Chapter 714

Group-Sequential Non-Inferiority Analysis for One Proportion

The corresponding sample size procedure, found in PASS Sample Size software, is Group-Sequential Non-Inferiority Tests for One Proportion (Simulation).

Introduction

This procedure is used to test non-inferiority of a single proportion to a null proportion, in stages (sometimes called looks or interim analyses), using group-sequential methods. Unless the stage boundaries are entered directly, the stage boundaries are defined using a specified spending function. Futility boundaries can be binding or non-binding. Futility boundaries are specified through a beta-spending function.

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

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

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

A group-sequential boundary and analysis graph is produced in this procedure.
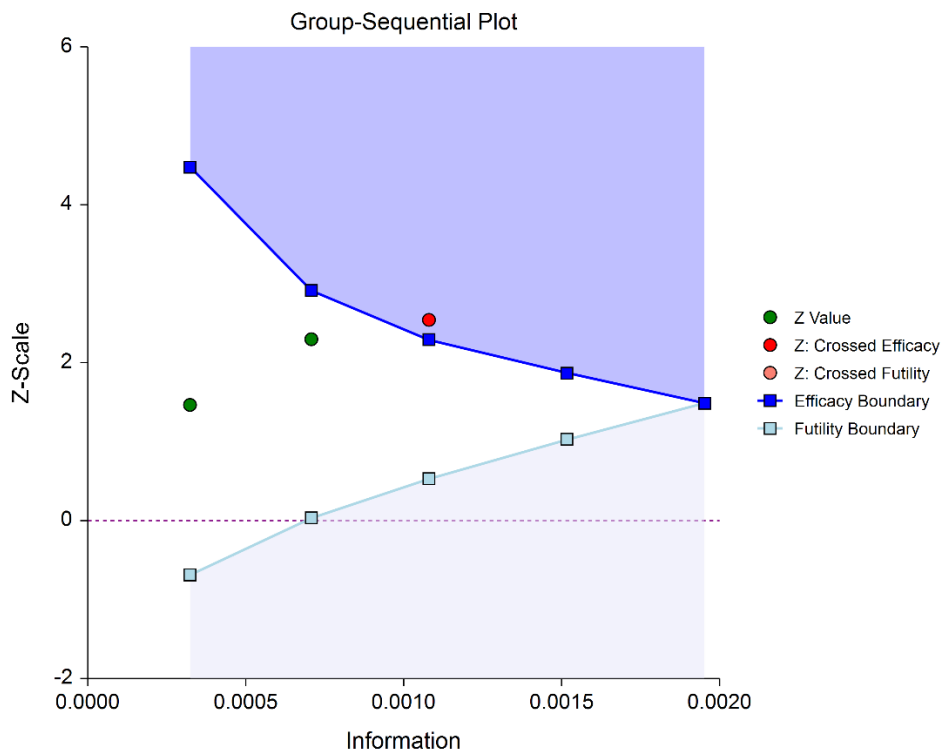
At each stage, stage-adjusted difference estimates, confidence intervals, and p-values are available.

The probabilities of crossing future boundaries may also be assessed, using simulation.

The format of the data for use in this procedure is three columns: one column for the response values, one column defining the two groups, and a third column defining the stage.

Outline of a Group-Sequential Study

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

- Design

- Group-Sequential Analysis

- Reporting

Design Phase – Determine the Number of Subjects

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

- Alpha

- Power

- Test Direction

- Types of boundaries (efficacy, binding futility, non-binding futility)

- Maximum number of stages

- Proportion of maximum information at each stage

- Spending functions

- Assumed proportion

- Non-inferiority margin

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

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

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

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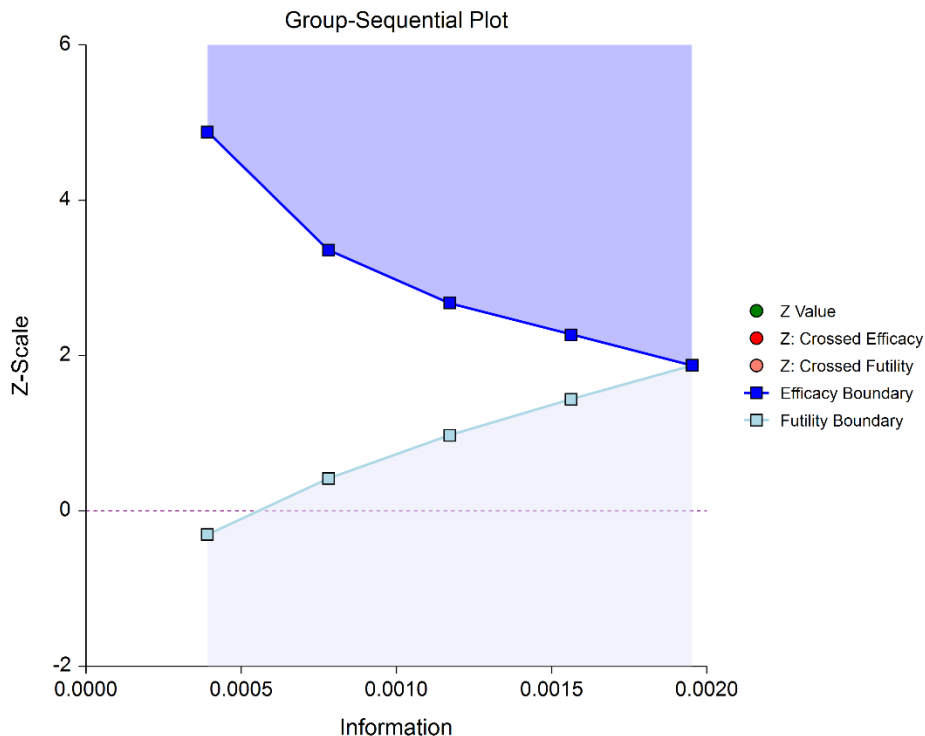
Group-Sequential Analysis Phase

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

First Interim Stage

The design phase gives the target number of subjects for the first stage. 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 proportion. The stage one *z*-statistic is compared to each of the stage one boundaries. Typically, if one of the boundaries is crossed, the study is stopped (non-binding futility boundaries may be an exception).

Group-Sequential Non-Inferiority Analysis for One Proportion
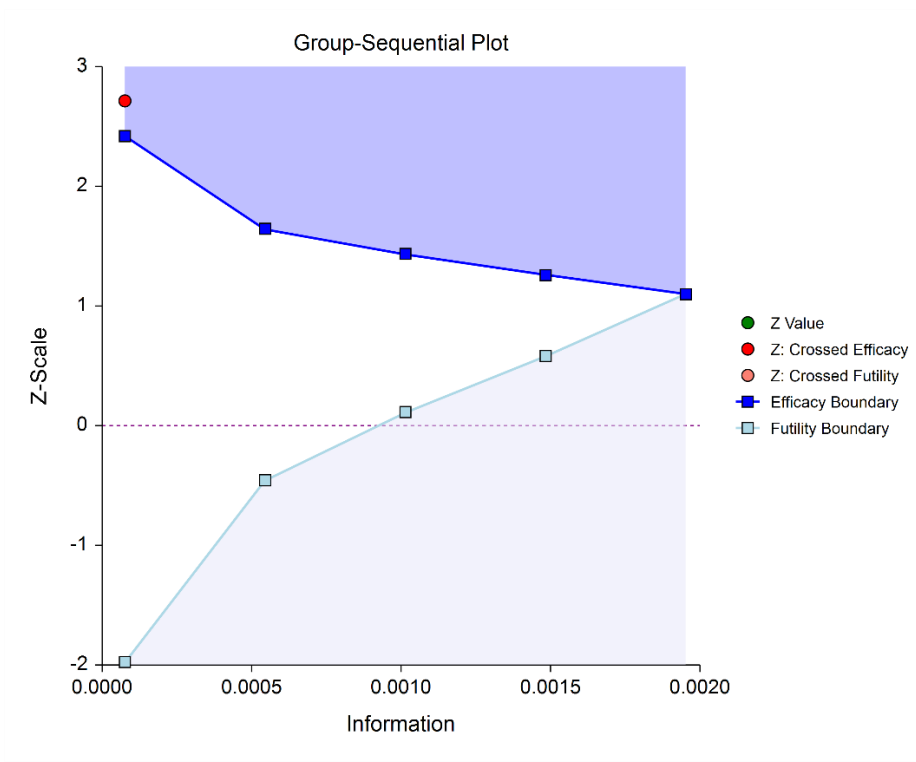
If none of the boundaries are crossed the study continues to the next stage.
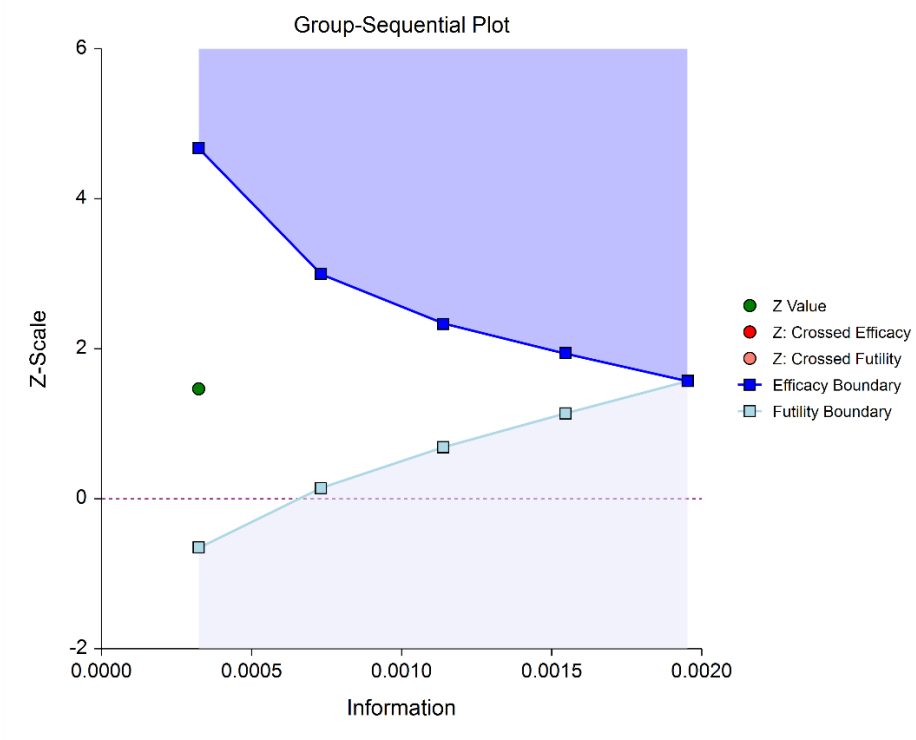
If none of the boundaries are crossed it may also be useful to examine the conditional power or stopping probabilities of future stages. Conditional power and stopping probabilities are based on the user-specified supposed true difference.

Second and other interim stages (if reached)

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 this procedure.

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

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

For either option, once the target information is determined for the next stage, revised target sample sizes are given, and the study continues until the decision is made to perform the next interim analysis on the cumulative response data. In the same manner as the first stage, the current stage information proportion is used with the spending function to determine alpha and/or beta spent at the current stage. The current stage boundaries are then computed. The *z*-statistic is calculated and compared to the boundaries, and a decision is made to stop or continue.

If a boundary is crossed, the study is typically stopped.
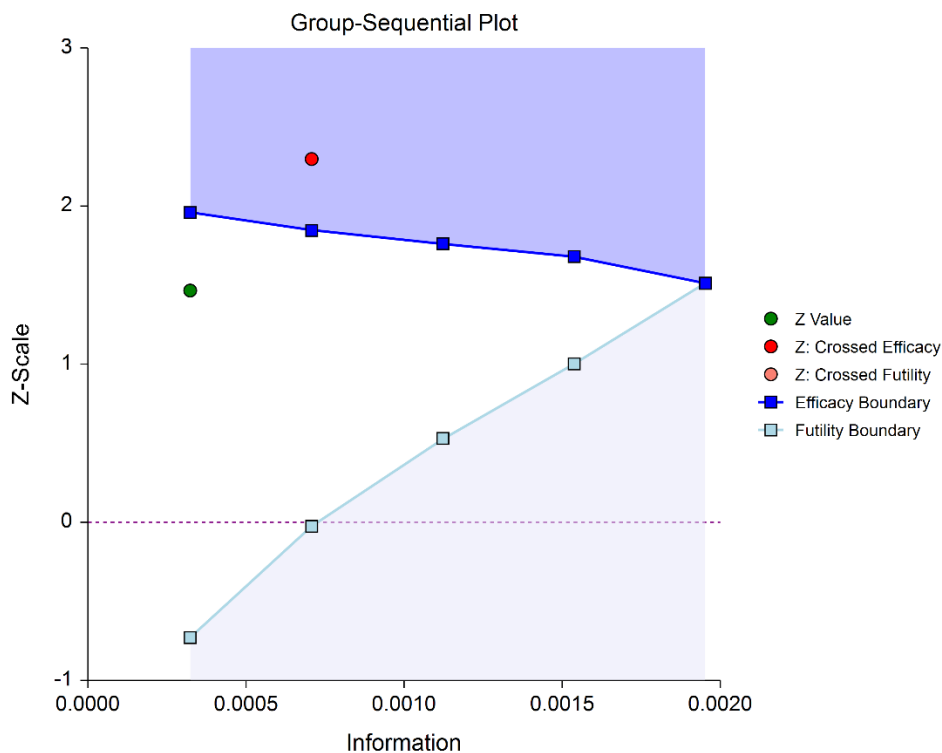
Group-Sequential Plot

If none of the boundaries are crossed the study continues to the next stage.
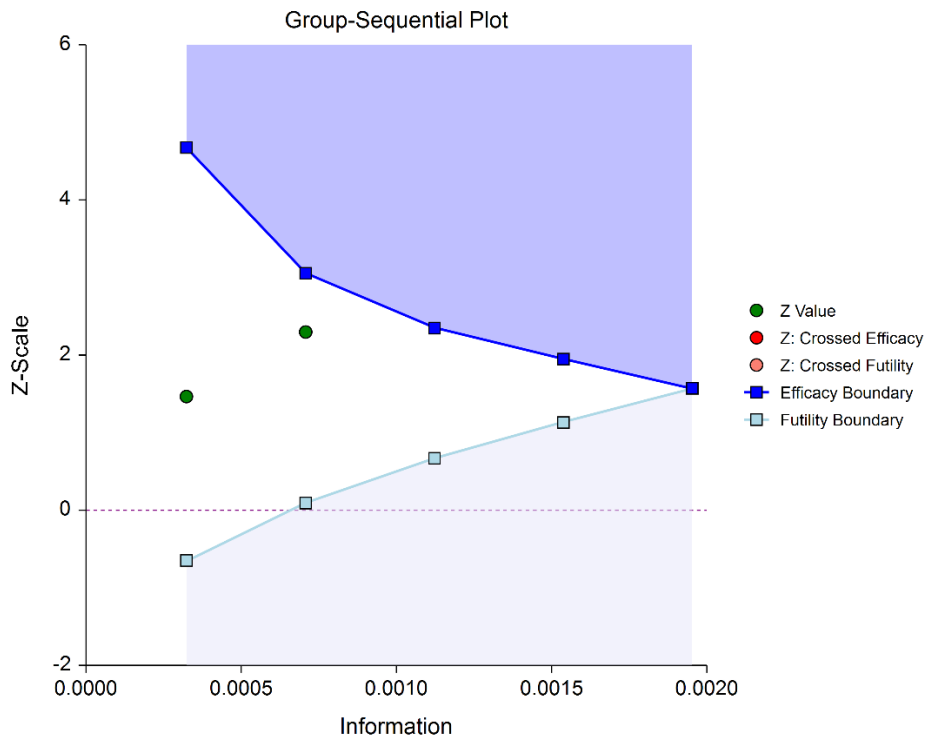
Once again, if no boundary is crossed, conditional power and stopping probabilities may be considered based on a choice of a supposed true difference.

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 proportion of the complete data. 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 proportion 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.
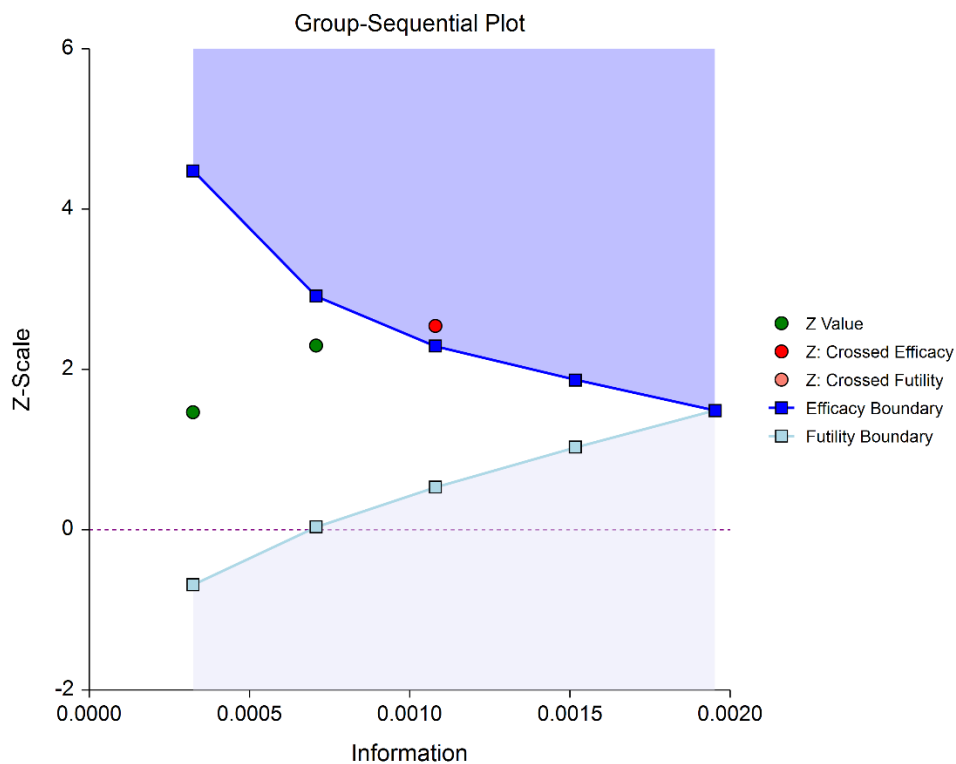
Adjusted confidence interval and estimate of the proportion difference

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

Sample size used

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

Technical Details

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

Null and Alternative Hypotheses

For non-inferiority tests of one proportion versus a null proportion, the appropriate null and alternative hypotheses depend on whether higher proportions are better or higher proportions are worse.

Case 1: Low Proportions Good

In this case, lower proportions are better. The hypotheses are arranged so that rejecting the null hypothesis implies that the proportion is no more than a small amount above the null proportion. 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

$H_0: P \geq P_0 + |M_{NI}|$ versus $H_1: P < P_0 + |M_{NI}|$

$H_0: P - P_0 \geq |M_{NI}|$ versus $H_1: P - P_0 < |M_{NI}|$

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

Case 2: High Proportions Good

In this case, higher proportions are better. The hypotheses are arranged so that rejecting the null hypothesis implies that the proportion is no less than a small amount below the null proportion. 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

$H_0: P \leq P_0 - |M_{NI}|$ versus $H_1: P > P_0 - |M_{NI}|$

$H_0: P - P_0 \leq -|M_{NI}|$ versus $H_1: P - P_0 > -|M_{NI}|$

$H_0: \delta \leq -|M_{NI}|$ 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.

When lower proportions are better, the formula for the test statistic is:

$$z_k = \frac{\hat{p}_k - P_0 - |NIM|}{\sqrt{\dfrac{P_0(1 - P_0)}{n_k}}}$$

and, when higher proportions are better:

$$z_k = \frac{\hat{p}_k - P_0 - (-|NIM|)}{\sqrt{\dfrac{P_0(1 - P_0)}{n_k}}} = \frac{\hat{p}_k - P_0 + |NIM|}{\sqrt{\dfrac{P_0(1 - P_0)}{n_k}}}$$

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 proportion.

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

Information and Total Information

In the group-sequential design phase, the information at any stage k may be calculated from the specified null proportion and the sample size, as

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

where

$$\sigma_{D_k} = \sqrt{\frac{P_0(1 - P_0)}{n_k}}$$

The final stage (K) or total (design) information is calculated from the specified proportions 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. As P_0 is the same for all information calculations, the proportion of the total information is determined solely by n_k. That is, the proportion of the total information is the same as the proportion of the total sample size.

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 $n_{K_{achieved}}$.

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.
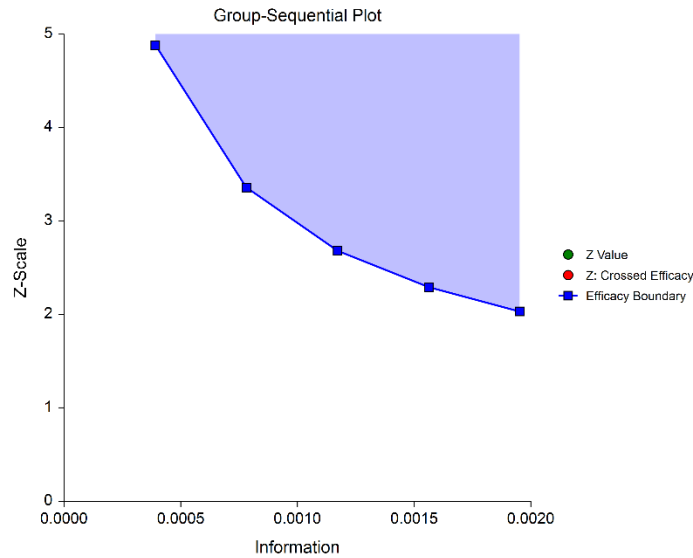
Efficacy and Binding Futility

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.
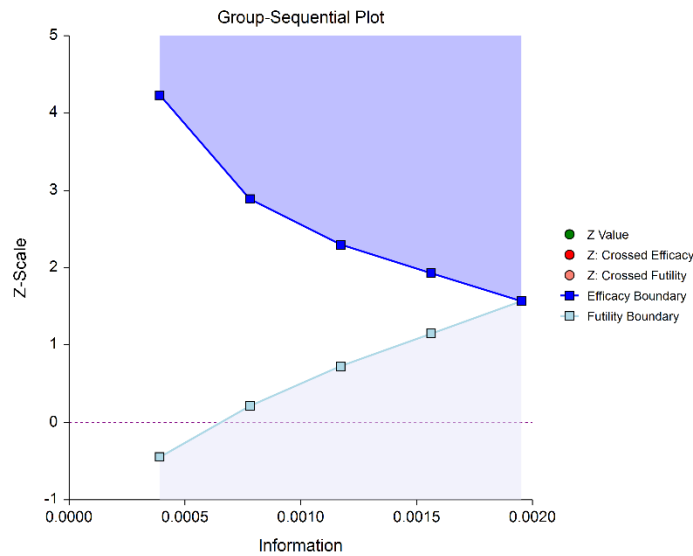
Efficacy and Non-Binding Futility

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).
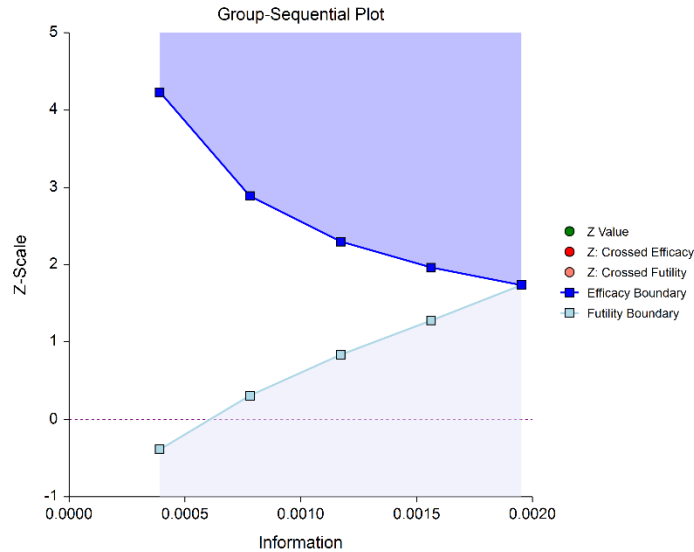
Futility Only

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.
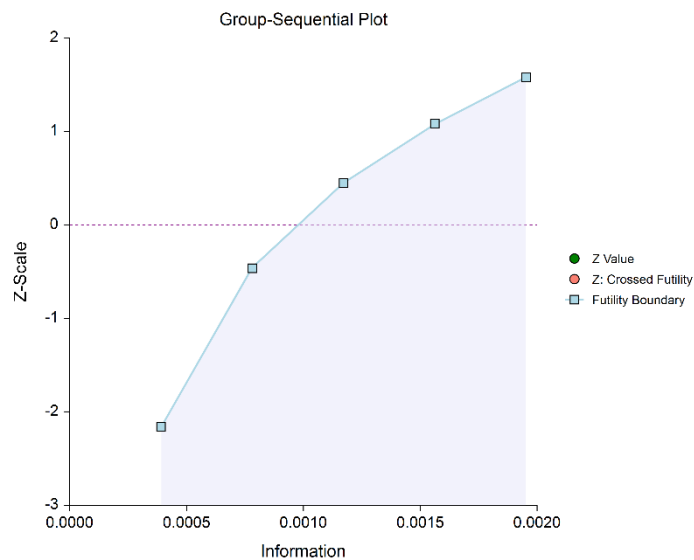
Boundary Calculations

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.

$$\alpha(0) = 0$$

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

$$\alpha(1) = \alpha$$
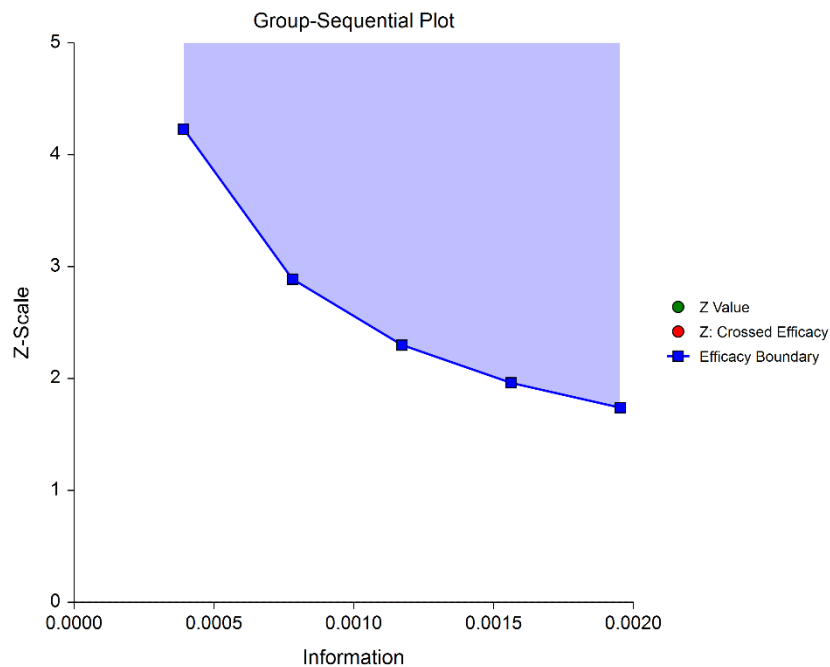
Pocock Analog

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.

$$\alpha(0) = 0$$

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

$$\alpha(1) = \alpha$$
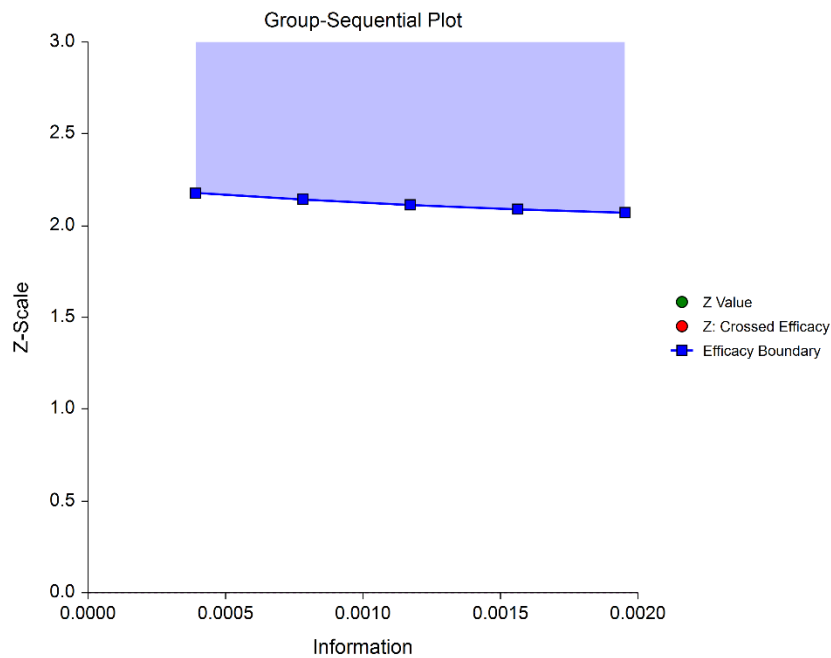
Power Family

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

$$\alpha(0) = 0$$

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

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

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.

Group-Sequential Non-Inferiority Analysis for One Proportion

$\rho = 1$

$\rho = 2$
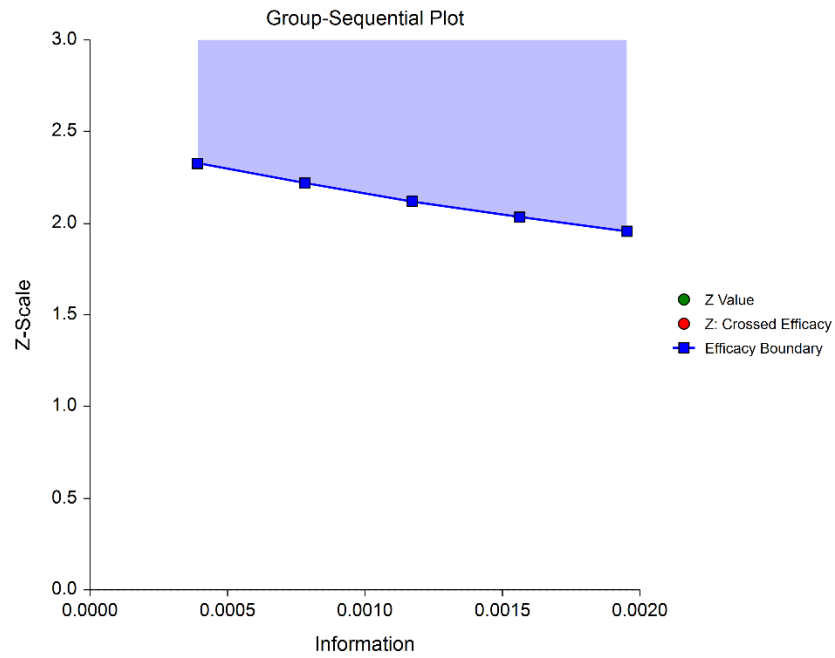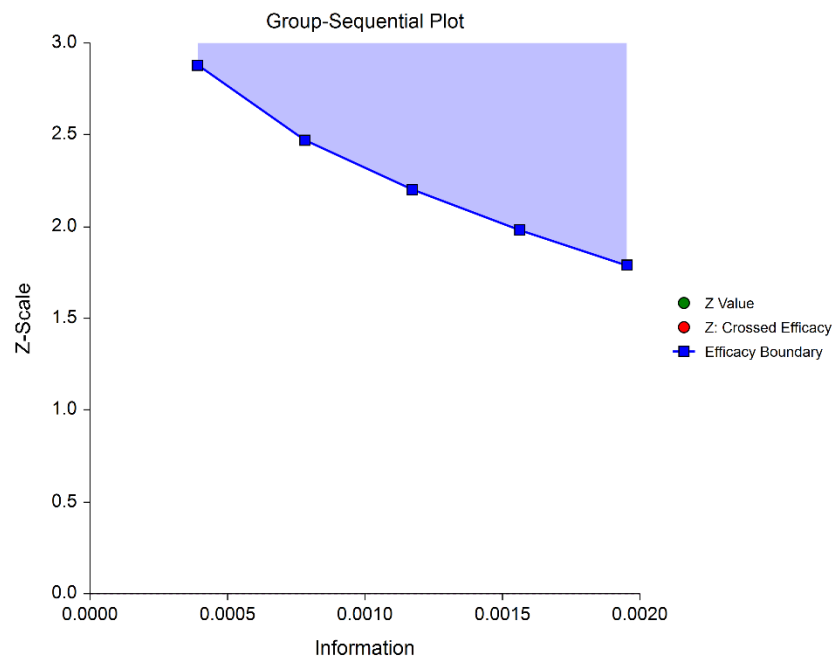
$\rho = 3$
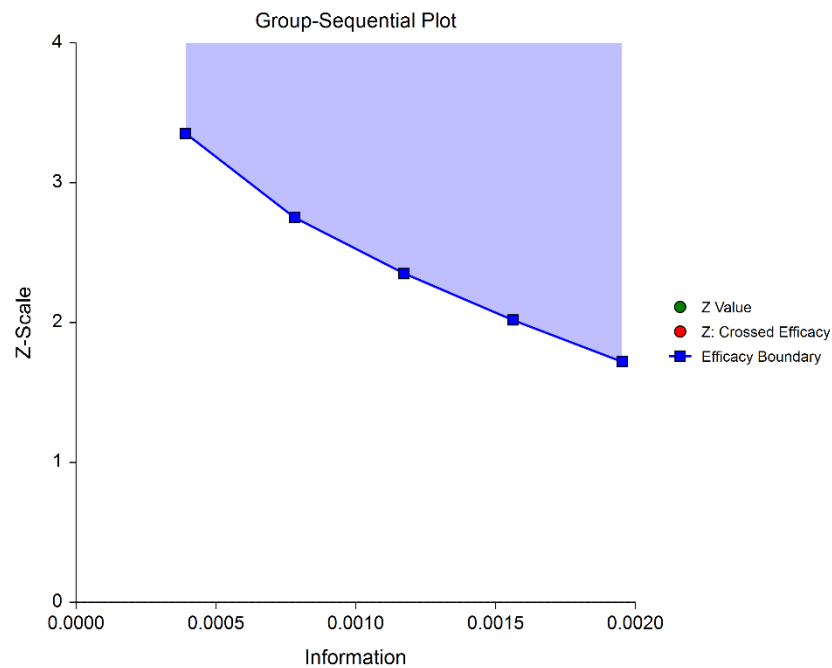
Hwang-Shih-DeCani (Gamma Family)

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

$$\alpha(0) = 0$$

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

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

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

Group-Sequential Non-Inferiority Analysis for One Proportion

$\gamma = -3$

$\gamma = -1$
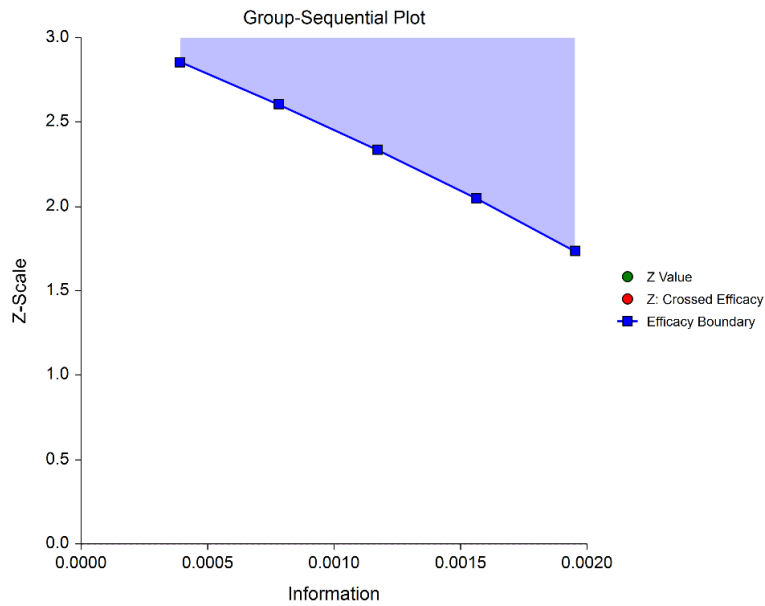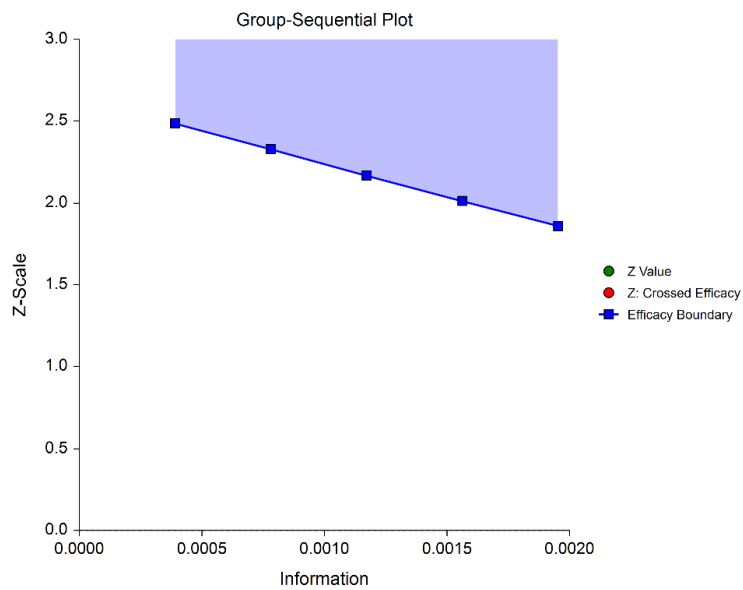
Group-Sequential Non-Inferiority Analysis for One Proportion

$\gamma = 1$
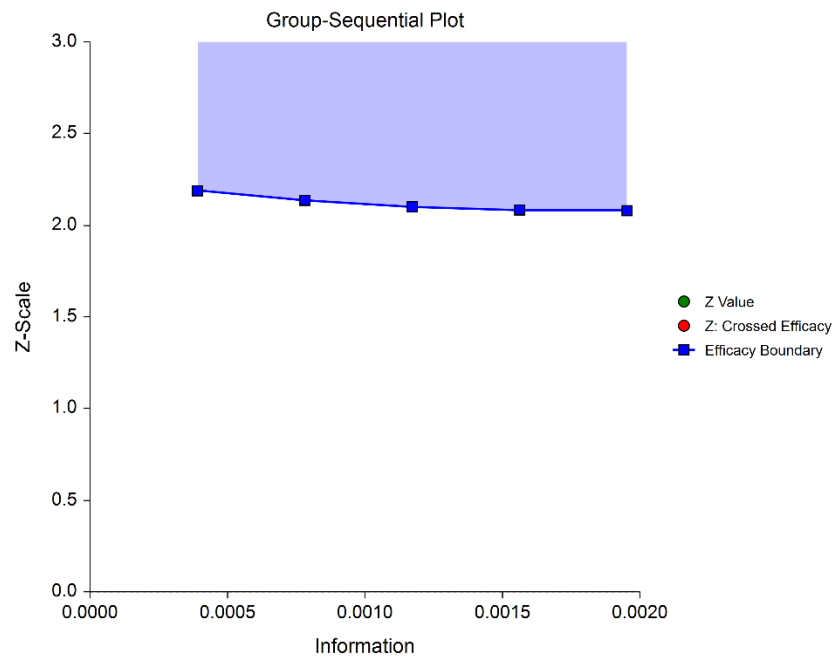
$\gamma = 3$
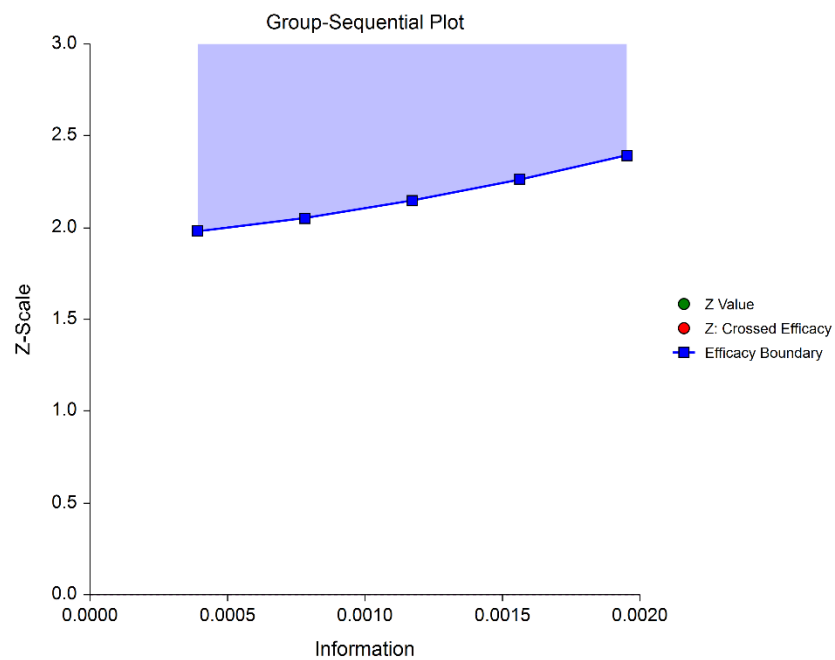
Adjusted Confidence Intervals

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

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

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

Adjusted 'p-values'

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

Adjusted Proportion Difference

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

Conditional Power

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

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

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

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

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

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

where

θ = the parameter being tested by the hypothesis

k = an interim stage at which the conditional power is computed (k = 1, …, K – 1)

K = the stage at which the study is terminated, and the final test computed

Z_k = the test statistic calculated from the observed data that has been collected up to stage k

I_k = the information level at stage k

I_K = the information level at the end of the study

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

For a non-inferiority test of a single proportion with null hypothesis $H_0: P = P_0 \pm |NIM|$, these components are computed in Chang (2008) page 70 as

$\theta = P - P_0 \pm |NIM|$ (the expected difference under the alternative hypothesis)

$Z_k = (p_k - P_0 \pm |NIM|)\sqrt{I_k}$ (the z-statistic computed from the observed data)

$I_k = \left(\dfrac{\sigma^2}{n_k}\right)^{-1}$ (the interim information level)

$I_K = \left(\dfrac{\sigma^2}{n_K}\right)^{-1}$ (the final information level)

$\sigma^2 = P_0(1 - P_0)$. (Note this is slightly different than the variance definition used in Chang (2008). It is used here to conform to the information definition.)

The values for P can come from the values used during the planning of the study, from similar studies, or from estimates made from the data that has emerged.

Predictive Power

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

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

The general lower one-sided predictive power at stage *k* is given by

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

The general two-sided predictive power at stage *k* is given by

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

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

Using Simulation to obtain Future Boundary Crossing Probabilities

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

1. From the data obtained to the current stage, obtain a current estimate of the information.

2. Determine the target (cumulative) sample sizes for each future stage, including the final stage. Fractional sample sizes are rounded up to the next integer.

3. For each simulation, append simulated values to the current sample data to obtain a data set with the final stage sample sizes. Simulated values correspond to the assumed proportion.

4. For each data set, determine which boundary or boundaries were crossed first (except in the case of non-binding futility boundaries). The proportion of simulations crossing each boundary (first) provides an estimate of the probability of crossing each boundary, given the specified assumed proportion.

Non-binding Futility Boundaries

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

Data Structure

The data for this procedure is entered in two columns. One column gives the individual responses. A second column defines the associated stage of each response. The column for stages must use numeric integers beginning with 1 (1, 2, 3, ...).

The two columns are assigned on the Variables tab of the procedure.

The software will assign the current stage as the highest value of the stage column. If the user wishes to exclude one or more (later) stages from the analysis, this may be done with the filter system.

Group-Sequential Analysis Data

Response	Stage
0	1
0	1
1	1
.	.
.	.
0	2
1	2
1	2
1	2
0	2
.	.
.	.

Alternative Data Structure

The data for this procedure may also be structured in summary form:

Group-Sequential Analysis Data

Response	Stage	Count
0	1	57
1	1	26
0	2	53
1	2	19
.	.	.
.	.	.

Example 1 – Group-Sequential Analysis

A childbirth study is conducted to determine whether a new approach during labor results in a proportion of C-sections that is no higher than the historical proportion of 0.269. The desired margin of non-inferiority is 0.05.The response for each patient is C-section or no C-section. A one-sided Z-test with alpha equal to 0.025 is used.

The null and alternative hypotheses are

$$H_0: P - P_0 = 0.05 \ (H_0: P = P_0 + 0.05)$$

versus

$$H_a: P - P_0 < 0.05 \ (H_a: P < P_0 + 0.05)$$

The design calls for five equally spaced stages if the final stage is reached. The current stage is the 3rd stage. In the design phase, a needed power of 0.90 called for 86 patients if the final stage is reached, based on an assumed proportion of 0.17. Both efficacy and non-binding futility boundaries are implemented. The efficacy (alpha-spending) spending function used is the O'Brien-Fleming analog. The Hwang-Shih-DeCani (Gamma) beta-spending function with gamma parameter 1.5 is used for futility.

The boundary plot for stage 2 appeared as
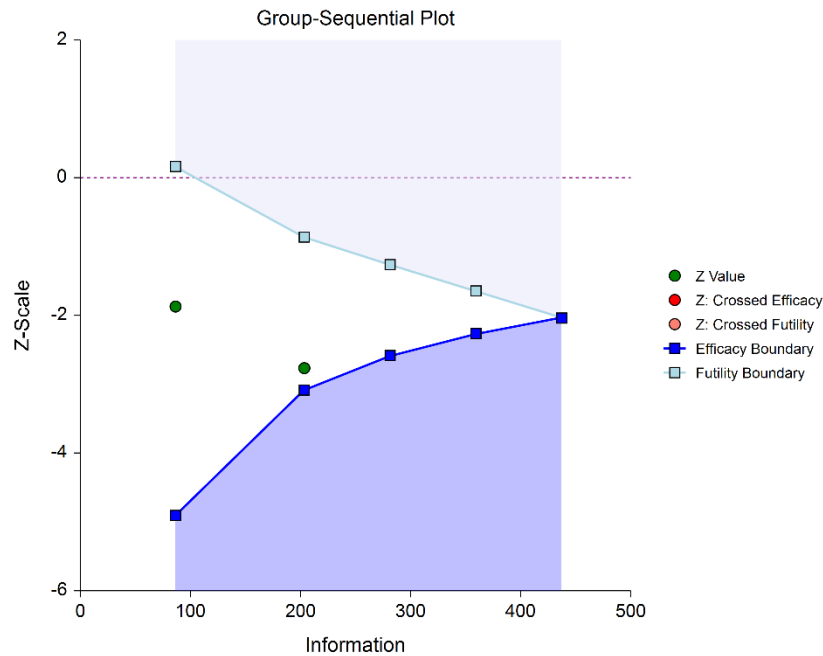
resulting in continuance of the study to stage 3.

Setup

To run this example, complete the following steps:

1   Open the CSection1 example dataset

- From the File menu of the NCSS Data window, select **Open Example Data**.
- Select **CSection1** and click **OK**.

2   Specify the Group-Sequential Non-Inferiority Analysis for One Proportion procedure options

- Find and open the **Group-Sequential Non-Inferiority Analysis for One Proportion** procedure using the menus or the Procedure Navigator.
- The settings 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.

Variables Tab

Response Variable ....**CSection**
  Zero Response Value ....**No**
  One Response Value....................................**Yes**
Stage Variable ....**Stage**
Maximum Number of Stages (K)....................**5**
Info. Proportion at each Stage ....**Equally incremented**
N..**86**
P **0.17**
P0 ....**0.269**
Non-Inferiority Margin (NIM) **0.05**
Future Stage Info. Adjustment ....**Adjust information proportions proportional to original design**
Boundaries Used ....**Efficacy with Futility**
Hypothesis Direction.......................................**Ha: P – P0 < |NIM| (Lower proportions are better)**
Boundary Specification ....**Spending Function Calculation**
Alpha **0.025**
Alpha Spending Function................................**O'Brien-Fleming Analog**
Skipped Efficacy Stages ....**<Empty>**
Beta **0.10**
Beta Spending Function ....**Hwang-Shih-DeCani (γ)**
  γ..**1.5**
Skipped Futility Stages ....**<Empty>**
Binding or Non-Binding Futility.......................**Non-Binding**

Reports Tab
───

Reports for Current Stage

All Reports ....**Checked**

Confidence Level...**95**

Number of Simulations **2000**

Random Seed..**6449600**

After Boundary Crossing................................**Hold Out**

All Three Boxes under Conditional ....**Checked**
and Predictive Power and Boundary
Crossing Probability Parameters

P **0.319**

Planning Stage (Stage 0) Reports

Summary using Z Scale...................................**Checked**

Plots...**Checked**

Plots Tab
───

Z-Statistic vs Information ....**Checked**

Note: You can add the stage number to the plot by checking the **small box on the Plot Format button** (under Z-Statistic vs Information). When the procedure is run, select the **Stage Notes** tab and press the **Add Stage Number** button.

3   Run the procedure

- Click the **Run** button to perform the calculations and generate the output.

Run Summary Report

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

Run Summary Report
───

Item	Value
Maximum Number of Stages (Design):	5
Current Stage:	3
Alternative Hypothesis:	P - P0 < |NIM|
Non-Inferiority Margin (NIM):	0.05
Alpha Spending Function:	O'Brien-Fleming Analog
Beta Spending Function:	Hwang-Shih-DeCani (γ = 1.5)
Futility Boundaries:	Non-Binding
Alpha:	0.0250
Maximum Information:	437.3497

───

Z-Values and Boundaries at Stage 3

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

Z-Values and Boundaries at Stage 3

Maximum Information: 437.3497
Alternative Hypothesis: P - P0 < |NIM|
Non-Inferiority Margin (NIM): 0.05
Futility Boundaries: Non-Binding

Stage	Z-Test Value	Boundaries		Information Proportion	Decision
		Efficacy	**Futility**		
1	-1.8722	-4.9070	0.1603	0.1977	Continue
2	-2.7669	-3.0861	-0.8668	0.4651	Continue
3	-3.4058	-2.5109	-1.3621	0.6744	Crossed Efficacy
4		-2.2466	-1.6766	0.8372	
5		-2.0460	-2.0460	1.0000	

Group-Sequential Boundary Plot at Stage 3

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

Group-Sequential Boundary Plot at Stage 3

P-Values and Boundaries at Stage 3

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

P-Values and Boundaries at Stage 3

Maximum Information: 437.3497
Alternative Hypothesis: P - P0 < |NIM|
Non-Inferiority Margin (NIM): 0.05
Futility Boundaries: Non-Binding

| | | Boundaries | | | |
| | Z-Test | | | Information | |
Stage	P-Value	Efficacy	Futility	Proportion	Decision
1	0.03059	0.00000	0.56367	0.1977	Continue
2	0.00283	0.00101	0.19303	0.4651	Continue
3	0.00033	0.00602	0.08658	0.6744	Crossed Efficacy
4		0.01233	0.04681	0.8372	
5		0.02038	0.02038	1.0000	

P-values and P-value boundaries are one-sided values.

Current Stage Results Adjusted for Sequential Analysis (Stage 3)

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

Current Stage Results Adjusted for Sequential Analysis (Stage 3)

		Group-Sequential Adjusted Difference			Conf. Level
	Actual	95.0% C.I. of Diff.			Where Upper
	Difference			C.I.	Boundary
Stage	Sample P - P0 - NIM	Lower	Upper	Midpoint	Is Zero
3	-0.19831	-0.37445	-0.08509	-0.23210	99.762%

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

Descriptive Statistics up to Stage 3

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

Descriptive Statistics up to Stage 3

Stage	N	X	P	P0	P - P0	SE
1	17	2	0.11765	0.26900	-0.15135	0.10755
2	40	5	0.12500	0.26900	-0.14400	0.07011
3	58	7	0.12069	0.26900	-0.14831	0.05823

Information Report at Stage 3

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

Information Report at Stage 3

Maximum Information: 437.3497
Alternative Hypothesis: P - P0 < |NIM|
Non-Inferiority Margin (NIM): 0.05
Alpha: 0.0250

Stage	Target Information Proportion	Achieved Information Proportion	Target Information	Achieved Information	N	P0
1	0.2000	0.1977	87.4699	86.4528	17.00	0.26900
2	0.4000	0.4651	174.9399	203.4184	40.00	0.26900
3	0.6000	0.6744	262.4098	294.9567	58.00	0.26900
4	0.8000	*0.8372	349.8797	*366.1532	*72.00	0.26900
5	1.0000	*1.0000	437.3497	*437.3497	*86.00	0.26900

* Projected value

Alpha Spending at Stage 3

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

Alpha Spending at Stage 3

Target Final Stage Alpha: 0.0250
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	0.1977	0.0000	0.0000	0.000000	0.0	0.0
2	0.4651	0.0010	0.0010	0.001014	4.1	4.1
3	0.6744	0.0053	0.0063	0.006021	21.3	25.4
4 *	0.8372	0.0080	0.0143	0.012331	31.8	57.2
5 *	1.0000	0.0107	0.0250	0.020379	42.8	100.0

* Projected

Beta Spending for Futility at Stage 3

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

Beta Spending for Futility at Stage 3

Target Cumulative Beta at Final Stage: 0.1000
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	0.1977	0.0330	0.0330	0.563673	33.0	33.0
2	0.4651	0.0316	0.0647	0.193030	31.6	64.7
3	0.6744	0.0173	0.0819	0.086577	17.3	81.9
4 *	0.8372	0.0101	0.0921	0.046811	10.1	92.1
5 *	1.0000	0.0079	0.1000	0.020379	7.9	100.0

* Projected

Conditional and Predictive Power Report at Stage 3

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

Conditional and Predictive Power Report at Stage 3

Maximum Information: 437.3497
Information this Stage: 294.9567
Proportion of Maximum Information: 0.6744
Predictive Power: 0.9992

δ Name	δ Value	Conditional Power
Design	-0.0990	0.9994
Data	-0.1483	0.9999
δ1	0.0500	0.9288

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

Boundary Probabilities for δ = -0.099

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

Boundary Probabilities for δ = -0.099
——

Number of Simulations:	2000
User-Entered Random Seed:	6449600
Futility Boundaries:	Non-Binding
After Efficacy Boundary Crossing:	Hold Out
After Non-Binding Futility Boundary Crossing:	Leave In
Alternative Hypothesis:	P - P0 < |NIM|
Non-Inferiority Margin (NIM):	0.05
P:	0.17
P0:	0.269
δ:	-0.099

——

			Efficacy		Futility	
Stage	**N**	**Z-Test Value**	**Boundary**	**Probability**	**Boundary**	**Probability**
1	17.00	-1.8722	-4.9070		0.1603	
2	40.00	-2.7669	-3.0861		-0.8668	
3	58.00	-3.4058	-2.5109		-1.3621	
4	*72.00		-2.2466	1.0000	-1.6766	0.0000
5	*86.00		-2.0460	0.0000	-2.0460	0.0000

——

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

Boundary Probabilities for δ = -0.1483103

This section estimates the probabilities of crossing future boundaries if the current sample proportion is assumed.

Boundary Probabilities for δ = -0.1483103
——

Number of Simulations:	2000
User-Entered Random Seed:	6449600
Futility Boundaries:	Non-Binding
After Efficacy Boundary Crossing:	Hold Out
After Non-Binding Futility Boundary Crossing:	Leave In
Alternative Hypothesis:	P - P0 < |NIM|
Non-Inferiority Margin (NIM):	0.05
P:	0.1206897
P0:	0.269
δ:	-0.1483103

——

			Efficacy		Futility	
Stage	**N**	**Z-Test Value**	**Boundary**	**Probability**	**Boundary**	**Probability**
1	17.00	-1.8722	-4.9070		0.1603	
2	40.00	-2.7669	-3.0861		-0.8668	
3	58.00	-3.4058	-2.5109		-1.3621	
4	*72.00		-2.2466	1.0000	-1.6766	0.0000
5	*86.00		-2.0460	0.0000	-2.0460	0.0000

——

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

Boundary Probabilities for δ = 0.05

This section estimates the probabilities of crossing future boundaries if the difference for the remaining looks is assumed to be 0.05 (the margin of non-inferiority).

Boundary Probabilities for δ = 0.05

Number of Simulations:	2000					
User-Entered Random Seed:	6449600					
Futility Boundaries:	Non-Binding					
After Efficacy Boundary Crossing:	Hold Out					
After Non-Binding Futility Boundary Crossing:	Leave In					
Alternative Hypothesis:	P - P0 < |NIM|					
Non-Inferiority Margin (NIM):	0.05					
P:	0.319					
P0:	0.269					
δ:	0.05					

			Efficacy		Futility	
Stage	N	Z-Test Value	Boundary	Probability	Boundary	Probability
1	17.00	-1.8722	-4.9070		0.1603	
2	40.00	-2.7669	-3.0861		-0.8668	
3	58.00	-3.4058	-2.5109		-1.3621	
4	*72.00		-2.2466	0.9570	-1.6766	0.0040
5	*86.00		-2.0460	0.0165	-2.0460	0.0700

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

Z-Values and Boundaries at Stage 0

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

Z-Values and Boundaries at Stage 0

Maximum Information:	437.3497			
Alternative Hypothesis:	P - P0 < |NIM|			
Non-Inferiority Margin (NIM):	0.05			
Futility Boundaries:	Non-Binding			

		Boundaries			
Stage	Z-Test Value	Efficacy	Futility	Information Proportion	Decision
1		-4.8769	0.1534	0.2000	
2		-3.3569	-0.5982	0.4000	
3		-2.6803	-1.1542	0.6000	
4		-2.2898	-1.6011	0.8000	
5		-2.0310	-2.0310	1.0000	

Group-Sequential Boundary Plot at Planning Stage (Stage 0)

This plot shows the projected boundaries at the planning stage.

Group-Sequential Boundary Plot at Planning Stage (Stage 0)
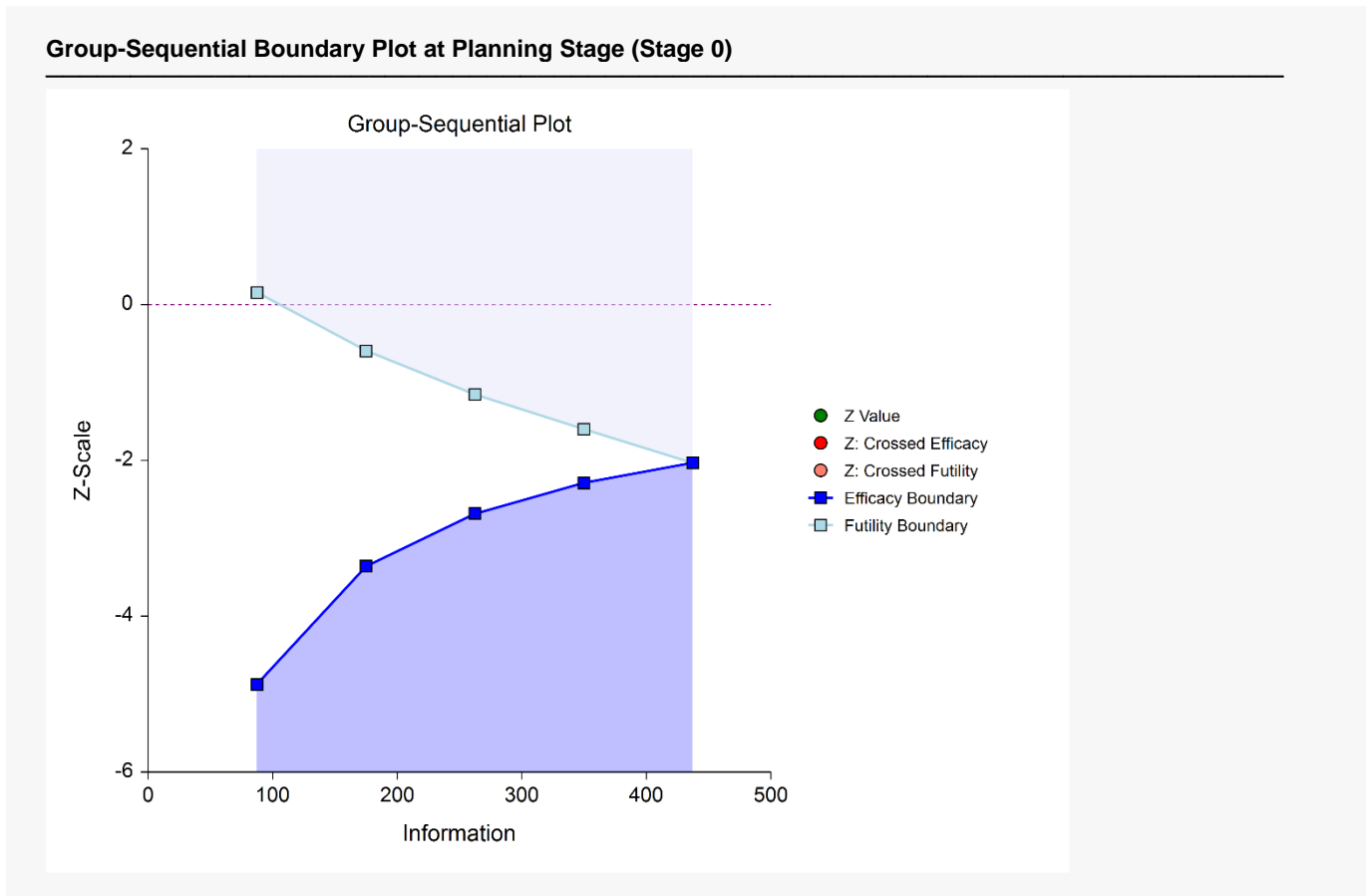
Example 2 – Skipping Stage Boundaries

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

Setup

To run this example, complete the following steps:

1   Open the CSection1 example dataset
  - From the File menu of the NCSS Data window, select **Open Example Data**.
  - Select **CSection1** and click **OK**.

2   Specify the Group-Sequential Non-Inferiority Analysis for One Proportion procedure options
  - Find and open the **Group-Sequential Non-Inferiority Analysis for One Proportion** procedure using the menus or the Procedure Navigator.
  - The settings 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.

   Variables Tab

   Skipped Futility Stages **1 2**

3   Run the procedure
  - Click the **Run** button to perform the calculations and generate the output.

Run Summary Report

The skipped futility stages are now reported.

Run Summary Report

Item	Value
Maximum Number of Stages (Design):	5
Skipped Futility Stage(s):	1 2
Current Stage:	3
Alternative Hypothesis:	P - P0 < |NIM|
Non-Inferiority Margin (NIM):	0.05
Alpha Spending Function:	O'Brien-Fleming Analog
Beta Spending Function:	Hwang-Shih-DeCani (γ = 1.5)
Futility Boundaries:	Non-Binding
Alpha:	0.0250
Maximum Information:	437.3497

Z-Values and Boundaries at Stage 3

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

Z-Values and Boundaries at Stage 3

Maximum Information: 437.3497
Alternative Hypothesis: P - P0 < |NIM|
Non-Inferiority Margin (NIM): 0.05
Futility Boundaries: Non-Binding

Stage	Z-Test Value	Boundaries		Information Proportion	Decision
		Efficacy	**Futility**		
1	-1.8722	-4.9070		0.1977	Continue
2	-2.7669	-3.0861		0.4651	Continue
3	-3.4058	-2.5109	-1.6243	0.6744	Crossed Efficacy
4		-2.2466	-1.7225	0.8372	
5		-2.0460	-2.0460	1.0000	

Group-Sequential Boundary Plot at Stage 3

The plot now has two futility boundaries skipped.

Group-Sequential Boundary Plot at Stage 3
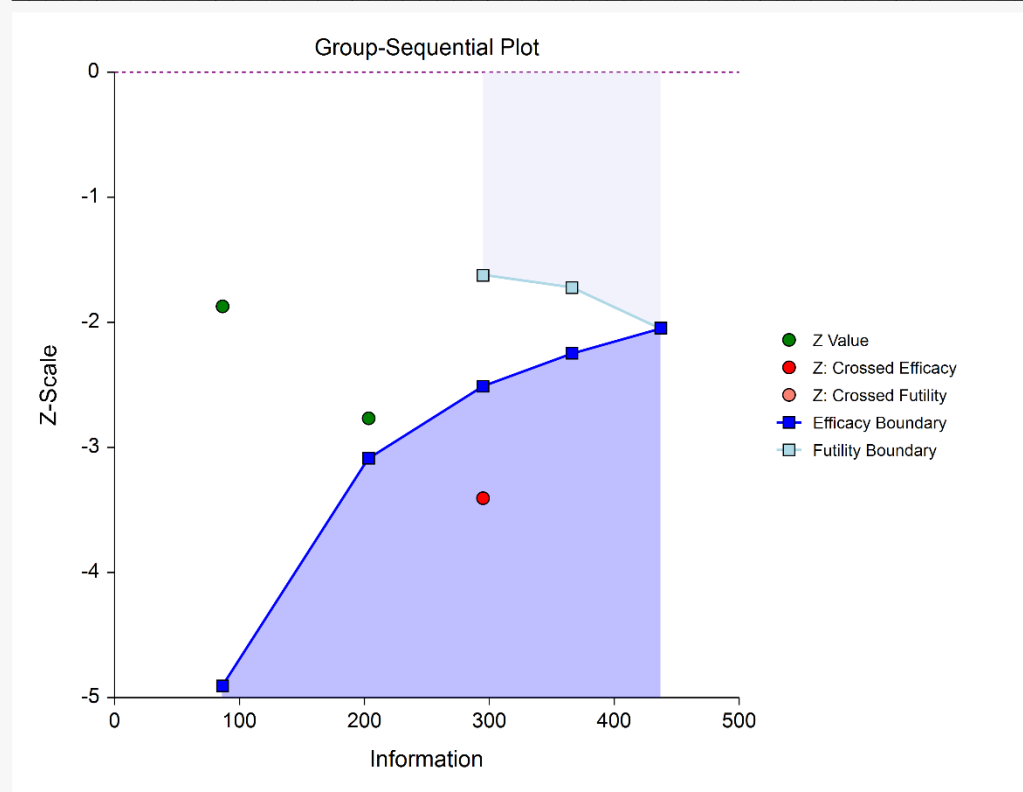
Example 3 – Sample Size Re-estimation and Boundary Probabilities

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

Setup

To run this example, complete the following steps:

1   Open the CSection1 2 Stages example dataset

- From the File menu of the NCSS Data window, select **Open Example Data**.
- Select CSection1 2 Stages and click OK.

2   Specify the Group-Sequential Non-Inferiority Analysis for One Proportion procedure options

- Find and open the **Group-Sequential Non-Inferiority Analysis for One Proportion** procedure using the menus or the Procedure Navigator.
- The settings 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.

Reports Tab

Random Seed..**4238623**

3   Run the procedure

- Click the **Run** button to perform the calculations and generate the output.

Run Summary Report

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

Run Summary Report

Item	Value
Maximum Number of Stages (Design):	5
Current Stage:	2
Alternative Hypothesis:	P - P0 < |NIM|
Non-Inferiority Margin (NIM):	0.05
Alpha Spending Function:	O'Brien-Fleming Analog
Beta Spending Function:	Hwang-Shih-DeCani (γ = 1.5)
Futility Boundaries:	Non-Binding
Alpha:	0.0250
Maximum Information:	437.3497

Z-Values and Boundaries at Stage 2

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

Z-Values and Boundaries at Stage 2

Maximum Information: 437.3497
Alternative Hypothesis: P - P0 < |NIM|
Non-Inferiority Margin (NIM): 0.05
Futility Boundaries: Non-Binding

| | | Boundaries | | | |
| | Z-Test | | | Information | |
Stage	Value	Efficacy	Futility	Proportion	Decision
1	-1.8722	-4.9070	0.1631	0.1977	Continue
2	-2.7669	-3.0861	-0.8624	0.4651	Continue
3		-2.5843	-1.2636	0.6434	
4		-2.2645	-1.6448	0.8217	
5		-2.0397	-2.0397	1.0000	

Group-Sequential Boundary Plot at Stage 2

This plot shows the Z-test values in the vicinity of the efficacy boundary side.

Group-Sequential Boundary Plot at Stage 2

P-Values and Boundaries at Stage 2

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

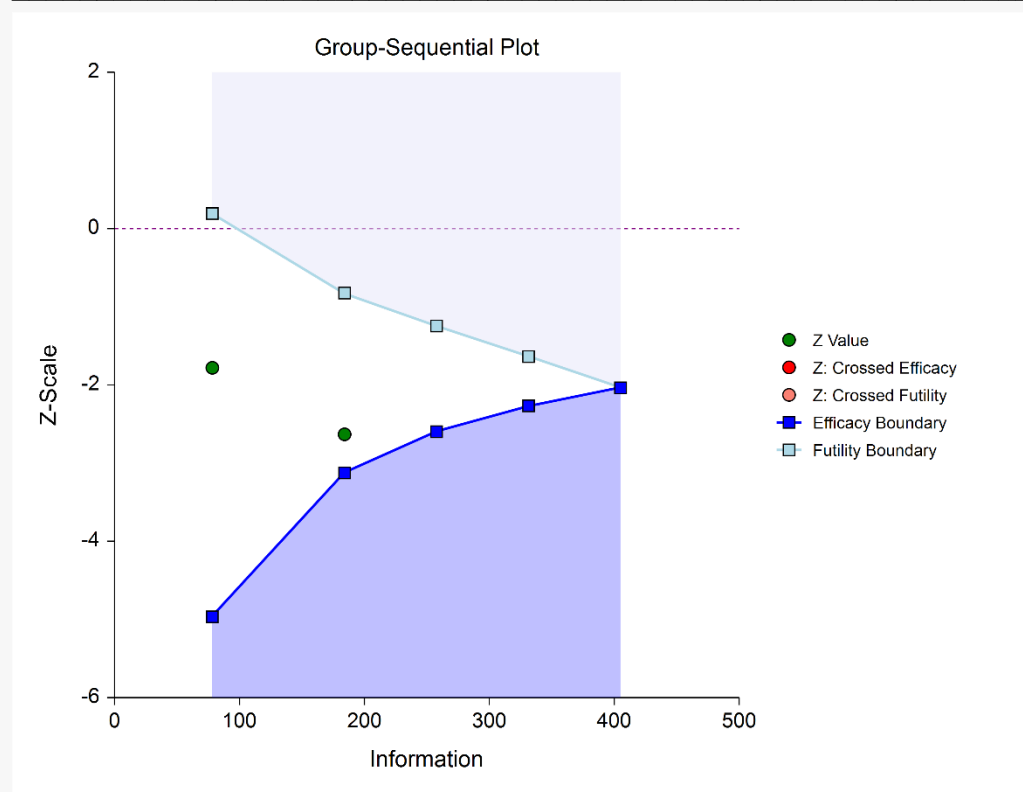**P-Values and Boundaries at Stage 2**

Maximum Information: 437.3497
Alternative Hypothesis: P - P0 < |NIM|
Non-Inferiority Margin (NIM): 0.05
Futility Boundaries: Non-Binding

Stage	Z-Test P-Value	Boundaries Efficacy	Boundaries Futility	Information Proportion	Decision
1	0.03059	0.00000	0.56479	0.1977	Continue
2	0.00283	0.00101	0.19423	0.4651	Continue
3		0.00488	0.10318	0.6434	
4		0.01177	0.05001	0.8217	
5		0.02069	0.02069	1.0000	

P-values and P-value boundaries are one-sided values.

Current Stage Results Adjusted for Sequential Analysis (Stage 2)

This section gives appropriate adjustments to the raw results to reflect the group-sequential nature of the analysis.

Current Stage Results Adjusted for Sequential Analysis (Stage 2)

Stage	Actual Difference Sample P - P0 - NIM	Group-Sequential Adjusted Difference 95.0% C.I. of Diff. Lower	Group-Sequential Adjusted Difference 95.0% C.I. of Diff. Upper	C.I. Midpoint	Conf. Level Where Upper Boundary Is Zero
2	-0.19400	-0.48596	-0.08296	-0.28446	99.434%

Descriptive Statistics up to Stage 2

Descriptive Statistics up to Stage 2

Stage	N	X	P	P0	P - P0	SE
1	17	2	0.11765	0.26900	-0.15135	0.10755
2	40	5	0.12500	0.26900	-0.14400	0.07011

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

This section shows that the target sample size for the next stage should be 56.

Information Report at Stage 2

Maximum Information: 437.3497
Alternative Hypothesis: P - P0 < |NIM|
Non-Inferiority Margin (NIM): 0.05
Alpha: 0.0250

Stage	Target Information Proportion	Achieved Information Proportion	Target Information	Achieved Information	N	P0
1	0.2000	0.1977	87.4699	86.4528	17.00	0.26900
2	0.4000	0.4651	174.9399	203.4184	40.00	0.26900
3	0.6000	*0.6434	262.4098	*281.3955	*55.33	0.26900
4	0.8000	*0.8217	349.8797	*359.3726	*70.67	0.26900
5	1.0000	*1.0000	437.3497	*437.3497	*86.00	0.26900

* Projected value

Alpha Spending at Stage 2

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

Alpha Spending at Stage 2

Target Final Stage Alpha: 0.0250
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	0.1977	0.0000	0.0000	0.000000	0.0	0.0
2	0.4651	0.0010	0.0010	0.001014	4.1	4.1
3 *	0.6434	0.0042	0.0052	0.004879	16.7	20.8
4 *	0.8217	0.0082	0.0134	0.011772	32.8	53.6
5 *	1.0000	0.0116	0.0250	0.020691	46.4	100.0

* Projected

Beta Spending for Futility at Stage 2

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

Beta Spending for Futility at Stage 2

Target Cumulative Beta at Final Stage: 0.1000
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	0.1977	0.0330	0.0330	0.564792	33.0	33.0
2	0.4651	0.0316	0.0647	0.194226	31.6	64.7
3 *	0.6434	0.0150	0.0797	0.103181	15.0	79.7
4 *	0.8217	0.0115	0.0912	0.050008	11.5	91.2
5 *	1.0000	0.0088	0.1000	0.020691	8.8	100.0

* Projected

Conditional and Predictive Power Report at Stage 2

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

Conditional and Predictive Power Report at Stage 2

Maximum Information: 437.3497
Information this Stage: 203.4184
Proportion of Maximum Information: 0.4651
Predictive Power: 0.9747

δ Name	δ Value	Conditional Power
Design	-0.0990	0.9853
Data	-0.1440	0.9979
δ1	0.0500	0.4603

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

Boundary Probabilities for δ = -0.099

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

Boundary Probabilities for δ = -0.099
_____

Number of Simulations:	2000
User-Entered Random Seed:	4238623
Futility Boundaries:	Non-Binding
After Efficacy Boundary Crossing:	Hold Out
After Non-Binding Futility Boundary Crossing:	Leave In
Alternative Hypothesis:	P - P0 < |NIM|
Non-Inferiority Margin (NIM):	0.05
P:	0.17
P0:	0.269
δ:	-0.099

Stage	N	Z-Test Value	Efficacy Boundary	Efficacy Probability	Futility Boundary	Futility Probability
1	17.00	-1.8722	-4.9070		0.1631	
2	40.00	-2.7669	-3.0861		-0.8624	
3	*55.33		-2.5843	0.8865	-1.2636	0.0010
4	*70.67		-2.2645	0.0975	-1.6448	0.0020
5	*86.00		-2.0397	0.0130	-2.0397	0.0080

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

Boundary Probabilities for δ = -0.144

This section estimates the probabilities of crossing future boundaries if the current sample proportion is assumed.

Boundary Probabilities for δ = -0.144
_____

Number of Simulations:	2000
User-Entered Random Seed:	4238623
Futility Boundaries:	Non-Binding
After Efficacy Boundary Crossing:	Hold Out
After Non-Binding Futility Boundary Crossing:	Leave In
Alternative Hypothesis:	P - P0 < |NIM|
Non-Inferiority Margin (NIM):	0.05
P:	0.125
P0:	0.269
δ:	-0.144

Stage	N	Z-Test Value	Efficacy Boundary	Efficacy Probability	Futility Boundary	Futility Probability
1	17.00	-1.8722	-4.9070		0.1631	
2	40.00	-2.7669	-3.0861		-0.8624	
3	*55.33		-2.5843	0.9635	-1.2636	0.0000
4	*70.67		-2.2645	0.0340	-1.6448	0.0000
5	*86.00		-2.0397	0.0025	-2.0397	0.0010

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

Boundary Probabilities for δ = 0.05

This section estimates the probabilities of crossing future boundaries if the difference for the remaining looks is assumed to be 0.05 (the non-inferiority margin).

Boundary Probabilities for δ = 0.05
───

Number of Simulations:	2000	
User-Entered Random Seed:	4238623	
Futility Boundaries:	Non-Binding	
After Efficacy Boundary Crossing:	Hold Out	
After Non-Binding Futility Boundary Crossing:	Leave In	
Alternative Hypothesis:	P - P0 < |NIM|	
Non-Inferiority Margin (NIM):	0.05	
P:	0.319	
P0:	0.269	
δ:	0.05	

			Efficacy		Futility	
Stage	**N**	**Z-Test Value**	**Boundary**	**Probability**	**Boundary**	**Probability**
1	17.00	-1.8722	-4.9070		0.1631	
2	40.00	-2.7669	-3.0861		-0.8624	
3	*55.33		-2.5843	0.3520	-1.2636	0.0410
4	*70.67		-2.2645	0.1500	-1.6448	0.2755
5	*86.00		-2.0397	0.0940	-2.0397	0.5420

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

Example 4 – Group-Sequential Analysis using Stage Counts

Suppose that the setup is the same as in Example 1, except that the data are arranged as stage counts rather than responses for individual observations. It is anticipated that the results should be the same as those of Example 1.

Setup

To run this example, complete the following steps:

1   Open the CSection1 Stage Counts example dataset

- From the File menu of the NCSS Data window, select **Open Example Data**.
- Select CSection1 Stage Counts and click OK.

2   Specify the Group-Sequential Non-Inferiority Analysis for One Proportion procedure options

- Find and open the **Group-Sequential Non-Inferiority Analysis for One Proportion** procedure using the menus or the Procedure Navigator.
- The settings 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.

  Variables Tab

  Frequency Variable..**Count**

3   Run the procedure

- Click the **Run** button to perform the calculations and generate the output.

Run Summary Report

The maximum information is the same as that of Example 1.

Run Summary Report

Item	Value
Maximum Number of Stages (Design):	5
Current Stage:	3
Alternative Hypothesis:	P - P0 < |NIM|
Non-Inferiority Margin (NIM):	0.05
Alpha Spending Function:	O'Brien-Fleming Analog
Beta Spending Function:	Hwang-Shih-DeCani (γ = 1.5)
Futility Boundaries:	Non-Binding
Alpha:	0.0250
Maximum Information:	437.3497

Z-Values and Boundaries at Stage 3

These results are the same as those of Example 1.
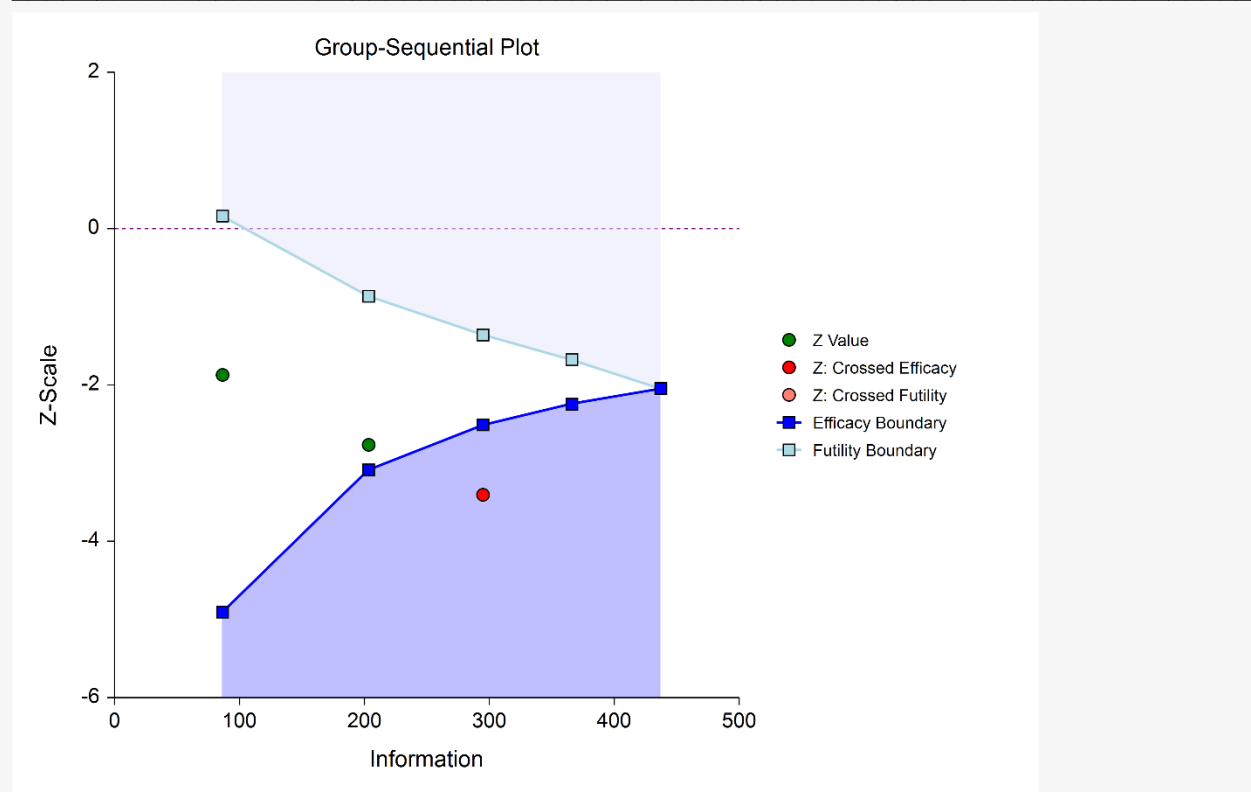
Z-Values and Boundaries at Stage 3

Maximum Information: 437.3497
Alternative Hypothesis: P - P0 < |NIM|
Non-Inferiority Margin (NIM):   0.05
Futility Boundaries: Non-Binding

| | | Boundaries | | | |
| | Z-Test | | | Information | |
Stage	Value	Efficacy	Futility	Proportion	Decision
1	-1.8722	-4.9070	0.1603	0.1977	Continue
2	-2.7669	-3.0861	-0.8668	0.4651	Continue
3	-3.4058	-2.5109	-1.3621	0.6744	Crossed Efficacy
4		-2.2466	-1.6766	0.8372	
5		-2.0460	-2.0460	1.0000	

Group-Sequential Boundary Plot at Stage 3

This plot is the same as that of Example 1.

Group-Sequential Boundary Plot at Stage 3

P-Values and Boundaries at Stage 3

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

P-Values and Boundaries at Stage 3

Maximum Information: 437.3497
Alternative Hypothesis: P - P0 < |NIM|
Non-Inferiority Margin (NIM): 0.05
Futility Boundaries: Non-Binding

Stage	Z-Test P-Value	Boundaries		Information Proportion	Decision
		Efficacy	Futility		
1	0.03059	0.00000	0.56367	0.1977	Continue
2	0.00283	0.00101	0.19303	0.4651	Continue
3	0.00033	0.00602	0.08658	0.6744	Crossed Efficacy
4		0.01233	0.04681	0.8372	
5		0.02038	0.02038	1.0000	

P-values and P-value boundaries are one-sided values.

Current Stage Results Adjusted for Sequential Analysis (Stage 3)

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

Current Stage Results Adjusted for Sequential Analysis (Stage 3)

Stage	Actual Difference Sample P - P0 - NIM	Group-Sequential Adjusted Difference			Conf. Level Where Upper Boundary Is Zero
		95.0% C.I. of Diff.		C.I. Midpoint	
		Lower	Upper		
3	-0.19831	-0.37445	-0.08509	-0.23210	99.762%

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

Descriptive Statistics up to Stage 3

These results are the same as those of Example 1.

Descriptive Statistics up to Stage 3

Stage	N	X	P	P0	P - P0	SE
1	17	2	0.11765	0.26900	-0.15135	0.10755
2	40	5	0.12500	0.26900	-0.14400	0.07011
3	58	7	0.12069	0.26900	-0.14831	0.05823

Information Report at Stage 3

The results of this section and all other output sections are the same as those of Example 1. Minor differences will exist for reports that use simulation.

Information Report at Stage 3

Maximum Information: 437.3497
Alternative Hypothesis: P - P0 < |NIM|
Non-Inferiority Margin (NIM):   0.05
Alpha: 0.0250

Stage	Target Information Proportion	Achieved Information Proportion	Target Information	Achieved Information	N	P0
1	0.2000	0.1977	87.4699	86.4528	17.00	0.26900
2	0.4000	0.4651	174.9399	203.4184	40.00	0.26900
3	0.6000	0.6744	262.4098	294.9567	58.00	0.26900
4	0.8000	*0.8372	349.8797	*366.1532	*72.00	0.26900
5	1.0000	*1.0000	437.3497	*437.3497	*86.00	0.26900

* Projected value