Chapter 785

Group-Sequential Superiority by a Margin Tests for One Hazard Rate (Simulation)

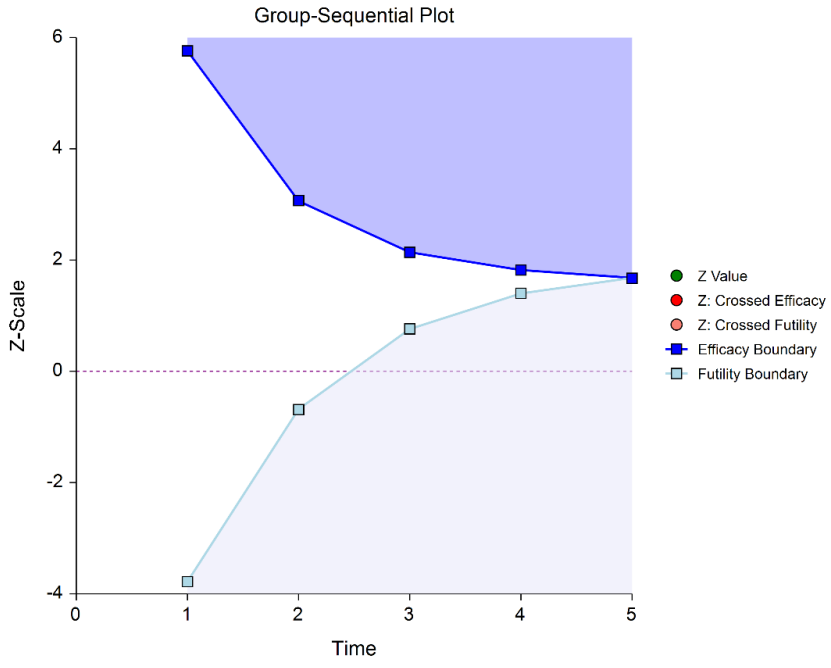
The corresponding analysis and sample size re-estimation procedure, found in NCSS Analysis and Graphics software, is *Group-Sequential Superiority by a Margin Analysis for One Hazard Rate*.

Introduction

This procedure can be used to determine power, sample size and/or boundaries for group-sequential superiority by a margin Z-tests comparing a single survival curve to a null hypothesized value. This methodology assumes an underlying Exponential model. 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 Superiority by a Margin Analysis for One Hazard Rate*. 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:

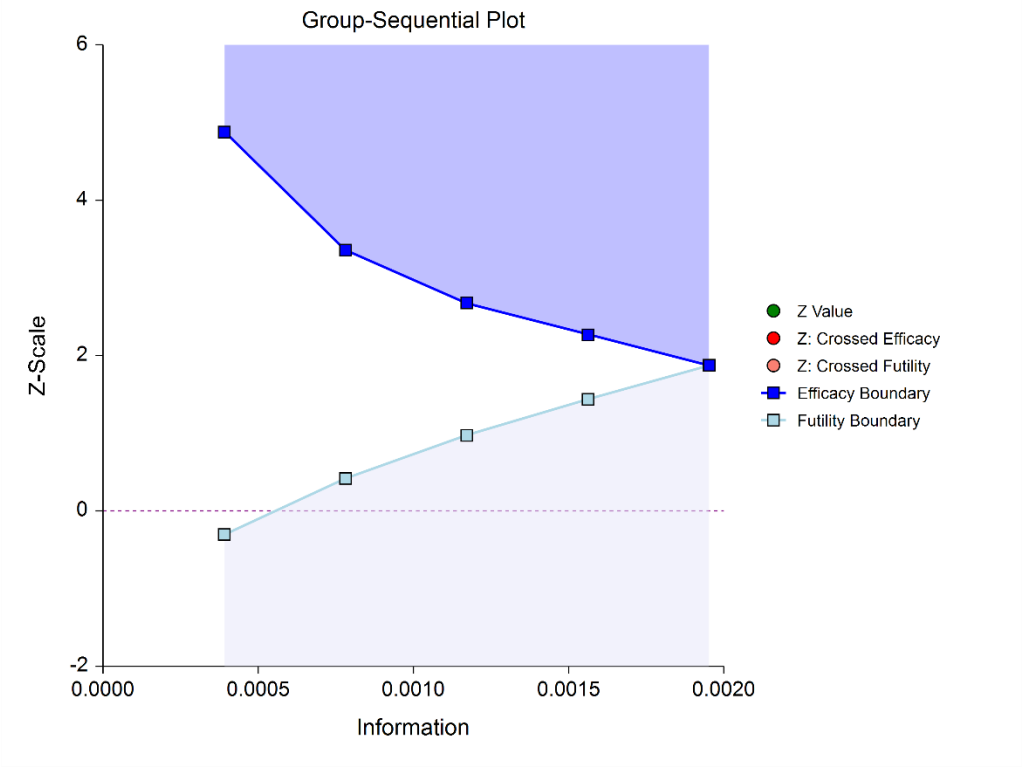
- Alpha
- Power
- Test Direction
- Types of boundaries (efficacy, binding futility, non-binding futility)
- Maximum number of stages
- Proportion of maximum information at each stage
- Spending functions
- Assumed survival rate
- Superiority margin

The design phase calculation is performed in this procedure. **PASS** software permits the user to easily try a range of survival rates, 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**.

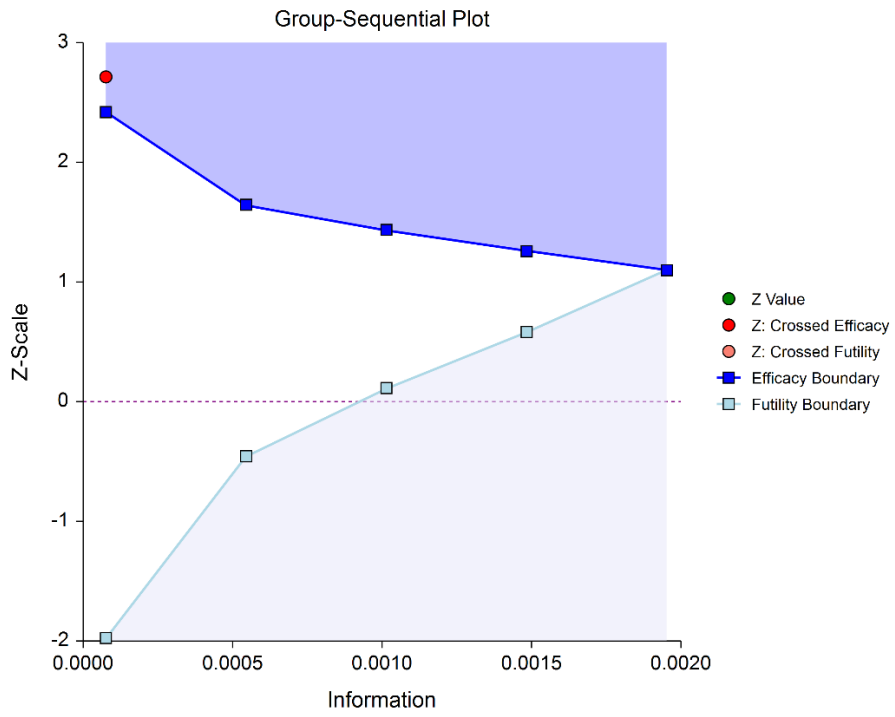
First Interim Stage

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.

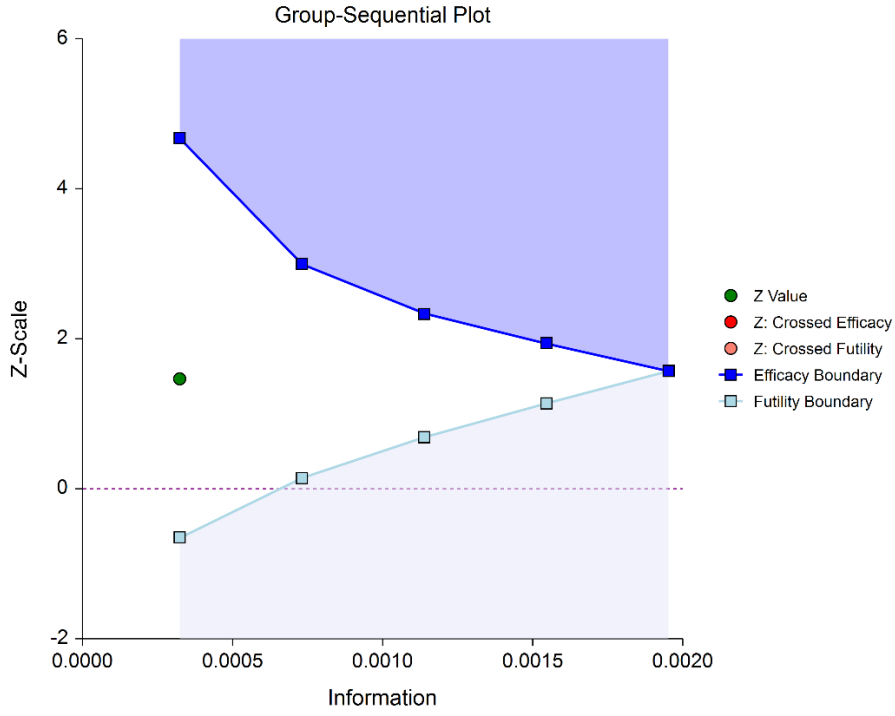
Unless the number of subjects and time at the first stage matches the design target for the first stage, the calculated information at the first stage will not exactly match the design information for the first stage. Generally, the calculated information will not differ too greatly from the design information,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

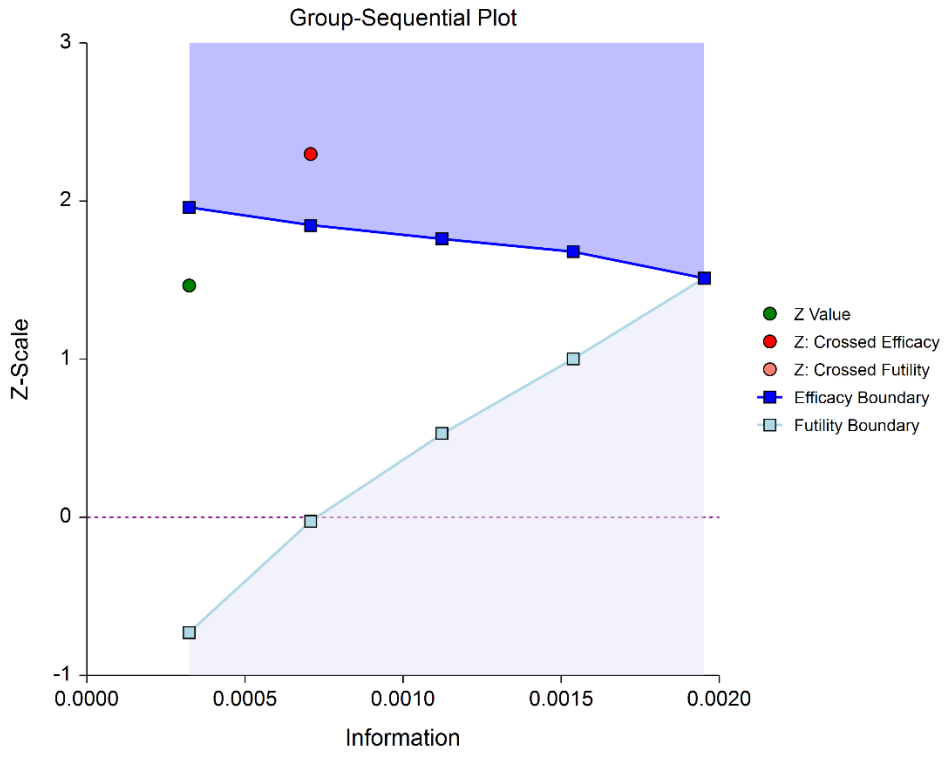
If the first stage time proportion is not equal to the design time proportion, a designation must be made at this point as to the target time of the second stage. Two options are available in the **NCSS** procedure.

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.

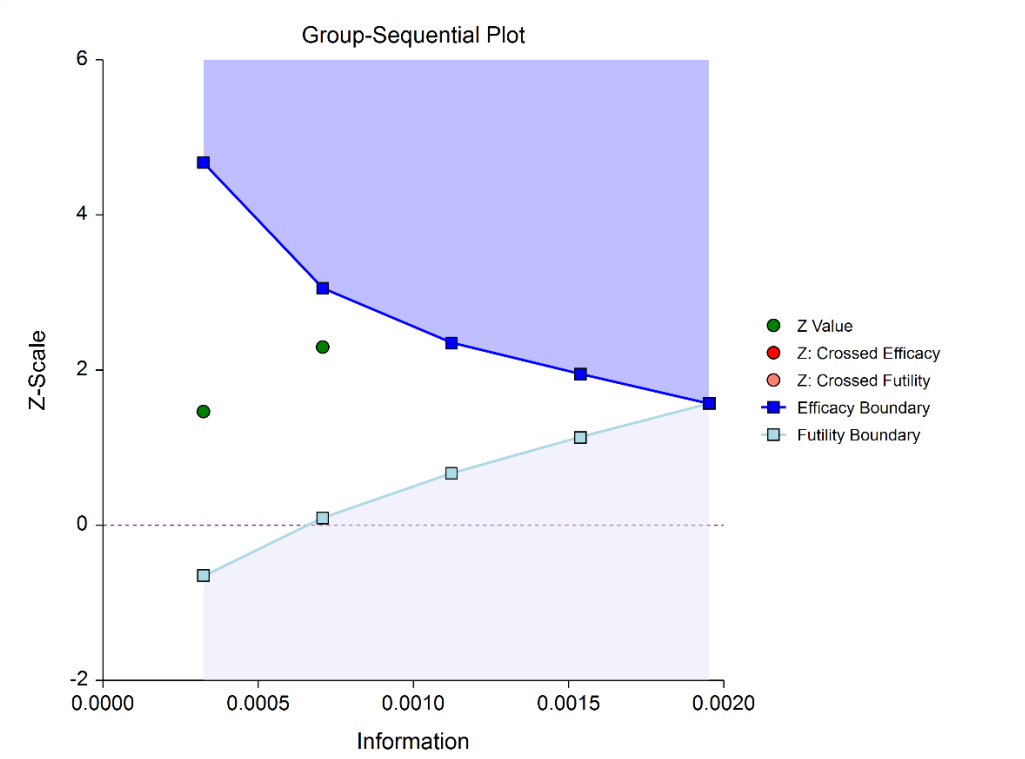
A second option is to adjust the target time proportionally to the remaining proportions. For this option, if the design proportions are 0.25, 0.50, 0.75, 1.0, and 0.22 is observed, the remaining 0.78 is distributed proportionally to the remaining stages. In this example, the remaining target proportions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

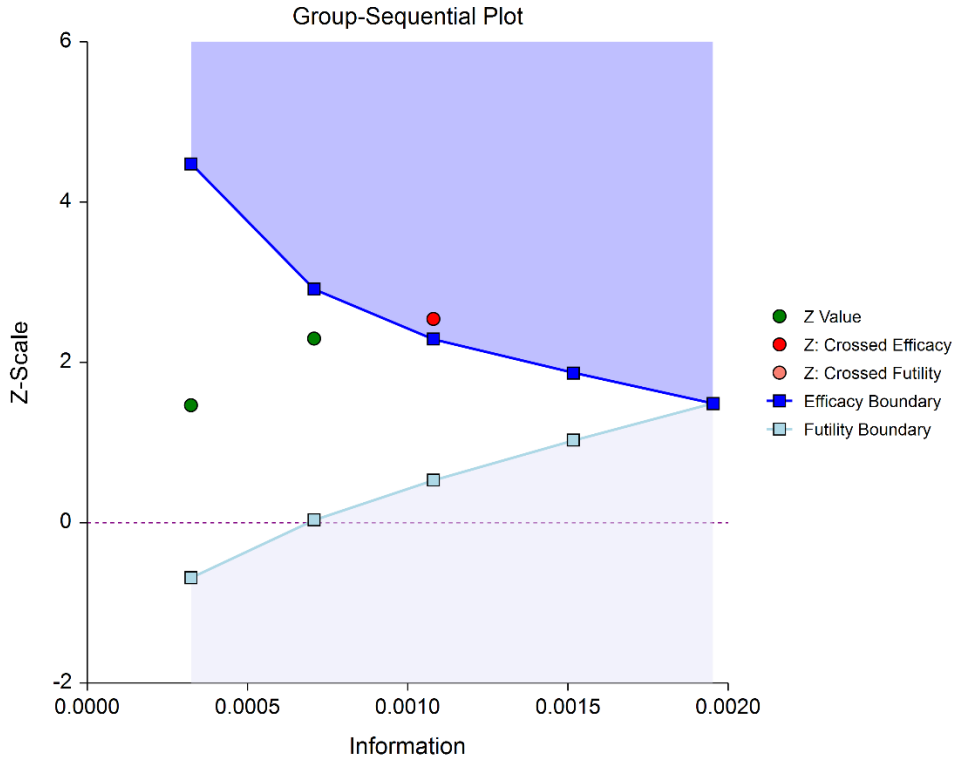
Reporting Phase

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 superiority by a margin tests of one hazard rate versus a null hazard rate, 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 hazard rate is less than the null hazard rate by at least the margin of superiority. The value of δ at which power is calculated must be less than $-|M_S|$. The null and alternative hypotheses, with superiority margin M_S, are

$H_0: h(T) \geq h_0(T) - |M_S|$ versus $H_1: h(T) < h_0(T) - |M_S|$

$H_0: h(T) - h_0(T) \geq -|M_S|$ versus $H_1: h(T) - h_0(T) < -|M_S|$

$H_0: \delta \geq -|M_S|$ versus $H_1: \delta < -|M_S|$

Case 2: High Hazard Rates Good

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

$H_0: h(T) \leq h_0(T) + |M_S|$ versus $H_1: h(T) > h_0(T) + |M_S|$

$H_0: h(T) - h_0(T) \leq |M_S|$ versus $H_1: h(T) - h_0(T) > |M_S|$

$H_0: \delta \leq |M_S|$ versus $H_1: \delta > |M_S|$

Stages in Group-Sequential Testing

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

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

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

Test Statistic (MLE)

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

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

$$z_k = \frac{\hat{h}_k - h_0 - (-|SM|)}{\sqrt{\hat{\sigma}_k^2(\hat{h}_k)}} = \frac{\hat{h}_k - h_0 + |SM|}{\sqrt{\hat{\sigma}_k^2(\hat{h}_k)}}$$

and, when higher hazard rates are better:

$$z_k = \frac{\hat{h}_k - h_0 - |SM|}{\sqrt{\hat{\sigma}_k^2(\hat{h}_k)}}$$

with

$$\hat{h}_k = \frac{\sum_{j=1}^{n_k} c_{jk}}{\sum_{j=1}^{n_k} x_{jk}}$$

$$\hat{\sigma}_k^2(\hat{h}_k) = \frac{\sum_{j=1}^{n_k} c_{jk}}{\left(\sum_{j=1}^{n_k} x_{jk}\right)^2} = \frac{\hat{h}_k^2}{\sum_{j=1}^{n_k} c_{jk}}$$

where

$\hat{h}_k$ is the estimated hazard rate at stage *k*

$\hat{\sigma}_k^2(\hat{h}_k)$ is the variance of the hazard rate estimator

c_{jk} is an indicator of censoring

x_{jk} 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 difference in hazard rates from the null value.

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

$$I_K^* = \frac{1}{\frac{\sigma_K^2(h_0, l, p)}{n_K}}$$

where

$\sigma_K^2(h_0, l, p)$ is the variance of the hazard rate estimator

h_0 is the null hypothesized hazard rate

l is the loss hazard rate

p is the patient entry parameter

and

$$\sigma_K^2(h_0, l, p) = h_0^2\left(\frac{h_0}{h_0 + l} + \frac{h_0 p e^{-(h_0+l)T}\left(1 - e^{(h_0+l-p)T_0}\right)}{(1 - e^{-pT_0})(h_0 + l)(h_0 + l - p)}\right)^{-1}$$

where

T_0 is the accrual time

T is the total time

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

$$\sigma_K^2(h_0, l, p) = h_0^2\left(\frac{h_0}{h_0 + l}\left[1 - \frac{e^{-(T-T_0)(h_0+l)} - e^{-T(h_0+l)}}{T_0(h_0 + l)}\right]\right)^{-1}$$

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

$$I_k = \frac{1}{\frac{\sigma_K^2(h_0, l, p)}{n_k}}$$

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

$$I_K = \frac{1}{\frac{\sigma_K^2(h_0, l, p)}{n_{K_{achieved}}}} \neq I_K^* = \frac{1}{\frac{\sigma_K^2(h_0, l, p)}{n_K}}$$

so that

$$p_K = \frac{I_K}{I_K^*} \neq 1$$

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

$$I_K^* = I_K$$

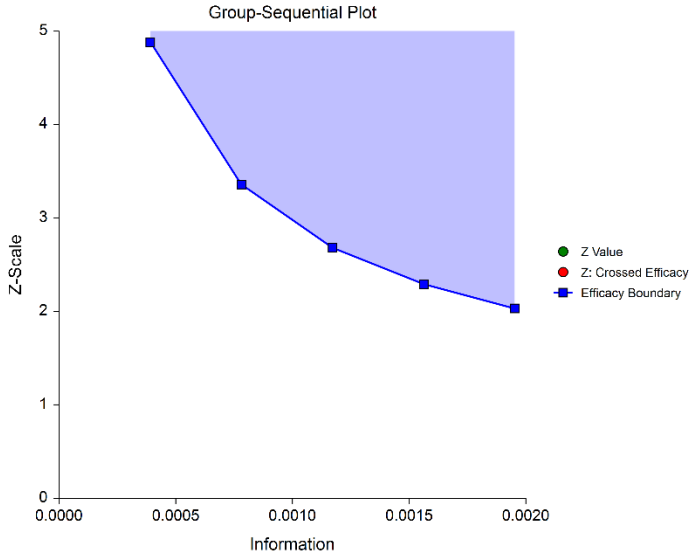
See the discussion in Wassmer and Brannath (2016), pages 78-79, or Jennison and Turnbull (2000), pages 153-154, 162.

Types of Boundaries

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

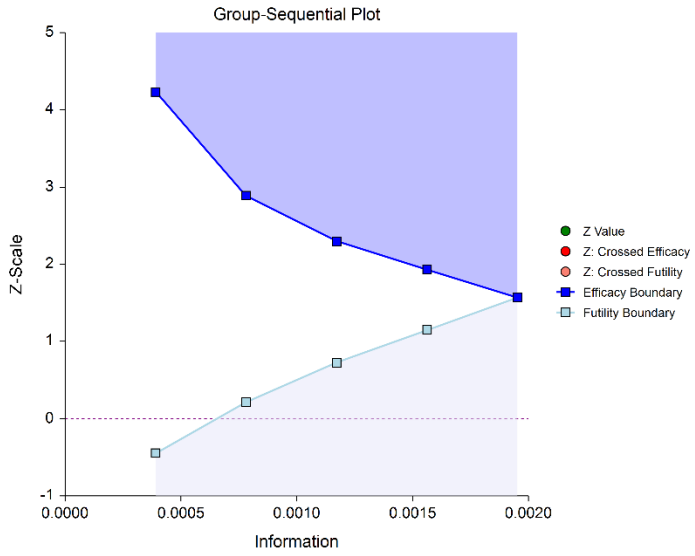
Efficacy Only

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



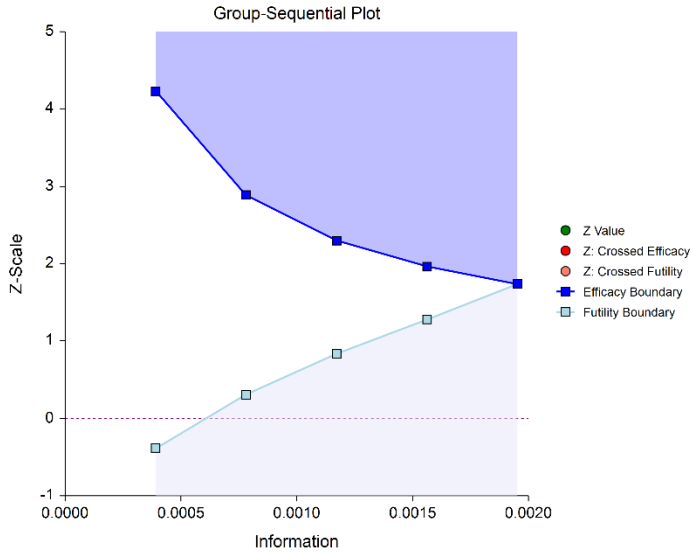
Efficacy and Binding Futility

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



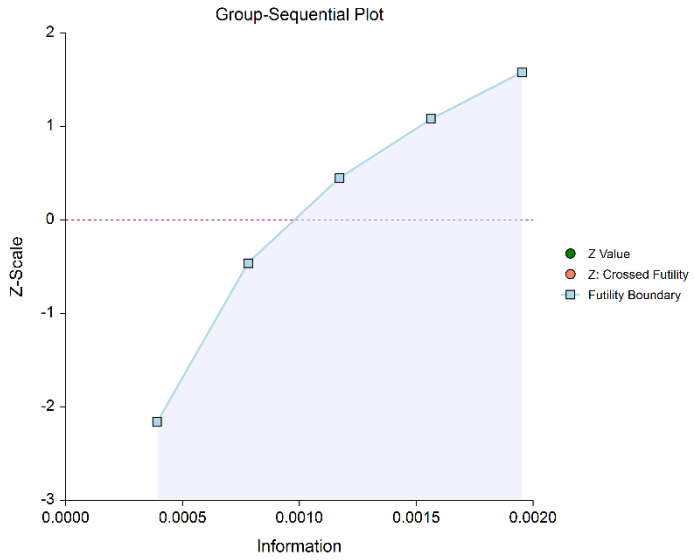
Efficacy and Non-Binding Futility

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



Futility Only

In this design, the interim analyses are used only for futility. Please be aware that, due to computational complexity, these boundaries may take several minutes to compute, particularly when some stages are skipped.



Boundary Calculations

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

Binding vs. Non-Binding Futility Boundaries

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

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

Spending Functions

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

Spending Function Characteristics

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

$$\alpha(0) = 0 \text{ (for alpha-spending)}$$

$$\beta(0) = 0 \text{ (for beta-spending)}$$

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

$$\alpha(1) = \alpha \text{ (for alpha-spending)}$$

$$\beta(1) = \beta \text{ (for beta-spending)}$$

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

Spending Functions Available in this Procedure

The following spending functions are shown as alpha-spending functions. The corresponding beta-spending function is given by replacing α with β.

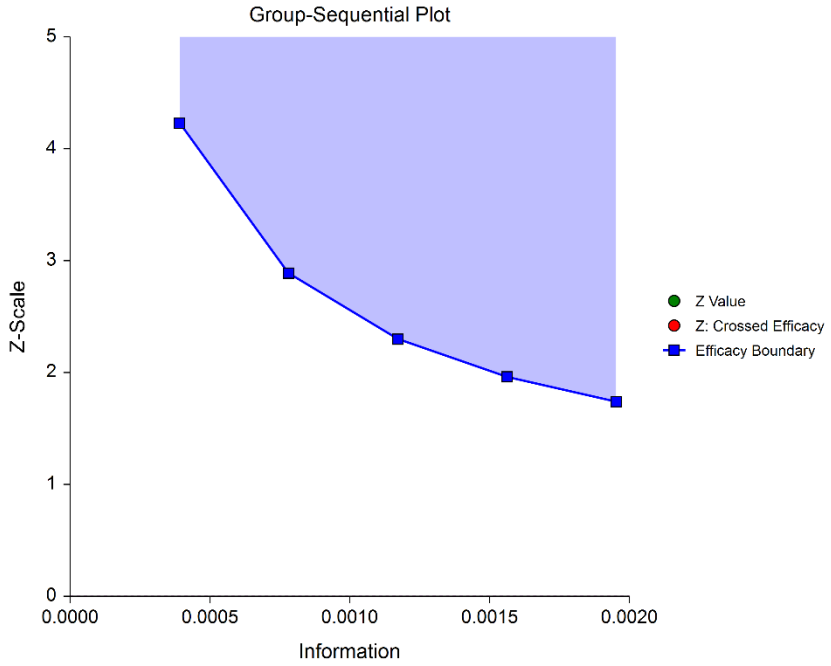
O'Brien-Fleming Analog

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.

$$\alpha(0) = 0$$

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

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



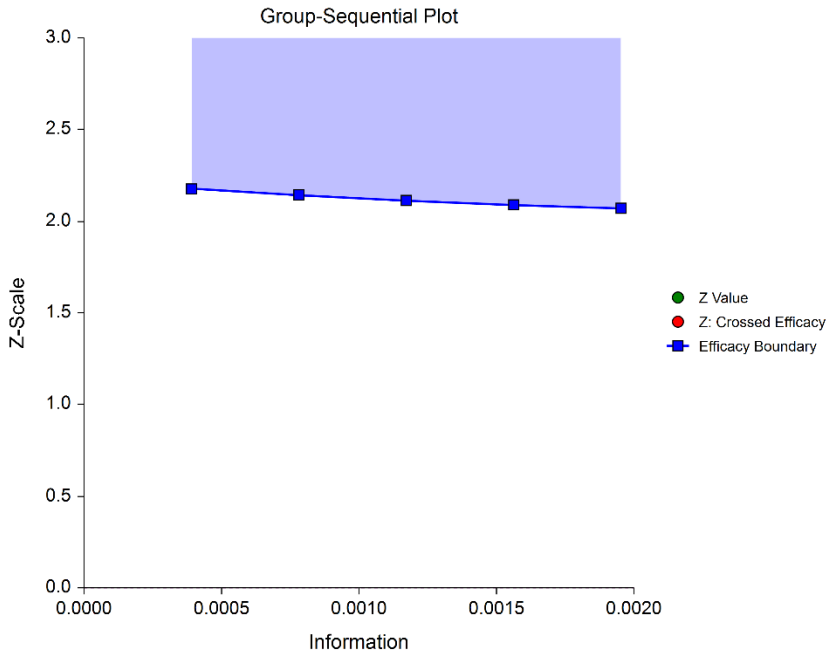
Pocock Analog

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.

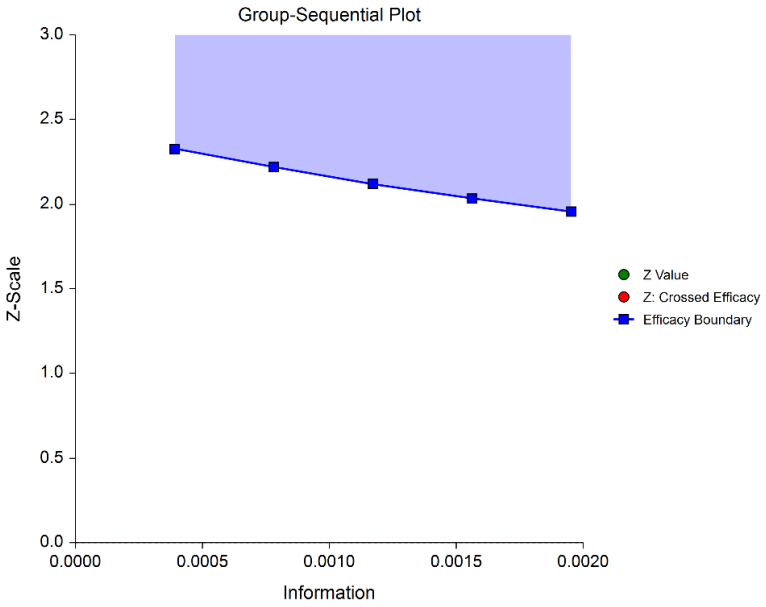
$$\alpha(0) = 0$$

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

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

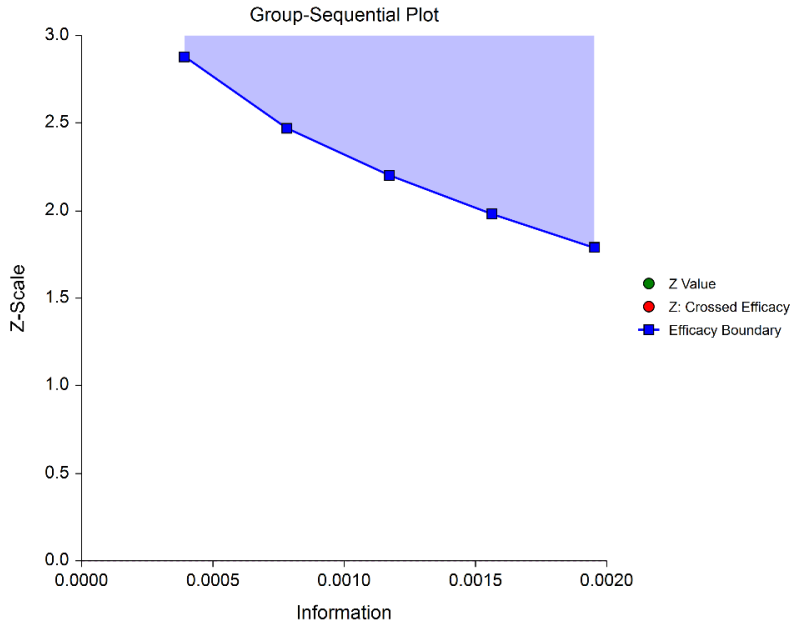
A power family spending function with a ρ of 1 is similar to a Pocock design, while a power family spending function with a ρ of 3 is more similar to an O'Brien-Fleming design.

$\rho = 1$

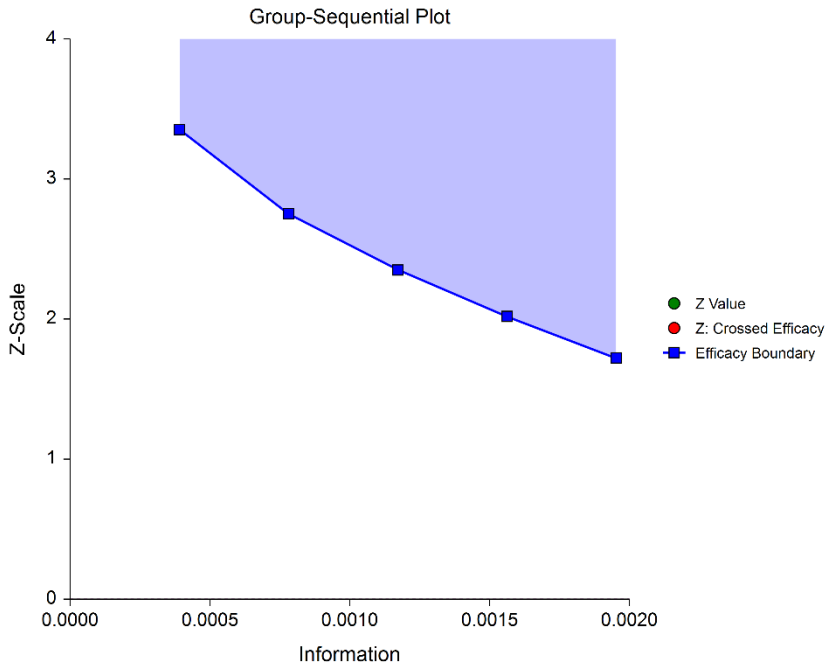


Group-Sequential Superiority by a Margin Tests for One Hazard Rate (Simulation)

$\rho = 2$



$\rho = 3$



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.

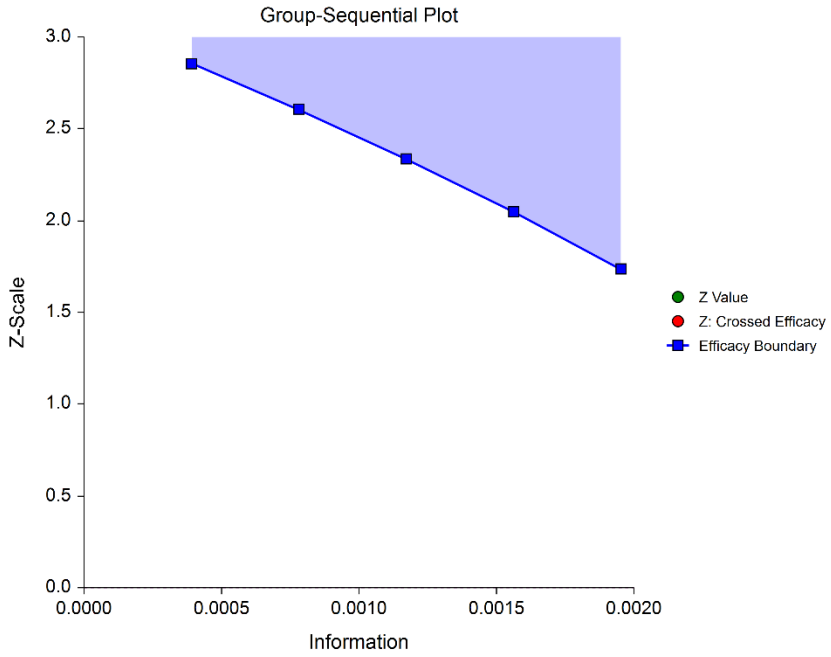
$$\alpha(0) = 0$$

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

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

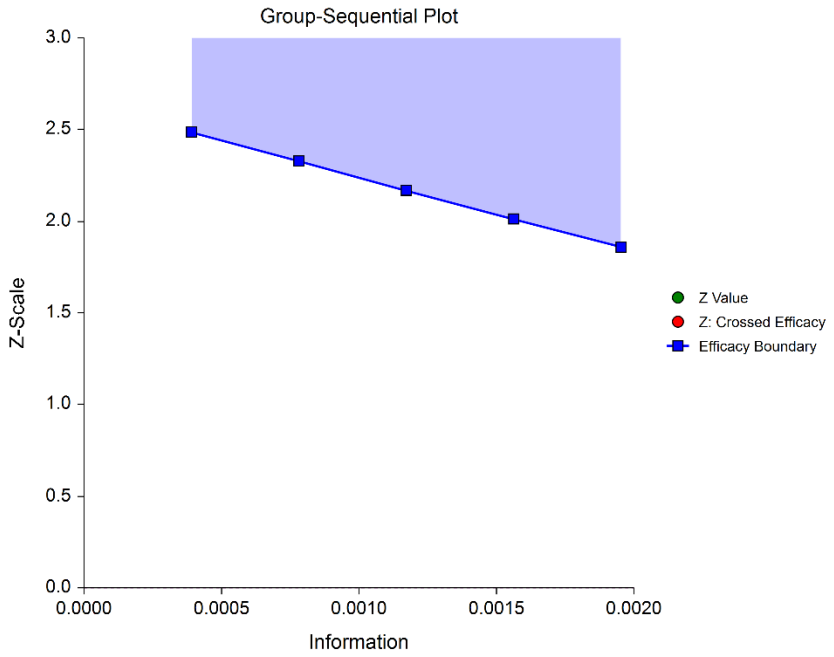
$$\alpha(1) = \alpha$$

$\gamma = -3$

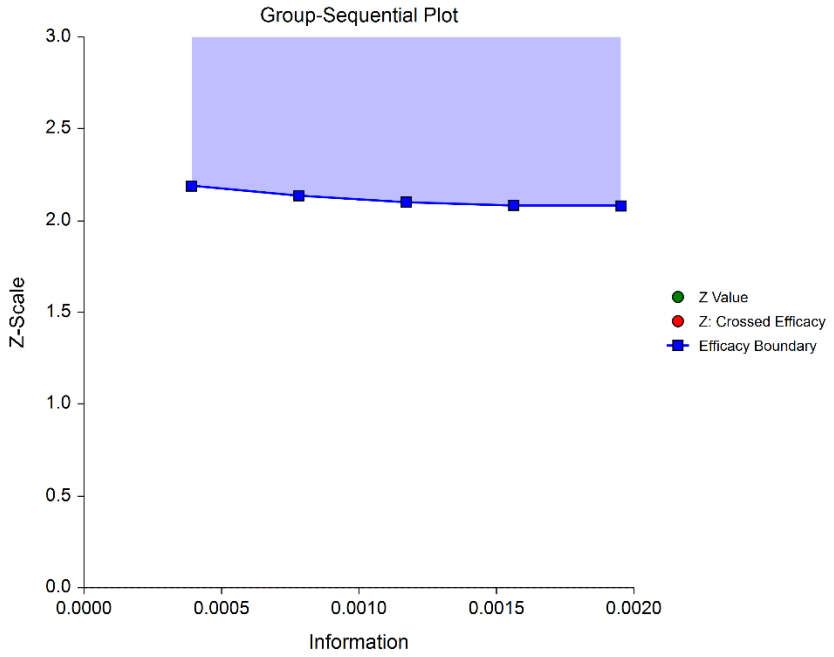


Group-Sequential Superiority by a Margin Tests for One Hazard Rate (Simulation)

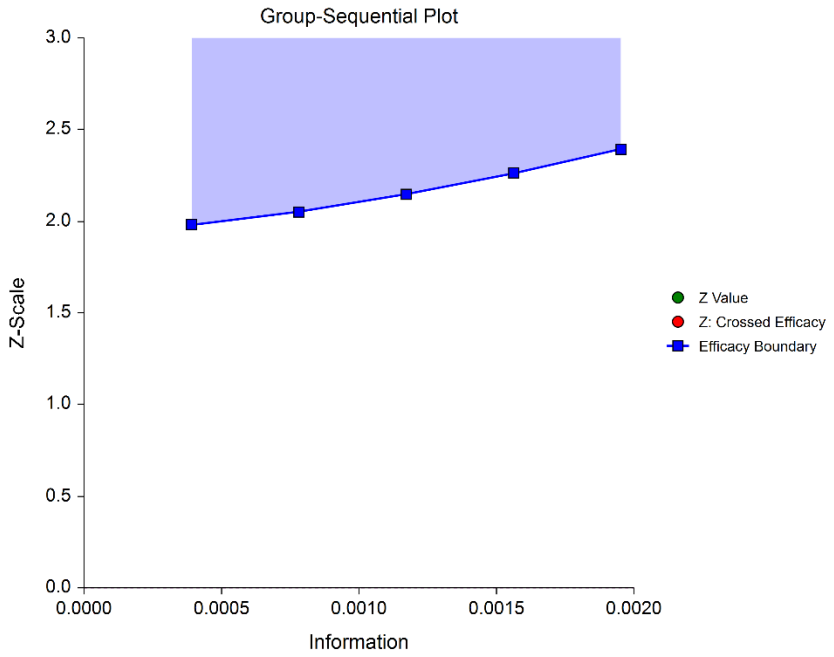
$\gamma = -1$



$\gamma = 1$



$\gamma = 3$



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 size. Simulated values are generated from Exponential distributions with a user-specified hazard rate.
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 rate.

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 hazard rate that is lower than the historical hazard rate of 0.913 by at least 0.2 (superiority margin). 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 the difference of a hazard rate to a null value, with superiority margin, will be used.

The null and alternative hypotheses are

$$H_0: h - h_0 = -0.2 \quad (H_0: h = h_0 - 0.2)$$

versus

$$H_a: h - h_0 < -0.2 \quad (H_a: h < h_0 - 0.2)$$

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 is assumed to be 0.03. A power of 0.90 is needed. 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**
L (Loss Hazard Rate)	**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**
h (Hazard Rate)	**0.3 0.4 0.5**
h0 (Null Hazard Rate)	**0.913**
SM (Superiority Margin)	**0.2**
Maximum Number of Stages (K)	**5**
Time Proportion at each Stage	**Equally incremented**
Boundaries Used	**Efficacy with Futility**

Group-Sequential Superiority by a Margin Tests for One Hazard Rate (Simulation)

Hypothesis Direction	**Ha: h - h0 < -|SM| (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 (γ)**
γ	**1.5**
Skipped Futility Stages	**<Empty>**
Binding or Non-Binding Futility	**Non-Binding**

Options Tab

Number of Simulations	**1000** (set for the sake of time, 100,000 or more are recommended)
Random Seed	**4415497** (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.

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 - h0 < -|SM|
Superiority Margin (SM)	0.2
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)	0.069
Hazard Rate (h)	0.3
Null Hazard Rate (h0)	0.913
Loss Hazard Rate	0.03
T0 (Accrual Time)	5
% of T0 Until 50% Accrual	50
Accrual Parameter	0
Total Time	5
N (if final stage reached)	20
Target Power	0.9
Power (from simulations)	0.914
Maximum Information	18.34724

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

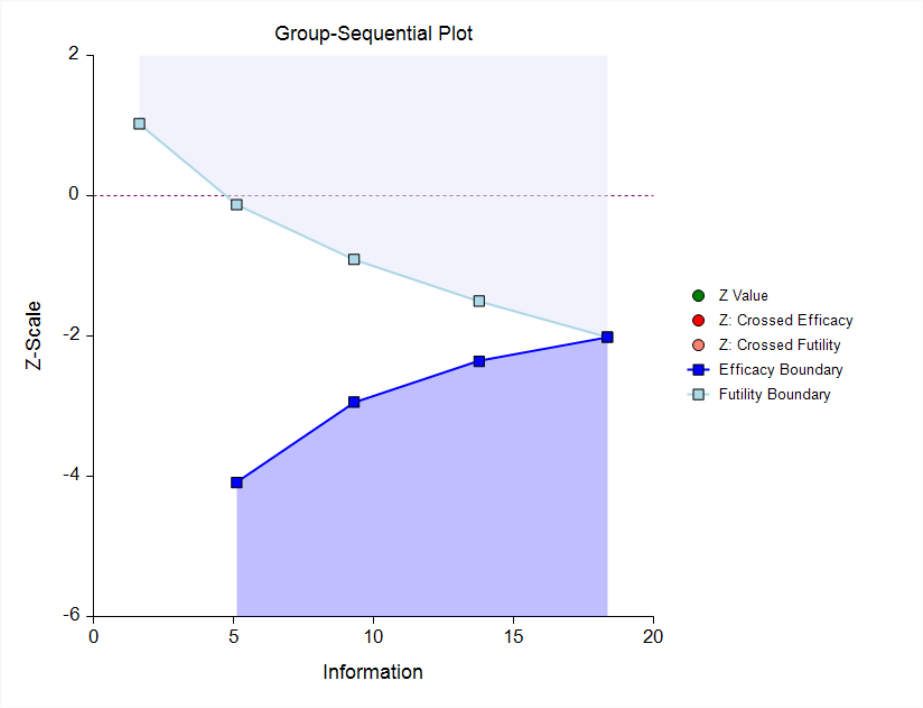
Maximum Information: 18.34724
Alternative Hypothesis: h - h0 < -|SM|
Futility Boundaries: Non-Binding

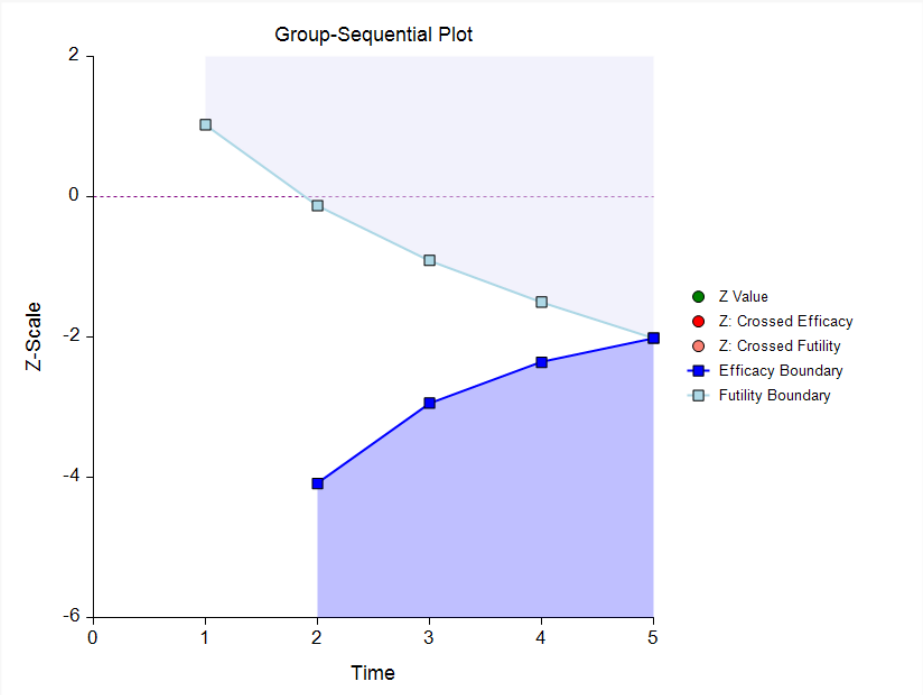
	Boundaries				
Stage	Efficacy	Futility	Time Proportion	Time	Information Proportion
1		1.02753	0.2	1	0.08928
2	-4.08792	-0.12585	0.4	2	0.27865
3	-2.94074	-0.90612	0.6	3	0.50701
4	-2.35946	-1.49951	0.8	4	0.75055
5	-2.01436	-2.01436	1.0	5	1.00000

Boundary Plot(s)

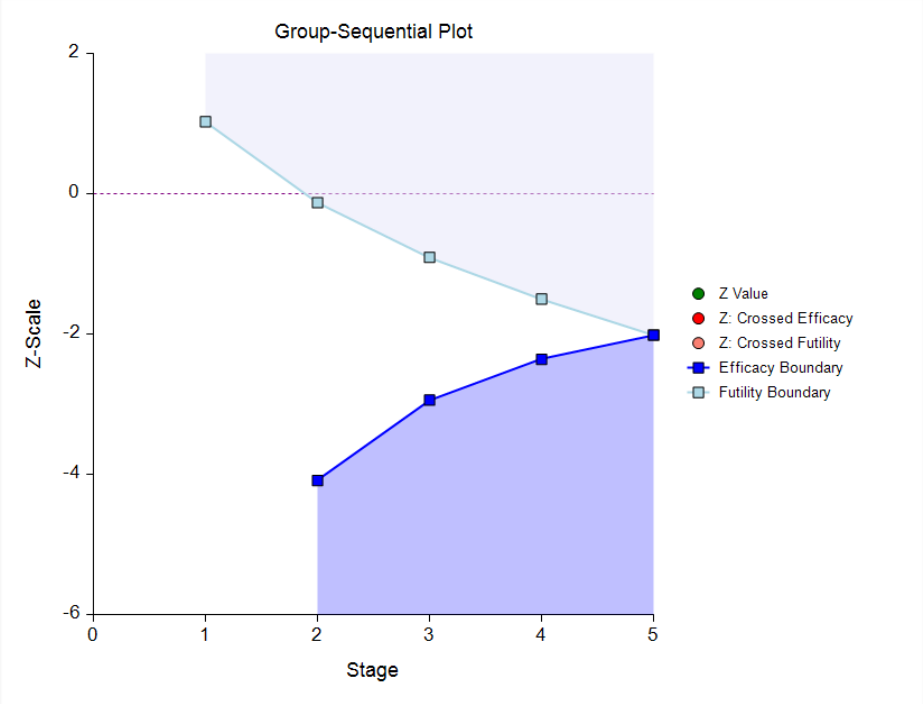
These plots show the efficacy and futility Z-statistic planning boundaries. It is anticipated that these boundaries will adjust to the actual information proportions as the data for each stage is realized. Because the stage one information proportion is so low, and the O-Brien-Fleming Analog Alpha spending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

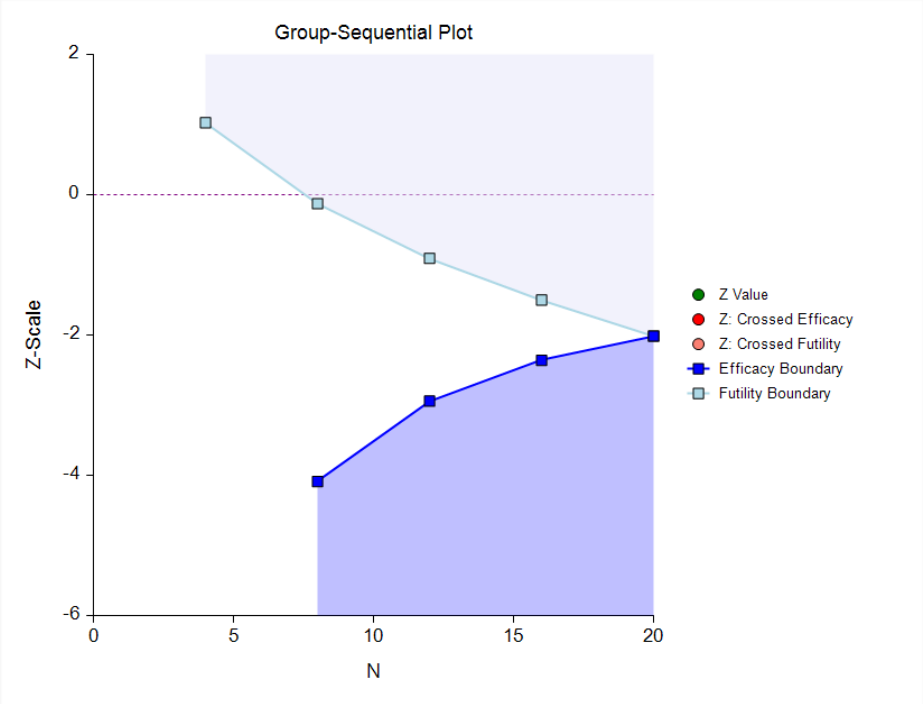
Boundary Plot(s)





Group-Sequential Superiority by a Margin Tests for One Hazard Rate (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: 18.34724
Alternative Hypothesis: h - h0 < -|SM|
Futility Boundaries: Non-Binding
P-value boundaries are one-sided values.

	Boundaries				
Stage	Efficacy	Futility	Time Proportion	Time	Information Proportion
1		0.84792	0.2	1	0.08928
2	0.00002	0.44993	0.4	2	0.27865
3	0.00164	0.18244	0.6	3	0.50701
4	0.00915	0.06687	0.8	4	0.75055
5	0.02199	0.02199	1.0	5	1.00000

Information Report

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

Information Report

Maximum Information: 18.34724
Alternative Hypothesis: h - h0 < -|SM|
Alpha: 0.025

Stage	Target Time Proportion	Target Time	Target Information Proportion	Target Information	Target Sample Size N	h0
1	0.2	1	0.08928	1.63796	4	0.913
2	0.4	2	0.27865	5.11244	8	0.913
3	0.6	3	0.50701	9.30217	12	0.913
4	0.8	4	0.75055	13.77046	16	0.913
5	1.0	5	1.00000	18.34724	20	0.913

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 *	0.08928	0.00000	0.00000	0.000000	0.0	0.0
2 *	0.27865	0.00002	0.00002	0.000022	0.1	0.1
3 *	0.50701	0.00162	0.00164	0.001637	6.5	6.6
4 *	0.75055	0.00803	0.00968	0.009151	32.1	38.7
5 *	1.00000	0.01532	0.02500	0.021986	61.3	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 *	0.08928	0.01613	0.01613	0.847915	16.1	16.1
2 *	0.27865	0.02784	0.04397	0.449925	27.8	44.0
3 *	0.50701	0.02458	0.06855	0.182435	24.6	68.6
4 *	0.75055	0.01841	0.08697	0.066871	18.4	87.0
5 *	1.00000	0.01303	0.10000	0.021986	13.0	100.0

* projected

Boundary Probabilities for δ = -0.613

Using simulation based on the specified hazard rate, this section gives the estimated probabilities of crossing each of the boundaries.

Boundary Probabilities for δ = -0.613

Number of Simulations:	1000
Random Seed:	4415497 (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: 584, Stage 2: 133, Stage 3: 11, Stage 4: 1, Stage 5: 0
Futility Boundaries:	Non-Binding
After Efficacy Boundary Crossing:	Hold Out
After Non-Binding Futility Boundary Crossing:	Leave In
Alternative Hypothesis:	h - h0 < -|SM|
Superiority Margin (SM):	0.2
Z Statistic:	MLE
h:	0.3
h0:	0.913
δ:	-0.613

		Efficacy		Futility	
Stage	N	Boundary	Probability	Boundary	Probability
1	*4		0.000	1.02753	0.006
2	*8	-4.08792	0.107	-0.12585	0.216
3	*12	-2.94074	0.370	-0.90612	0.118
4	*16	-2.35946	0.294	-1.49951	0.114
5	*20	-2.01436	0.143	-2.01436	0.097

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

Event Summary for δ = -0.613

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

Event Summary for δ = -0.613

Number of Simulations:	1000
Random Seed:	4415497 (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: 584, Stage 2: 133, Stage 3: 11, Stage 4: 1, Stage 5: 0
h:	0.3
h0:	0.913
δ:	-0.613

Stage	Average Cumulative Number of Events E
1	0.51
2	1.86
3	3.93
4	6.42
5	9.23

Boundary Probabilities for δ = -|SM| (Alpha)

This section estimates the probabilities of crossing each boundary if the hazard rate difference is assumed to be the negative of the superiority margin.

Boundary Probabilities for δ = -|SM| (Alpha)

Number of Simulations:	1000
Random Seed:	4415497 (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: 304, Stage 2: 21, 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 - h0 < -|SM|
Superiority Margin (SM):	0.2
Z Statistic:	MLE
h:	0.913 - |SM| = 0.913 - 0.2 = 0.713
h0:	0.913
δ:	-|SM| = -0.2

		Efficacy		Futility	
Stage	N	Boundary	Probability	Boundary	Probability
1	*4		0.000	1.02753	0.083
2	*8	-4.08792	0.006	-0.12585	0.557
3	*12	-2.94074	0.017	-0.90612	0.793
4	*16	-2.35946	0.024	-1.49951	0.909
5	*20	-2.01436	0.022	-2.01436	0.953

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

Event Summary for δ = -|SM| (Alpha)

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

Event Summary for δ = -|SM| (Alpha)

Number of Simulations:	1000
Random Seed:	4415497 (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: 304, Stage 2: 21, Stage 3: 0, Stage 4: 0, Stage 5: 0
h:	0.913 - |SM| = 0.913 - 0.2 = 0.713
h0:	0.913
δ:	-|SM| = -0.2

Stage	Average Cumulative Number of Events E
1	1.15
2	3.60
3	6.85
4	10.62
5	14.49

Scenario 2

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

Scenario 3

All of the same boundary reports are given for Scenario 3, corresponding to an h 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:	h - h0 < -|SM|
Alpha Spending Function:	O'Brien-Fleming Analog
Beta Spending Function:	Hwang-Shih-DeCani (γ = 1.5)
Number of Simulations:	1000
Random Seed:	4415497 (User-Entered)

Target Power	Sim Power	N	h	h0	SM	Target Alpha	Sim Alpha
0.9	0.914	20	0.3	0.913	0.2	0.025	0.069
0.9	0.906	45	0.4	0.913	0.2	0.025	0.049
0.9	0.904	122	0.5	0.913	0.2	0.025	0.029

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.
N	The anticipated total number of individuals if the final stage is reached.
h	The assumed hazard rate of the population for power calculation simulations.
h0	The null hypothesized hazard rate. h0 +/- |SM| is also the assumed hazard rate of the population for alpha calculation simulations.
SM	The superiority 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 single-group group-sequential design with a maximum of 5 stages (where lower hazard rates are considered better) will be used to test whether the hazard rate is superior to the null (standard) hazard rate 0.913 by a margin, with a superiority margin of 0.2 (H0: h - 0.913 ≥ -0.2 versus H1: h - 0.913 < -0.2). The comparison will be made at each stage using a one-sample MLE hazard rate 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 loss hazard rate will be 0.03. To detect a hazard rate of 0.3 (difference of -0.613) with 90% power, the number of needed subjects at the final stage will be 20.

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.

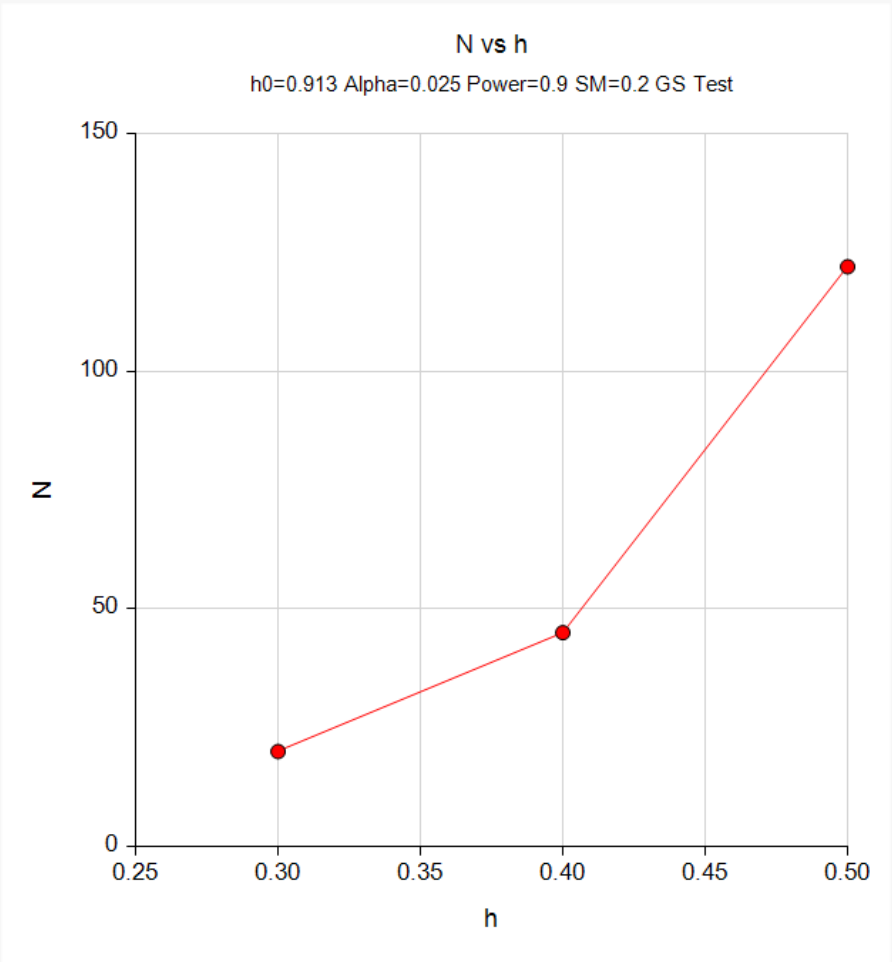
Reboussin, D.M., DeMets, D.L., Kim, K., and Lan, K.K.G. 1992. 'Programs for computing group sequential boundaries using the Lan-DeMets Method.' Technical Report 60, Department of Biostatistics, University of Wisconsin-Madison.

This report shows the values of each of the parameters, one scenario per row. The 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**
L (Loss Hazard Rate)	**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**
h (Hazard Rate)	**0.3 0.4 0.5**
h0 (Null Hazard Rate)	**0.913**
SM (Superiority Margin)	**0.2**
Maximum Number of Stages (K)	**5**
Time Proportion at each Stage	**Equally incremented**
Boundaries Used	**Efficacy with Futility**
Hypothesis Direction	**Ha: h - h0 < -|SM| (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 (γ)**
γ	**1.5**
Skipped Futility Stages	**1 2**
Binding or Non-Binding Futility	**Non-Binding**

Options Tab	
Number of Simulations	**1000** (set for the sake of time, 100,000 or more are recommended)
Random Seed	**5013913** (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	h - h0 < -|SM|
Superiority Margin (SM)	0.2
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)	0.061
Hazard Rate (h)	0.3
Null Hazard Rate (h0)	0.913
Loss Hazard Rate	0.03
T0 (Accrual Time)	5
% of T0 Until 50% Accrual	50
Accrual Parameter	0
Total Time	5
N (if final stage reached)	21
Target Power	0.9
Power (from simulations)	0.921
Maximum Information	19.26461

Z-Value Boundaries

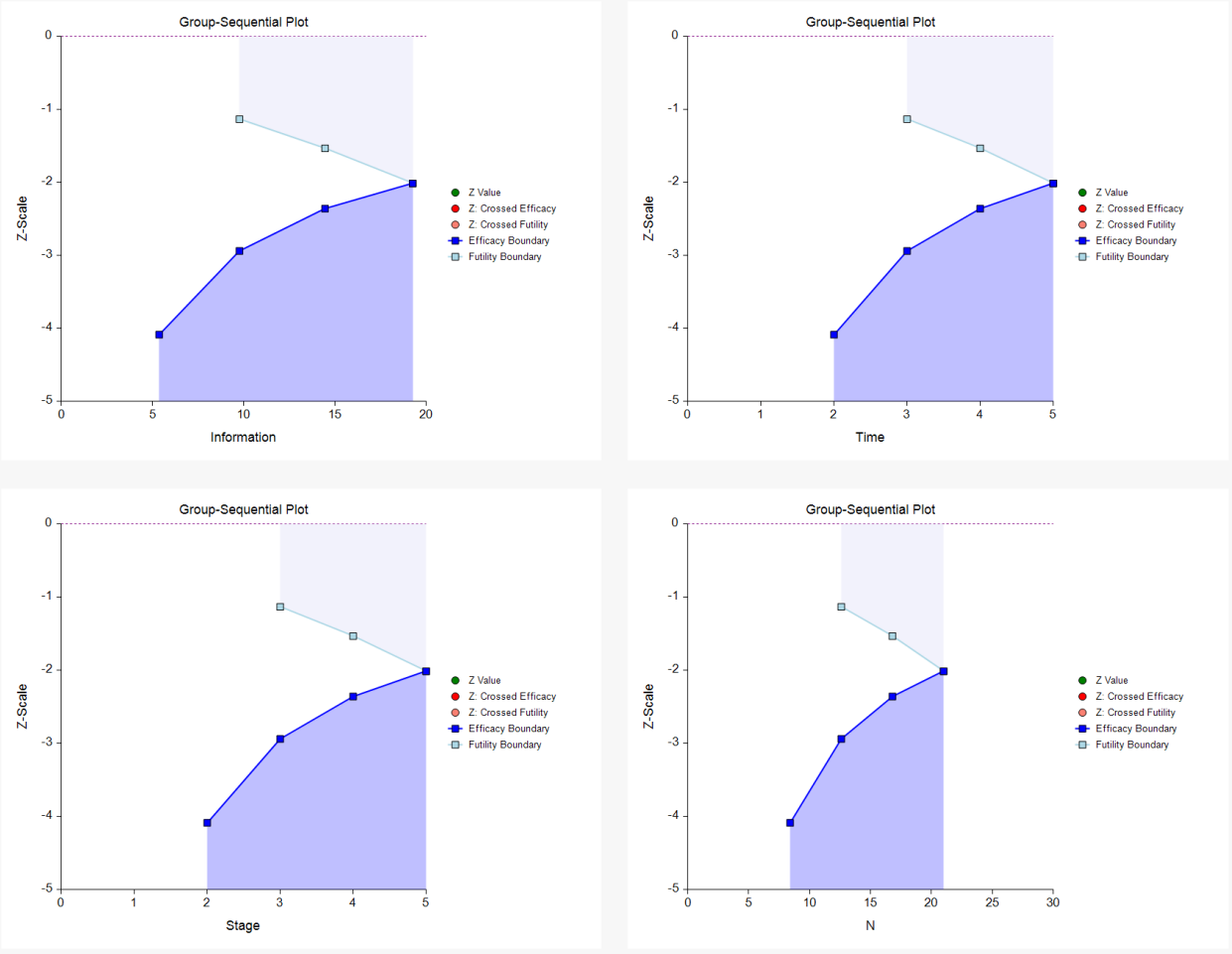
Z-Value Boundaries

Maximum Information: 19.26461
Alternative Hypothesis: h - h0 < -|SM|
Futility Boundaries: Non-Binding

	Boundaries				
Stage	Efficacy	Futility	Time Proportion	Time	Information Proportion
1			0.2	1	0.08928
2	-4.08792		0.4	2	0.27865
3	-2.94074	-1.13352	0.6	3	0.50701
4	-2.35946	-1.53358	0.8	4	0.75055
5	-2.01436	-2.01436	1.0	5	1.00000

Boundary Plot(s)

Boundary Plot(s)



P-Value Boundaries

P-Value Boundaries

Maximum Information: 19.26461
Alternative Hypothesis: h - h0 < -|SM|
Futility Boundaries: Non-Binding
P-value boundaries are one-sided values.

	Boundaries				
Stage	Efficacy	Futility	Time Proportion	Time	Information Proportion
1			0.2	1	0.08928
2	0.00002		0.4	2	0.27865
3	0.00164	0.12850	0.6	3	0.50701
4	0.00915	0.06257	0.8	4	0.75055
5	0.02199	0.02199	1.0	5	1.00000

Information Report

Information Report

Maximum Information: 19.26461
Alternative Hypothesis: h - h0 < -|SM|
Alpha: 0.025

Stage	Target Time Proportion	Target Time	Target Information Proportion	Target Information	Target Sample Size N	h0
1	0.2	1	0.08928	1.71985	4.2	0.913
2	0.4	2	0.27865	5.36806	8.4	0.913
3	0.6	3	0.50701	9.76728	12.6	0.913
4	0.8	4	0.75055	14.45899	16.8	0.913
5	1.0	5	1.00000	19.26461	21.0	0.913

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 *	0.08928	0.00000	0.00000	0.000000	0.0	0.0
2 *	0.27865	0.00002	0.00002	0.000022	0.1	0.1
3 *	0.50701	0.00162	0.00164	0.001637	6.5	6.6
4 *	0.75055	0.00803	0.00968	0.009151	32.1	38.7
5 *	1.00000	0.01532	0.02500	0.021986	61.3	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 *	0.08928	0.00000	0.00000	1.000000	0.0	0.0
2 *	0.27865	0.00000	0.00000	1.000000	0.0	0.0
3 *	0.50701	0.06855	0.06855	0.128498	68.6	68.6
4 *	0.75055	0.01841	0.08697	0.062567	18.4	87.0
5 *	1.00000	0.01303	0.10000	0.021986	13.0	100.0

* projected

Boundary Probabilities for δ = -0.613

Boundary Probabilities for δ = -0.613

Number of Simulations:	1000
Random Seed:	5013913 (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: 576, Stage 2: 134, Stage 3: 9, 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 - h0 < -|SM|
Superiority Margin (SM):	0.2
Z Statistic:	MLE
h:	0.3
h0:	0.913
δ:	-0.613

		Efficacy		Futility	
Stage	N	Boundary	Probability	Boundary	Probability
1	*4.2		0.000		0.000
2	*8.4	-4.08792	0.108		0.000
3	*12.6	-2.94074	0.363	-1.13352	0.150
4	*16.8	-2.35946	0.301	-1.53358	0.114
5	*21.0	-2.01436	0.149	-2.01436	0.094

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

Event Summary for δ = -0.613

Event Summary for δ = -0.613

Number of Simulations:	1000
Random Seed:	5013913 (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: 576, Stage 2: 134, Stage 3: 9, Stage 4: 0, Stage 5: 0
h:	0.3
h0:	0.913
δ:	-0.613

Stage	Average Cumulative Number of Events E
1	0.54
2	2.06
3	4.20
4	6.81
5	9.79

Boundary Probabilities for δ = -|SM| (Alpha)

Boundary Probabilities for δ = -|SM| (Alpha)

Number of Simulations:	1000
Random Seed:	5013913 (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: 277, Stage 2: 16, 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 - h0 < -|SM|
Superiority Margin (SM):	0.2
Z Statistic:	MLE
h:	0.913 - |SM| = 0.913 - 0.2 = 0.713
h0:	0.913
δ:	-|SM| = -0.2

		Efficacy		Futility	
Stage	N	Boundary	Probability	Boundary	Probability
1	*4.2		0.000		0.000
2	*8.4	-4.08792	0.004		0.000
3	*12.6	-2.94074	0.021	-1.13352	0.828
4	*16.8	-2.35946	0.016	-1.53358	0.909
5	*21.0	-2.01436	0.020	-2.01436	0.963

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

Event Summary for δ = -|SM| (Alpha)

Event Summary for δ = -|SM| (Alpha)

Number of Simulations:	1000
Random Seed:	5013913 (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: 277, Stage 2: 16, Stage 3: 0, Stage 4: 0, Stage 5: 0
h:	0.913 - |SM| = 0.913 - 0.2 = 0.713
h0:	0.913
δ:	-|SM| = -0.2

Stage	Average Cumulative Number of Events E
1	1.23
2	3.91
3	7.38
4	11.31
5	15.37

Scenario 2

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

Scenario 3

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

Power and Sample Size Summary

Power and Sample Size Summary

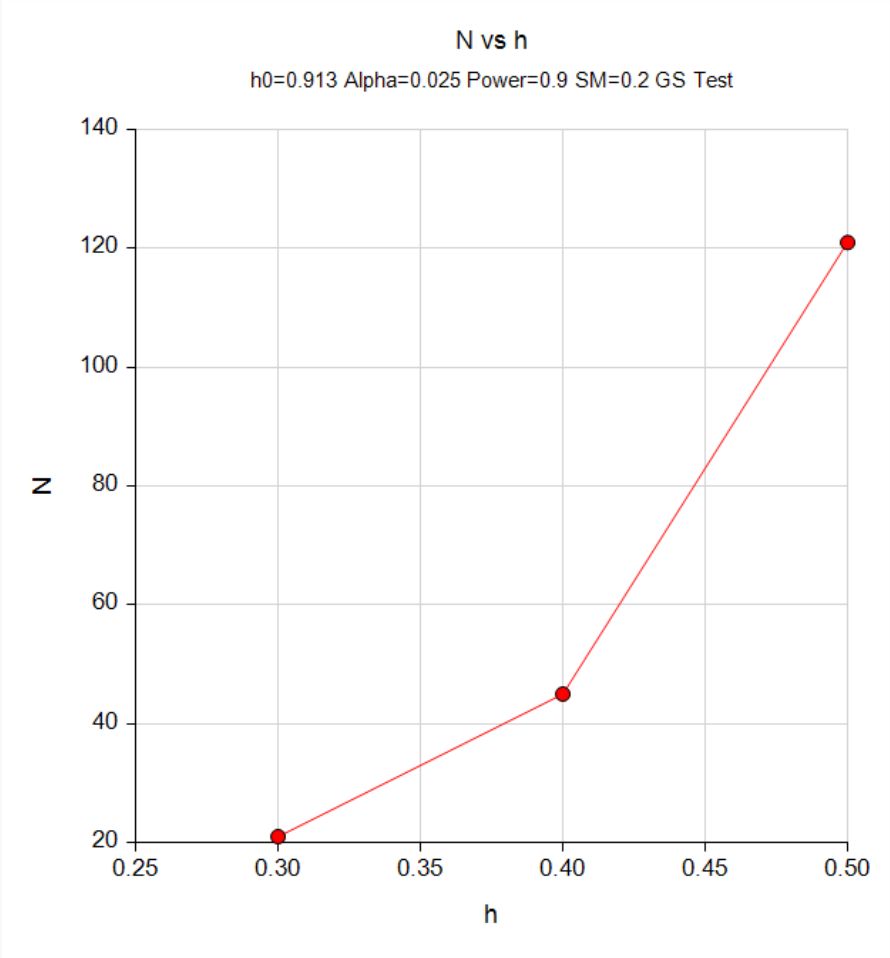
Solve For:	Sample Size
Maximum Number of Stages:	5
Skipped Futility Stage(s):	1 2
Alternative Hypothesis:	h - h0 < -|SM|
Alpha Spending Function:	O'Brien-Fleming Analog
Beta Spending Function:	Hwang-Shih-DeCani (γ = 1.5)
Number of Simulations:	1000
Random Seed:	5013913 (User-Entered)

Target Power	Sim Power	N	h	h0	SM	Target Alpha	Sim Alpha
0.9	0.921	21	0.3	0.913	0.2	0.025	0.061
0.9	0.902	45	0.4	0.913	0.2	0.025	0.043
0.9	0.906	121	0.5	0.913	0.2	0.025	0.037

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 10 to 100.

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**
N	**10 to 100 by 10**
L (Loss Hazard Rate)	**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**
h (Hazard Rate)	**0.3 0.4 0.5**
h0 (Null Hazard Rate)	**0.913**
SM (Superiority Margin)	**0.2**
Maximum Number of Stages (K)	**5**
Time Proportion at each Stage	**Equally incremented**
Boundaries Used	**Efficacy with Futility**
Hypothesis Direction	**Ha: h - h0 < -|SM| (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 (γ)**
γ	**1.5**
Skipped Futility Stages	**<Empty>**
Binding or Non-Binding Futility	**Non-Binding**

Options Tab	
Number of Simulations	**1000** (set for the sake of time, 100,000 or more are recommended)
Random Seed	**5093553** (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

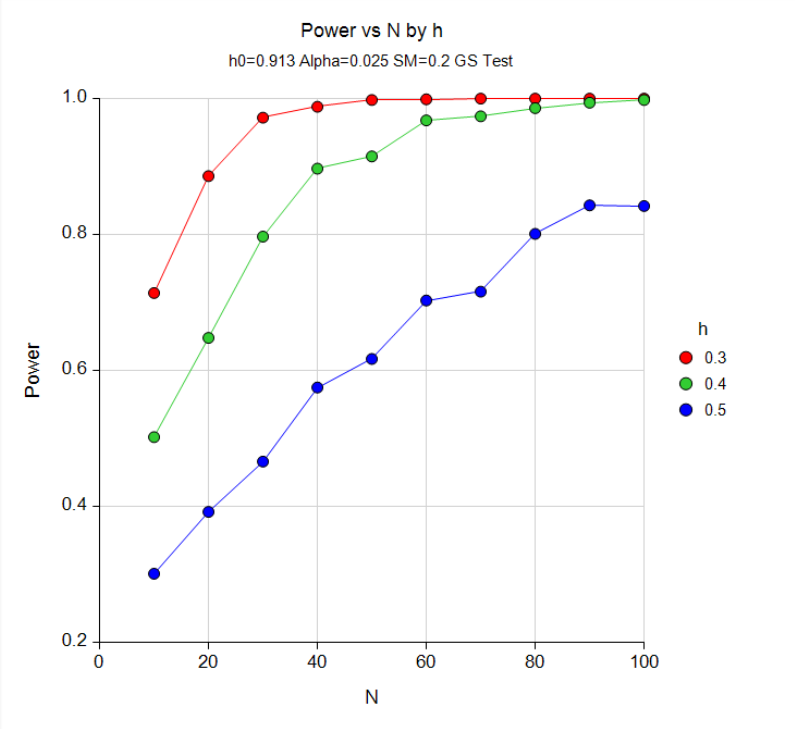
Power and Sample Size Summary

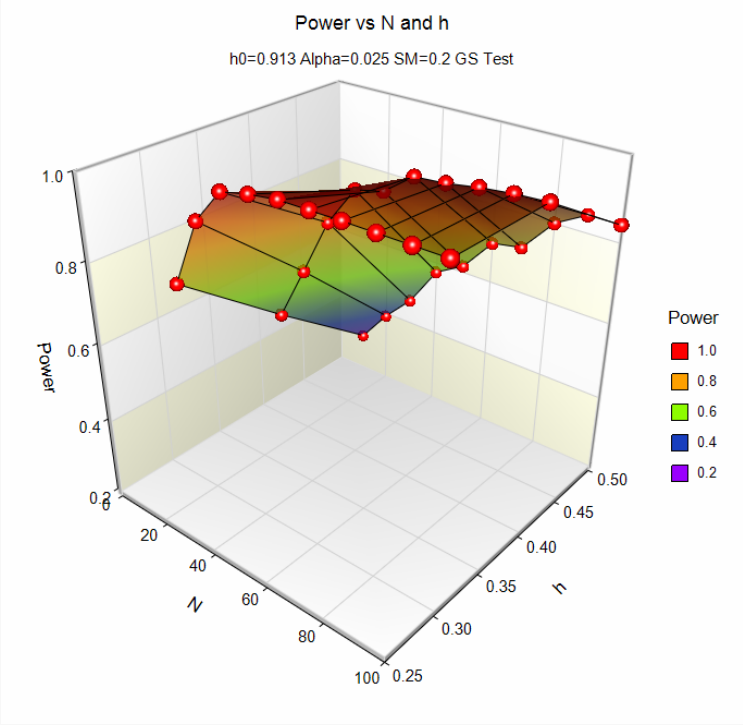
Solve For:	Power
Maximum Number of Stages:	5
Alternative Hypothesis:	h - h0 < -|SM|
Alpha Spending Function:	O'Brien-Fleming Analog
Beta Spending Function:	Hwang-Shih-DeCani (γ = 1.5)
Number of Simulations:	1000
Random Seed:	5093553 (User-Entered)

Sim Power	N	h	h0	SM	Target Alpha	Sim Alpha
0.714	10	0.3	0.913	0.2	0.025	0.074
0.886	20	0.3	0.913	0.2	0.025	0.064
0.972	30	0.3	0.913	0.2	0.025	0.051
0.988	40	0.3	0.913	0.2	0.025	0.051
0.998	50	0.3	0.913	0.2	0.025	0.037
0.999	60	0.3	0.913	0.2	0.025	0.041
1.000	70	0.3	0.913	0.2	0.025	0.047
1.000	80	0.3	0.913	0.2	0.025	0.038
1.000	90	0.3	0.913	0.2	0.025	0.043
1.000	100	0.3	0.913	0.2	0.025	0.041
0.502	10	0.4	0.913	0.2	0.025	0.089
0.648	20	0.4	0.913	0.2	0.025	0.067
0.797	30	0.4	0.913	0.2	0.025	0.061
0.897	40	0.4	0.913	0.2	0.025	0.064
0.915	50	0.4	0.913	0.2	0.025	0.048
0.968	60	0.4	0.913	0.2	0.025	0.042
0.974	70	0.4	0.913	0.2	0.025	0.039
0.986	80	0.4	0.913	0.2	0.025	0.043
0.994	90	0.4	0.913	0.2	0.025	0.042
0.998	100	0.4	0.913	0.2	0.025	0.045
0.301	10	0.5	0.913	0.2	0.025	0.089
0.392	20	0.5	0.913	0.2	0.025	0.055
0.466	30	0.5	0.913	0.2	0.025	0.065
0.575	40	0.5	0.913	0.2	0.025	0.046
0.617	50	0.5	0.913	0.2	0.025	0.032
0.703	60	0.5	0.913	0.2	0.025	0.046
0.716	70	0.5	0.913	0.2	0.025	0.050
0.801	80	0.5	0.913	0.2	0.025	0.041
0.843	90	0.5	0.913	0.2	0.025	0.035
0.842	100	0.5	0.913	0.2	0.025	0.040

Plots Section for Power and Sample Size Summary

Plots





The power curve plot shows the effect of sample size and hazard rate 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**
N	**10 to 100 by 10**
L (Loss Hazard Rate)	**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**
h (Hazard Rate)	**0.3 0.4 0.5**
h0 (Null Hazard Rate)	**0.913**
SM (Superiority Margin)	**0.2**
Maximum Number of Stages (K)	**5**
Time Proportion at each Stage	**Equally incremented**
Boundaries Used	**Efficacy with Futility**
Hypothesis Direction	**Ha: h - h0 < -|SM| (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 (γ)**
γ	**1.5**
Skipped Futility Stages	**<Empty>**
Binding or Non-Binding Futility	**Binding**

Options Tab	
Number of Simulations	**1000** (set for the sake of time, 100,000 or more are recommended)
Random Seed	**5122421** (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

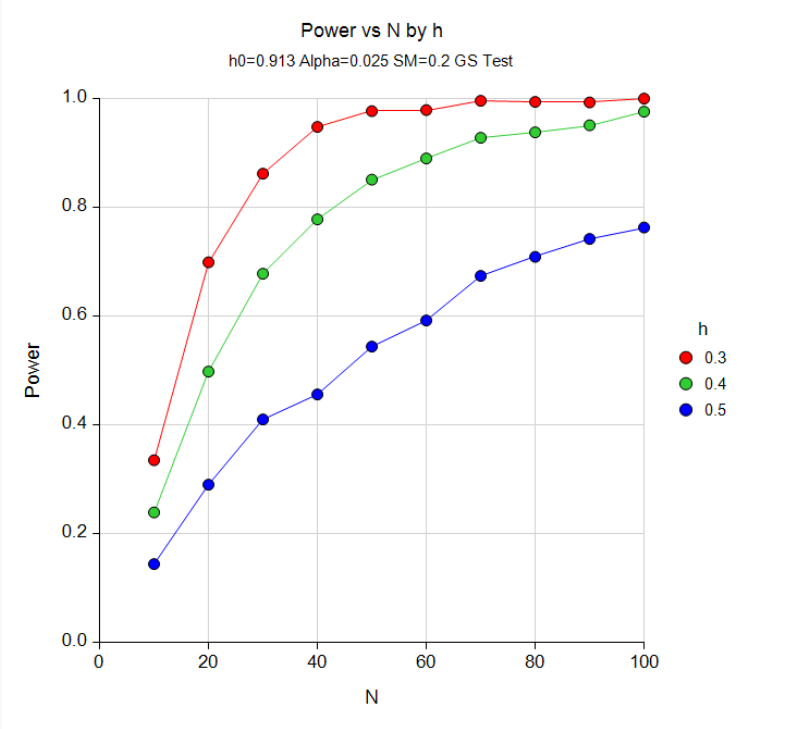
Power and Sample Size Summary

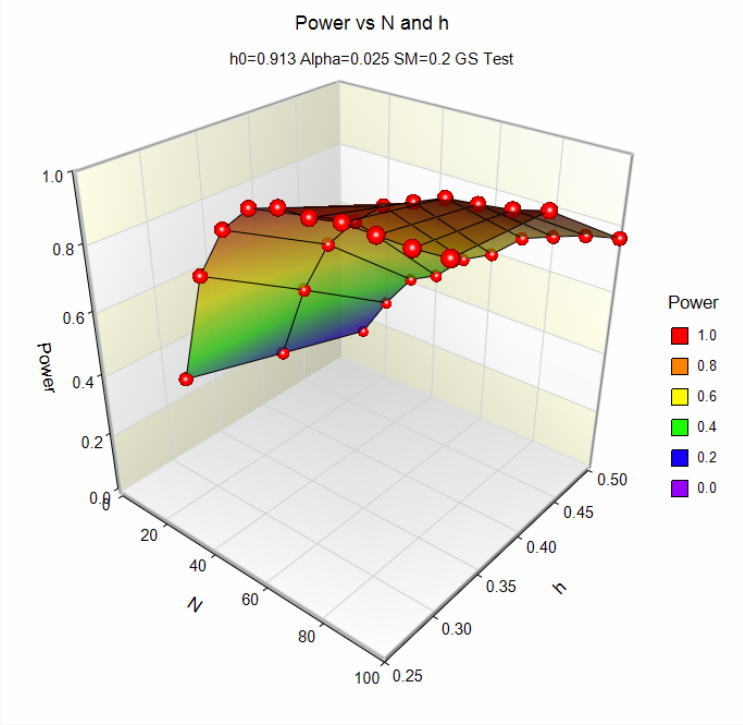
Solve For:	Power
Maximum Number of Stages:	5
Alternative Hypothesis:	h - h0 < -|SM|
Alpha Spending Function:	O'Brien-Fleming Analog
Beta Spending Function:	Hwang-Shih-DeCani (γ = 1.5)
Number of Simulations:	1000
Random Seed:	5122421 (User-Entered)

Sim Power	N	h	h0	SM	Target Alpha	Sim Alpha
0.335	10	0.3	0.913	0.2	0.025	0.028
0.699	20	0.3	0.913	0.2	0.025	0.043
0.862	30	0.3	0.913	0.2	0.025	0.052
0.948	40	0.3	0.913	0.2	0.025	0.039
0.977	50	0.3	0.913	0.2	0.025	0.052
0.979	60	0.3	0.913	0.2	0.025	0.036
0.996	70	0.3	0.913	0.2	0.025	0.035
0.994	80	0.3	0.913	0.2	0.025	0.032
0.993	90	0.3	0.913	0.2	0.025	0.038
1.000	100	0.3	0.913	0.2	0.025	0.030
0.239	10	0.4	0.913	0.2	0.025	0.023
0.498	20	0.4	0.913	0.2	0.025	0.049
0.678	30	0.4	0.913	0.2	0.025	0.042
0.778	40	0.4	0.913	0.2	0.025	0.037
0.851	50	0.4	0.913	0.2	0.025	0.042
0.890	60	0.4	0.913	0.2	0.025	0.040
0.928	70	0.4	0.913	0.2	0.025	0.037
0.938	80	0.4	0.913	0.2	0.025	0.033
0.951	90	0.4	0.913	0.2	0.025	0.048
0.976	100	0.4	0.913	0.2	0.025	0.043
0.144	10	0.5	0.913	0.2	0.025	0.038
0.290	20	0.5	0.913	0.2	0.025	0.047
0.410	30	0.5	0.913	0.2	0.025	0.048
0.456	40	0.5	0.913	0.2	0.025	0.041
0.544	50	0.5	0.913	0.2	0.025	0.033
0.592	60	0.5	0.913	0.2	0.025	0.048
0.674	70	0.5	0.913	0.2	0.025	0.035
0.709	80	0.5	0.913	0.2	0.025	0.037
0.742	90	0.5	0.913	0.2	0.025	0.033
0.763	100	0.5	0.913	0.2	0.025	0.031

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 of 0.4 and a sample size of 30 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**
N	**30**
L (Loss Hazard Rate)	**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**
h (Hazard Rate)	**0.4**
h0 (Null Hazard Rate)	**0.913**
SM (Superiority Margin)	**0.2**
Maximum Number of Stages (K)	**2** (Also run with **3**, **4**, **5**, **10**, and **20**)
Time Proportion at each Stage	**Equally incremented**
Boundaries Used	**Efficacy with Futility**
Hypothesis Direction	**Ha: h - h0 < -|SM| (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 (γ)**
γ	**1.5**
Skipped Futility Stages	**<Empty>**
Binding or Non-Binding Futility	**Non-Binding**

Options Tab	
Number of Simulations	**100000**
Random Seed	**5306956** (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.

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 - h0 < -|SM|
Alpha Spending Function:	O'Brien-Fleming Analog
Beta Spending Function:	Hwang-Shih-DeCani (γ = 1.5)
Number of Simulations:	100000
Random Seed:	5306956 (User-Entered)

Sim Power	N	h	h0	SM	Target Alpha	Sim Alpha	Number of Stages
0.79126	30	0.4	0.913	0.2	0.025	0.04591	2
0.79245	30	0.4	0.913	0.2	0.025	0.049	3
0.79392	30	0.4	0.913	0.2	0.025	0.05092	4
0.79552	30	0.4	0.913	0.2	0.025	0.05577	5
0.79948	30	0.4	0.913	0.2	0.025	0.0625	10
0.80479	30	0.4	0.913	0.2	0.025	0.07093	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 sample size of 13,000, hazard rates of 0.3 (h) and 0.9 (h0), a superiority margin of 0.2, no futility boundaries, and 7,000 simulations. The alpha-spending will be compared to the results of the simulated boundary crossings.

Note: As the sample size is quite large, this validation simulation will take several minutes to run.

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	**0.025**
N	**13000**
L (Loss Hazard Rate)	**0**
T0 (Accrual or Recruitment Time)	**5**
Accrual Parameter Entry	**Calculate Accrual Parameter**
Percent of T0 Until 50% are Accrued	**50**
T (Total Time)	**5**
h (Hazard Rate)	**0.3**
h0 (Null Hazard Rate)	**0.9**
SM (Superiority Margin)	**0.2**
Maximum Number of Stages (K)	**5**
Time Proportion at each Stage	**Equally incremented**
Boundaries Used	**Efficacy Only**
Hypothesis Direction	**Ha: h - h0 < -|SM| (Lower hazard rates are better)**
Boundary Specification	**Spending Function Calculation**
Alpha Spending Function	**O'Brien-Fleming Analog**
Skipped Efficacy Stages	**<Empty>**

Options Tab	
Number of Simulations	**3000** (set for the sake of time, 100,000 or more are recommended)
Random Seed	**5592305** (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	h - h0 < -|SM|
Superiority Margin (SM)	0.2
Alpha Spending Function	O'Brien-Fleming Analog
Target Alpha	0.025
Alpha (from simulations)	0.024
Hazard Rate (h)	0.3
Null Hazard Rate (h0)	0.9
Loss Hazard Rate	0
T0 (Accrual Time)	5
% of T0 Until 50% Accrual	50
Accrual Parameter	0
Total Time	5
N (if final stage reached)	13000
Power (from simulations)	1
Maximum Information	12522.47379

Z-Value Boundaries

Z-Value Boundaries

Maximum Information: 12522.47379
Alternative Hypothesis: h - h0 < -|SM|

Stage	Efficacy Boundary	Time Proportion	Time	Information Proportion
1		0.2	1	0.08731
2	-4.11740	0.4	2	0.27493
3	-2.95285	0.6	3	0.50332
4	-2.36310	0.8	4	0.74829
5	-2.01369	1.0	5	1.00000

Information Report

Information Report

Maximum Information: 12522.47379
Alternative Hypothesis: h - h0 < -|SM|
Alpha: 0.025

Stage	Target Time Proportion	Target Time	Target Information Proportion	Target Information	Target Sample Size N	h0
1	0.2	1	0.08731	1093.38973	2600	0.9
2	0.4	2	0.27493	3442.76695	5200	0.9
3	0.6	3	0.50332	6302.79058	7800	0.9
4	0.8	4	0.74829	9370.42754	10400	0.9
5	1.0	5	1.00000	12522.47379	13000	0.9

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 *	0.08731	0.00000	0.00000	0.000000	0.0	0.0
2 *	0.27493	0.00002	0.00002	0.000019	0.1	0.1
3 *	0.50332	0.00156	0.00158	0.001574	6.2	6.3
4 *	0.74829	0.00799	0.00957	0.009061	31.9	38.3
5 *	1.00000	0.01543	0.02500	0.022021	61.7	100.0

* projected

The Alpha Spent this Stage is compared to the results of the simulations, found in the section Boundary Probabilities for δ = -|SM| (Alpha).

Boundary Probabilities for δ = -|SM| (Alpha)

Boundary Probabilities for δ = -|SM| (Alpha)

Number of Simulations:	3000
Random Seed:	5592305 (User-Entered)
After Efficacy Boundary Crossing:	Hold Out
Alternative Hypothesis:	h - h0 < -|SM|
Superiority Margin (SM):	0.2
Z Statistic:	MLE
h:	0.9 - |SM| = 0.9 - 0.2 = 0.7
h0:	0.9
δ:	-|SM| = -0.2

Stage	N	Efficacy Boundary	Boundary Probability
1	*2600		0.00000
2	*5200	-4.11740	0.00033
3	*7800	-2.95285	0.00200
4	*10400	-2.36310	0.00500
5	*13000	-2.01369	0.01667

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

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