Chapter 768

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

In this procedure, boundaries are calculated analytically, while simulation is used for the calculation of power (and sample size). A variety of futility boundary options are available.

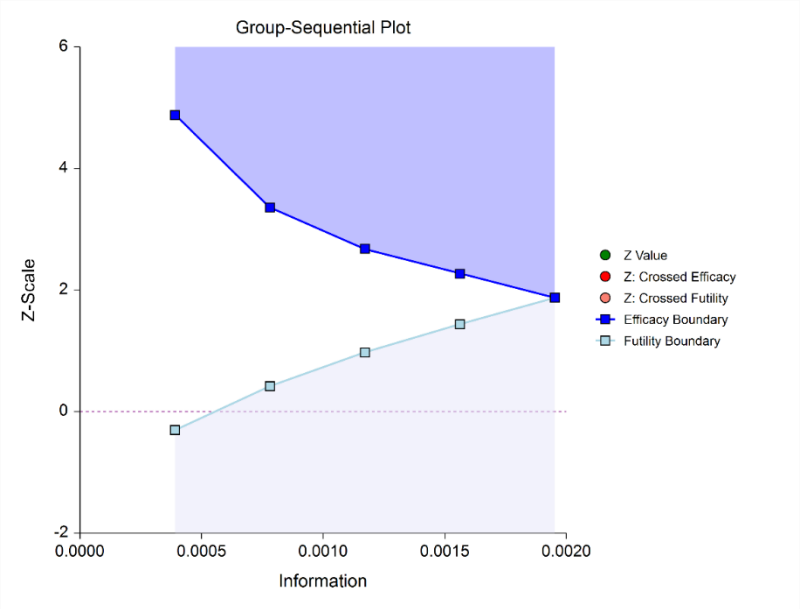
The corresponding analysis and sample size re-estimation procedure, found in NCSS Analysis and Graphics software, is Group-Sequential Non-Inferiority Analysis for Two Poisson Rates.

Introduction

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

This procedure is used as the planning tool for determining sample size and initial boundaries. Stage data, as it is obtained, can be evaluated using the companion procedure *Group-Sequential Non-Inferiority Analysis for Two Poisson 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:

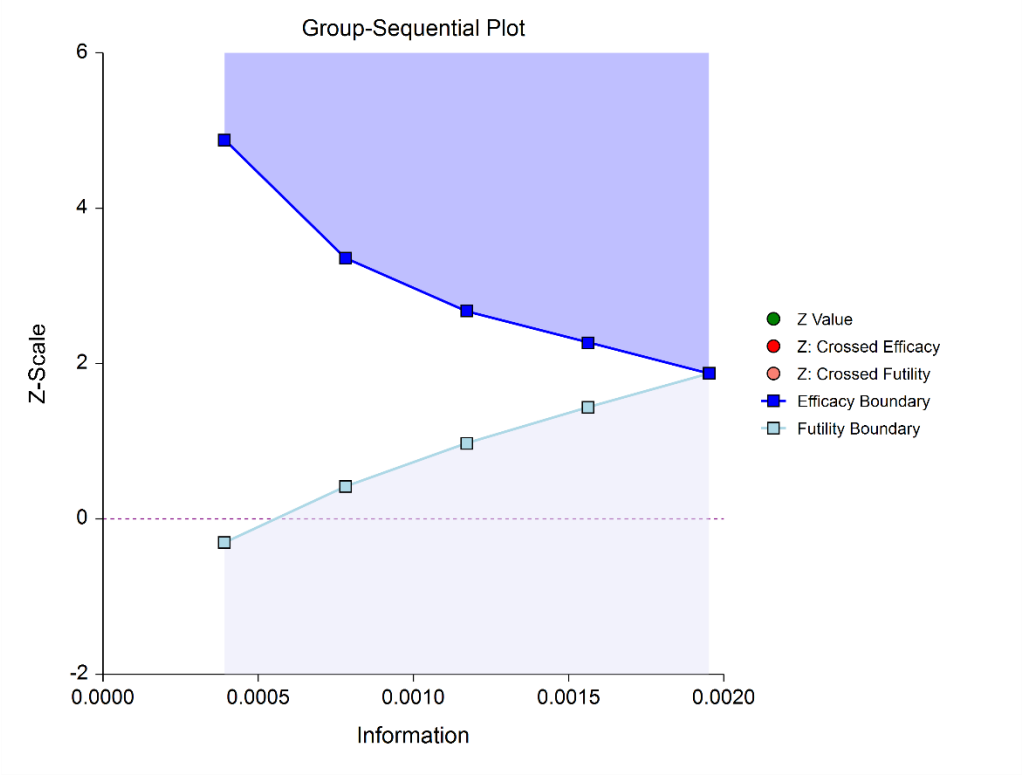
- Alpha
- Power
- Test Direction
- Types of boundaries (efficacy, binding futility, non-binding futility)
- Maximum number of stages
- Proportion of maximum information at each stage
- Spending functions
- Assumed Poisson rates
- Non-inferiority margin

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

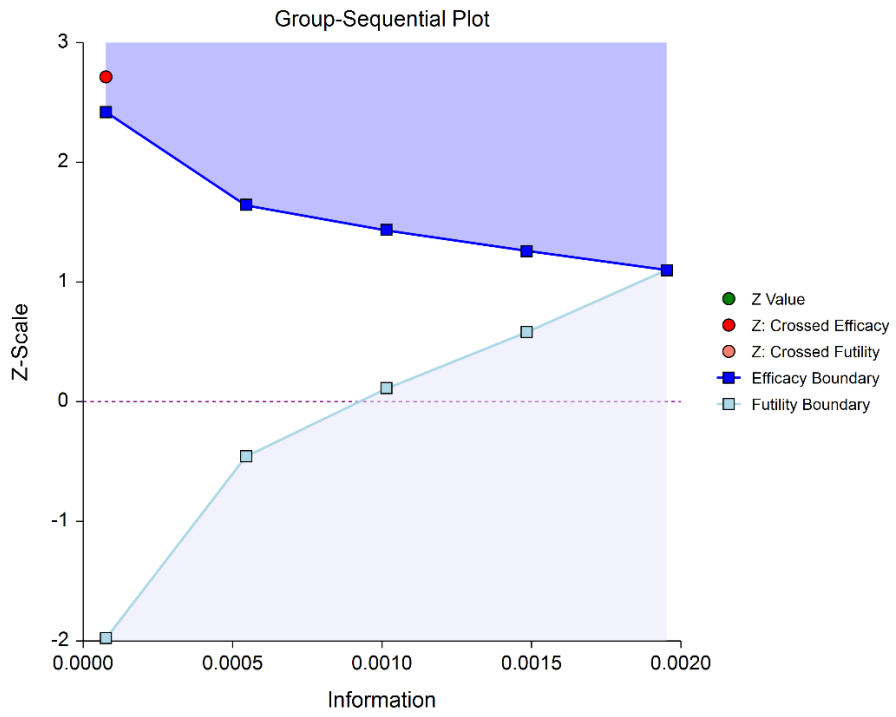
First Interim Stage

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

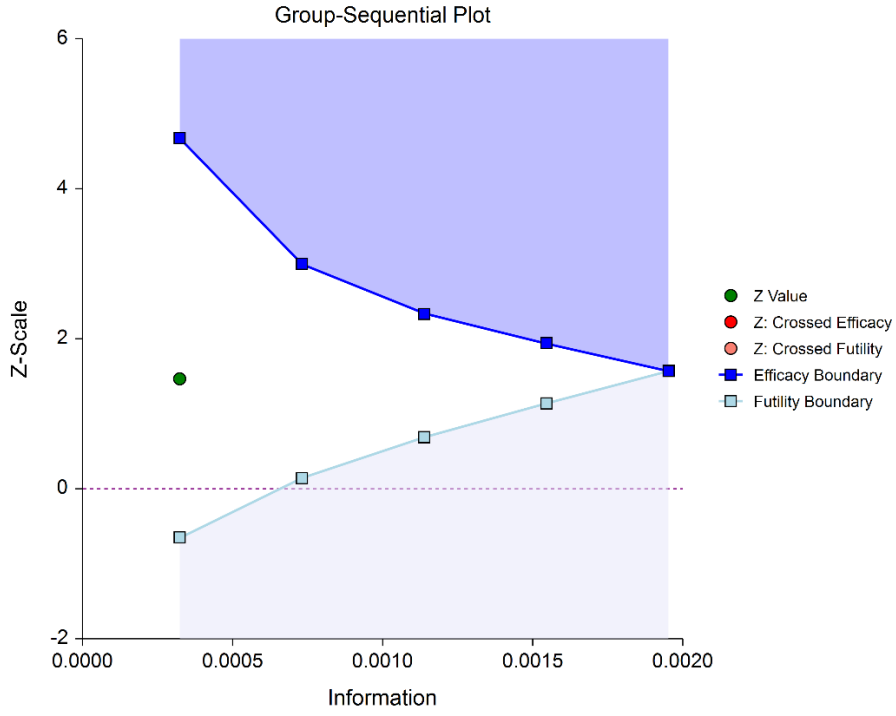
Unless the number of subjects at the first stage matches the design target for the first stage, the calculated information at the first stage will not exactly match the design information for the first stage. Generally, the calculated information will not differ too greatly from the design information,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

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

A *z*-statistic is calculated from the raw Poisson 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)

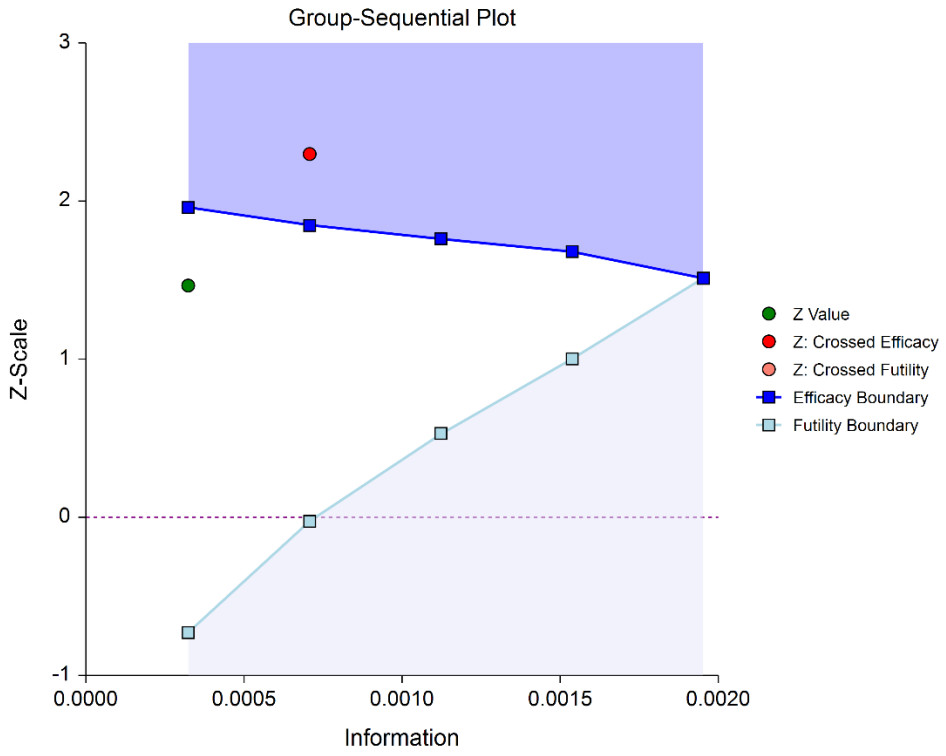
Since the first stage information proportion is not equal to the design information proportion, a designation must be made at this point as to the target information of the second stage. Two options are available in the **NCSS** procedure.

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

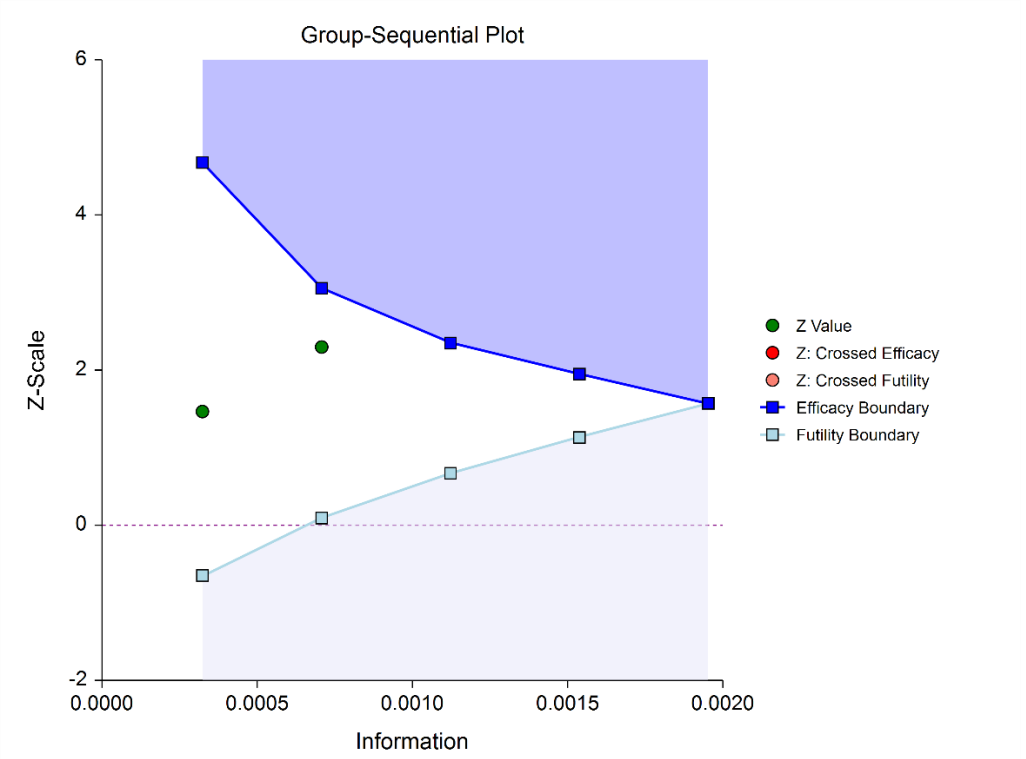
A second option is to adjust the target information proportionally to the remaining proportions. For this option, if the design proportions are 0.25, 0.50, 0.75, 1.0, and 0.22 is observed, the remaining 0.78 is distributed proportionally to the remaining stages. In this example, the remaining target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

For either option, once the target information is determined for the next stage, revised target sample sizes are given (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 Poisson 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.

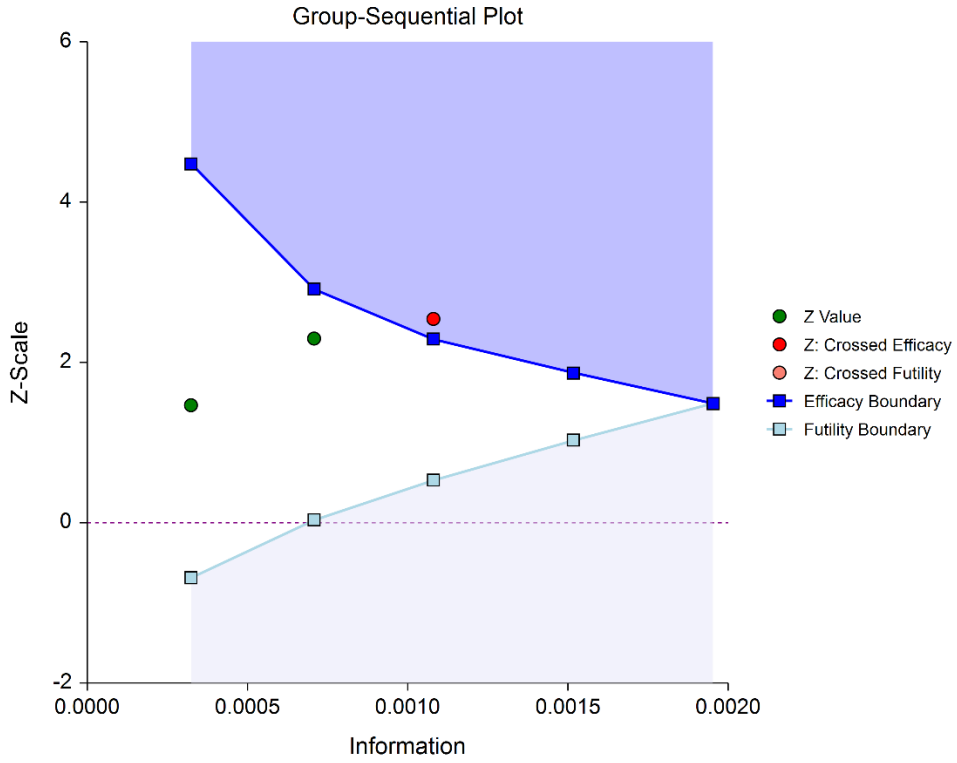
Reporting Phase

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 Poisson 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 Poisson rate difference

Due to the bias that is introduced in the group-sequential analysis process, the raw data confidence interval of the difference in Poisson rates should not be used. An adjusted confidence interval should be used instead.

Sample size used

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

Technical Details

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

Null and Alternative Hypotheses

For non-inferiority tests of two Poisson rates, the appropriate null and alternative hypotheses depend on whether higher Poisson rates are better or higher Poisson rates are worse.

Case 1: Low Poisson rates Good

In this case, lower Poisson rates are better. The hypotheses are arranged so that rejecting the null hypothesis implies that the treatment Poisson rate is no more than a small amount above the reference Poisson rate. The value of δ at which power is calculated is often set to zero. The null and alternative hypotheses, with non-inferiority margin M_{NI}, are

$H_0: \lambda_1 \geq \lambda_2 + |M_{NI}|$ versus $H_1: \lambda_1 < \lambda_2 + |M_{NI}|$

$H_0: \lambda_1 - \lambda_2 \geq |M_{NI}|$ versus $H_1: \lambda_1 - \lambda_2 < |M_{NI}|$

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

Case 2: High Poisson rates Good

In this case, higher Poisson rates are better. The hypotheses are arranged so that rejecting the null hypothesis implies that the treatment Poisson rate (1) is no less than a small amount below the reference Poisson rate (2). The value of δ at which power is calculated is often set to zero. The null and alternative hypotheses, with non-inferiority margin M_{NI}, are

$H_0: \lambda_1 \leq \lambda_2 - |M_{NI}|$ versus $H_1: \lambda_1 > \lambda_2 - |M_{NI}|$

$H_0: \lambda_1 - \lambda_2 \leq -|M_{NI}|$ versus $H_1: \lambda_1 - \lambda_2 > -|M_{NI}|$

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

Stages in Group-Sequential Testing

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

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

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

Test Statistic

The *z*-statistic for any stage *k* is obtained from all the accumulated data up to and including that stage, using, when lower Poisson rates are better:

$$z_k = \frac{\hat{\lambda}_{1k} - \hat{\lambda}_{2k} - |NIM|}{\hat{\sigma}_{D_k}}$$

and, when higher Poisson rates are better:

$$z_k = \frac{\hat{\lambda}_{1k} - \hat{\lambda}_{2k} - (-|NIM|)}{\hat{\sigma}_{D_k}} = \frac{\hat{\lambda}_{1k} - \hat{\lambda}_{2k} + |NIM|}{\hat{\sigma}_{D_k}}$$

with

$$\hat{\sigma}_{D_k} = \sqrt{\frac{\hat{\lambda}_{1k}}{n_{1k}} + \frac{\hat{\lambda}_{2k}}{n_{2k}}}$$

where $\hat{\lambda}_{1k}$ and $\hat{\lambda}_{2k}$ are the averages of the subject or experimental unit counts for each group at stage k.

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

$$I_k = \frac{1}{\sigma_{D_k}^2}$$

where

$$\sigma_{D_k} = \sqrt{\frac{\lambda_{1k}}{n_{1k}} + \frac{\lambda_{2k}}{n_{2k}}}$$

The planning λ_1 and λ_2 are used for λ_{1k} and λ_{2k}, since realized values are not available before data is collected. When the analysis is carried out, the sample estimates $\hat{\lambda}_{1k}$ and $\hat{\lambda}_{2k}$ will be used in place of λ_{1k} and λ_{2k}. The final stage (*K*) or total (design) information is calculated from the specified Poisson rates and the final sample sizes, as

$$I_K^* = \frac{1}{\sigma_{D_K}^2}$$

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

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

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 $prop_K = 1$. However, if the final stage is reached, we see that

$$I_K = \frac{1}{\sigma_{D_{K_{achieved}}}^2} \neq I_K^* = \frac{1}{\sigma_{D_K}^2}$$

so that

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

$\sigma_{D_{K_{achieved}}}^2$ is based on $n_{1K_{achieved}}$ and $n_{2K_{achieved}}$.

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

$$I_K^* = I_K$$

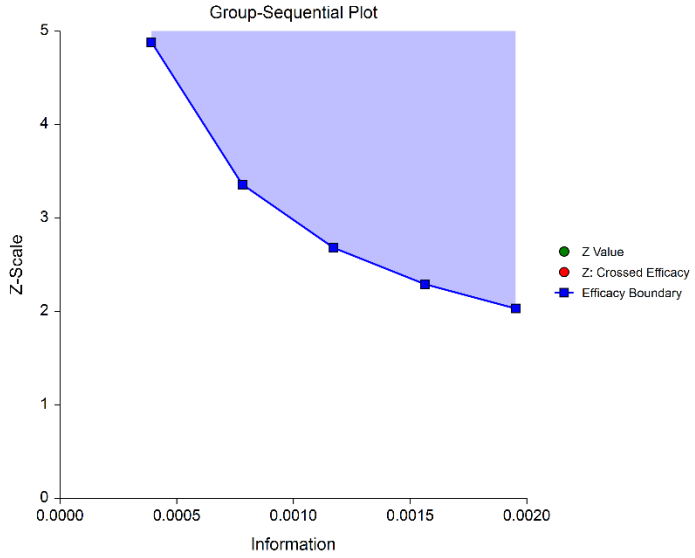
See the discussion in Wassmer and Brannath (2016), pages 78-79, or Jennison and Turnbull (2000), pages 153-154, 162.

Types of Boundaries

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

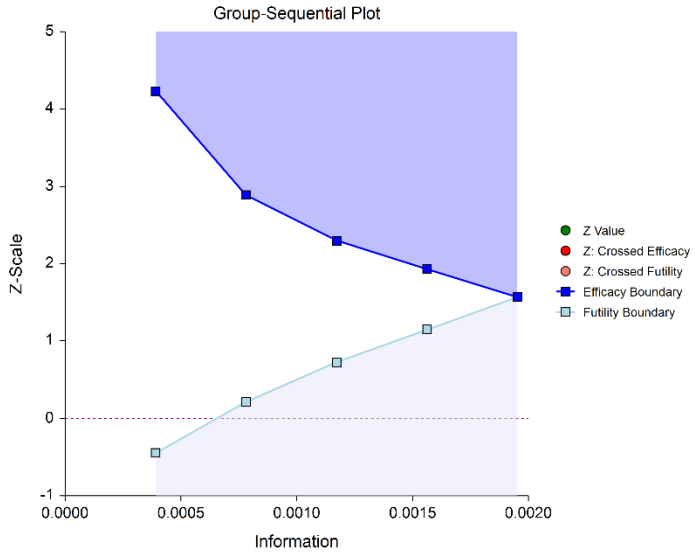
Efficacy Only

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



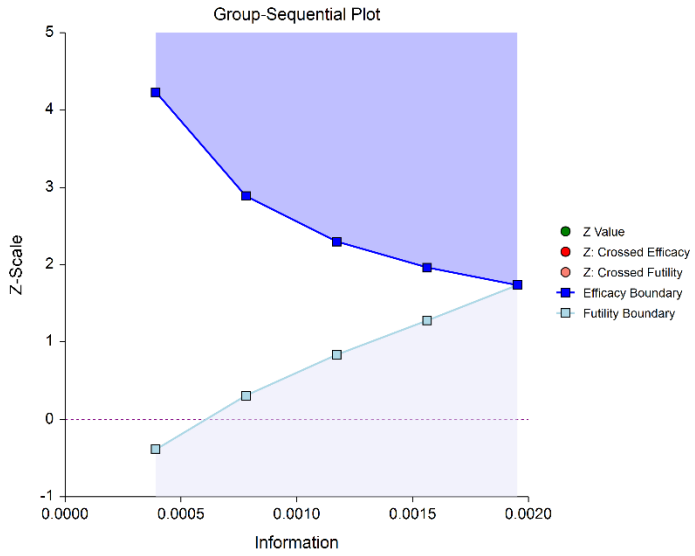
Efficacy and Binding Futility

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.



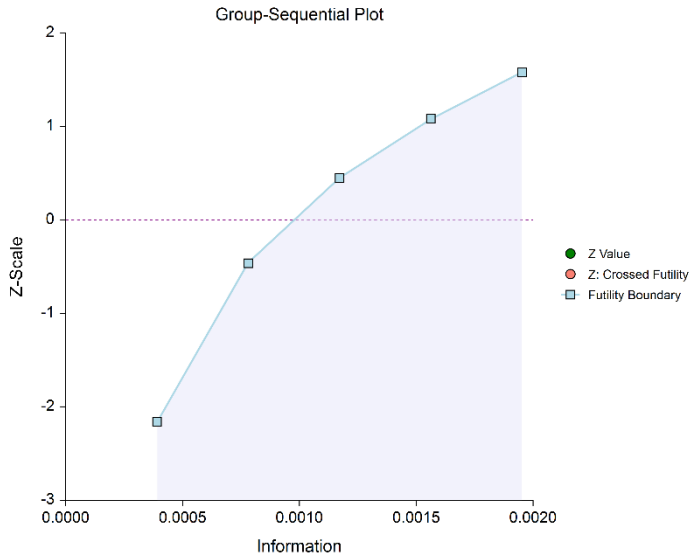
Efficacy and Non-Binding Futility

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.

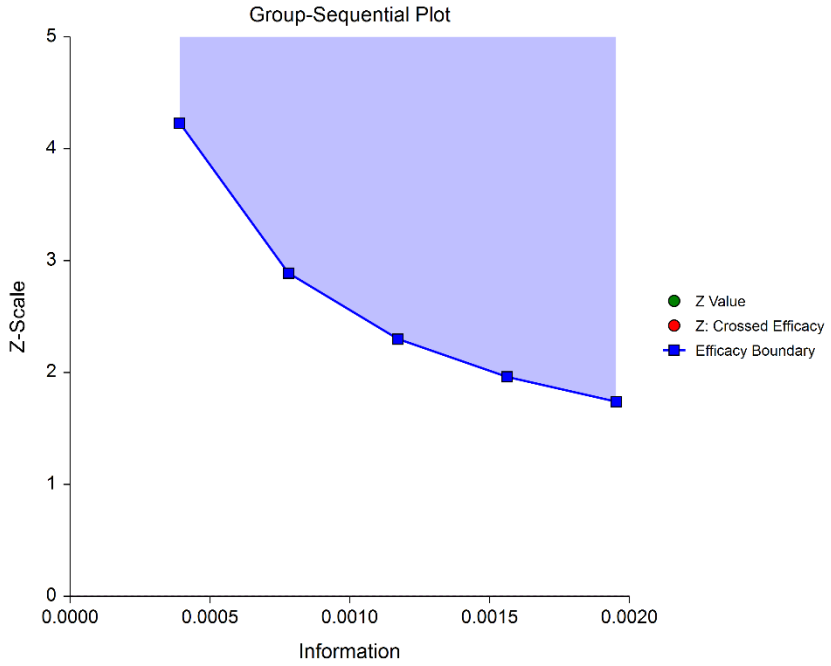
O'Brien-Fleming Analog

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.

$$\alpha(0) = 0$$

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

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



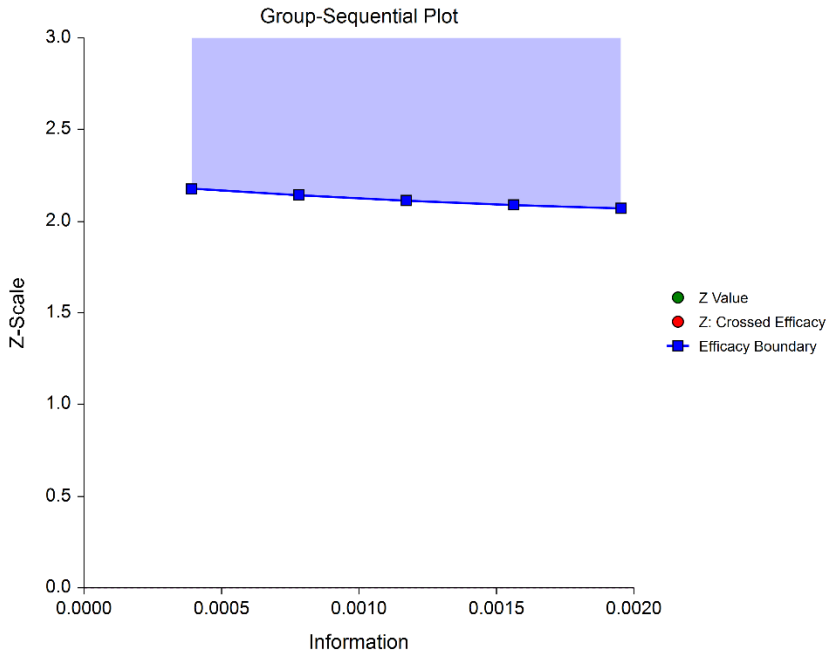
Pocock Analog

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.

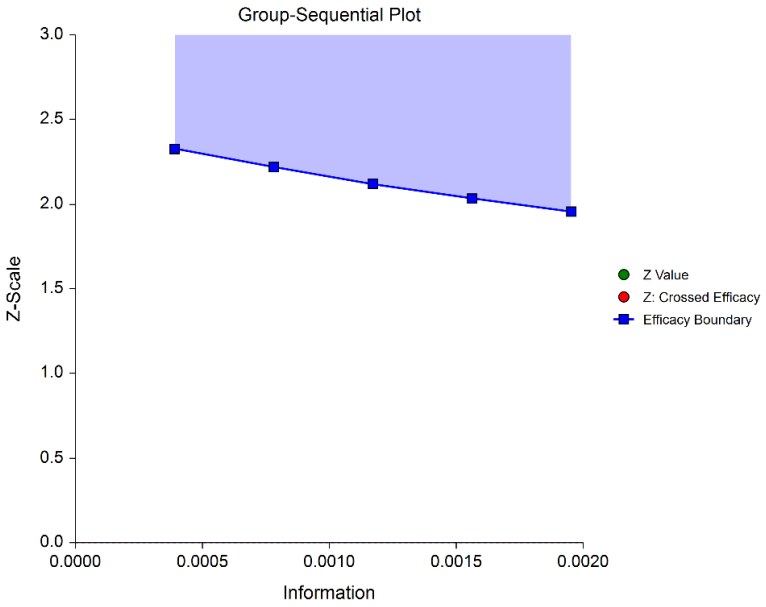
$$\alpha(0) = 0$$

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

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

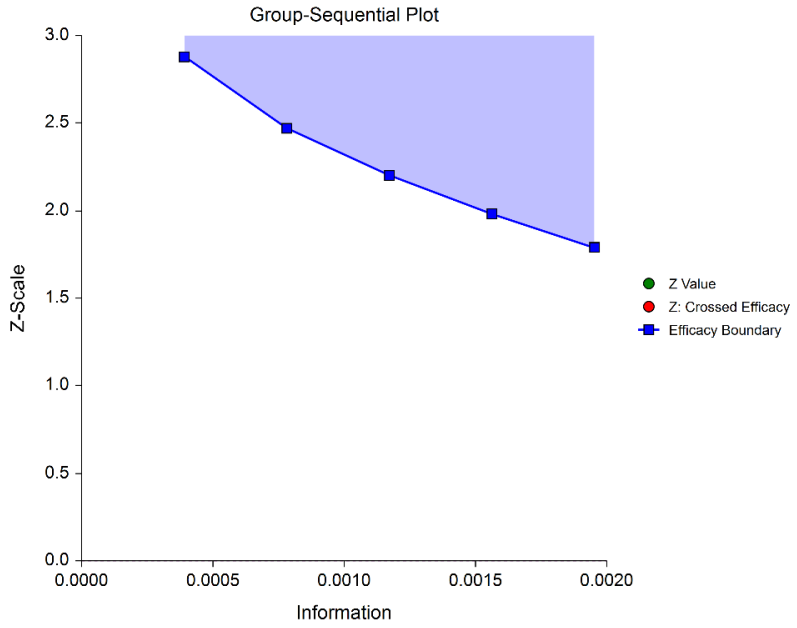
A power family spending function with a ρ of 1 is similar to a Pocock design, while a power family spending function with a ρ of 3 is more similar to an O'Brien-Fleming design.

$\rho = 1$

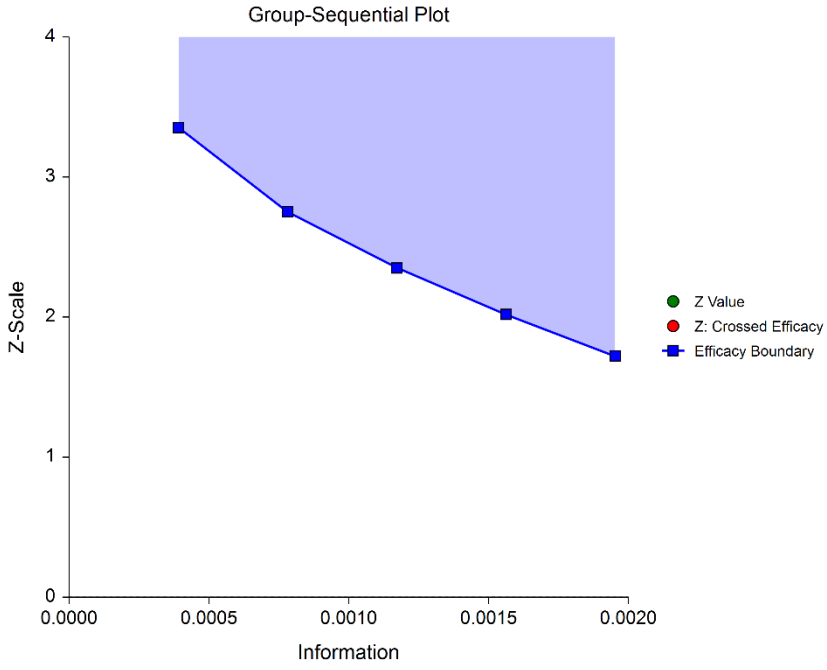


Group-Sequential Non-Inferiority Tests for Two Poisson Rates (Simulation)

$\rho = 2$



$\rho = 3$



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.

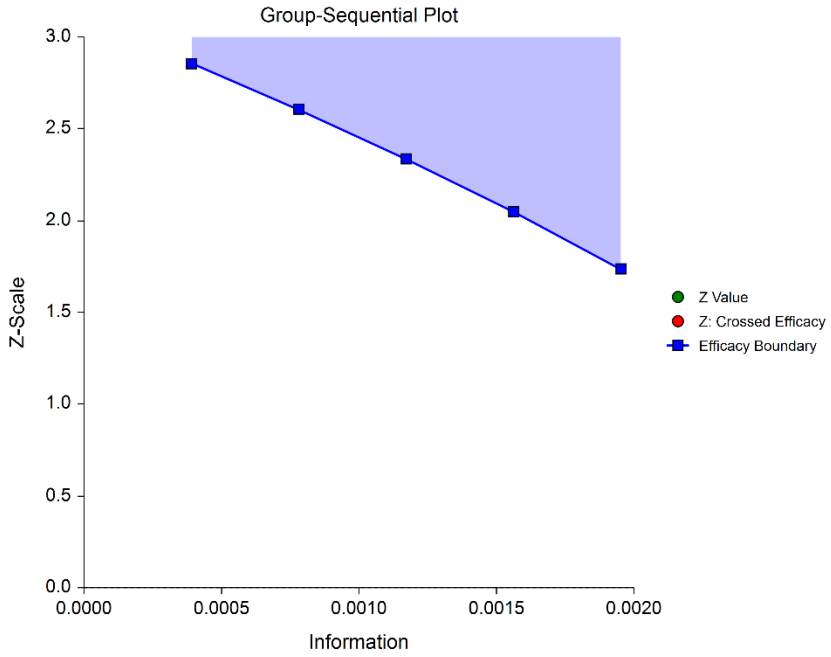
$$\alpha(0) = 0$$

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

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

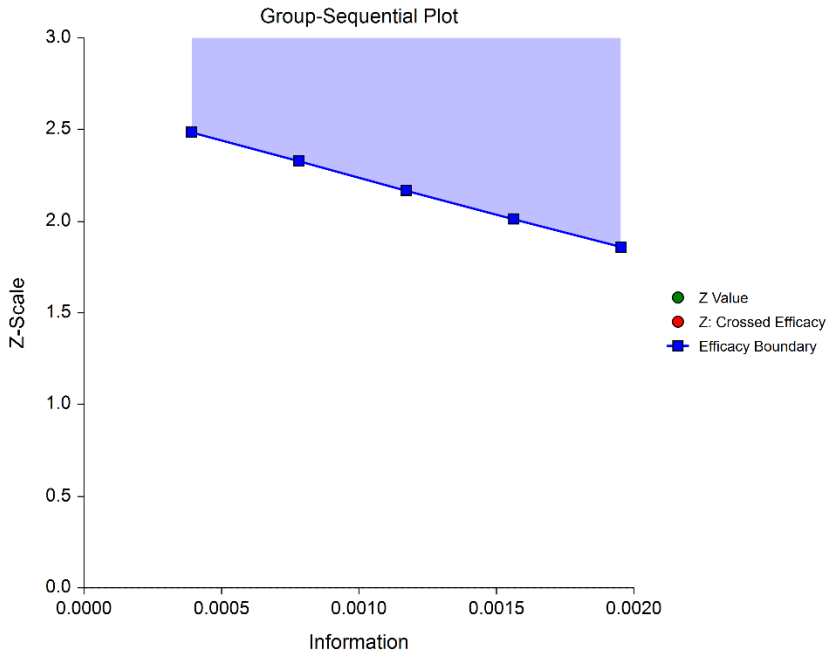
$$\alpha(1) = \alpha$$

$\gamma = -3$

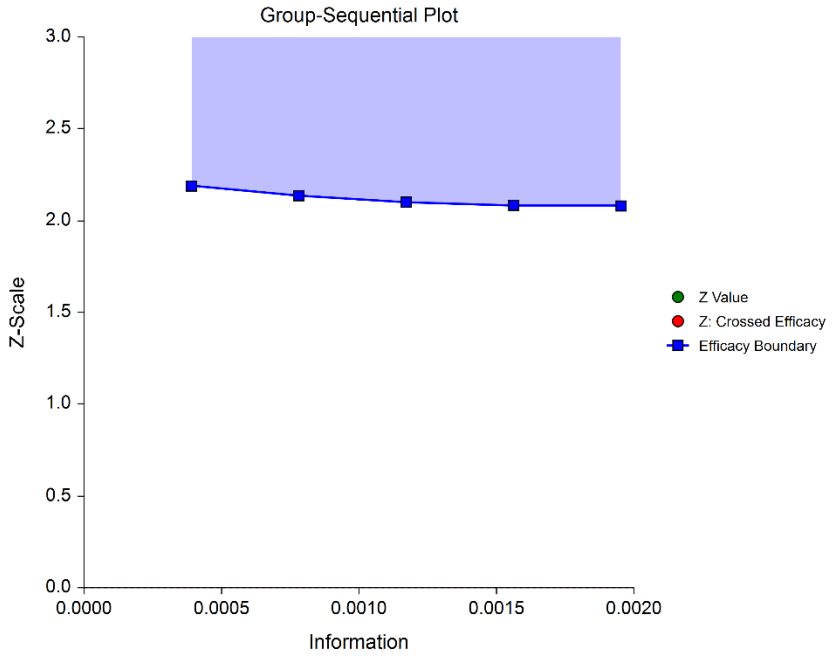


Group-Sequential Non-Inferiority Tests for Two Poisson Rates (Simulation)

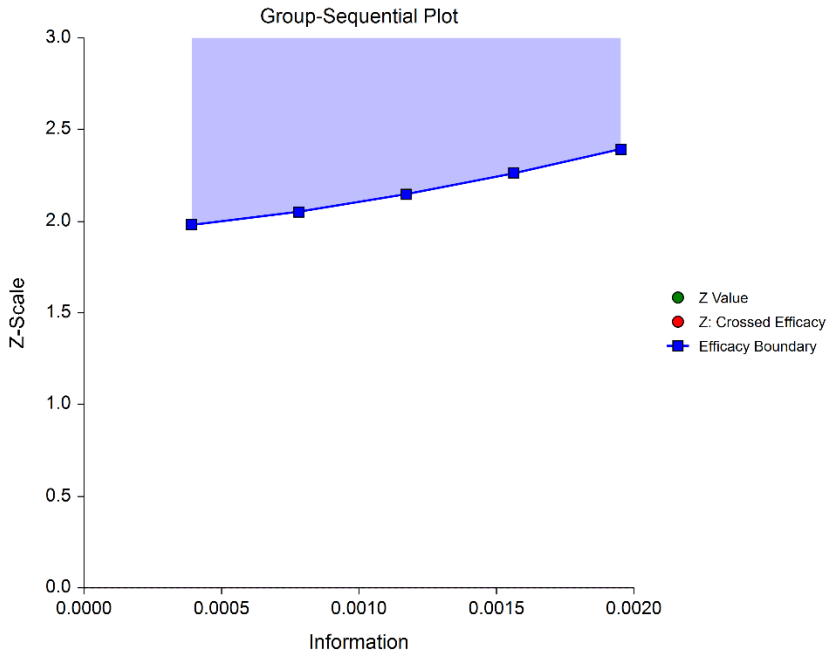
$\gamma = -1$



$\gamma = 1$



$\gamma = 3$



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 Poisson rates. The following steps are used to estimate these probabilities using simulation:

1. Determine the target (cumulative) sample sizes 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 Poisson distributions with user-specified Poisson 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 Poisson 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

An epidemiological study is to be conducted to determine whether a new antiviral medicine results in an average number of transmissions (infections) that is no higher than the current medication. The desired margin of non-inferiority is 0.3. The response for each patient is the number of viral transmissions. A one-sided MLE Z-Test for the difference in Poisson rates, with alpha equal to 0.025, is used.

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

$$H_0: \lambda_1 - \lambda_2 = 0.3 \quad (H_0: \lambda_{New} = \lambda_{Std} + 0.3)$$

versus

$$H_a: \lambda_1 - \lambda_2 < 0.3 \quad (H_a: \lambda_{New} < \lambda_{Std} + 0.3)$$

The design calls for five equally spaced stages if the final stage is reached. A power of 0.90 is needed. The assumed Poisson rate for the standard approach is 2.97. Researchers wish to examine the sample sizes needed for new approach Poisson rates of 2.4, 2.6, and 2.8. 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)**
λ1	**2.4 2.6 2.8**
λ2	**2.97**
NIM (Non-Inferiority Margin)	**0.3**
Maximum Number of Stages (K)	**5**
Info. Proportion at each Stage	**Equally incremented**
Boundaries Used	**Efficacy with Futility**
Hypothesis Direction	**Ha: λ1 - λ2 < |NIM| (Lower Poisson 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..... **10000**
Random Seed..... **6382224** (for Reproducibility)
After Boundary Crossing..... **Hold out**

Boundary Reports Tab

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

Boundary Plots Tab

Z-Statistic vs Information ..... **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	λ1 - λ2 < |NIM|
Non-Inferiority Margin (NIM)	0.3
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)	0.026
λ1	2.4
λ2	2.97
N1 (if final stage reached)	76
N2 (if final stage reached)	76
Target Power	0.9
Power (from simulations)	0.903
Maximum Information	14.1527

Z-Value Boundaries

This section gives the planning stage Z-statistic boundaries, numerically. These values are reflected in the group-sequential boundary plot.

Z-Value Boundaries

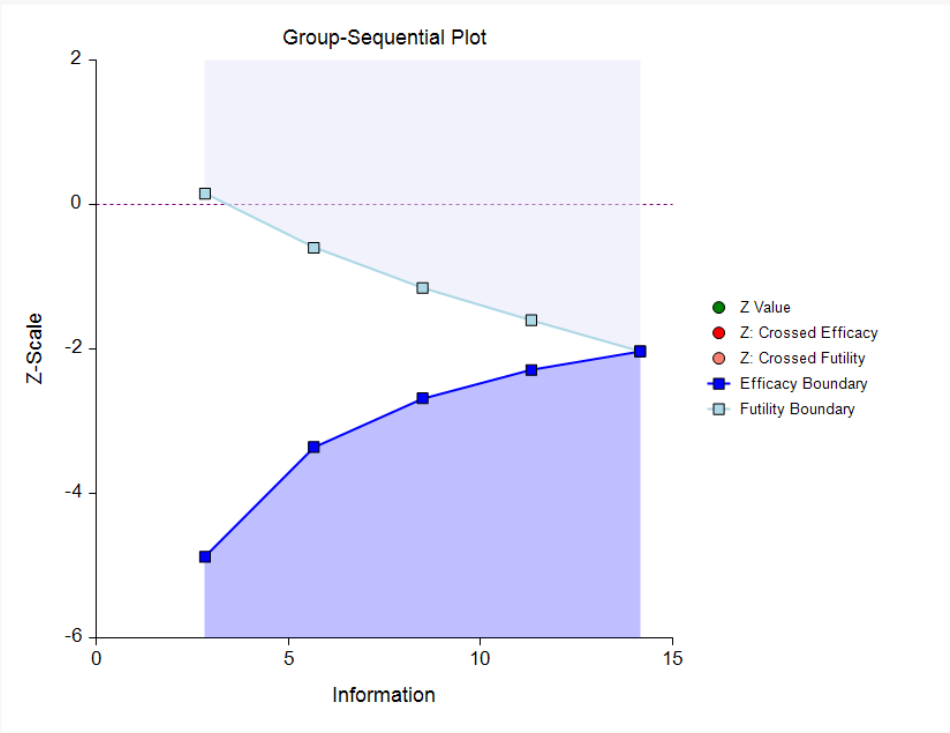
Maximum Information: 14.1527
Alternative Hypothesis: λ1 - λ2 < |NIM|
Futility Boundaries: Non-Binding

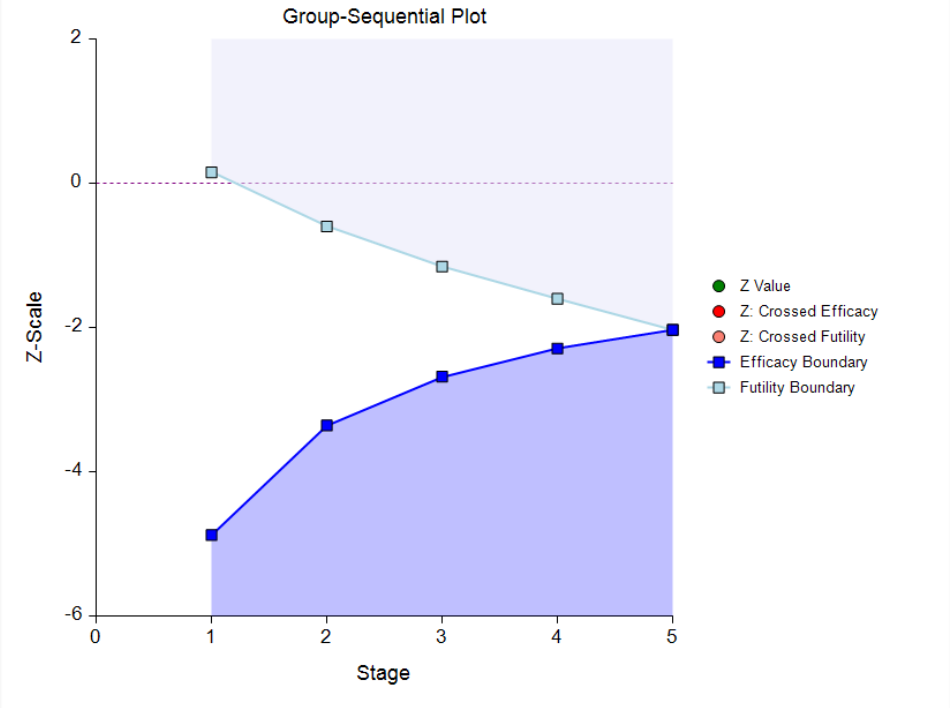
	Boundaries		
Stage	Efficacy	Futility	Information Proportion
1	-4.87688	0.15338	0.2
2	-3.35695	-0.59824	0.4
3	-2.68026	-1.15421	0.6
4	-2.28979	-1.60111	0.8
5	-2.03100	-2.03100	1.0

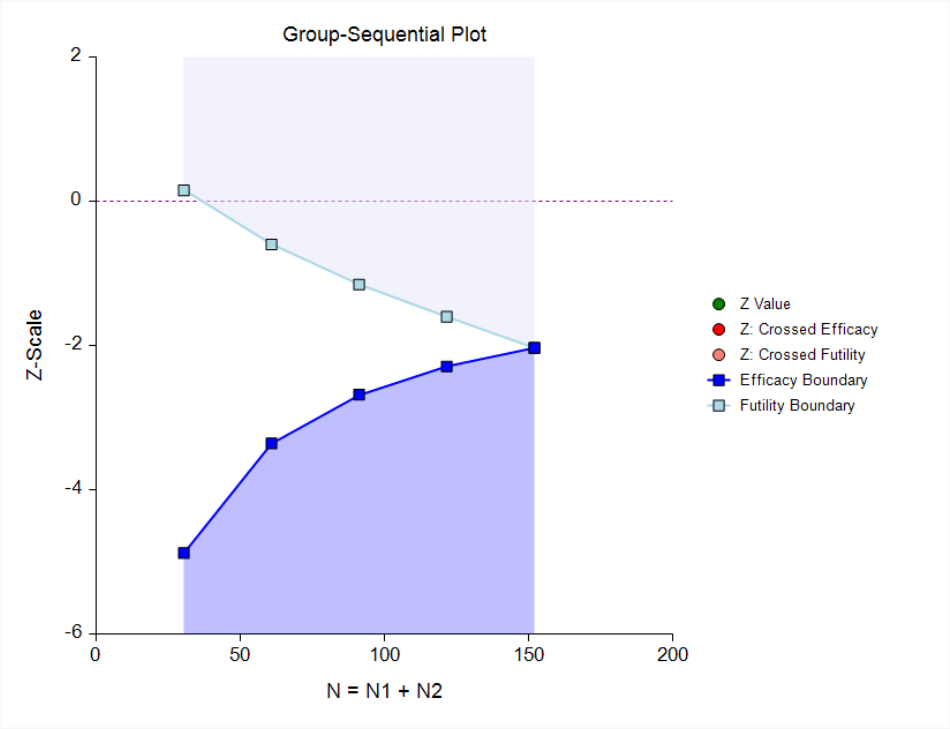
Boundary Plot(s)

This plot shows 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.

Boundary Plot(s)







P-Value Boundaries

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

P-Value Boundaries

Maximum Information: 14.1527
Alternative Hypothesis: λ1 - λ2 < |NIM|
Futility Boundaries: Non-Binding
P-value boundaries are one-sided values.

	Boundaries		
Stage	Efficacy	Futility	Information Proportion
1	0.00000	0.56095	0.2
2	0.00039	0.27484	0.4
3	0.00368	0.12421	0.6
4	0.01102	0.05468	0.8
5	0.02113	0.02113	1.0

Information Report

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

Information Report

Maximum Information: 14.1527
Alternative Hypothesis: λ1 - λ2 < |NIM|
Alpha: 0.025

Stage	Target Information Proportion	Target Information	Target Sample Size N1	Target Sample Size N2	λ1	λ2
1	0.2	2.83054	15.2	15.2	2.4	2.97
2	0.4	5.66108	30.4	30.4	2.4	2.97
3	0.6	8.49162	45.6	45.6	2.4	2.97
4	0.8	11.32216	60.8	60.8	2.4	2.97
5	1.0	14.15270	76.0	76.0	2.4	2.97

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 *	0.2	0.00000	0.00000	0.000001	0.0	0.0
2 *	0.4	0.00039	0.00039	0.000394	1.6	1.6
3 *	0.6	0.00341	0.00381	0.003678	13.7	15.2
4 *	0.8	0.00840	0.01221	0.011017	33.6	48.8
5 *	1.0	0.01279	0.02500	0.021128	51.2	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 *	0.2	0.03336	0.03336	0.560952	33.4	33.4
2 *	0.4	0.02472	0.05808	0.274840	24.7	58.1
3 *	0.6	0.01831	0.07639	0.124207	18.3	76.4
4 *	0.8	0.01356	0.08995	0.054676	13.6	90.0
5 *	1.0	0.01005	0.10000	0.021128	10.0	100.0

* projected

Boundary Probabilities for δ = -0.57

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

Boundary Probabilities for δ = -0.57

Number of Simulations: 10000
Random Seed: 6382224 (User-Entered)
Futility Boundaries: Non-Binding
After Efficacy Boundary Crossing: Hold Out
After Non-Binding Futility Boundary Crossing: Leave In
Alternative Hypothesis: λ1 - λ2 < |NIM|
Non-Inferiority Margin (NIM): 0.3
λ1: 2.4
λ2: 2.97
δ: -0.57

			Efficacy		Futility	
Stage	N1	N2	Boundary	Probability	Boundary	Probability
1	*15.2	*15.2	-4.87688	0.0007	0.15338	0.0466
2	*30.4	*30.4	-3.35695	0.1035	-0.59824	0.0673
3	*45.6	*45.6	-2.68026	0.3427	-1.15421	0.0826
4	*60.8	*60.8	-2.28979	0.3019	-1.60111	0.0916
5	*76.0	*76.0	-2.03100	0.1542	-2.03100	0.1028

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

Average N1: 56.23088
Average N2: 56.23088

Boundary Probabilities for δ = |NIM| (Alpha)

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

Boundary Probabilities for δ = |NIM| (Alpha)

Number of Simulations:	10000
Random Seed:	6382224 (User-Entered)
Futility Boundaries:	Non-Binding
After Efficacy Boundary Crossing:	Hold Out
After Non-Binding Futility Boundary Crossing:	Leave In
Alternative Hypothesis:	λ1 - λ2 < |NIM|
Non-Inferiority Margin (NIM):	0.3
λ1:	2.97 + |NIM| = 2.97 + 0.3 = 3.27
λ2:	2.97
δ:	|NIM| = 0.3

			Efficacy		Futility	
Stage	N1	N2	Boundary	Probability	Boundary	Probability
1	*15.2	*15.2	-4.87688	0.0000	0.15338	0.4341
2	*30.4	*30.4	-3.35695	0.0004	-0.59824	0.7291
3	*45.6	*45.6	-2.68026	0.0039	-1.15421	0.8772
4	*60.8	*60.8	-2.28979	0.0092	-1.60111	0.9461
5	*76.0	*76.0	-2.03100	0.0125	-2.03100	0.9772

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

Average N1: 75.72336
Average N2: 75.72336

Scenario 2

All of the same boundary reports are given for Scenario 2, corresponding to a λ1 value of 2.6.

Scenario 3

All of the same boundary reports are given for Scenario 3, corresponding to a λ1 value of 2.8.

Power and Sample Size Summary

Power and Sample Size Summary

Solve For:	Sample Size
Maximum Number of Stages:	5
Alternative Hypothesis:	λ1 - λ2 < |NIM|
Alpha Spending Function:	O'Brien-Fleming Analog
Beta Spending Function:	Hwang-Shih-DeCani (γ = 1.5)
Number of Simulations:	10000
Random Seed:	6382224 (User-Entered)

Target Power	Sim Power	N1	N2	N	λ1	λ2	NIM	Target Alpha	Sim Alpha
0.9	0.9030	76	76	152	2.4	2.97	0.3	0.025	0.0260
0.9	0.9026	134	134	268	2.6	2.97	0.3	0.025	0.0234
0.9	0.9044	282	282	564	2.8	2.97	0.3	0.025	0.0263

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.
λ1	The assumed Poisson rate of population 1 for power calculation simulations.
λ2	The assumed Poisson rate of population 2 for power calculation simulations. λ2 +/- |NIM| is also the assumed Poisson rate of populations 1 for alpha calculation simulations.
NIM	The non-inferiority margin.
Target Alpha	The alpha used in the computation of the boundaries. The desired overall probability of a Type 1 error.
Sim Alpha	The proportion of null simulation z-values that cross an efficacy boundary. Because "After Boundary Crossing" is set to "Hold out," it is the sum of the individual boundary crossing proportions.

Summary Statements

A parallel, two-group, group-sequential design with a maximum of 5 stages (where lower Poisson rates are considered better) will be used to test whether the Group 1 (treatment) Poisson rate is non-inferior to the Group 2 (control) Poisson rate, with a non-inferiority margin of 0.3 (H0: λ1 - λ2 ≥ 0.3 versus H1: λ1 - λ2 < 0.3). The comparison will be made at each stage using a two-sample 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. To detect a Group 1 Poisson rate of 2.4 and a Group 2 Poisson rate of 2.97 (difference of -0.57), with 90% power, the number of needed subjects at the final stage will be 76 in Group 1 and 76 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.

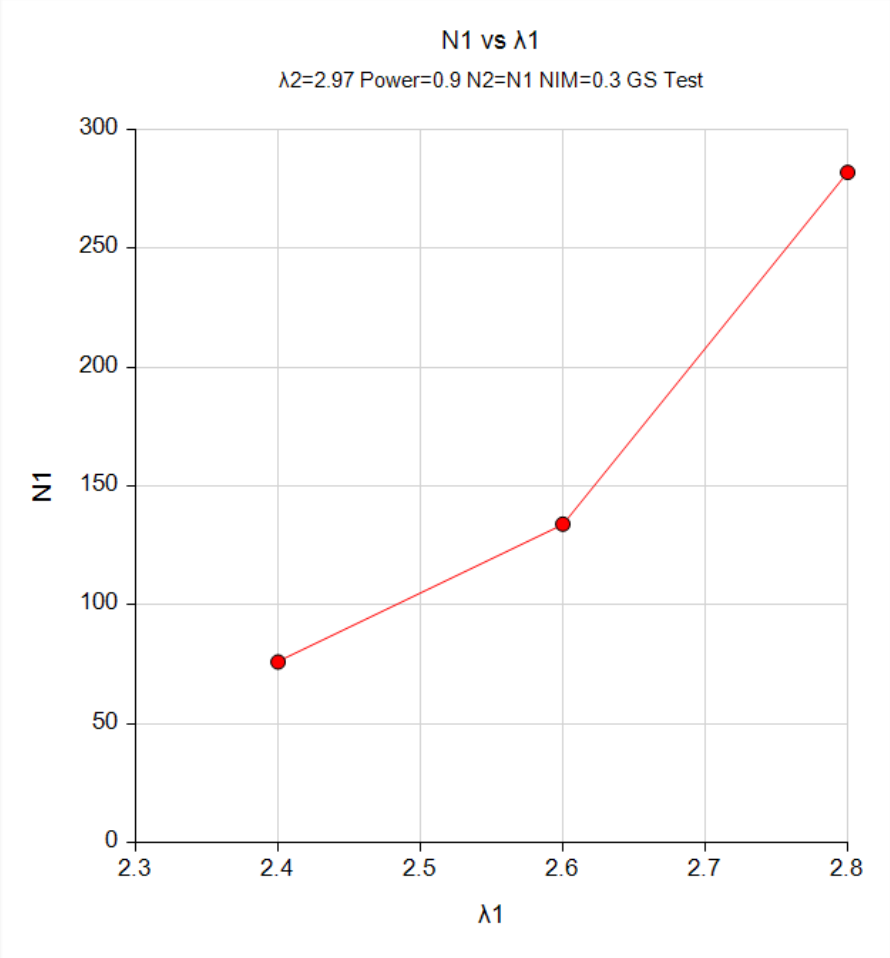
Reboussin, D.M., DeMets, D.L., Kim, K., and Lan, K.K.G. 1992. 'Programs for computing group sequential boundaries using the Lan-DeMets Method.' Technical Report 60, Department of Biostatistics, University of Wisconsin-Madison.

This report shows the values of each of the parameters, one scenario per row. The 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)**
λ1	**2.4 2.6 2.8**
λ2	**2.97**
NIM (Non-Inferiority Margin)	**0.3**
Maximum Number of Stages (K)	**5**
Info. Proportion at each Stage	**Equally incremented**
Boundaries Used	**Efficacy with Futility**
Hypothesis Direction	**Ha: λ1 - λ2 < |NIM| (Lower Poisson 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	**10000**
Random Seed	**5355924** (for Reproducibility)
After Boundary Crossing	**Hold out**

Boundary Reports Tab	
All Reports	**Checked**

Boundary Plots Tab	
Z-Statistic vs Information	**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	λ1 - λ2 < |NIM|
Non-Inferiority Margin (NIM)	0.3
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)	0.0273
λ1	2.4
λ2	2.97
N1 (if final stage reached)	76
N2 (if final stage reached)	76
Target Power	0.9
Power (from simulations)	0.9012
Maximum Information	14.1527

Z-Value Boundaries

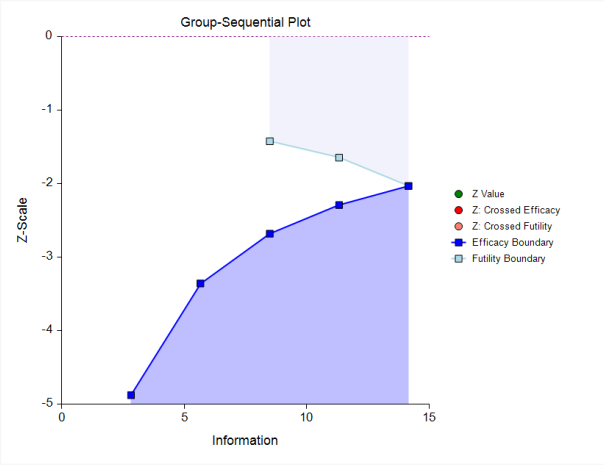
Z-Value Boundaries

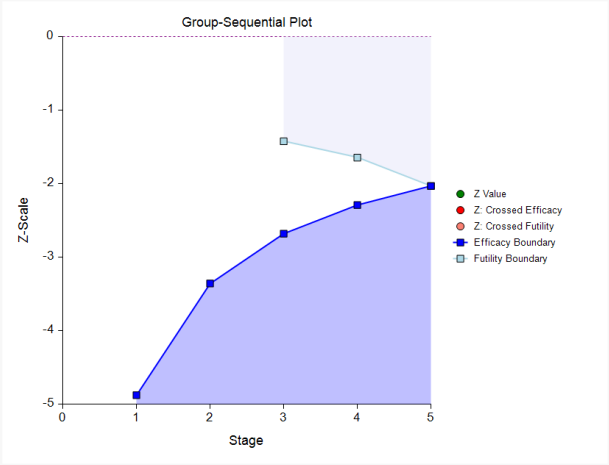
Maximum Information: 14.1527
Alternative Hypothesis: λ1 - λ2 < |NIM|
Futility Boundaries: Non-Binding

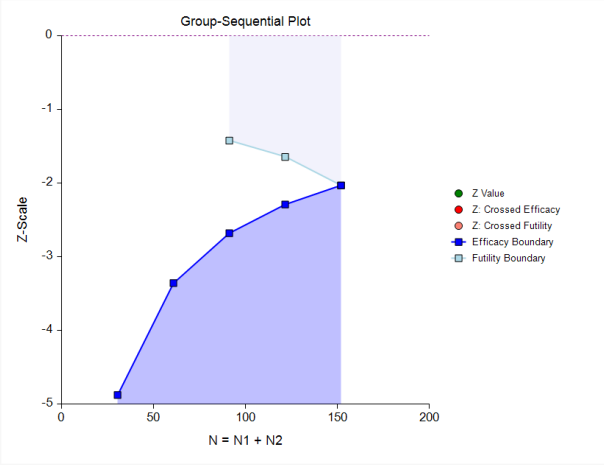
	Boundaries		
Stage	Efficacy	Futility	Information Proportion
1	-4.87688		0.2
2	-3.35695		0.4
3	-2.68026	-1.42324	0.6
4	-2.28979	-1.64431	0.8
5	-2.03100	-2.03100	1.0

Boundary Plot(s)

Boundary Plot(s)







P-Value Boundaries

P-Value Boundaries

Maximum Information: 14.1527
Alternative Hypothesis: λ1 - λ2 < |NIM|
Futility Boundaries: Non-Binding
P-value boundaries are one-sided values.

	Boundaries		
Stage	Efficacy	Futility	Information Proportion
1	0.00000		0.2
2	0.00039		0.4
3	0.00368	0.07733	0.6
4	0.01102	0.05006	0.8
5	0.02113	0.02113	1.0

Information Report

Information Report

Maximum Information: 14.1527
Alternative Hypothesis: λ1 - λ2 < |NIM|
Alpha: 0.025

			Target Sample Size			
Stage	Target Information Proportion	Target Information	N1	N2	λ1	λ2
1	0.2	2.83054	15.2	15.2	2.4	2.97
2	0.4	5.66108	30.4	30.4	2.4	2.97
3	0.6	8.49162	45.6	45.6	2.4	2.97
4	0.8	11.32216	60.8	60.8	2.4	2.97
5	1.0	14.15270	76.0	76.0	2.4	2.97

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 *	0.2	0.00000	0.00000	0.000001	0.0	0.0
2 *	0.4	0.00039	0.00039	0.000394	1.6	1.6
3 *	0.6	0.00341	0.00381	0.003678	13.7	15.2
4 *	0.8	0.00840	0.01221	0.011017	33.6	48.8
5 *	1.0	0.01279	0.02500	0.021128	51.2	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 *	0.2	0.00000	0.00000	1.000000	0.0	0.0
2 *	0.4	0.00000	0.00000	1.000000	0.0	0.0
3 *	0.6	0.07639	0.07639	0.077334	76.4	76.4
4 *	0.8	0.01356	0.08995	0.050056	13.6	90.0
5 *	1.0	0.01005	0.10000	0.021128	10.0	100.0

* projected

Boundary Probabilities for δ = -0.57

Boundary Probabilities for δ = -0.57

Number of Simulations:	10000
Random Seed:	5355924 (User-Entered)
Futility Boundaries:	Non-Binding
After Efficacy Boundary Crossing:	Hold Out
After Non-Binding Futility Boundary Crossing:	Leave In
Alternative Hypothesis:	λ1 - λ2 < |NIM|
Non-Inferiority Margin (NIM):	0.3
λ1:	2.4
λ2:	2.97
δ:	-0.57

			Efficacy		Futility	
Stage	N1	N2	Boundary	Probability	Boundary	Probability
1	*15.2	*15.2	-4.87688	0.0003		0.0000
2	*30.4	*30.4	-3.35695	0.1026		0.0000
3	*45.6	*45.6	-2.68026	0.3558	-1.42324	0.1252
4	*60.8	*60.8	-2.28979	0.2914	-1.64431	0.0933
5	*76.0	*76.0	-2.03100	0.1511	-2.03100	0.1035

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

Average N1: 56.0576
Average N2: 56.0576

Boundary Probabilities for δ = |NIM| (Alpha)

Boundary Probabilities for δ = |NIM| (Alpha)

Number of Simulations:	10000
Random Seed:	5355924 (User-Entered)
Futility Boundaries:	Non-Binding
After Efficacy Boundary Crossing:	Hold Out
After Non-Binding Futility Boundary Crossing:	Leave In
Alternative Hypothesis:	λ1 - λ2 < |NIM|
Non-Inferiority Margin (NIM):	0.3
λ1:	2.97 + |NIM| = 2.97 + 0.3 = 3.27
λ2:	2.97
δ:	|NIM| = 0.3

			Efficacy		Futility	
Stage	N1	N2	Boundary	Probability	Boundary	Probability
1	*15.2	*15.2	-4.87688	0.0000		0.0000
2	*30.4	*30.4	-3.35695	0.0005		0.0000
3	*45.6	*45.6	-2.68026	0.0037	-1.42324	0.9232
4	*60.8	*60.8	-2.28979	0.0091	-1.64431	0.9479
5	*76.0	*76.0	-2.03100	0.0140	-2.03100	0.9769

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

Average N1: 75.7264
Average N2: 75.7264

Scenario 2

All of the same boundary reports are given for Scenario 2, corresponding to a λ1 value of 2.6.

Scenario 3

All of the same boundary reports are given for Scenario 3, corresponding to a λ1 value of 2.8.

Power and Sample Size Summary

Power and Sample Size Summary

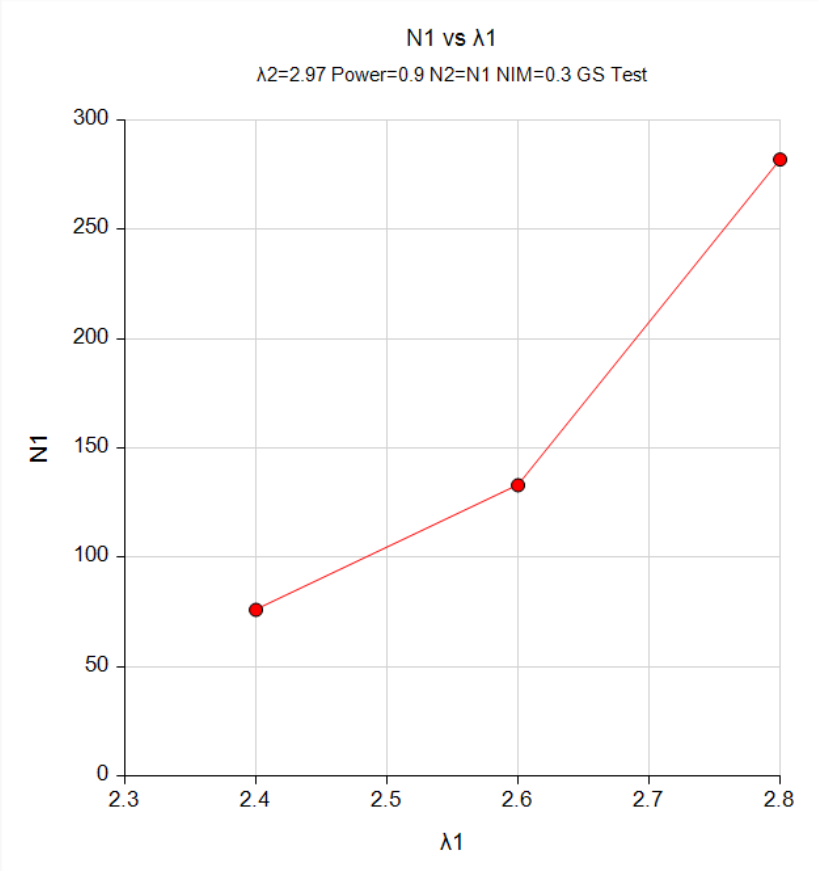
Solve For:	Sample Size
Maximum Number of Stages:	5
Skipped Futility Stage(s):	1 2
Alternative Hypothesis:	λ1 - λ2 < |NIM|
Alpha Spending Function:	O'Brien-Fleming Analog
Beta Spending Function:	Hwang-Shih-DeCani (γ = 1.5)
Number of Simulations:	10000
Random Seed:	5355924 (User-Entered)

Target Power	Sim Power	N1	N2	N	λ1	λ2	NIM	Target Alpha	Sim Alpha
0.9	0.9012	76	76	152	2.4	2.97	0.3	0.025	0.0273
0.9	0.9002	133	133	266	2.6	2.97	0.3	0.025	0.0231
0.9	0.9022	282	282	564	2.8	2.97	0.3	0.025	0.0270

This report shows little 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 50, 100, 150, 200, and 250 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	**50 100 150 200 250**
λ1	**2.4 2.6 2.8**
λ2	**2.97**
NIM (Non-Inferiority Margin)	**0.3**
Maximum Number of Stages (K)	**5**
Info. Proportion at each Stage	**Equally incremented**
Boundaries Used	**Efficacy with Futility**
Hypothesis Direction	**Ha: λ1 - λ2 < |NIM| (Lower Poisson 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	**10000**
Random Seed	**6044953** (for Reproducibility)
After Boundary Crossing	**Hold out**

Boundary Reports Tab	
All Reports	**Checked**

Boundary Plots Tab	
Z-Statistic vs Information	**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 15 scenarios are generated in the output, but they are not shown here.

Power and Sample Size Summary

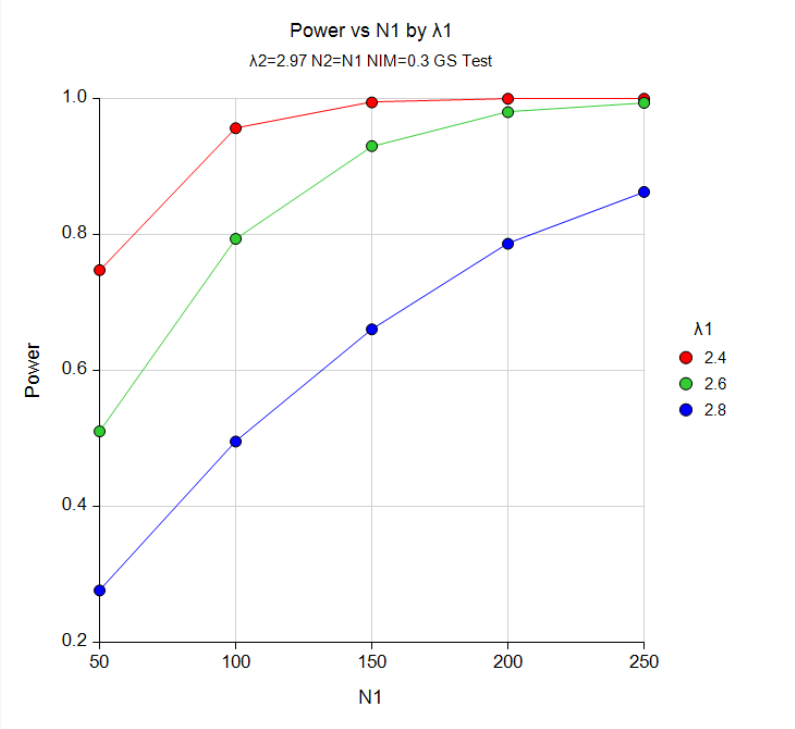
Power and Sample Size Summary

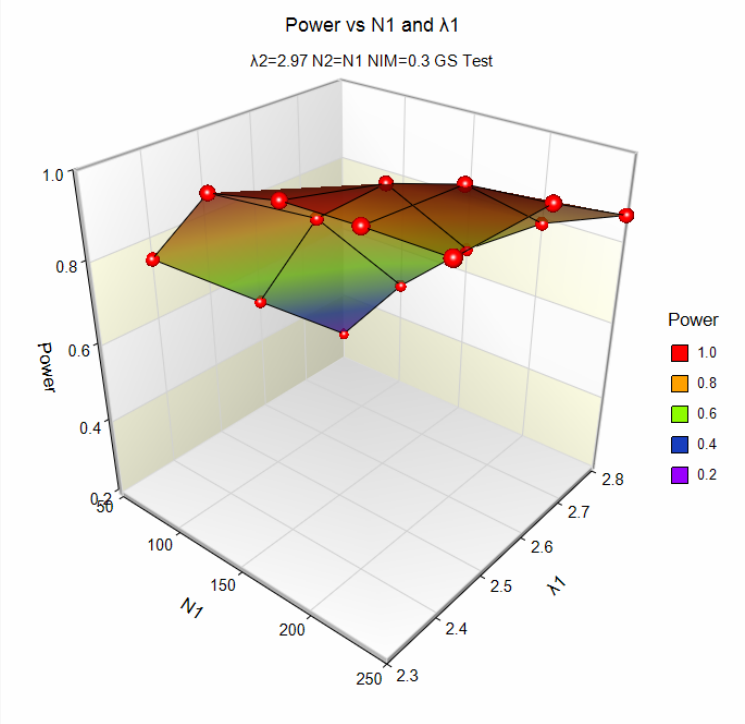
Solve For:	Power
Maximum Number of Stages:	5
Alternative Hypothesis:	λ1 - λ2 < |NIM|
Alpha Spending Function:	O'Brien-Fleming Analog
Beta Spending Function:	Hwang-Shih-DeCani (γ = 1.5)
Number of Simulations:	10000
Random Seed:	6044953 (User-Entered)

Sim Power	N1	N2	N	λ1	λ2	NIM	Target Alpha	Sim Alpha
0.7477	50	50	100	2.4	2.97	0.3	0.025	0.0255
0.9565	100	100	200	2.4	2.97	0.3	0.025	0.0240
0.9944	150	150	300	2.4	2.97	0.3	0.025	0.0238
0.9998	200	200	400	2.4	2.97	0.3	0.025	0.0272
0.9998	250	250	500	2.4	2.97	0.3	0.025	0.0247
0.5105	50	50	100	2.6	2.97	0.3	0.025	0.0240
0.7937	100	100	200	2.6	2.97	0.3	0.025	0.0235
0.9302	150	150	300	2.6	2.97	0.3	0.025	0.0274
0.9801	200	200	400	2.6	2.97	0.3	0.025	0.0244
0.9938	250	250	500	2.6	2.97	0.3	0.025	0.0248
0.2764	50	50	100	2.8	2.97	0.3	0.025	0.0252
0.4955	100	100	200	2.8	2.97	0.3	0.025	0.0247
0.6606	150	150	300	2.8	2.97	0.3	0.025	0.0235
0.7865	200	200	400	2.8	2.97	0.3	0.025	0.0225
0.8627	250	250	500	2.8	2.97	0.3	0.025	0.0234

Plots Section for Power and Sample Size Summary

Plots





The power curve plot shows the effect of sample size and Poisson 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	**50 100 150 200 250**
λ1	**2.4 2.6 2.8**
λ2	**2.97**
NIM (Non-Inferiority Margin)	**0.3**
Maximum Number of Stages (K)	**5**
Info. Proportion at each Stage	**Equally incremented**
Boundaries Used	**Efficacy with Futility**
Hypothesis Direction	**Ha: λ1 - λ2 < |NIM| (Lower Poisson 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	**10000**
Random Seed	**6091193** (for Reproducibility)
After Boundary Crossing	**Hold out**

Boundary Reports Tab	
All Reports	**Checked**

Boundary Plots Tab	
Z-Statistic vs Information	**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 15 scenarios are generated in the output, but they are not shown here.

Power and Sample Size Summary

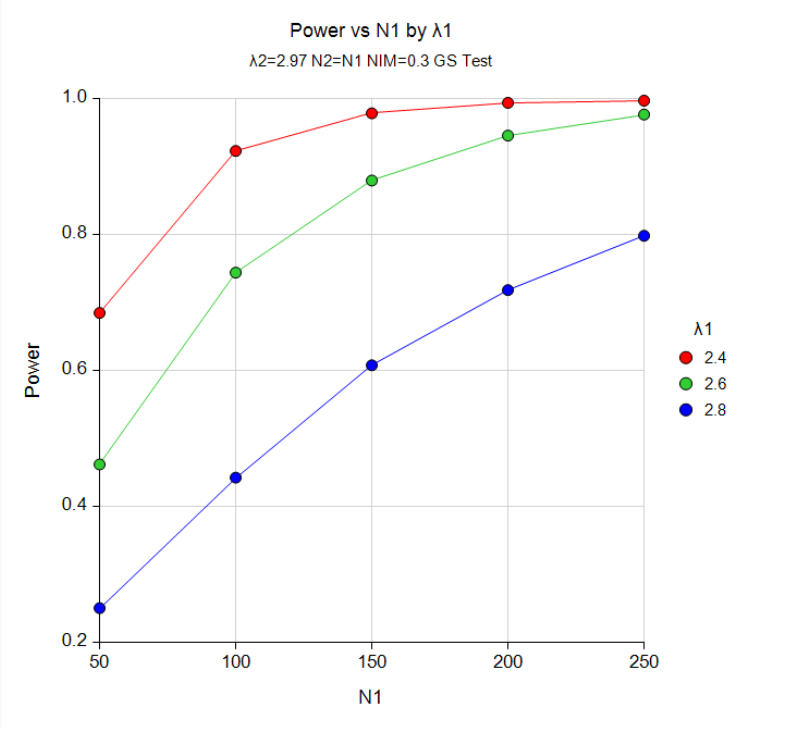
Power and Sample Size Summary

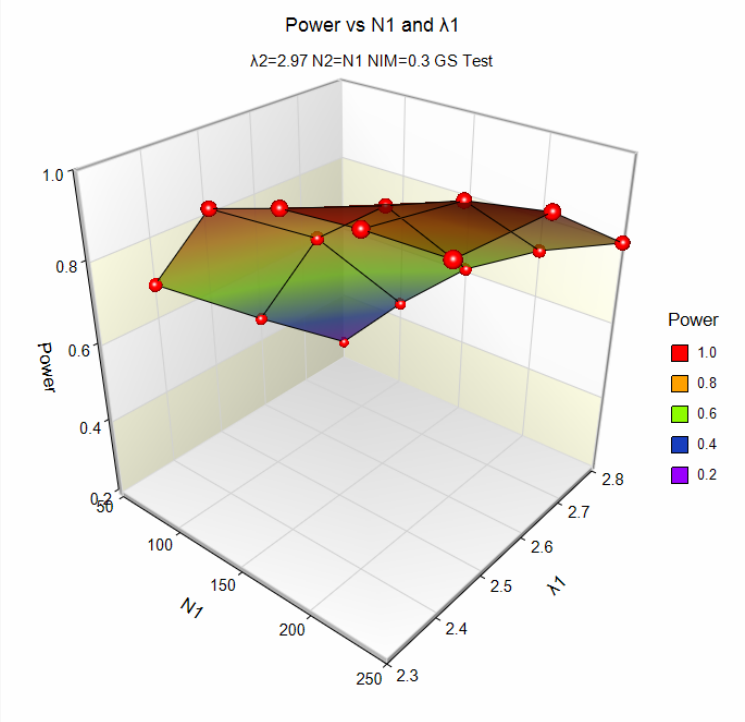
Solve For:	Power
Maximum Number of Stages:	5
Alternative Hypothesis:	λ1 - λ2 < |NIM|
Alpha Spending Function:	O'Brien-Fleming Analog
Beta Spending Function:	Hwang-Shih-DeCani (γ = 1.5)
Number of Simulations:	10000
Random Seed:	6091193 (User-Entered)

Sim Power	N1	N2	N	λ1	λ2	NIM	Target Alpha	Sim Alpha
0.6847	50	50	100	2.4	2.97	0.3	0.025	0.0279
0.9230	100	100	200	2.4	2.97	0.3	0.025	0.0247
0.9784	150	150	300	2.4	2.97	0.3	0.025	0.0235
0.9938	200	200	400	2.4	2.97	0.3	0.025	0.0271
0.9970	250	250	500	2.4	2.97	0.3	0.025	0.0236
0.4618	50	50	100	2.6	2.97	0.3	0.025	0.0242
0.7440	100	100	200	2.6	2.97	0.3	0.025	0.0264
0.8795	150	150	300	2.6	2.97	0.3	0.025	0.0245
0.9456	200	200	400	2.6	2.97	0.3	0.025	0.0252
0.9766	250	250	500	2.6	2.97	0.3	0.025	0.0246
0.2504	50	50	100	2.8	2.97	0.3	0.025	0.0255
0.4424	100	100	200	2.8	2.97	0.3	0.025	0.0251
0.6077	150	150	300	2.8	2.97	0.3	0.025	0.0233
0.7183	200	200	400	2.8	2.97	0.3	0.025	0.0263
0.7982	250	250	500	2.8	2.97	0.3	0.025	0.0263

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 Poisson rate for Group 1 of 2.6 and a sample size of 100 per group will be considered.

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**
λ1	**2.6**
λ2	**2.97**
NIM (Non-Inferiority Margin)	**0.3**
Maximum Number of Stages (K)	**2** (Also run with **3**, **4**, **5**, **10**, and **20**)
Info. Proportion at each Stage	**Equally incremented**
Boundaries Used	**Efficacy with Futility**
Hypothesis Direction	**Ha: λ1 - λ2 < |NIM| (Lower Poisson 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	**10000**
Random Seed	**6142748** (for Reproducibility)
After Boundary Crossing	**Hold out**

Boundary Reports Tab	
All Reports	**Checked**

Boundary Plots Tab	
Z-Statistic vs Information	**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:	λ1 - λ2 < |NIM|
Alpha Spending Function:	O'Brien-Fleming Analog
Beta Spending Function:	Hwang-Shih-DeCani (γ = 1.5)
Number of Simulations:	10000
Random Seed:	6142748 (User-Entered)

Sim Power	N1	N2	N	λ1	λ2	NIM	Target Alpha	Sim Alpha	Number of Stages
0.8102	100	100	200	2.6	2.97	0.3	0.025	0.0262	2
0.8086	100	100	200	2.6	2.97	0.3	0.025	0.0263	3
0.8077	100	100	200	2.6	2.97	0.3	0.025	0.0265	4
0.8059	100	100	200	2.6	2.97	0.3	0.025	0.0258	5
0.7983	100	100	200	2.6	2.97	0.3	0.025	0.0258	10
0.7948	100	100	200	2.6	2.97	0.3	0.025	0.0247	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 500 per group, Poisson rates of 2.5 (λ1) and 2.6 (λ2), no futility boundaries, and 20,000 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 some time 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**
Group Allocation	**Equal (N1 = N2)**
Sample Size Per Group	**500**
λ1	**2.8**
λ2	**2.6**
NIM (Non-Inferiority Margin)	**0.3**
Maximum Number of Stages (K)	**5**
Info. Proportion at each Stage	**Equally incremented**
Boundaries Used	**Efficacy Only**
Hypothesis Direction	**Ha: λ1 - λ2 < |NIM| (Lower Poisson rates are better)**
Boundary Specification	**Spending Function Calculation**
Alpha Spending Function	**O'Brien-Fleming Analog**
Skipped Efficacy Stages	**<Empty>**

Options Tab	
Number of Simulations	**20000**
Random Seed	**6282500** (for Reproducibility)
After Boundary Crossing	**Hold out**

Boundary Reports Tab	
Boundaries using Z Scale	**Checked**
Information Report	**Checked**
Alpha Spending	**Checked**

Boundary Plots Tab	
Z-Statistic vs N	**Checked**

Summary Reports Tab	
All Reports	**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

Run Summary Report

Item	Value
Solve For	Power
Maximum Number of Stages (Design)	5
Current Stage	0
Alternative Hypothesis	λ1 - λ2 < |NIM|
Non-Inferiority Margin (NIM)	0.3
Alpha Spending Function	O'Brien-Fleming Analog
Target Alpha	0.025
Alpha (from simulations)	0.025
λ1	2.8
λ2	2.6
N1 (if final stage reached)	500
N2 (if final stage reached)	500
Power (from simulations)	0.15495
Maximum Information	92.59259

Z-Value Boundaries

Z-Value Boundaries

Maximum Information: 92.59259
Alternative Hypothesis: λ1 - λ2 < |NIM|

Stage	Efficacy Boundary	Information Proportion
1	-4.87688	0.2
2	-3.35695	0.4
3	-2.68026	0.6
4	-2.28979	0.8
5	-2.03100	1.0

Information Report

Information Report

Maximum Information: 92.59259
Alternative Hypothesis: λ1 - λ2 < |NIM|
Alpha: 0.025

Stage	Target Information Proportion	Target Information	Target Sample Size N1	Target Sample Size N2	λ1	λ2
1	0.2	18.51852	100	100	2.8	2.6
2	0.4	37.03704	200	200	2.8	2.6
3	0.6	55.55556	300	300	2.8	2.6
4	0.8	74.07407	400	400	2.8	2.6
5	1.0	92.59259	500	500	2.8	2.6

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 *	0.2	0.00000	0.00000	0.000001	0.0	0.0
2 *	0.4	0.00039	0.00039	0.000394	1.6	1.6
3 *	0.6	0.00341	0.00381	0.003678	13.7	15.2
4 *	0.8	0.00840	0.01221	0.011017	33.6	48.8
5 *	1.0	0.01279	0.02500	0.021128	51.2	100.0

* projected

Boundary Probabilities for δ = |NIM| (Alpha)

Boundary Probabilities for δ = |NIM| (Alpha)

Number of Simulations:	20000
Random Seed:	6282500 (User-Entered)
After Efficacy Boundary Crossing:	Hold Out
Alternative Hypothesis:	λ1 - λ2 < |NIM|
Non-Inferiority Margin (NIM):	0.3
λ1:	2.6 + |NIM| = 2.6 + 0.3 = 2.9
λ2:	2.6
δ:	|NIM| = 0.3

Stage	N1	N2	Efficacy Boundary	Boundary Probability
1	*100	*100	-4.87688	0.00000
2	*200	*200	-3.35695	0.00040
3	*300	*300	-2.68026	0.00375
4	*400	*400	-2.28979	0.00830
5	*500	*500	-2.03100	0.01255

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

Average N1: 498.3
Average N2: 498.3

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