \neq \textit{Hypothesized Difference}$$

$$H_a: h_1(T) - h_2(T) < \textit{Hypothesized Difference}$$

$$H_a: h_1(T) - h_2(T) > \textit{Hypothesized Difference}$$

For testing these hypotheses with a hypothesized difference, the non-inferiority or superiority by a margin procedure should be used instead.

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

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

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

Test Statistics (Logrank Type)

The general form of the Logrank-type test statistic is

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

where

D is the number of distinct event times

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

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

Y_i is the combined number at risk at time t_i

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

d_i is the combined number of events at time t_i

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

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

The following table describes each of these tests:

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

This table uses the following definitions.

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

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

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

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

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

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

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

$$I_K^* = I_K$$

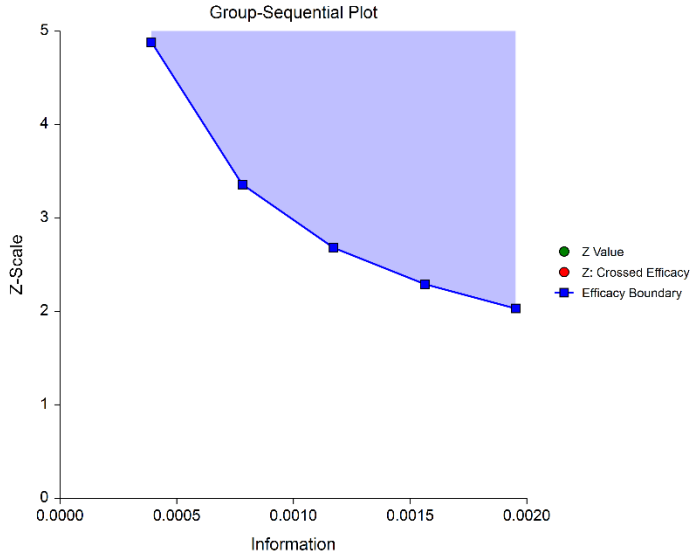
See the discussion in Wassmer and Brannath (2016), pages 78-79, or Jennison and Turnbull (2000), pages 153-154, 162.

Types of Boundaries

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

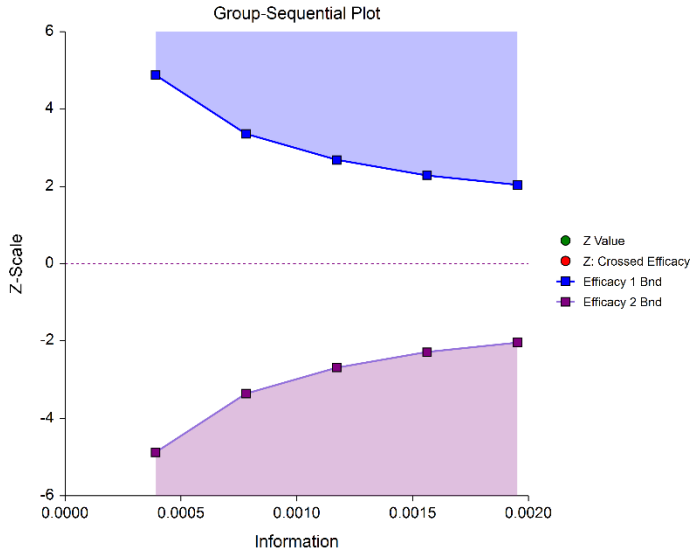
Efficacy Only (One-Sided)

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



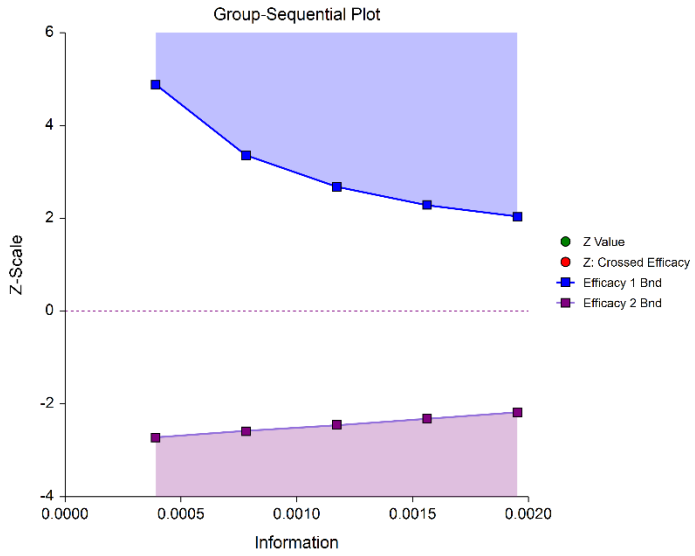
Efficacy Only (Two-Sided, Symmetric)

This boundary type would be used if the goal is to compare treatments, and it is not known in advance which treatment should be better.



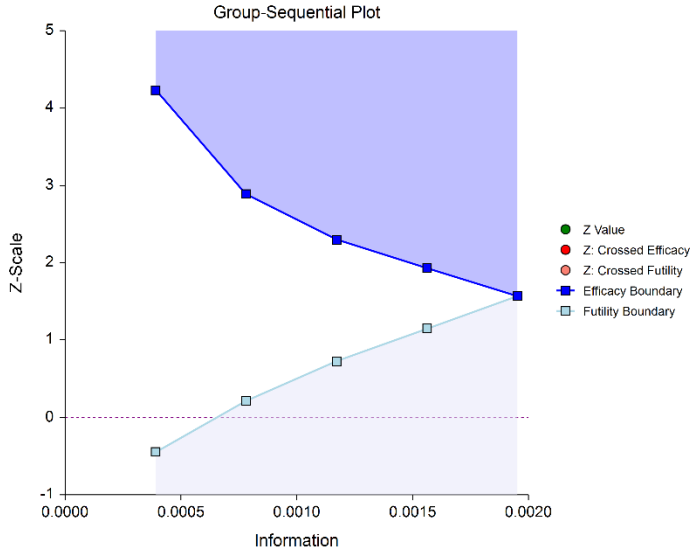
Efficacy 1 and Efficacy 2 / Harm (Two-Sided, Asymmetric)

These boundaries might be used to show efficacy on one side or harm on the other side. This design might be used in place of a one-sided efficacy and futility design if showing harm has additional benefit over stopping early for futility.



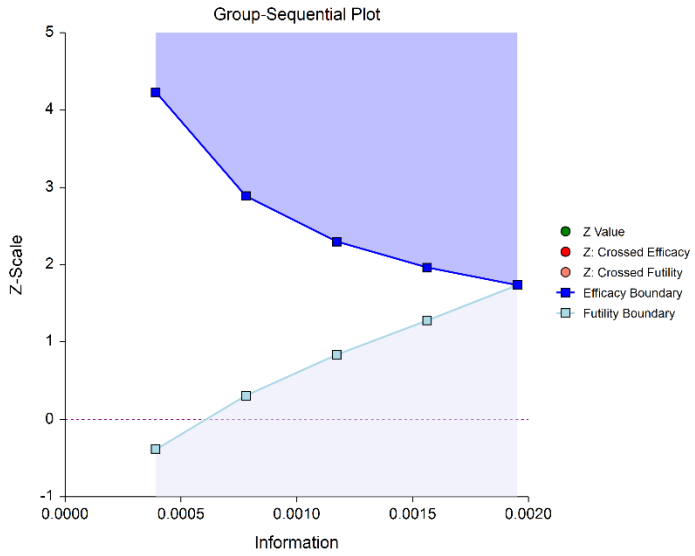
Efficacy and Binding Futility (One-Sided)

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.



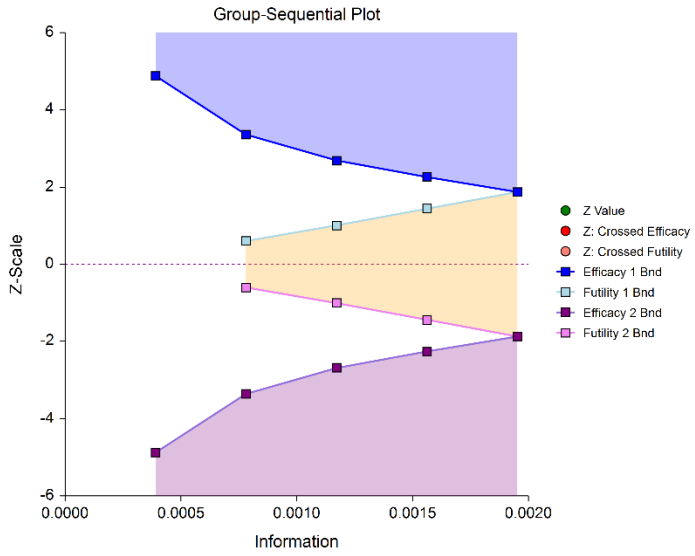
Efficacy and Non-Binding Futility (One-Sided)

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).



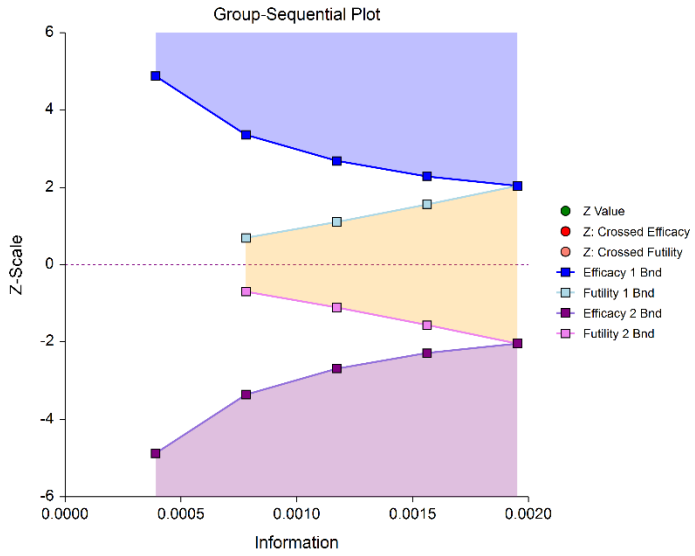
Efficacy and Binding Futility (Two-Sided, Symmetric)

This design allows early stopping for either efficacy or futility on either side. Alpha is preserved only if crossing of futility boundaries strictly leads to early stopping for futility. In early looks of this design, the futility boundaries may overlap. Overlapping futility boundaries may be skipped or left as they are.



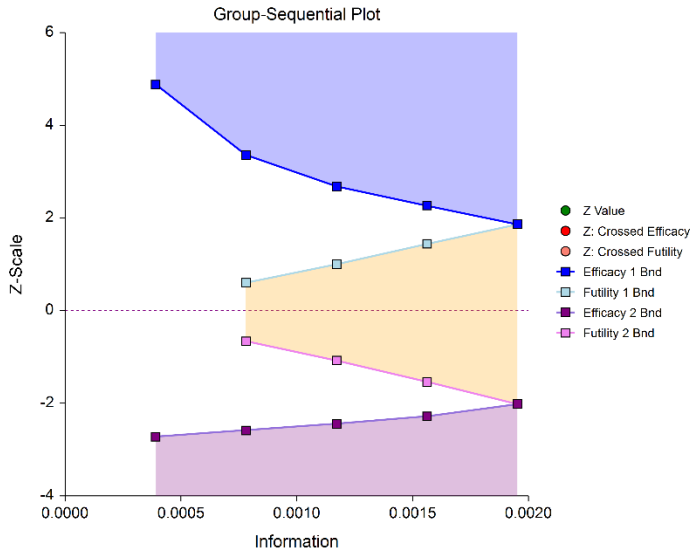
Efficacy and Non-Binding Futility (Two-Sided, Symmetric)

This design allows early stopping for either efficacy or futility on either side. Alpha is preserved even when the study is allowed to continue after crossing a futility boundary. In early looks of this design, the futility boundaries may overlap. Overlapping futility boundaries may be skipped or left as they are.



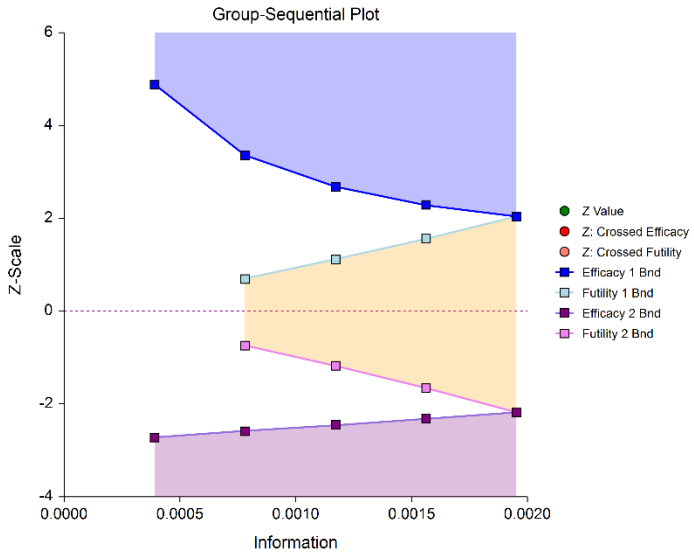
Efficacy 1, Efficacy 2 / Harm, and Binding Futility (Two-Sided, Asymmetric)

This design allows early stopping for efficacy and efficacy futility, and for harm and harm futility (or efficacy 2 and efficacy 2 futility). Binding futility boundaries require that the study is stopped when a binding futility boundary is crossed. In early looks of this design, the futility boundaries may overlap. Overlapping futility boundaries may be skipped or left as they are.



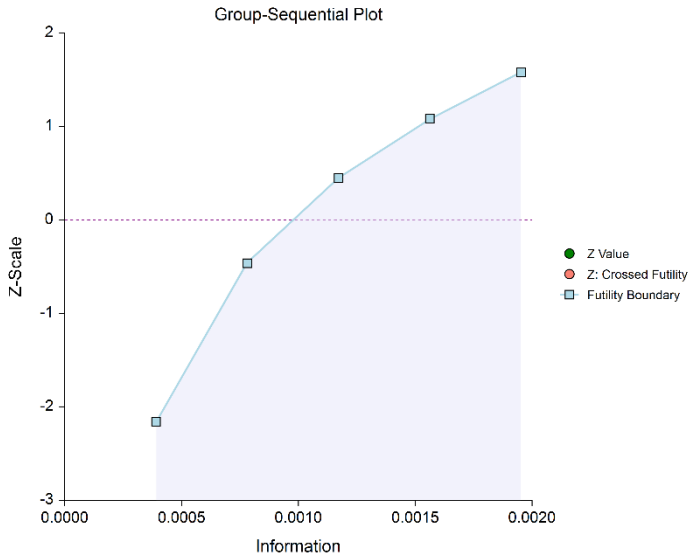
Efficacy 1, Efficacy 2 / Harm, and Non-Binding Futility (Two-Sided, Asymmetric)

This design allows early stopping for efficacy and efficacy futility, and for harm and harm futility (or efficacy 2 and efficacy 2 futility). Non-binding futility boundaries do not require that the study is stopped when a binding futility boundary is crossed, but the study design is conservative. In early looks of this design, the futility boundaries may overlap. Overlapping futility boundaries may be skipped or left as they are.



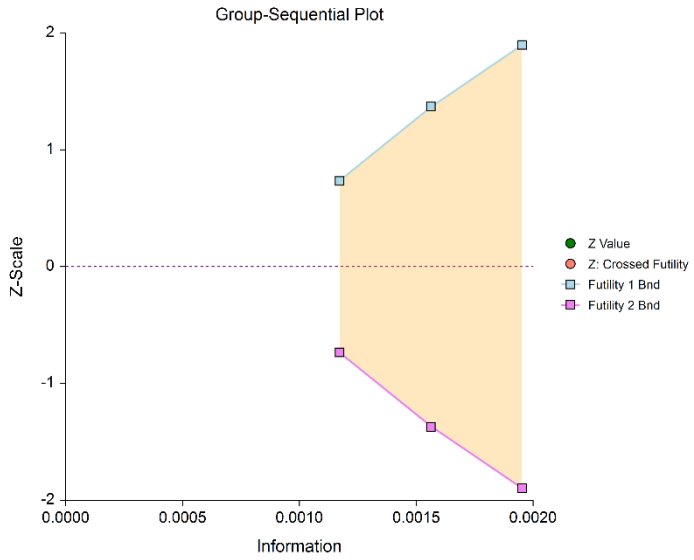
Futility Only (One-Sided)

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.



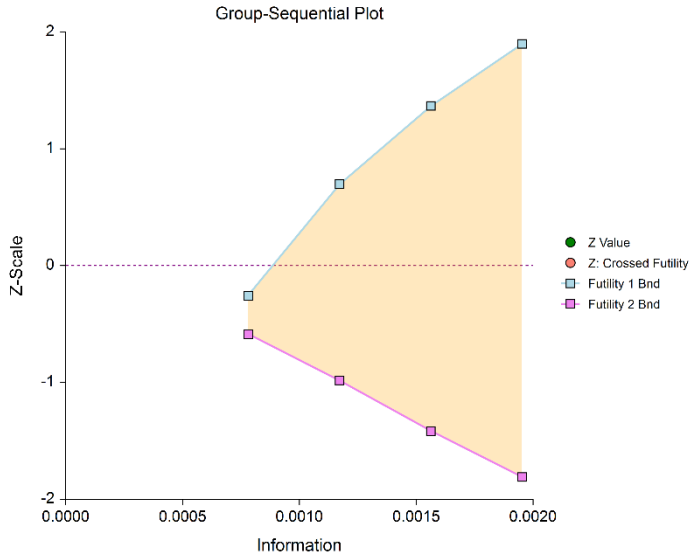
Futility Only (Two-Sided, Symmetric)

In this design, the study is stopped early only for futility. Overlapping futility boundaries may be skipped or left as they are. Please be aware that, due to computational complexity, these boundaries may take several minutes to compute, particularly when overlapping boundaries are removed or some stages are skipped.



Futility Only (Two-Sided, Asymmetric)

In this design, all stages previous to the final stage are used only for futility. Overlapping futility boundaries may be skipped or left as they are. Please be aware that, due to computational complexity, these boundaries may take several minutes to compute, particularly when overlapping boundaries are removed or 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 α with β.

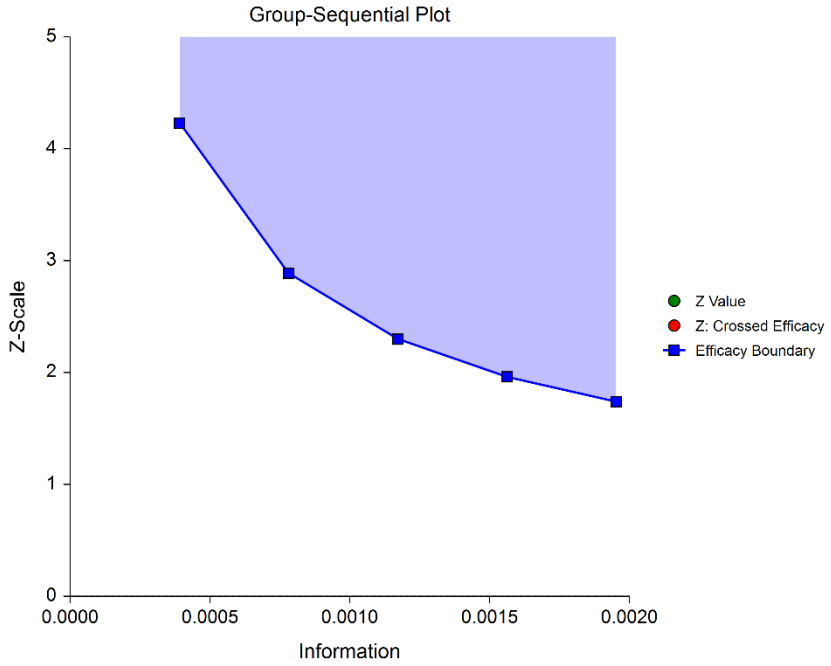
O'Brien-Fleming Analog

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.

$$\alpha(0) = 0$$

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

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



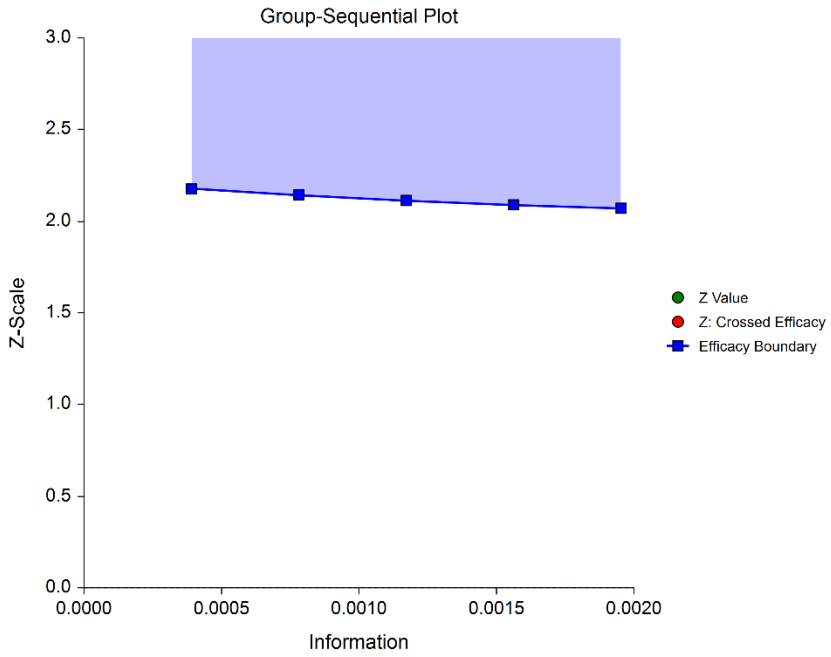
Pocock Analog

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 ρ parameter that gives flexibility in the spending function shape.

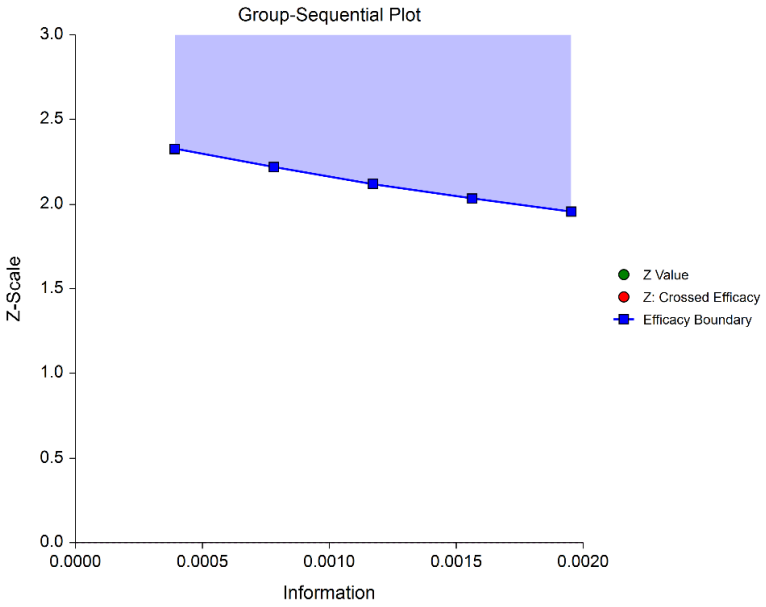
$$\alpha(0) = 0$$

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

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

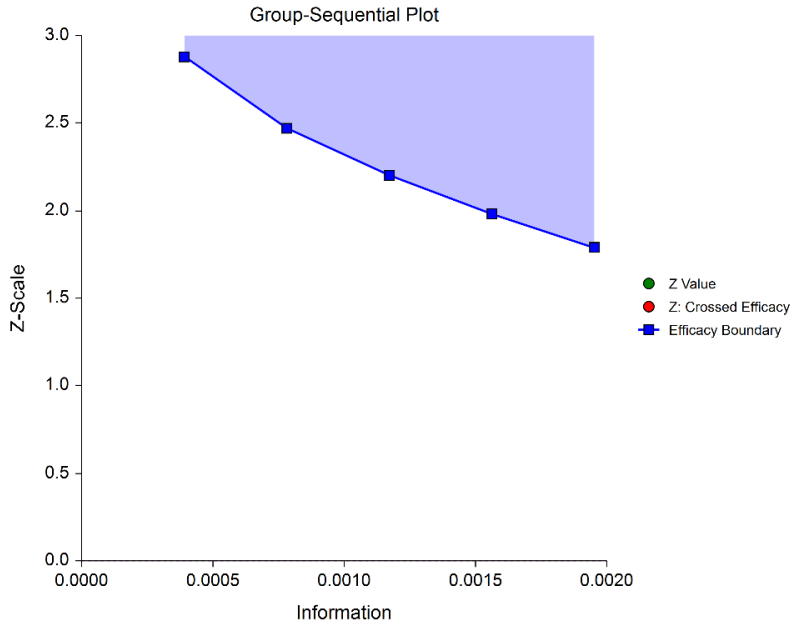
A power family spending function with a ρ of 1 is similar to a Pocock design, while a power family spending function with a ρ of 3 is more similar to an O'Brien-Fleming design.

$\rho = 1$

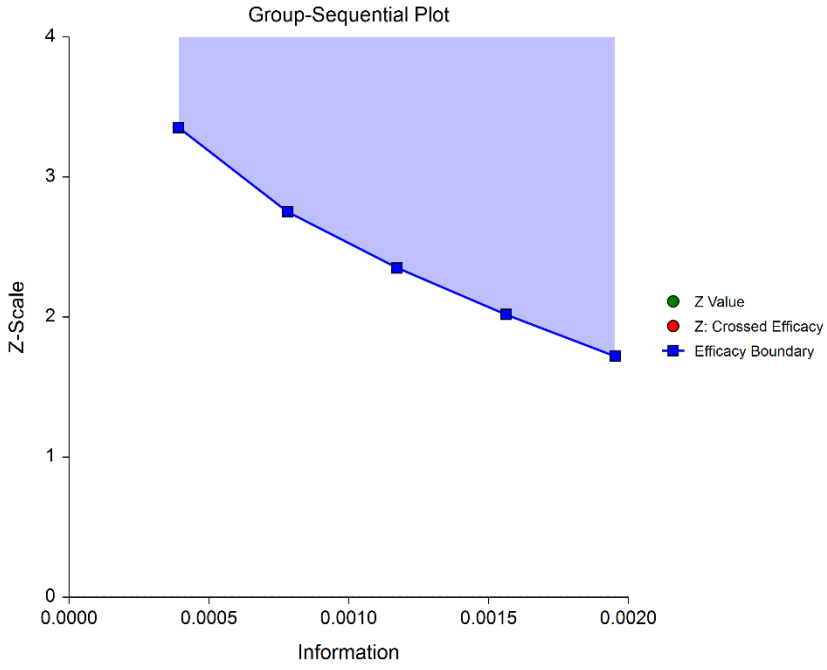


Group-Sequential Tests for Two Hazard Rates (Simulation)

$\rho = 2$



$\rho = 3$



Hwang-Shih-DeCani (Gamma Family)

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

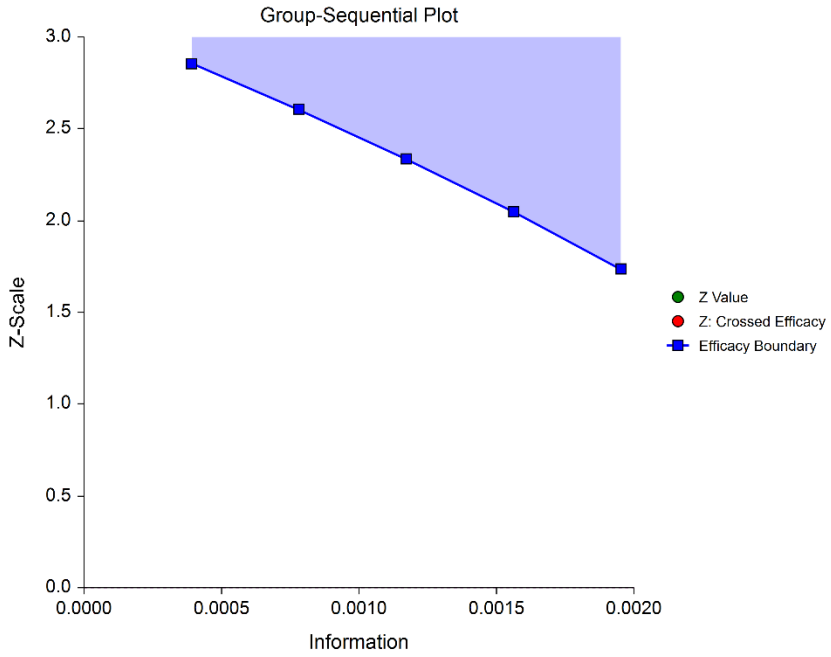
$$\alpha(0) = 0$$

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

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

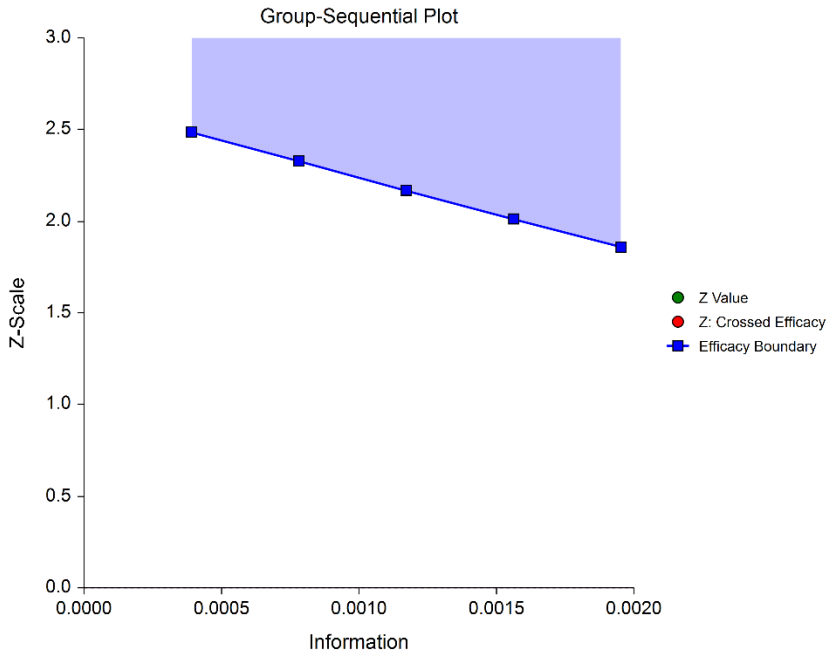
$$\alpha(1) = \alpha$$

$\gamma = -3$

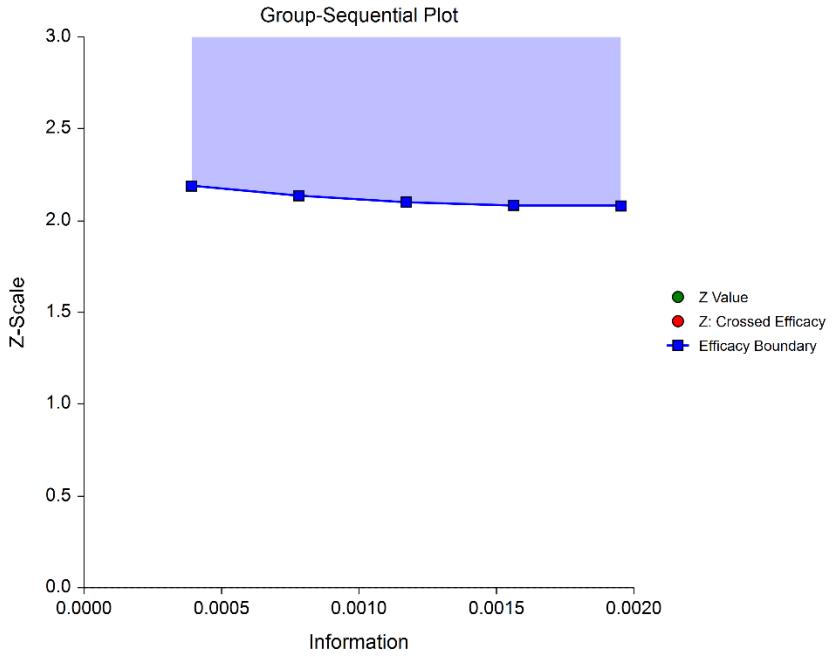


Group-Sequential Tests for Two Hazard Rates (Simulation)

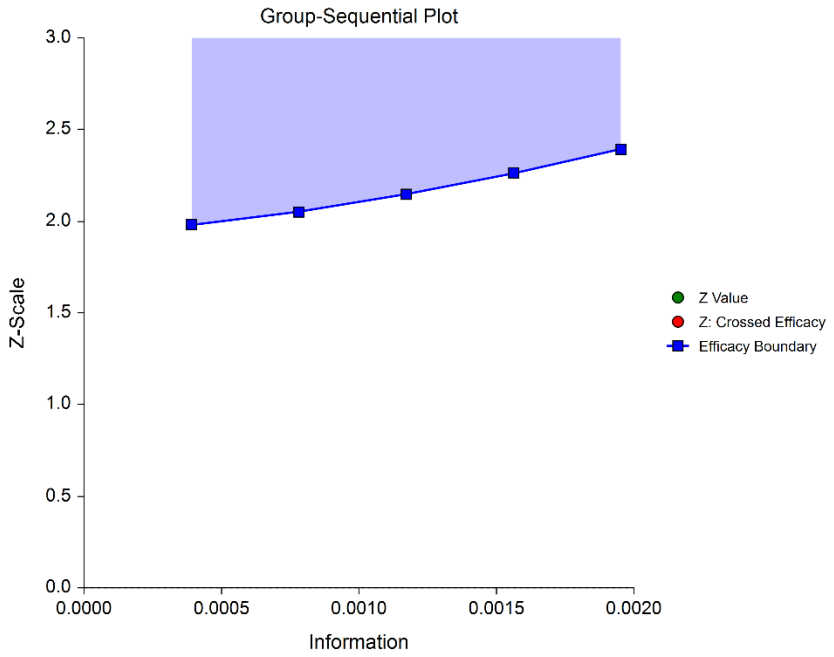
$\gamma = -1$



$\gamma = 1$



$\gamma = 3$



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.

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 longer time before tumor recurrence (lesser hazard rate). The new treatment will be compared to the current standard treatment. 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

$$H_0: h_1 - h_2 = 0 \quad (H_0: h_{New} = h_{Std})$$

versus

$$H_a: h_1 - h_2 < 0 \quad (H_a: h_{New} < h_{Std})$$

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 0.3, 0.4, and 0.5. 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	**Sample Size**
Power	**0.90**
Alpha	**0.025**
Group Allocation	**Equal (N1 = N2)**
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)	**0.3 0.4 0.5**
h2 (Hazard Rate of Group 2)	**0.7**
Maximum Number of Stages (K)	**5**
Time Proportion at each Stage	**Equally incremented**

Boundaries Used	**One-sided Efficacy with Futility**
Hypothesis Direction	**Ha: h1 - h2 < 0**
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 (γ)**
γ	**1.5**
Skipped Futility Stages	**<Empty>**
Binding or Non-Binding Futility	**Non-Binding**

Options Tab

Test Type	**MLE**
Number of Simulations	**10000** (set for the sake of time, 100,000 or more are recommended)
Random Seed	**5433788** (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	h1 - h2 < 0 (one-sided)
Alpha Spending Function	O'Brien-Fleming Analog
Beta Spending Function	Hwang-Shih-DeCani (γ = 1.5)
Futility Boundaries	Non-Binding
Target Alpha	0.025
Alpha (from simulations)	0.0202
Hazard Rate of Group 1	0.3
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)	53
N2 (if final stage reached)	53
Target Power	0.9
Power (from simulations)	0.9005
Maximum Information	59.4847

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

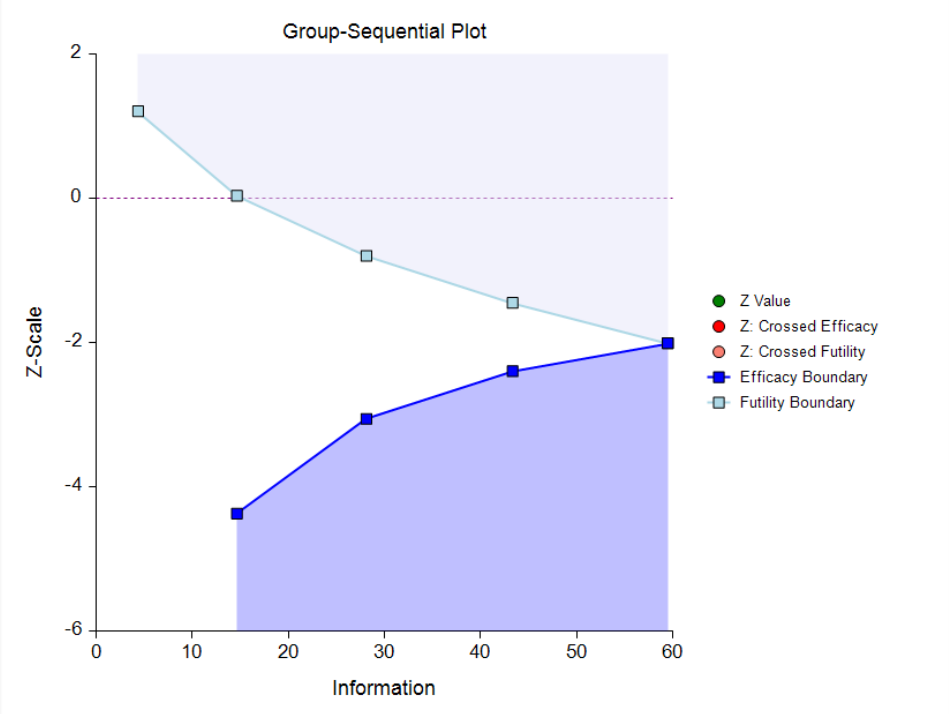
Maximum Information: 59.4847
Alternative Hypothesis: h1 - h2 < 0 (one-sided)
Futility Boundaries: Non-Binding

	Boundaries				
Stage	Efficacy	Futility	Time Proportion	Time	Information Proportion
1		1.2078	0.2	1	0.0734
2	-4.3709	0.0350	0.4	2	0.2463
3	-3.0582	-0.7983	0.6	3	0.4728
4	-2.3966	-1.4486	0.8	4	0.7285
5	-2.0081	-2.0081	1.0	5	1.0000

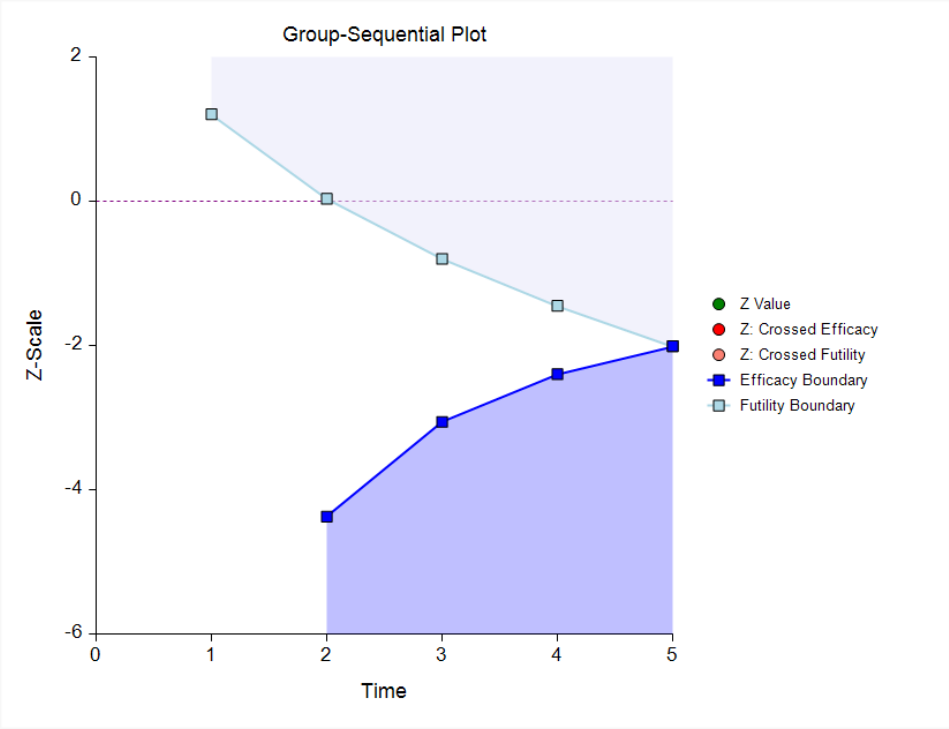
Boundary Plot(s)

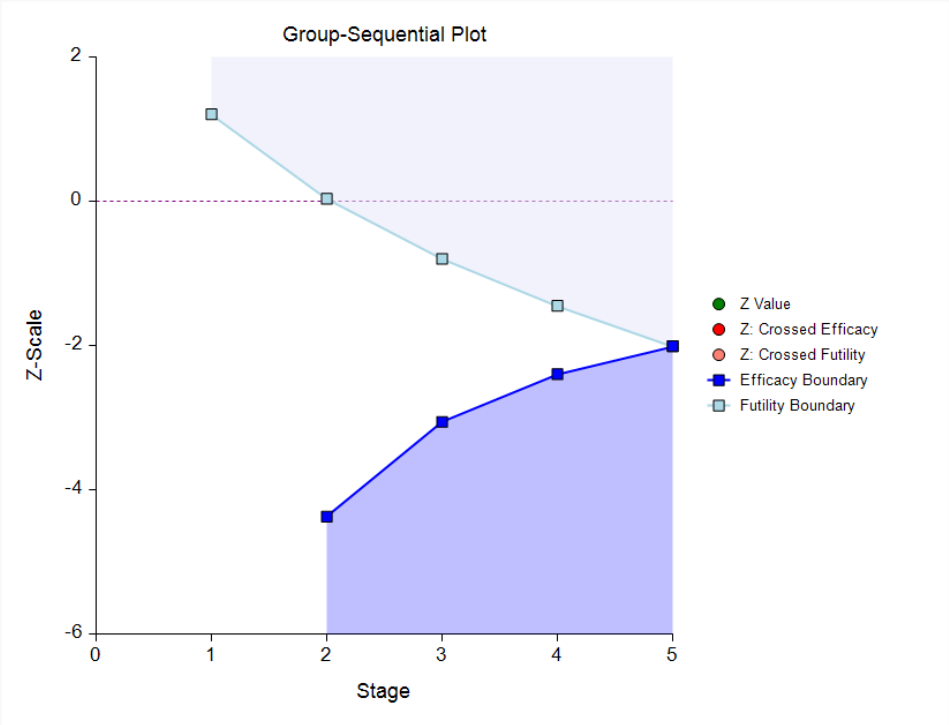
These plots show the efficacy and futility Z-statistic planning boundaries. It is anticipated that these boundaries will adjust to the actual information proportions as the data for each stage is realized. Because the stage one information proportion is so low, and the O-Brien-Fleming Analog Alpha spending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

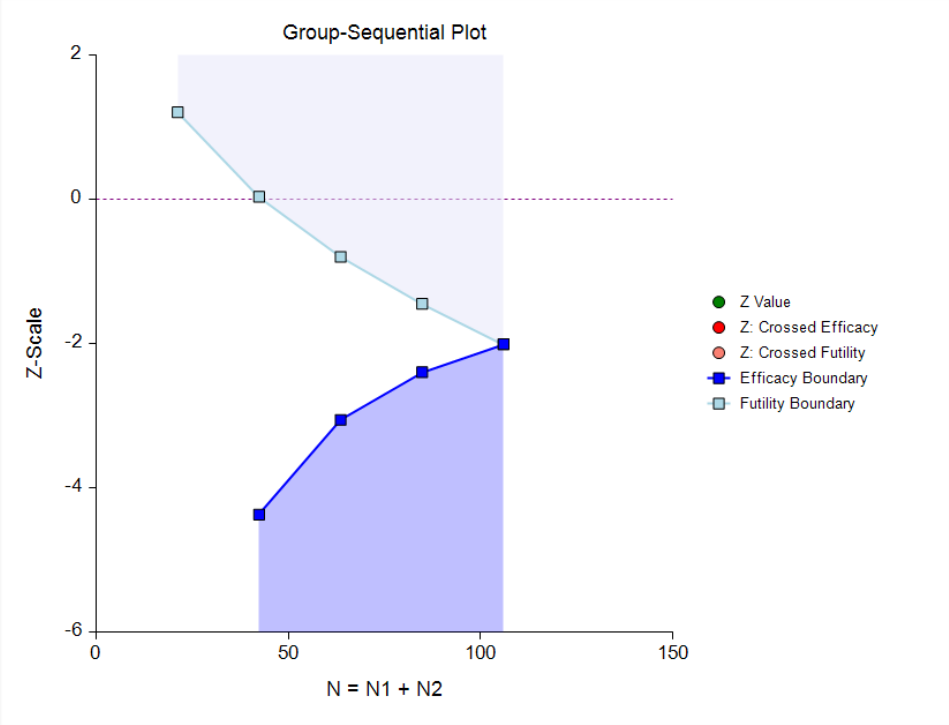
Boundary Plot(s)



Group-Sequential 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: 59.4847
Alternative Hypothesis: h1 - h2 < 0 (one-sided)
Futility Boundaries: Non-Binding
P-value boundaries are one-sided values.

	Boundaries				
Stage	Efficacy	Futility	Time Proportion	Time	Information Proportion
1		0.88645	0.2	1	0.0734
2	0.00001	0.51396	0.4	2	0.2463
3	0.00111	0.21235	0.6	3	0.4728
4	0.00828	0.07373	0.8	4	0.7285
5	0.02232	0.02232	1.0	5	1.0000

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:	59.4847
Alternative Hypothesis:	h1 - h2 < 0 (one-sided)
Alpha:	0.025

Stage	Target Time Proportion	Target Time	Target Information Proportion	Target Information	Target Sample Size N1	Target Sample Size N2	h1	h2
1	0.2	1	0.0734	4.3655	10.6	10.6	0.3	0.7
2	0.4	2	0.2463	14.6488	21.2	21.2	0.3	0.7
3	0.6	3	0.4728	28.1258	31.8	31.8	0.3	0.7
4	0.8	4	0.7285	43.3323	42.4	42.4	0.3	0.7
5	1.0	5	1.0000	59.4847	53.0	53.0	0.3	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 *	0.0734	0.0000	0.0000	0.000000	0.0	0.0
2 *	0.2463	0.0000	0.0000	0.000006	0.0	0.0
3 *	0.4728	0.0011	0.0011	0.001113	4.4	4.5
4 *	0.7285	0.0075	0.0086	0.008275	30.1	34.5
5 *	1.0000	0.0164	0.0250	0.022316	65.5	100.0

* projected

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 (γ = 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 *	0.0734	0.0134	0.0134	0.886446	13.4	13.4
2 *	0.2463	0.0263	0.0398	0.513959	26.3	39.8
3 *	0.4728	0.0256	0.0654	0.212351	25.6	65.4
4 *	0.7285	0.0202	0.0856	0.073728	20.2	85.6
5 *	1.0000	0.0144	0.1000	0.022316	14.4	100.0

* projected

Boundary Probabilities for δ = -0.4

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 δ = -0.4

Number of Simulations:	10000
Random Seed:	5433788 (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: 130, 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 < 0 (one-sided)
Z Statistic:	MLE
h1:	0.3
h2:	0.7
δ:	-0.4

			Efficacy		Futility	
Stage	N1	N2	Boundary	Probability	Boundary	Probability
1	*10.6	*10.6		0.0000	1.2078	0.0294
2	*21.2	*21.2	-4.3709	0.0000	0.0350	0.0563
3	*31.8	*31.8	-3.0582	0.1187	-0.7983	0.0800
4	*42.4	*42.4	-2.3966	0.4969	-1.4486	0.0929
5	*53.0	*53.0	-2.0081	0.2849	-2.0081	0.1029

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

Event Summary for δ = -0.4

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

Event Summary for δ = -0.4

Number of Simulations:	10000
Random Seed:	5433788 (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: 130, Stage 2: 0, Stage 3: 0, Stage 4: 0, Stage 5: 0
h1:	0.3
h2:	0.7
δ:	-0.4

	Average Cumulative Number of Events	
Stage	E1	E2
1	1.43	2.92
2	5.19	9.61
3	10.55	18.16
4	17.13	27.47
5	24.55	37.30

Boundary Probabilities for δ = 0 (Alpha)

This section estimates the probabilities of crossing each boundary if the difference for the remaining stages is assumed to be zero (the hazard rates are assumed to be the same).

Boundary Probabilities for δ = 0 (Alpha)

Number of Simulations:	10000
Random Seed:	5433788 (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: 19, 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 < 0 (one-sided)
Z Statistic:	MLE
h1:	0.7
h2:	0.7
δ:	0

			Efficacy		Futility	
Stage	N1	N2	Boundary	Probability	Boundary	Probability
1	*10.6	*10.6		0.0000	1.2078	0.1171
2	*21.2	*21.2	-4.3709	0.0000	0.0350	0.4901
3	*31.8	*31.8	-3.0582	0.0003	-0.7983	0.7834
4	*42.4	*42.4	-2.3966	0.0050	-1.4486	0.9310
5	*53.0	*53.0	-2.0081	0.0149	-2.0081	0.9812

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

Event Summary for δ = 0 (Alpha)

This section gives the estimated cumulative number of events at each stage when both hazard rates are the same.

Event Summary for δ = 0 (Alpha)

Number of Simulations:	10000
Random Seed:	5433788 (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: 19, Stage 2: 0, Stage 3: 0, Stage 4: 0, Stage 5: 0
h1:	0.7
h2:	0.7
δ:	0

	Average Cumulative Number of Events	
Stage	E1	E2
1	2.96	2.97
2	9.68	9.67
3	18.15	18.12
4	27.50	27.44
5	37.24	37.22

Scenario 2

All of the same boundary reports are given for Scenario 2, corresponding to an h1 value of 0.4.

Scenario 3

All of the same boundary reports are given for Scenario 3, corresponding to an h1 value of 0.5.

Power and Sample Size Summary

Power and Sample Size Summary

Solve For:	Sample Size
Maximum Number of Stages:	5
Alternative Hypothesis:	h1 - h2 < 0 (one-sided)
Alpha Spending Function:	O'Brien-Fleming Analog
Beta Spending Function:	Hwang-Shih-DeCani (γ = 1.5)
Number of Simulations:	10000
Random Seed:	5433788 (User-Entered)

Target Power	Sim Power	N1	N2	N	h1	h2	Target Alpha	Sim Alpha
0.9	0.9005	53	53	106	0.3	0.7	0.025	0.0202
0.9	0.9040	112	112	224	0.4	0.7	0.025	0.0248
0.9	0.9022	290	290	580	0.5	0.7	0.025	0.0229

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. h2 is also the assumed hazard rate of populations 1 and 2 for alpha calculation simulations.
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 will be used to test whether the Group 1 hazard rate is less than the Group 2 hazard rate (H0: h1 - h2 ≥ 0 versus H1: h1 - h2 < 0). The comparison will be made at each stage using a two-sample MLE hazard rate difference Z-test, with efficacy and futility boundary values calculated from the designated spending functions. The target cumulative Type I error rate (α) 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 0.3 and a Group 2 hazard rate of 0.7 (difference of -0.4), with 90% power, the number of needed subjects at the final stage will be 53 in Group 1 and 53 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.

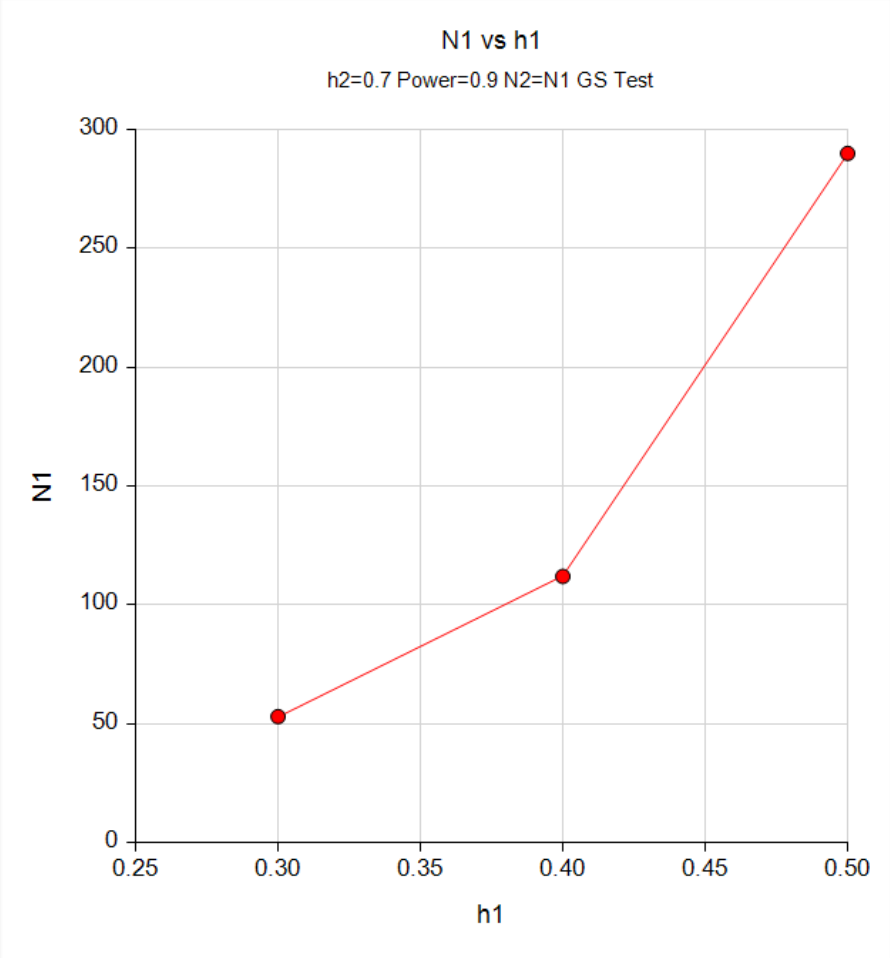
Reboussin, D.M., DeMets, D.L., Kim, K., and Lan, K.K.G. 1992. 'Programs for computing group sequential boundaries using the Lan-DeMets Method.' Technical Report 60, Department of Biostatistics, University of Wisconsin-Madison.

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	**Sample Size**
Power	**0.90**
Alpha	**0.025**
Group Allocation	**Equal (N1 = N2)**
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)	**0.3 0.4 0.5**
h2 (Hazard Rate of Group 2)	**0.7**
Maximum Number of Stages (K)	**5**
Time Proportion at each Stage	**Equally incremented**
Boundaries Used	**One-sided Efficacy with Futility**
Hypothesis Direction	**Ha: h1 - h2 < 0**
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 (γ)**
γ	**1.5**
Skipped Futility Stages	**1 2**
Binding or Non-Binding Futility	**Non-Binding**

Options Tab	
Test Type	**MLE**
Number of Simulations	**10000** (set for the sake of time, 100,000 or more are recommended)
Random Seed	**5516884** (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. 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	h1 - h2 < 0 (one-sided)
Alpha Spending Function	O'Brien-Fleming Analog
Beta Spending Function	Hwang-Shih-DeCani (γ = 1.5)
Futility Boundaries	Non-Binding
Target Alpha	0.025
Alpha (from simulations)	0.0251
Hazard Rate of Group 1	0.3
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)	53
N2 (if final stage reached)	53
Target Power	0.9
Power (from simulations)	0.9026
Maximum Information	59.4847

Z-Value Boundaries

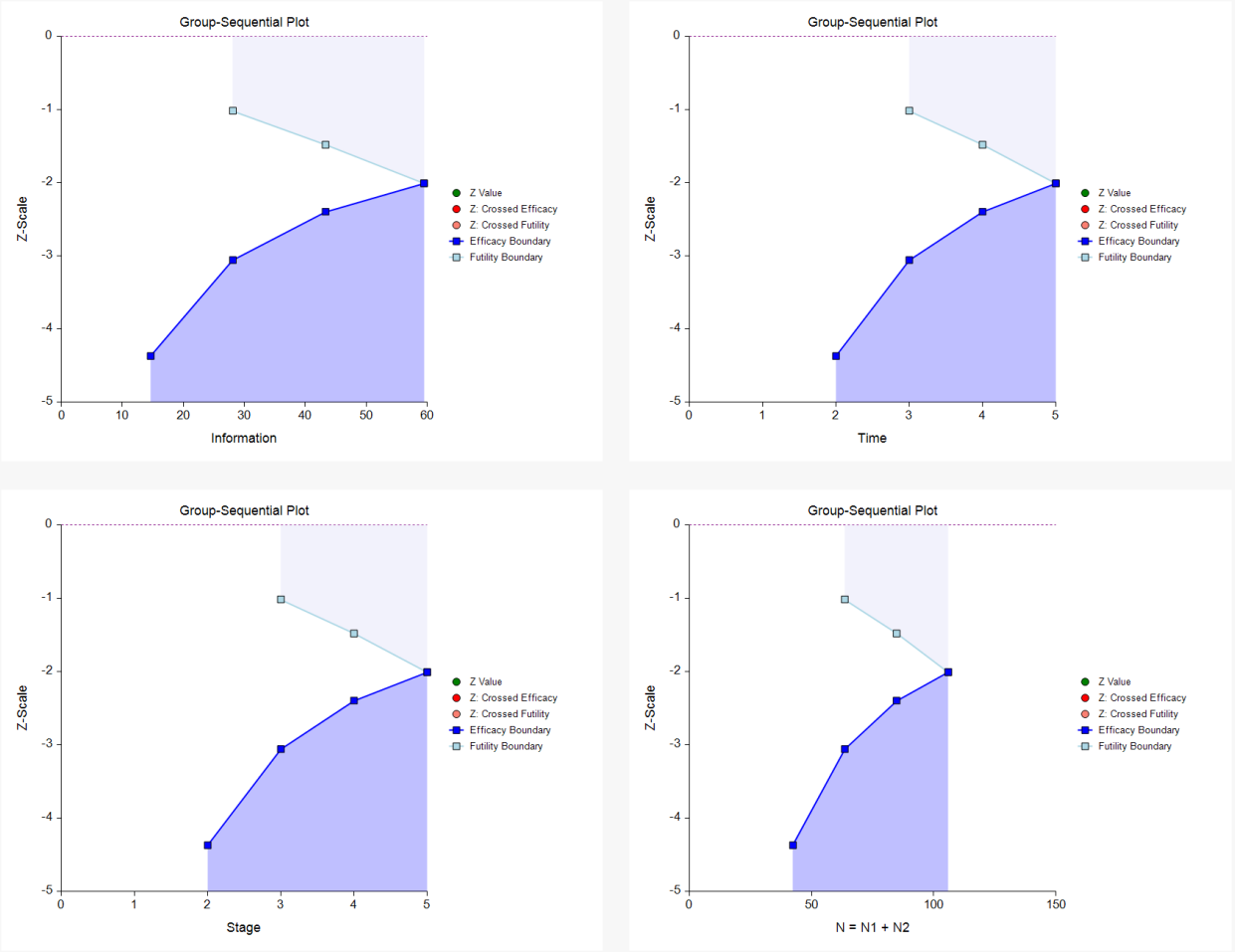
Z-Value Boundaries

Maximum Information: 59.4847
Alternative Hypothesis: h1 - h2 < 0 (one-sided)
Futility Boundaries: Non-Binding

	Boundaries				
Stage	Efficacy	Futility	Time Proportion	Time	Information Proportion
1			0.2	1	0.0734
2	-4.3709		0.4	2	0.2463
3	-3.0582	-1.0153	0.6	3	0.4728
4	-2.3966	-1.4803	0.8	4	0.7285
5	-2.0081	-2.0081	1.0	5	1.0000

Boundary Plot(s)

Boundary Plot(s)



P-Value Boundaries

P-Value Boundaries

Maximum Information: 59.4847
Alternative Hypothesis: h1 - h2 < 0 (one-sided)
Futility Boundaries: Non-Binding
P-value boundaries are one-sided values.

	Boundaries				
Stage	Efficacy	Futility	Time Proportion	Time	Information Proportion
1			0.2	1	0.0734
2	0.00001		0.4	2	0.2463
3	0.00111	0.15499	0.6	3	0.4728
4	0.00828	0.06940	0.8	4	0.7285
5	0.02232	0.02232	1.0	5	1.0000

Information Report

Information Report

Maximum Information: 59.4847
Alternative Hypothesis: h1 - h2 < 0 (one-sided)
Alpha: 0.025

Stage	Target Time Proportion	Target Time	Target Information Proportion	Target Information	Target Sample Size N1	Target Sample Size N2	h1	h2
1	0.2	1	0.0734	4.3655	10.6	10.6	0.3	0.7
2	0.4	2	0.2463	14.6488	21.2	21.2	0.3	0.7
3	0.6	3	0.4728	28.1258	31.8	31.8	0.3	0.7
4	0.8	4	0.7285	43.3323	42.4	42.4	0.3	0.7
5	1.0	5	1.0000	59.4847	53.0	53.0	0.3	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 *	0.0734	0.0000	0.0000	0.000000	0.0	0.0
2 *	0.2463	0.0000	0.0000	0.000006	0.0	0.0
3 *	0.4728	0.0011	0.0011	0.001113	4.4	4.5
4 *	0.7285	0.0075	0.0086	0.008275	30.1	34.5
5 *	1.0000	0.0164	0.0250	0.022316	65.5	100.0

* projected

Beta Spending for Futility

Beta Spending for Futility

Target Cumulative Beta at Final Stage: 0.1
Spending Function for Futility: Hwang-Shih-DeCani (γ = 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 *	0.0734	0.0000	0.0000	1.000000	0.0	0.0
2 *	0.2463	0.0000	0.0000	1.000000	0.0	0.0
3 *	0.4728	0.0654	0.0654	0.154992	65.4	65.4
4 *	0.7285	0.0202	0.0856	0.069395	20.2	85.6
5 *	1.0000	0.0144	0.1000	0.022316	14.4	100.0

* projected

Boundary Probabilities for δ = -0.4

Boundary Probabilities for δ = -0.4

Number of Simulations: 10000
Random Seed: 5516884 (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: 115, 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 < 0 (one-sided)
Z Statistic: MLE
h1: 0.3
h2: 0.7
δ: -0.4

			Efficacy		Futility	
Stage	N1	N2	Boundary	Probability	Boundary	Probability
1	*10.6	*10.6		0.0000		0.0000
2	*21.2	*21.2	-4.3709	0.0001		0.0000
3	*31.8	*31.8	-3.0582	0.1145	-1.0153	0.1111
4	*42.4	*42.4	-2.3966	0.5080	-1.4803	0.0923
5	*53.0	*53.0	-2.0081	0.2800	-2.0081	0.1007

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

Event Summary for δ = -0.4

Event Summary for δ = -0.4

Number of Simulations:	10000
Random Seed:	5516884 (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: 115, Stage 2: 0, Stage 3: 0, Stage 4: 0, Stage 5: 0
h1:	0.3
h2:	0.7
δ:	-0.4

	Average Cumulative Number of Events	
Stage	**E1**	**E2**
1	1.43	2.94
2	5.15	9.68
3	10.56	18.16
4	17.14	27.48
5	24.58	37.27

Boundary Probabilities for δ = 0 (Alpha)

Boundary Probabilities for δ = 0 (Alpha)

Number of Simulations:	10000
Random Seed:	5516884 (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: 20, 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 < 0 (one-sided)
Z Statistic:	MLE
h1:	0.7
h2:	0.7
δ:	0

			Efficacy		Futility	
Stage	**N1**	**N2**	**Boundary**	**Probability**	**Boundary**	**Probability**
1	*10.6	*10.6		0.0000		0.0000
2	*21.2	*21.2	-4.3709	0.0000		0.0000
3	*31.8	*31.8	-3.0582	0.0004	-1.0153	0.8363
4	*42.4	*42.4	-2.3966	0.0070	-1.4803	0.9324
5	*53.0	*53.0	-2.0081	0.0177	-2.0081	0.9769

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

Event Summary for δ = 0 (Alpha)

Event Summary for δ = 0 (Alpha)

Number of Simulations:	10000
Random Seed:	5516884 (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: 20, Stage 2: 0, Stage 3: 0, Stage 4: 0, Stage 5: 0
h1:	0.7
h2:	0.7
δ:	0

	Average Cumulative Number of Events	
Stage	E1	E2
1	2.95	2.96
2	9.67	9.63
3	18.12	18.14
4	27.50	27.51
5	37.26	37.27

Scenario 2

All of the same boundary reports are given for Scenario 2, corresponding to an h1 value of 0.4.

Scenario 3

All of the same boundary reports are given for Scenario 3, corresponding to an h1 value of 0.5.

Power and Sample Size Summary

Power and Sample Size Summary

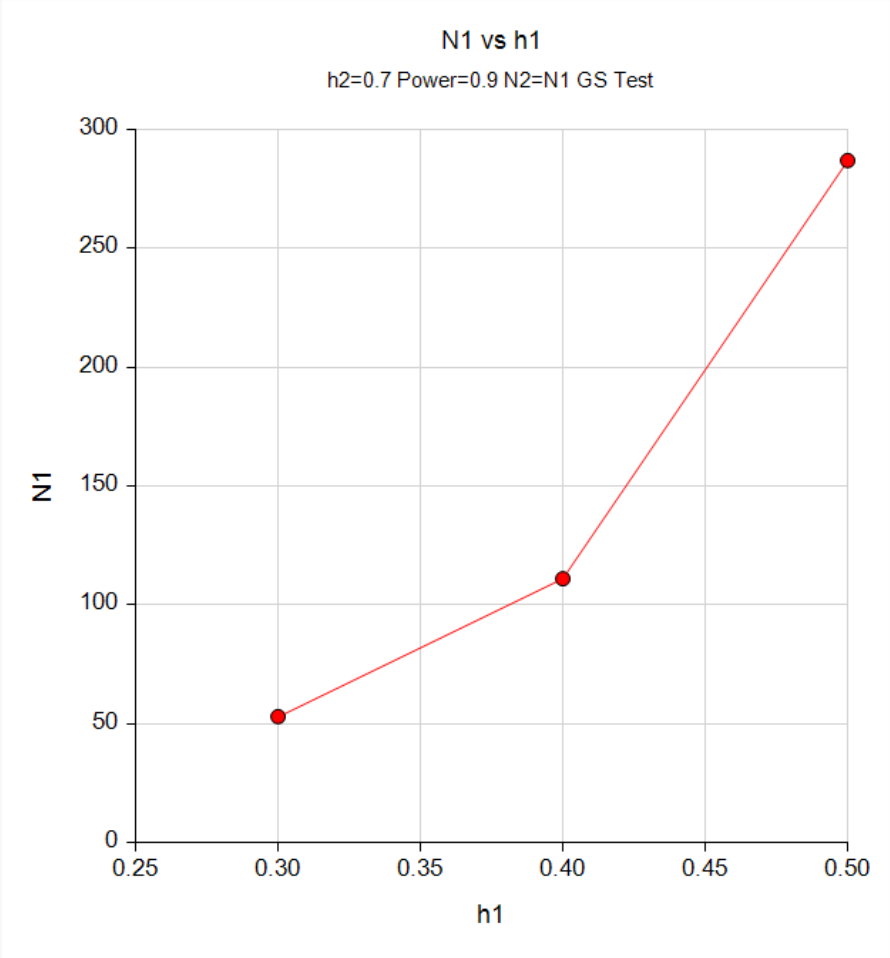
Solve For:	Sample Size
Maximum Number of Stages:	5
Skipped Futility Stage(s):	1 2
Alternative Hypothesis:	h1 - h2 < 0 (one-sided)
Alpha Spending Function:	O'Brien-Fleming Analog
Beta Spending Function:	Hwang-Shih-DeCani (γ = 1.5)
Number of Simulations:	10000
Random Seed:	5516884 (User-Entered)

Target Power	Sim Power	N1	N2	N	h1	h2	Target Alpha	Sim Alpha
0.9	0.9026	53	53	106	0.3	0.7	0.025	0.0251
0.9	0.9012	111	111	222	0.4	0.7	0.025	0.0230
0.9	0.9015	287	287	574	0.5	0.7	0.025	0.0216

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)	**0.3 0.4 0.5**
h2 (Hazard Rate of Group 2)	**0.7**
Maximum Number of Stages (K)	**5**
Time Proportion at each Stage	**Equally incremented**
Boundaries Used	**One-sided Efficacy with Futility**
Hypothesis Direction	**Ha: h1 - h2 < 0**
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 (γ)**
γ	**1.5**
Skipped Futility Stages	**<Empty>**
Binding or Non-Binding Futility	**Non-Binding**

Options Tab	
Test Type	**MLE**
Number of Simulations	**10000** (set for the sake of time, 100,000 or more are recommended)
Random Seed	**20163488** (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**

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.

Power and Sample Size Summary

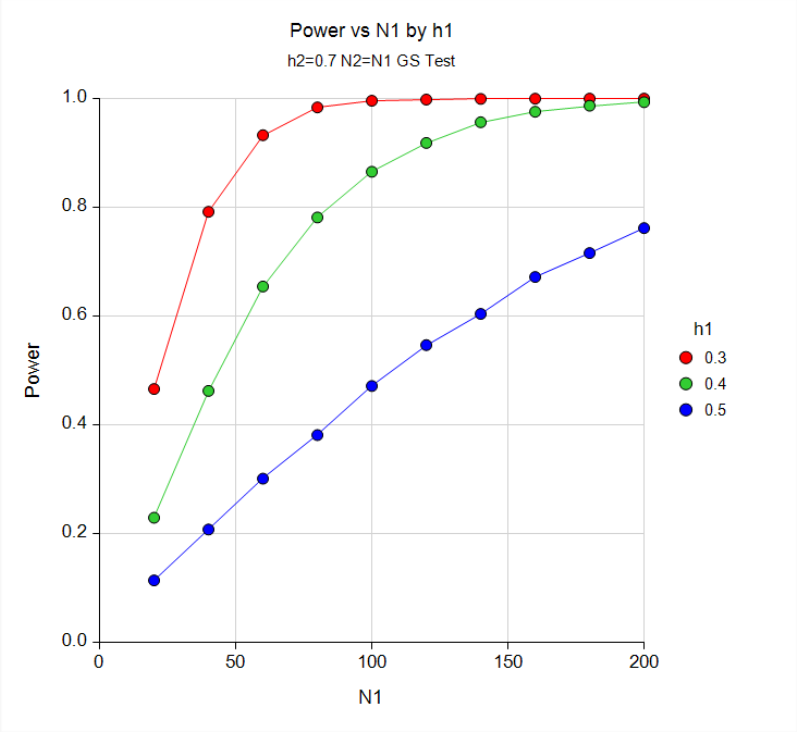
Power and Sample Size Summary

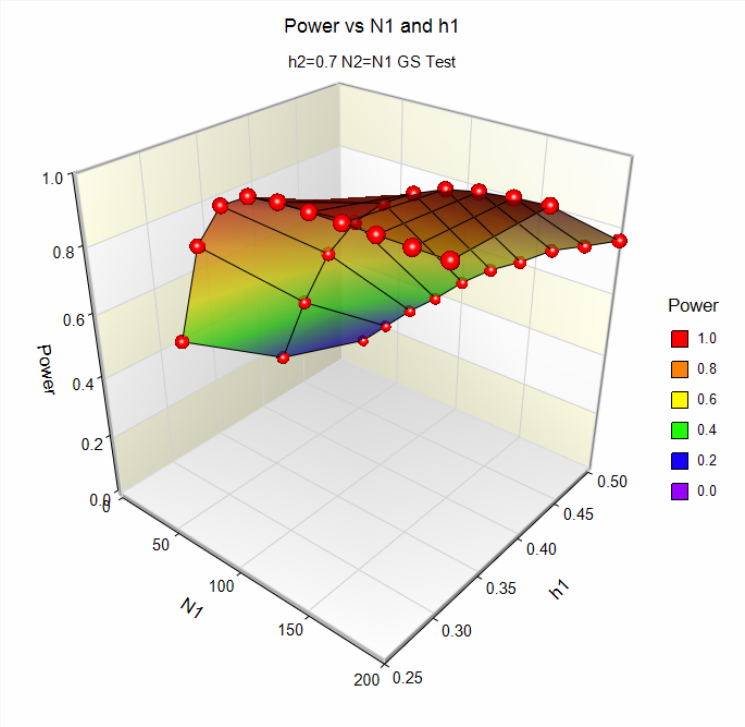
Solve For:	Power
Maximum Number of Stages:	5
Alternative Hypothesis:	h1 - h2 < 0 (one-sided)
Alpha Spending Function:	O'Brien-Fleming Analog
Beta Spending Function:	Hwang-Shih-DeCani (γ = 1.5)
Number of Simulations:	10000
Random Seed:	20163488 (User-Entered)

Sim Power	N1	N2	N	h1	h2	Target Alpha	Sim Alpha
0.4660	20	20	40	0.3	0.7	0.025	0.0267
0.7919	40	40	80	0.3	0.7	0.025	0.0226
0.9328	60	60	120	0.3	0.7	0.025	0.0229
0.9839	80	80	160	0.3	0.7	0.025	0.0202
0.9962	100	100	200	0.3	0.7	0.025	0.0193
0.9983	120	120	240	0.3	0.7	0.025	0.0218
0.9995	140	140	280	0.3	0.7	0.025	0.0270
0.9999	160	160	320	0.3	0.7	0.025	0.0252
1.0000	180	180	360	0.3	0.7	0.025	0.0232
1.0000	200	200	400	0.3	0.7	0.025	0.0235
0.2293	20	20	40	0.4	0.7	0.025	0.0256
0.4625	40	40	80	0.4	0.7	0.025	0.0198
0.6545	60	60	120	0.4	0.7	0.025	0.0178
0.7816	80	80	160	0.4	0.7	0.025	0.0240
0.8656	100	100	200	0.4	0.7	0.025	0.0247
0.9186	120	120	240	0.4	0.7	0.025	0.0225
0.9567	140	140	280	0.4	0.7	0.025	0.0222
0.9759	160	160	320	0.4	0.7	0.025	0.0233
0.9870	180	180	360	0.4	0.7	0.025	0.0254
0.9935	200	200	400	0.4	0.7	0.025	0.0232
0.1140	20	20	40	0.5	0.7	0.025	0.0280
0.2077	40	40	80	0.5	0.7	0.025	0.0202
0.3012	60	60	120	0.5	0.7	0.025	0.0219
0.3813	80	80	160	0.5	0.7	0.025	0.0227
0.4715	100	100	200	0.5	0.7	0.025	0.0265
0.5468	120	120	240	0.5	0.7	0.025	0.0257
0.6042	140	140	280	0.5	0.7	0.025	0.0219
0.6720	160	160	320	0.5	0.7	0.025	0.0243
0.7160	180	180	360	0.5	0.7	0.025	0.0231
0.7619	200	200	400	0.5	0.7	0.025	0.0260

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	**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)	**0.3 0.4 0.5**
h2 (Hazard Rate of Group 2)	**0.7**
Maximum Number of Stages (K)	**5**
Time Proportion at each Stage	**Equally incremented**
Boundaries Used	**One-sided Efficacy with Futility**
Hypothesis Direction	**Ha: h1 - h2 < 0**
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 (γ)**
γ	**1.5**
Skipped Futility Stages	**<Empty>**
Binding or Non-Binding Futility	**Binding**

Options Tab

Test Type	**MLE**
Number of Simulations	**10000** (set for the sake of time, 100,000 or more are recommended)
Random Seed	**2310507** (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**

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.

Power and Sample Size Summary

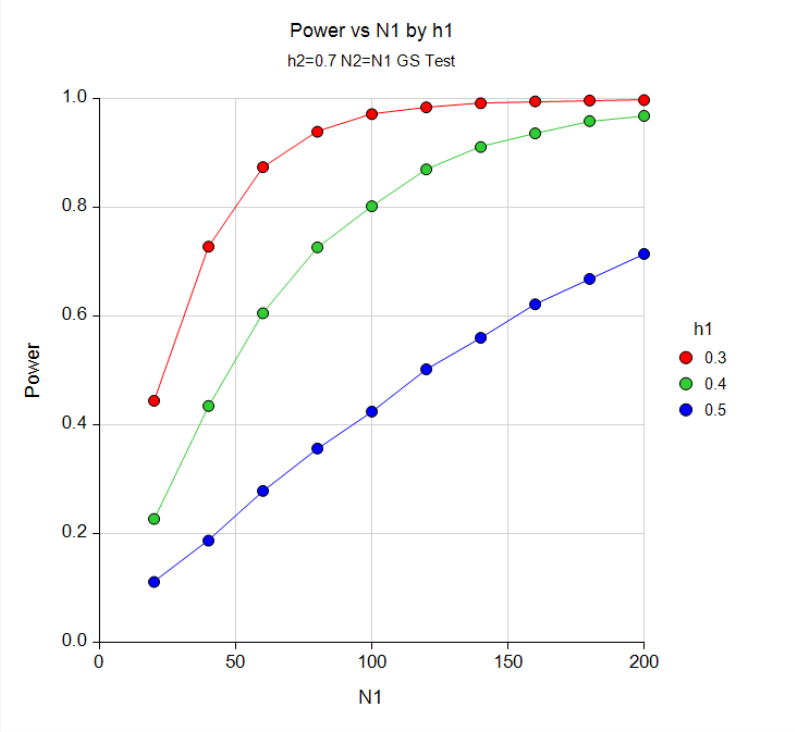
Power and Sample Size Summary

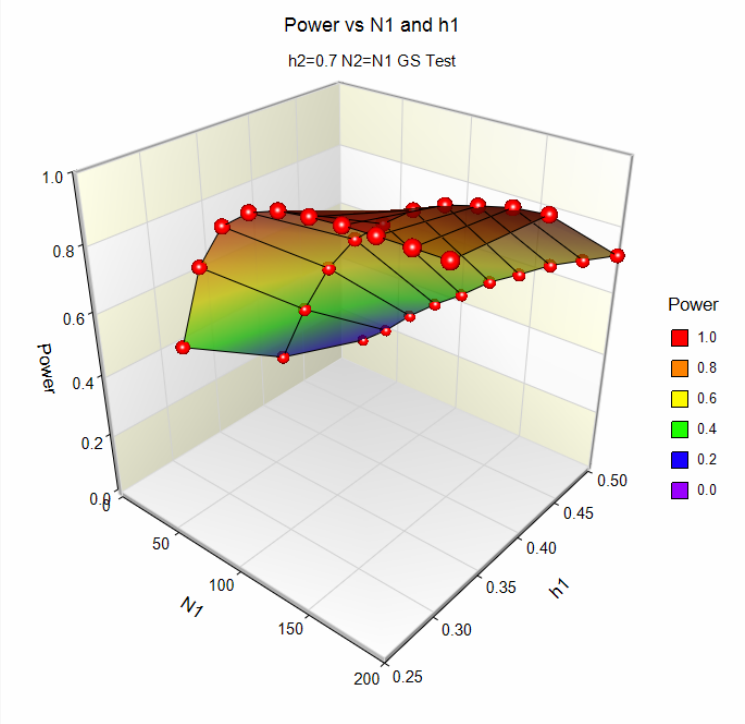
Solve For:	Power
Maximum Number of Stages:	5
Alternative Hypothesis:	h1 - h2 < 0 (one-sided)
Alpha Spending Function:	O'Brien-Fleming Analog
Beta Spending Function:	Hwang-Shih-DeCani (γ = 1.5)
Number of Simulations:	10000
Random Seed:	2310507 (User-Entered)

Sim Power	N1	N2	N	h1	h2	Target Alpha	Sim Alpha
0.4444	20	20	40	0.3	0.7	0.025	0.0290
0.7278	40	40	80	0.3	0.7	0.025	0.0219
0.8741	60	60	120	0.3	0.7	0.025	0.0238
0.9392	80	80	160	0.3	0.7	0.025	0.0218
0.9716	100	100	200	0.3	0.7	0.025	0.0246
0.9840	120	120	240	0.3	0.7	0.025	0.0233
0.9915	140	140	280	0.3	0.7	0.025	0.0246
0.9949	160	160	320	0.3	0.7	0.025	0.0243
0.9965	180	180	360	0.3	0.7	0.025	0.0234
0.9973	200	200	400	0.3	0.7	0.025	0.0242
0.2270	20	20	40	0.4	0.7	0.025	0.0279
0.4348	40	40	80	0.4	0.7	0.025	0.0219
0.6054	60	60	120	0.4	0.7	0.025	0.0235
0.7265	80	80	160	0.4	0.7	0.025	0.0216
0.8022	100	100	200	0.4	0.7	0.025	0.0232
0.8699	120	120	240	0.4	0.7	0.025	0.0235
0.9111	140	140	280	0.4	0.7	0.025	0.0224
0.9362	160	160	320	0.4	0.7	0.025	0.0231
0.9588	180	180	360	0.4	0.7	0.025	0.0228
0.9683	200	200	400	0.4	0.7	0.025	0.0255
0.1112	20	20	40	0.5	0.7	0.025	0.0246
0.1872	40	40	80	0.5	0.7	0.025	0.0228
0.2785	60	60	120	0.5	0.7	0.025	0.0206
0.3566	80	80	160	0.5	0.7	0.025	0.0235
0.4244	100	100	200	0.5	0.7	0.025	0.0280
0.5023	120	120	240	0.5	0.7	0.025	0.0248
0.5602	140	140	280	0.5	0.7	0.025	0.0289
0.6218	160	160	320	0.5	0.7	0.025	0.0246
0.6684	180	180	360	0.5	0.7	0.025	0.0256
0.7144	200	200	400	0.5	0.7	0.025	0.0241

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 0.4 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	**Power**
Alpha	**0.025**
Group Allocation	**Equal (N1 = N2)**
Sample Size Per Group	**100**
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)	**0.4**
h2 (Hazard Rate of Group 2)	**0.7**
Maximum Number of Stages (K)	**2** (Also run with **3**, **4**, **5**, **10**, and **20**)
Time Proportion at each Stage	**Equally incremented**
Boundaries Used	**One-sided Efficacy with Futility**
Hypothesis Direction	**Ha: h1 - h2 < 0**
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 (γ)**
γ	**1.5**
Skipped Futility Stages	**<Empty>**
Binding or Non-Binding Futility	**Non-Binding**

Options Tab

Test Type	**MLE**
Number of Simulations	**100000**
Random Seed	**Random**
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. 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:	h1 - h2 < 0 (one-sided)
Alpha Spending Function:	O'Brien-Fleming Analog
Beta Spending Function:	Hwang-Shih-DeCani (γ = 1.5)
Number of Simulations:	100000

Sim Power	N1	N2	N	h1	h2	Target Alpha	Sim Alpha	Number of Stages
0.87285	100	100	200	0.4	0.7	0.025	0.0235	2
0.87184	100	100	200	0.4	0.7	0.025	0.0232	3
0.86983	100	100	200	0.4	0.7	0.025	0.0231	4
0.86846	100	100	200	0.4	0.7	0.025	0.0235	5
0.86099	100	100	200	0.4	0.7	0.025	0.0229	10
0.85861	100	100	200	0.4	0.7	0.025	0.0248	20

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

Example 6 – Two-Sided Boundaries

Suppose that the scenario is similar to the setup of Example 3, but the boundary structure is changed to two-sided boundaries with an alpha of 0.05.

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	**Power**
Alpha	**0.05**
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)	**0.3 0.4 0.5**
h2 (Hazard Rate of Group 2)	**0.7**
Maximum Number of Stages (K)	**5**
Time Proportion at each Stage	**Equally incremented**
Boundaries Used	**Two-sided Efficacy with Futility (Symmetric)**
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 (γ)**
γ	**1.5**
Skipped Futility Stages	**<Empty>**
Binding or Non-Binding Futility	**Non-Binding**
Overlapped Futility Boundaries	**Remove (skip) overlapped futility boundaries**

Options Tab	
Test Type	**MLE**
Number of Simulations	**10000** (set for the sake of time, 100,000 or more are recommended)
Random Seed	**3168484** (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**

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 – Scenario 1

Run Summary Report - Scenario 1

Item	Value
Solve For	Power
Maximum Number of Stages (Design)	5
Current Stage	0
Alternative Hypothesis	h1 - h2 ≠ 0 (two-sided, symmetric)
Alpha Spending Function	O'Brien-Fleming Analog
Beta Spending Function	Hwang-Shih-DeCani (γ = 1.5)
Futility Boundaries	Non-Binding
Target Alpha	0.05
Alpha (from simulations)	0.0439
Hazard Rate of Group 1	0.3
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)	20
N2 (if final stage reached)	20
Power (from simulations)	0.3826
Maximum Information	22.4471

Z-Value Boundaries – Scenario 1

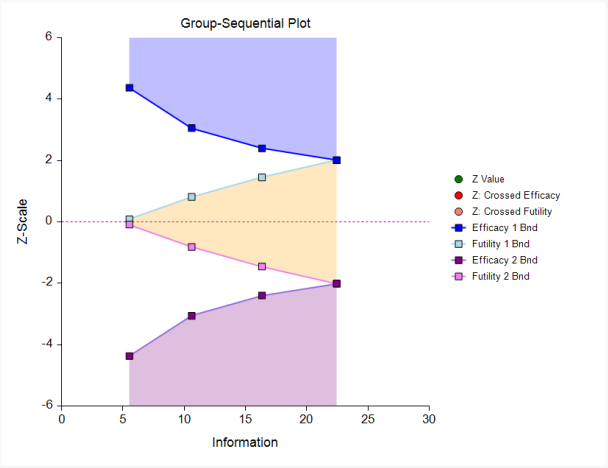
Z-Value Boundaries

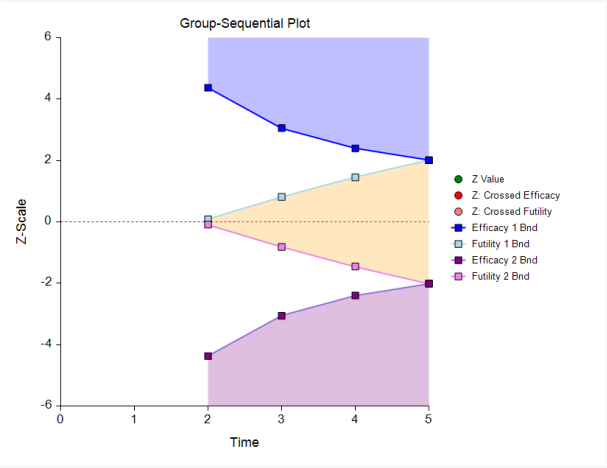
Maximum Information: 22.4471
Alternative Hypothesis: h1 - h2 ≠ 0 (two-sided, symmetric)
Futility Boundaries: Non-Binding

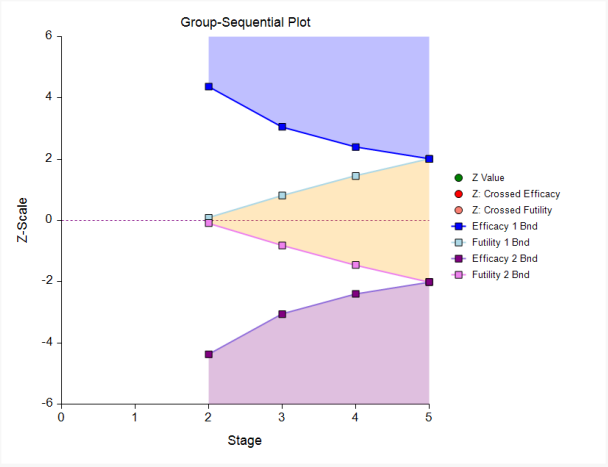
	Boundaries						
	Upper Side		Lower Side				
Stage	Efficacy 1	Futility 1	Efficacy 2	Futility 2	Time Proportion	Time	Information Proportion
1					0.2	1	0.0734
2	4.3709	0.0853	-4.3709	-0.0853	0.4	2	0.2463
3	3.0582	0.8157	-3.0582	-0.8157	0.6	3	0.4728
4	2.3966	1.4531	-2.3966	-1.4531	0.8	4	0.7285
5	2.0081	2.0081	-2.0081	-2.0081	1.0	5	1.0000

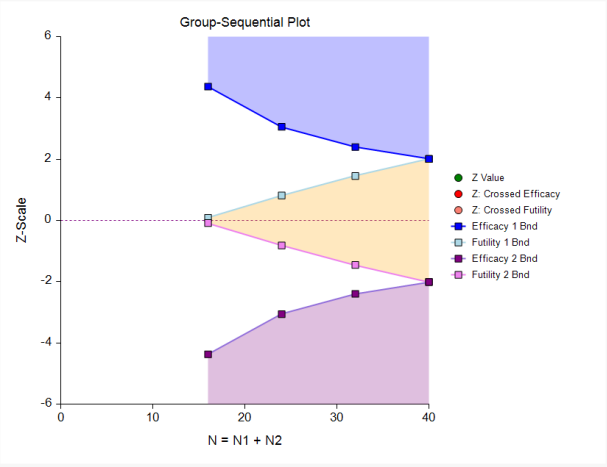
Boundary Plot(s) – Scenario 1

Boundary Plot(s)









Other Scenario Reports

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

Power and Sample Size Summary

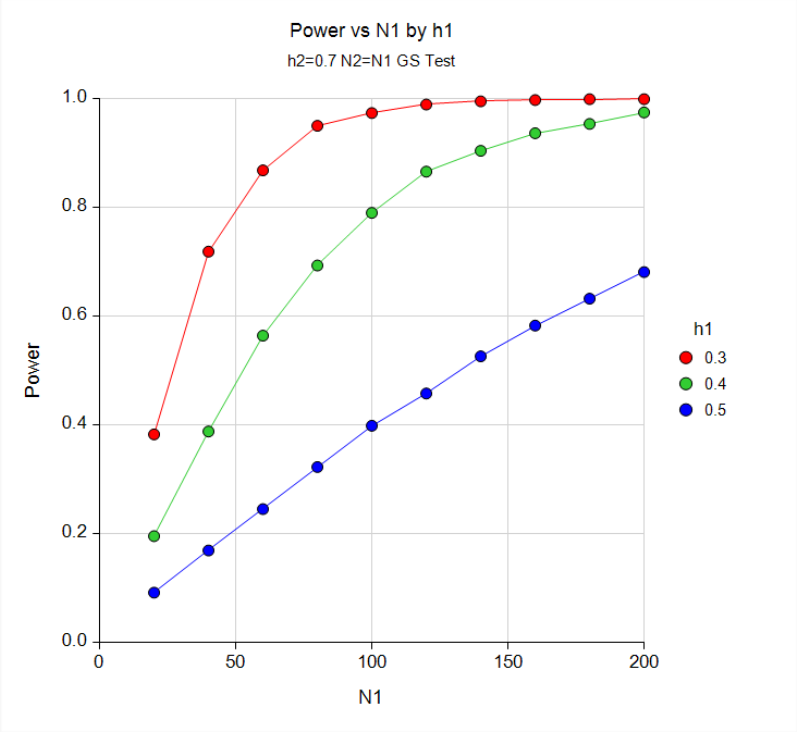
Power and Sample Size Summary

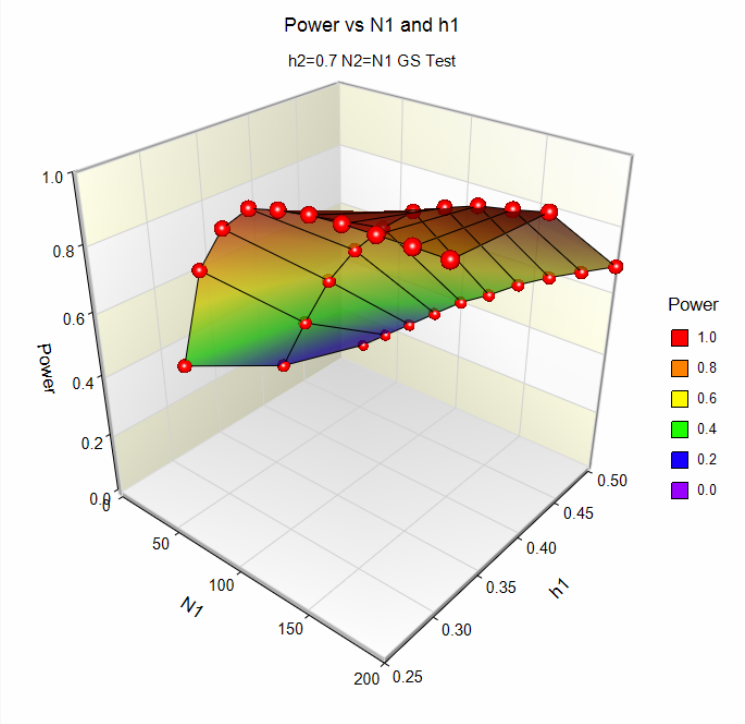
Solve For:	Power
Maximum Number of Stages:	5
Alternative Hypothesis:	h1 - h2 ≠ 0 (two-sided, symmetric)
Alpha Spending Function:	O'Brien-Fleming Analog
Beta Spending Function:	Hwang-Shih-DeCani (γ = 1.5)
Number of Simulations:	10000
Random Seed:	3168484 (User-Entered)

Sim Power	N1	N2	N	h1	h2	Target Alpha	Sim Alpha
0.3826	20	20	40	0.3	0.7	0.05	0.0439
0.7187	40	40	80	0.3	0.7	0.05	0.0340
0.8682	60	60	120	0.3	0.7	0.05	0.0356
0.9500	80	80	160	0.3	0.7	0.05	0.0365
0.9735	100	100	200	0.3	0.7	0.05	0.0377
0.9892	120	120	240	0.3	0.7	0.05	0.0395
0.9950	140	140	280	0.3	0.7	0.05	0.0376
0.9974	160	160	320	0.3	0.7	0.05	0.0340
0.9990	180	180	360	0.3	0.7	0.05	0.0380
0.9991	200	200	400	0.3	0.7	0.05	0.0359
0.1954	20	20	40	0.4	0.7	0.05	0.0431
0.3879	40	40	80	0.4	0.7	0.05	0.0313
0.5642	60	60	120	0.4	0.7	0.05	0.0324
0.6932	80	80	160	0.4	0.7	0.05	0.0344
0.7899	100	100	200	0.4	0.7	0.05	0.0362
0.8658	120	120	240	0.4	0.7	0.05	0.0353
0.9041	140	140	280	0.4	0.7	0.05	0.0336
0.9364	160	160	320	0.4	0.7	0.05	0.0399
0.9535	180	180	360	0.4	0.7	0.05	0.0375
0.9747	200	200	400	0.4	0.7	0.05	0.0372
0.0916	20	20	40	0.5	0.7	0.05	0.0422
0.1691	40	40	80	0.5	0.7	0.05	0.0312
0.2452	60	60	120	0.5	0.7	0.05	0.0310
0.3225	80	80	160	0.5	0.7	0.05	0.0312
0.3984	100	100	200	0.5	0.7	0.05	0.0337
0.4578	120	120	240	0.5	0.7	0.05	0.0344
0.5262	140	140	280	0.5	0.7	0.05	0.0376
0.5827	160	160	320	0.5	0.7	0.05	0.0364
0.6322	180	180	360	0.5	0.7	0.05	0.0376
0.6811	200	200	400	0.5	0.7	0.05	0.0385

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 7 – 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 0.4 and 0.7, 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 7** 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	**100**
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)	**0.4**
h2 (Hazard Rate of Group 2)	**0.7**
Maximum Number of Stages (K)	**5**
Time Proportion at each Stage	**Equally incremented**
Boundaries Used	**One-sided Efficacy with Futility**
Hypothesis Direction	**Ha: h1 - h2 < 0**
Boundary Specification	**Spending Function Calculation**
Alpha Spending Function	**O'Brien-Fleming Analog**
Skipped Efficacy Stages	**<Empty>**
Design Beta	**0.20**
Beta Spending Function	**Hwang-Shih-DeCani (γ)**
γ	**1.5**
Skipped Futility Stages	**<Empty>**
Binding or Non-Binding Futility	**Binding**

Options Tab	
Test Type	**MLE**
Number of Simulations	**100000**
Random Seed	**2380115** (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. 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	h1 - h2 < 0 (one-sided)
Alpha Spending Function	O'Brien-Fleming Analog
Beta Spending Function	Hwang-Shih-DeCani (γ = 1.5)
Futility Boundaries	Binding
Target Alpha	0.025
Alpha (from simulations)	0.02403
Hazard Rate of Group 1	0.4
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)	0.79795
Maximum Information	101.1139

Z-Value Boundaries

Z-Value Boundaries

Maximum Information: 101.1139
Alternative Hypothesis: h1 - h2 < 0 (one-sided)
Futility Boundaries: Binding

	Boundaries				
Stage	Efficacy	Futility	Time Proportion	Time	Information Proportion
1		1.0870	0.2	1	0.0738
2	-4.3563	-0.0065	0.4	2	0.2472
3	-3.0527	-0.7683	0.6	3	0.4739
4	-2.3743	-1.3492	0.8	4	0.7292
5	-1.8294	-1.8294	1.0	5	1.0000

Information Report

Information Report

Maximum Information: 101.1139
Alternative Hypothesis: h1 - h2 < 0 (one-sided)
Alpha: 0.025

					Target Sample Size			
Stage	Target Time Proportion	Target Time	Target Information Proportion	Target Information	N1	N2	h1	h2
1	0.2	1	0.0738	7.4655	20	20	0.4	0.7
2	0.4	2	0.2472	24.9978	40	40	0.4	0.7
3	0.6	3	0.4739	47.9198	60	60	0.4	0.7
4	0.8	4	0.7292	73.7351	80	80	0.4	0.7
5	1.0	5	1.0000	101.1139	100	100	0.4	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 *	0.0738	0.0000	0.0000	0.000000	0.0	0.0
2 *	0.2472	0.0000	0.0000	0.000007	0.0	0.0
3 *	0.4739	0.0011	0.0011	0.001134	4.5	4.5
4 *	0.7292	0.0075	0.0087	0.008791	30.2	34.7
5 *	1.0000	0.0163	0.0250	0.033667	65.3	100.0

* projected

The Alpha Spent this Stage is compared to the results of the simulations, found in the section Boundary Probabilities for $\delta = 0$ (Alpha).

Boundary Probabilities for δ = 0 (Alpha)

Boundary Probabilities for δ = 0 (Alpha)

Number of Simulations:	100000
Random Seed:	2380115 (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: 1, 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:	h1 - h2 < 0 (one-sided)
Z Statistic:	MLE
h1:	0.7
h2:	0.7
δ:	0

			Efficacy		Futility	
Stage	N1	N2	Boundary	Probability	Boundary	Probability
1	*20	*20		0.0000	1.0870	0.1398
2	*40	*40	-4.3563	0.0000	-0.0065	0.3844
3	*60	*60	-3.0527	0.0006	-0.7683	0.2837
4	*80	*80	-2.3743	0.0069	-1.3492	0.1249
5	*100	*100	-1.8294	0.0166	-1.8294	0.0432

* 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.

Beta Spending for Futility

Beta Spending for Futility

Target Cumulative Beta at Final Stage: 0.2
Spending Function for Futility: Hwang-Shih-DeCani (γ = 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 *	0.0738	0.0270	0.0270	0.861482	13.5	13.5
2 *	0.2472	0.0528	0.0798	0.497417	26.4	39.9
3 *	0.4739	0.0512	0.1310	0.221141	25.6	65.5
4 *	0.7292	0.0402	0.1712	0.088631	20.1	85.6
5 *	1.0000	0.0288	0.2000	0.033667	14.4	100.0

* projected

Similarly, the Beta Spent this Stage is compared to the results of the simulations, found in the section Boundary Probabilities for δ = 0.3.

Boundary Probabilities for δ = -0.3

Boundary Probabilities for δ = -0.3

Number of Simulations: 100000
Random Seed: 2380115 (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: 12, 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: h1 - h2 < 0 (one-sided)
Z Statistic: MLE
h1: 0.4
h2: 0.7
δ: -0.3

			Efficacy		Futility	
Stage	N1	N2	Boundary	Probability	Boundary	Probability
1	*20	*20		0.0000	1.0870	0.0300
2	*40	*40	-4.3563	0.0001	-0.0065	0.0541
3	*60	*60	-3.0527	0.1332	-0.7683	0.0507
4	*80	*80	-2.3743	0.4373	-1.3492	0.0384
5	*100	*100	-1.8294	0.2273	-1.8294	0.0288

* 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.