Chapter 702

Group-Sequential Non-Inferiority Analysis for Two Means with Known Variances

The corresponding sample size procedure, found in PASS Sample Size software, is Group-Sequential Non-Inferiority Tests for Two Means with Known Variances (Simulation).

Introduction

This procedure is used to test non-inferiority for the difference of two means in stages (sometimes called looks or interim analyses) when the variances are known. 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
- Within group standard deviations
- Assumed difference in means

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 standard deviations and mean 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.

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 mean difference and sample standard deviations. 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. 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.
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 means and standard deviations 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 mean 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 mean difference

Due to the bias that is introduced in the group-sequential analysis process, the raw data confidence interval of the difference in means 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 means. 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 two means, the appropriate null and alternative hypotheses depend on whether higher means are better or higher means are worse.

**Case 1: Low Values Good**

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

\[
H_0: \mu_1 \geq \mu_2 + |M_{NI}| \quad \text{versus} \quad H_1: \mu_1 < \mu_2 + |M_{NI}|
\]

\[
H_0: \mu_1 - \mu_2 \geq |M_{NI}| \quad \text{versus} \quad H_1: \mu_1 - \mu_2 < |M_{NI}|
\]

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

**Case 2: High Values Good**

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

\[
H_0: \mu_1 \leq \mu_2 - |M_{NI}| \quad \text{versus} \quad H_1: \mu_1 > \mu_2 - |M_{NI}|
\]

\[
H_0: \mu_1 - \mu_2 \leq -|M_{NI}| \quad \text{versus} \quad H_1: \mu_1 - \mu_2 > -|M_{NI}|
\]

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

Stages in Group-Sequential Testing

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

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

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

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

$$z_k = \frac{\bar{X}_{1k} - \bar{X}_{2k} - |NIM|}{\sqrt{\frac{\sigma_1^2}{n_{1k}} + \frac{\sigma_2^2}{n_{2k}}}}$$

and, when higher means are better:

$$z_k = \frac{\bar{X}_{1k} - \bar{X}_{2k} - (-|NIM|)}{\sqrt{\frac{\sigma_1^2}{n_{1k}} + \frac{\sigma_2^2}{n_{2k}}}} = \frac{\bar{X}_{1k} - \bar{X}_{2k} + |NIM|}{\sqrt{\frac{\sigma_1^2}{n_{1k}} + \frac{\sigma_2^2}{n_{2k}}}}$$

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, the anticipated standard deviations, and an estimate of the true difference in means.

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 final stage ($K$) or total (design) information is calculated from the specified standard deviations and the final sample sizes, as

$$I_K^* = \frac{1}{\frac{\sigma_1^2}{n_{1K}} + \frac{\sigma_2^2}{n_{2K}}}$$

The information at any stage $k$ may be calculated from all the accumulated data up to and including that stage, as

$$I_k = \frac{1}{\frac{\sigma_1^2}{n_{1k}} + \frac{\sigma_2^2}{n_{2k}}}$$

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

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

The information fractions are used in conjunction with the spending function(s) to define the alpha and/or beta to be spent at each stage.

To properly use the spending function at the final stage, it is required that $p_K = 1$. However, if the final stage is reached, we see that

$$I_K = \frac{1}{\frac{\sigma_1^2}{n_{1K,achieved}} + \frac{\sigma_2^2}{n_{2K,achieved}}} \neq I_K^* = \frac{1}{\frac{\sigma_1^2}{n_{1K}} + \frac{\sigma_2^2}{n_{2K}}}$$
so that

\[ p_K = \frac{I_K}{I_K^*} \neq 1 \]

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

\[ I_K^{*} = I_K \]

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

**Types of Boundaries**

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

**Efficacy Only**

The simplest group-sequential test involves a single set of stage boundaries with early stopping for efficacy.
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 (One-Sided)**

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

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**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.

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**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).

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**Spending Functions**

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

- Spending functions give a value of zero when the proportion of accumulated information is zero.
  \[ \alpha(0) = 0 \text{ (for alpha-spending)} \]
  \[ \beta(0) = 0 \text{ (for beta-spending)} \]

- Spending functions are increasing functions.

- Spending functions give a value of alpha (or beta) when the proportion of accumulated information is one.
  \[ \alpha(1) = \alpha \text{ (for alpha-spending)} \]
  \[ \beta(1) = \beta \text{ (for beta-spending)} \]

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

Spending Functions Available in this Procedure

The following spending functions are shown as alpha-spending functions. The corresponding beta-spending function is given by replacing \( \alpha \) with \( \beta \).

O'Brien-Fleming Analog

The O'Brien Fleming Analog (Lan & DeMets, 1983) roughly mimics the O'Brien-Fleming (non-spending function) design, with the key attribute that only a small proportion of alpha is spent early. Its popularity comes from it proportioning enough alpha to the final stage that the final stage boundary is not too different from the fixed-sample (non-group-sequential) boundary.

\[ \alpha(0) = 0 \]

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

\[ \alpha(1) = \alpha \]
**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.

\[ \alpha(0) = 0 \]
\[ \alpha(p_k) = \alpha \ln(1 + (e - 1)p_k) \]
\[ \alpha(1) = \alpha \]

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**Power Family**

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

\[ \alpha(0) = 0 \]
\[ \alpha(p_k) = p_k^\rho, \quad \rho > 0 \]
\[ \alpha(1) = \alpha \]

A power family spending function with a \( \rho \) of 1 is similar to a Pocock design, while a power family spending function with a \( \rho \) of 3 is more similar to an O’Brien-Fleming design.
\[ \rho = 1 \]

\[ \rho = 2 \]
\( \rho = 3 \)

**Hwang-Shih-DeCani (Gamma Family)**

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

\[
\alpha(0) = 0 \\
\alpha(p_k) = \alpha \left( \frac{1 - e^{-\gamma p_k}}{1 - e^{-\gamma}} \right), \quad \gamma \neq 0 \\
\alpha(p_k) = \alpha p_k, \quad \gamma = 0 \\
\alpha(1) = \alpha
\]
\[ \gamma = -3 \]

\[ \gamma = -1 \]
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$\gamma = 1$

$\gamma = 3$
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 Mean Difference

The adjusted mean 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 $\theta$ 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

$\theta$ = the parameter being tested by the hypothesis

$k$ = an interim stage at which the conditional power is computed $(k = 1, \ldots, K - 1)$

$K$ = the stage at which the study is terminated, and the final test computed
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\( Z_k = \) 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 \( \alpha \).

For a test of a two means with null hypothesis \( H_0: \mu_1 = \mu_2 \), where \( \mu_1 \) and \( \mu_2 \) are the population means in groups 1 and 2, respectively, under the alternative hypothesis, these components are computed in Chang (2008) page 70 as

\[ \theta = \mu_1 - \mu_2 \pm |NIM| \]  

(the expected difference under the alternative hypothesis)

\[ Z_k = (\bar{x}_{1k} - \bar{x}_{2k} \pm |NIM|)\sqrt{I_k} \]  

(the \( z \) statistic computed from the observed data)

\[ I_k = \left( \frac{\sigma_1^2}{n_{1k}} + \frac{\sigma_2^2}{n_{2k}} \right)^{-1} \]  

(the interim information level)

\[ I_K = \left( \frac{\sigma_1^2}{n_1} + \frac{\sigma_2^2}{n_2} \right)^{-1} \]  

(the final information level)

where

\( \bar{x}_{jk} \) is the sample mean for group \( j \), estimating \( \mu_j \) at stage \( k \)

\( \hat{I}_k \) is the estimated information from the sample at stage \( k \)

\( n_{jk} \) is the sample size in group \( j \) at stage \( k \)

\( n_j \) is the final sample size in group \( j \)

\( \sigma_j^2 \) is the variance of group \( j \)

### 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

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

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 means. 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 user-specified standard deviations and the assumed means.
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 means.

### 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 three columns. One column gives the individual responses. Another column identifies the group of the patient, individual, or experimental unit. A third column defines the associated stage of each response. The column for stages must use numeric integers beginning with 1 (1, 2, 3, …).

The three columns are assigned on the Variables tab of the procedure. Groups 1 and 2 are also assigned on the Variables tab.

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.
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Group-Sequential Analysis Data

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<thead>
<tr>
<th>Response</th>
<th>Group</th>
<th>Stage</th>
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<tr>
<td>37.6</td>
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<td>Placebo</td>
<td>1</td>
</tr>
<tr>
<td>35.7</td>
<td>Treatment</td>
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</tr>
<tr>
<td>53.4</td>
<td>Placebo</td>
<td>1</td>
</tr>
<tr>
<td>31.8</td>
<td>Treatment</td>
<td>1</td>
</tr>
<tr>
<td>38.4</td>
<td>Placebo</td>
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Procedure Options

This section describes the options available in this procedure. To find out more about using a procedure in general, go to the Procedures chapter.

Variables Tab

Variables

Response Variable
Specify the column containing the response data.

The response data is divided into groups and into stages using the values of the Group Variable and the Stage Variable.

Response: Group Stage
12 Trt 1
35 Cntrl 1
19 Cntrl 1
24 Trt 1
. . .
. . .
26 Cntrl 2
44 Cntrl 2
36 Trt 2
33 Cntrl 2
. . .
. . .
**Group Variable**
Specify the column defining the grouping of the response data. The Group Variable values are assigned to Group 1 and Group 2 using the Group 1 Value and Group 2 Value entries.

<table>
<thead>
<tr>
<th>Response</th>
<th>Group</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Trt</td>
<td>1</td>
</tr>
<tr>
<td>35</td>
<td>Cntrl</td>
<td>1</td>
</tr>
<tr>
<td>19</td>
<td>Cntrl</td>
<td>1</td>
</tr>
<tr>
<td>24</td>
<td>Trt</td>
<td>1</td>
</tr>
<tr>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>26</td>
<td>Cntrl</td>
<td>2</td>
</tr>
<tr>
<td>44</td>
<td>Cntrl</td>
<td>2</td>
</tr>
<tr>
<td>36</td>
<td>Trt</td>
<td>2</td>
</tr>
<tr>
<td>33</td>
<td>Cntrl</td>
<td>2</td>
</tr>
<tr>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
</tbody>
</table>

**Group 1 Value**
Enter the value of the Group Variable column that designates Group 1. For example, if the Group Variable column is filled with Trt and Cntrl, enter Trt as the Group 1 Value to designate all Trt rows as Group 1. Do not put quotes around the Group 1 Value.

**Group 2 Value**
Enter the value of the Group Variable column that designates Group 2. For example, if the Group Variable column is filled with Trt and Cntrl, enter Cntrl as the Group 2 Value to designate all Cntrl rows as Group 2. Do not put quotes around the Group 2 Value.

**Stage Variable**
Specify the column that specifies the stage of each response. The values of the Stage Variable column must be integers between 1 and the current stage, inclusive. The procedure uses the highest integer in the Stage Variable column as the current stage.

<table>
<thead>
<tr>
<th>Response</th>
<th>Group</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Trt</td>
<td>1</td>
</tr>
<tr>
<td>35</td>
<td>Cntrl</td>
<td>1</td>
</tr>
<tr>
<td>19</td>
<td>Cntrl</td>
<td>1</td>
</tr>
<tr>
<td>24</td>
<td>Trt</td>
<td>1</td>
</tr>
<tr>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>26</td>
<td>Cntrl</td>
<td>2</td>
</tr>
<tr>
<td>44</td>
<td>Cntrl</td>
<td>2</td>
</tr>
<tr>
<td>36</td>
<td>Trt</td>
<td>2</td>
</tr>
<tr>
<td>33</td>
<td>Cntrl</td>
<td>2</td>
</tr>
<tr>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
</tbody>
</table>

**Design**

**Maximum Number of Stages (K)**
Enter an integer value indicating the number of stages in the planning design if the final stage is reached.

**Information Proportion at each Stage**
Specify whether stages are intended to reflect evenly spaced increments in information, or whether custom spacing is to be used.
• Equally incremented
  For this selection, the increment in information at each stage is the same for all stages. For example, if the maximum number of stages is 4, the information proportion at each stage is planned to be 0.25, 0.50, 0.75, 1.00.

• Custom (Enter cumulative information proportions)
  Select this option to enter specific cumulative information proportions for each stage. The values entered should be between 0 and 1, increasing in value, and the final value should be 1. The number of proportions entered should equal the Maximum Number of Stages.

Cumulative Information Proportions
When Information Proportion at each stage is set to Custom, this option appears to allow the user to enter specific cumulative information proportions for each stage.

The values entered should be between 0 and 1, increasing in value, and the final value should be 1. The number of proportions should equal the Maximum Number of Stages. The values may be separated by spaces or commas.

N's if Final Stage Reached
Enter the sample sizes N1 and N2 corresponding to the planned group-sequential analysis study if the final stage is reached. For example, these values might be obtained through the PASS sample size software. These values are also used in the calculation of the maximum information.

Means (δ = μ1 − μ2): (μ1 and μ2)
Enter the planning design means upon which the power and sample size calculations were based. These means may be used in calculations of conditional power, predictive power, future stage stopping probabilities, and future stage estimates of needed sample size.

Standard Deviations (σ0’s)
Enter the planning design within-group standard deviations σ10 and σ20 upon which the power and sample size calculations were based. These standard deviations are used in the calculation of the maximum information. They are also used in the calculation of the z-statistics of each stage, as well as simulation z-statistics.

Non-Inferiority Margin

NIM (Non-Inferiority Margin)
Enter the value for the non-inferiority margin. The sign of the non-inferiority margin is determined by the direction of the alternative hypothesis:

• Ha: μ1 - μ2 < |NIM| (Lower values are better)
  In this case, rejecting the null hypothesis implies that the treatment mean is no more than a small amount (NIM) above the reference/control/standard mean.

• Ha: μ1 - μ2 > -|NIM| (Higher values are better)
  In this case, rejecting the null hypothesis implies that the treatment mean is no less than a small amount (NIM) below the reference/control/standard mean.

Information

Future Stage Information Adjustment
At each stage, the information is not likely to match the original design information. The Future Stage Information Adjustment specifies how future stage information proportions will be determined.
• **Adjust information proportions proportional to original design**
  For this selection, the target information proportion for each future stage is calculated 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.

• **Keep original design information proportions exactly**
  For this choice, target information proportion for each future stage is left as that specified by 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 selection would 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. If the next information proportion is less than the current stage information proportion, the software will automatically switch to adjusting the information proportions proportional to the original design.

---

**Boundaries**

This section is used to specify the details of the types of boundaries, the direction of the alternative hypothesis, and alpha and beta spending.

---

**Boundaries – Boundary Structure**

**Boundaries Used**

Use this option to determine whether boundaries are for efficacy only, futility only, or both. To see example images of each of the boundary types, see the Type of Boundaries section of the documentation.

• **Efficacy Only**
  The simplest group-sequential test involves a single set of stage boundaries with early stopping for efficacy (Rejecting H0).

• **Efficacy with Futility**
  This design allows early stopping for either efficacy (Reject H0) or futility (Accept H0). The final stage boundary is equal for the two sets of boundaries.

• **Futility Only**
  In this one-sided design, the interim analyses are used only for futility. Please be aware that these boundaries may take several minutes to compute, particularly when one or more stages are skipped.

**Hypothesis Direction**

Specify the direction of the alternative hypothesis. This procedure is set up to assume that group 1 is the treatment/new method group, and group 2 is the reference/control/standard group.

• **Ha: μ1 – μ2 < |NIM| (Lower values are better)**
  In this case, rejecting the null hypothesis implies that the treatment mean is no more than a small amount (NIM) above the reference/control/standard mean.

• **Ha: μ1 – μ2 > -|NIM| (Higher values are better)**
  In this case, rejecting the null hypothesis implies that the treatment mean is no less than a small amount (NIM) below the reference/control/standard mean.
Boundary Specification
Specify whether the boundaries are calculated based on spending functions or input directly.

- **Spending Function Calculation**
  Spending function methods are now mainstream methods since they are flexible to the proportion of information at each stage, and there is a wide variety of spending functions available.

- **Enter Boundaries Directly**
  In some cases, it may be useful to enter specific Z-value boundaries. This selection provides that option.

**Alpha**
Alpha is the significance level used in the hypothesis tests. It is the overall probability of a Type I error. Alpha is divided among the stages of the study according the spending function. A value of 0.05 is most commonly used for two-sided tests, and 0.025 is commonly used for one-sided tests, but 0.01, 0.1, and other values are sometimes used.

**Beta**
Beta is the probability of a Type II error during the course of the study. Power is one minus beta. Beta is divided among the stages of the study according the selected spending function. Beta values of 0.2 and 0.1 are common, but any value between 0 and 1 is eligible.

**Spending Function (Alpha or Beta)**
The alpha- and beta-spending functions determine how alpha and/or beta are distributed across the stages. See the Spending Function section of the documentation for more details.

- **Hwang-Shih-DeCani (Gamma Family)**
The Hwang-Shih-DeCani gamma family of spending function has a $\gamma$ parameter that allows for a variety of spending functions. The $\gamma$ parameter can be positive, negative, or 0.

- **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 or beta is spent early. Its popularity comes from it proportioning enough alpha (or beta) to the final stage that the final stage boundary is not too different from the fixed-sample (non-group-sequential) boundary.

- **Pocock Analog**
The Pocock Analog (Lan & DeMets, 1983) roughly mimics the Pocock (non-spending function) design, with the key attribute that alpha and/or beta are spent roughly equally across all stages.

- **Power Family**
The power family of spending functions has a $\rho$ parameter that gives flexibility in the spending function shape. The $\rho$ parameter must be greater than 0. A power family spending function with a $\rho$ of 1 is similar to a Pocock design, while a power family spending function with a $\rho$ of 3 is more similar to an O’Brien-Fleming design.

- **Custom**
Select this option to enter specific cumulative alpha (or beta) values for each stage. The values entered should be between 0 and alpha (or half alpha for two-sided tests) or beta, increasing in value, and the final value should be alpha (or half alpha) or beta. The number of custom cumulative alpha (or beta) spent values should equal the Maximum Number of Stages.
γ (Gamma)

γ is used to define the Hwang-Shih-DeCani (γ) spending function. Negative values of γ spend more of alpha or beta at later looks, values near 0 spend alpha or beta evenly, and positive values of γ spend more of alpha or beta at earlier looks.

ρ

ρ is used to define the power family spending function. Only positive values for ρ are permitted. Values of ρ near zero spend more of alpha or beta at earlier looks, values near 1 spend alpha or beta evenly, and larger values of ρ spend more of alpha or beta at later looks. 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.

Custom Cumulative Alpha or Beta Spent

Enter a series of cumulative alpha or beta values, separated by spaces. The number of values should equal the Maximum Number of Stages. As cumulative values, the values must be increasing. The final value could be set to equal alpha or beta. Otherwise, the values will be scaled so that the final value is equal to alpha or beta.

Boundary Z Values (Entered Directly)

Enter a Z value for each stage of this boundary, separated by spaces or commas. The number of Z values entered should match the Maximum Number of Stages (K).

Skipped Stages

Specify the stages that will be skipped, if any, for this boundary. The final stage cannot be skipped. The stage numbers should be separated by spaces or commas. For example, if the maximum number of stages is 5, but a boundary analysis at stages 2 and 4 is to be skipped, 2 4 may be entered here. The spending function accounts for the amount of alpha or beta that should be spent at a stage following a skipped stage.

Binding or Non-Binding Futility

This option specifies whether the futility boundaries are binding or non-binding.

- Binding
  Binding futility boundaries are computed in concert with significance boundaries. They are called binding because they require the stopping of a trial if they are crossed. If the trial is not stopped, the probability of a false positive will exceed alpha.

- Non-Binding
  When Non-binding futility boundaries are computed, the significance boundaries are first computed, ignoring the futility boundaries. The futility boundaries are then computed. These futility boundaries are non-binding because continuing the trial after they are crossed will not affect the overall probability of a false positive declaration. One 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).

Reports Tab

The options on this panel specify which reports will be included in the output.

Reports for Current Stage

Summary using Z Scale

This report gives the Z-Test statistics and corresponding decision, as well as the boundary values, and the information proportion at each stage.
Summary using P-Value Scale
This report gives the Z-Test p-values and corresponding decision, as well as the boundary p-values, and the information proportion at each stage.

Current Stage Results Adjusted for Sequential Analysis
This section provides the raw mean difference, the group-sequential adjusted confidence interval and difference, and the confidence level at which the adjusted confidence interval boundary is zero. These group-sequential adjusted results are based on the assumption that a stopping decision has been made. See more details near the end of the Technical Details section of the documentation.

Confidence Level
This is the confidence level used in the group-sequential adjusted confidence interval of the difference.

Descriptive Statistics
This section provides the sample sizes and raw sample means, sample standard deviations, and sample mean differences at each stage. The data used at each stage is the cumulative data.

Information Report
The Information Report gives the target and achieved information, and target and achieved information proportions. Projected informations and sample sizes are given for future stages.

Alpha Spending
This report shows the amount and percentage of alpha spent at each stage, both individually and cumulatively. Projected values are given for future stages. The report is blank if boundaries are input directly.

Beta Spending
This report shows the amount and percentage of beta spent at each stage, both individually and cumulatively. Projected values are given for future stages. The report is blank if there are no futility boundaries or if boundaries are input directly.

Conditional and Predictive Power
This report gives the predictive power and conditional power based on the current $z$-statistic and the proportion of the information to the maximum information. The conditional power is based on the specified differences, while the predictive power is not.

Future Boundary Crossing Probabilities using Simulation
This report gives the various probabilities of crossing all future boundaries. These probabilities are calculated as proportions of a large number of simulated data sets. For two-sided boundary scenarios, such as ‘Two-sided Efficacy with Futility (Asymmetric)’, the comparisons of the simulation Z-statistics to the two (upper and lower) sides are made independently. For more details, see the description at the end of the Technical Details section of the documentation.

Number of Simulations
Increasing the number of simulations improves the accuracy of the estimated probabilities of boundary crossing, but it also increases the computation time. One suggestion is to first run the procedure with a small number of simulations, such as 1,000 or 10,000. The simulation time can then be estimated and a reasonable increase in simulations can be made before a second run. A decent lower number of simulations is 100,000, but more is better when feasible.

After Boundary Crossing
This option specifies whether simulation Z-values are ‘held out’ after crossing a boundary, or whether simulation Z-values are compared to boundaries at all future stages, regardless of whether a boundary was crossed at a previous stage. For two-sided boundary scenarios, such as ‘Two-sided Efficacy with Futility (Asymmetric)’, the comparisons of the simulation Z-statistics to the two (upper and lower) sides are made independently.
Hold out
For this selection, once a simulation Z-statistic crosses an efficacy boundary or a binding futility boundary, it is removed from consideration for future stages. For non-binding futility boundaries, simulation Z-statistics remain in the simulation for future stages, regardless of whether ‘After Boundary Crossing’ is set to ‘Hold out’ or ‘Leave in’.

Leave In
For this choice, simulation Z-statistics at all future stages are compared to the boundary values, regardless of whether a boundary was crossed at a previous stage.

Reports for Current Stage – Conditional and Predictive Power and Boundary Crossing Probability Parameters

Design Means ($\delta = \mu_1 - \mu_2$)
The design difference in means is typically the difference upon which the sample size calculation is based. The design means are specified in the Design section of the Variables tab. The difference in design means is used for conditional power. For future boundary crossing probability simulations, values are simulated from Normal distributions with these means.

Data Means ($\delta = \bar{x}_1 - \bar{x}_2$)
The data difference in means is the difference in sample means at the current stage. The difference in data means is used for conditional power. For future boundary crossing probability simulations, values are simulated from Normal distributions with these means.

Custom Means ($\delta = \mu_1 - \mu_2$)
Custom differences in means by specifying custom $\mu_1$ and $\mu_2$ may be used to determine their effect on conditional power or future boundary crossing probabilities. The difference in means is used for conditional power. For future boundary crossing probability simulations, values are simulated from Normal distributions with these means. Multiple values may be separated by spaces or commas. A separate report will be generated for each mean combination.

Custom $\mu_1$ and $\mu_2$
Enter one or more values for $\mu_1$ and $\mu_2$. The difference in means is used for conditional power. For future boundary crossing probability simulations, values are simulated from Normal distributions with these means. When more than one value is entered, a separate analysis is made for each combination of $\mu_1$ and $\mu_2$.

Planning Stage (Stage 0) Reports

Various Reports
Check the box to include this planning stage report. The reports are the same as those of the current stage reports, except that no stage results are given.

Past Reports for Previous Stages

Various Reports
Check the box to include this previous stage report. These reports are the same as those of the current stage reports, except that the results are given for each previous stage.
Report Options Tab

The options on this panel control the label and decimal options of the reports.

Report Options

Variable Names
This option lets you select whether to display only variable names, variable labels, or both.

Value Labels
This option applies to the Group Variable. It lets you select whether to display data values, value labels, or both. Use this option if you want the output to automatically attach labels to the values (like 1=Yes, 2=No, etc.). See the section on specifying Value Labels elsewhere in this manual.

Decimal Places

Decimals
This option allows the user to specify the number of decimal places directly or based on the significant digits (auto).

If one of the auto options is used, the ending zero digits are not shown. For example, if ‘Auto (Up to 7)’ is chosen, 0.0500 is displayed as 0.05
1.314583689 is displayed as 1.314584

The output formatting system is not designed to accommodate ‘Auto (Up to 13)’, and if chosen, this will likely lead to lines that run on to a second line. This option is included, however, for the rare case when a very large number of decimals is needed. Sometimes Auto (Up to 7) doesn’t show well and causes formatting problems as well.

Plots Tab

The options on this panel control the inclusion and appearance of the plots. The set of available plots depends upon the choice of ‘Boundaries Used’.

Group-Sequential Boundary Plots

Z-Statistic vs Information / Stage / N
Check the boxes to display the plot. Click the plot format button to change the plot settings. To edit the plot with live data, check the box in the top-right corner before running the procedure.

Use care when adding Stage Notes (notes for each stage just above the X-axis). These notes should only be added with live data, as their position is based on the X-axis values.
Example 1 – Group-Sequential Analysis

A blood pressure treatment study is conducted to determine whether a new drug results in patient blood pressure readings that are no higher than a current standard. The desired margin to maintain non-inferiority is 7. The response for each patient is a resting systolic blood pressure. A one-sided test with alpha equal to 0.025 is used.

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

\[ H_0: \mu_1 - \mu_2 = 7 \ (H_0: \mu_{\text{New}} = \mu_{\text{Std}} + 7) \]

versus

\[ H_a: \mu_1 - \mu_2 < 7 \ (H_a: \mu_{\text{New}} < \mu_{\text{Std}} + 7) \]

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 213 patients per group if the final stage is reached, based on known standard deviations of 22 for each group and assumed means of 124 for both the new and standard treatments. 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.
You may follow along here by making the appropriate entries or load the completed template **Example 1** by clicking on Open Example Template from the File menu on the procedure window.

1 **Open the BP NI dataset.**
   - From the File menu of the NCSS Data window, select **Open Example Data**.
   - Click on the file **BP NI.NCSS**.
   - Click **Open**.

2 **Open the procedure window.**
   - Using the Analysis menu or the Procedure Navigator, find and select this procedure.
   - On the menus, select **File**, then **New Template**. This will fill the procedure with the default template.

3 **Specify the variables.**
   - Select the **Variables** tab.
   - Click the small **Column Selection button** to the right of **Response Variable**. Select **Systolic_BP** and click Ok. The column name ‘Systolic_BP’ will appear in the Response Variable box.
   - Click the small **Column Selection button** to the right of **Group Variable**. Select **Treatment** and click Ok. The column name ‘Treatment’ will appear in the Group Variable box.
   - For **Group 1 Value**, enter **New**.
   - For **Group 2 Value**, enter **Standard**.
   - Click the small **Column Selection button** to the right of **Stage Variable**. Select **Stage** and click Ok. The column name ‘Stage’ will appear in the Stage Variable box.

4 **Specify the design.**
   - Set **Maximum Number of Stages (K)** to **5**.
   - Set **Information Proportion at each Stage** to **Equally incremented**.
   - Enter **213** and **213** for **N1** and **N2**.
   - Enter **124** and **124** for **μ1** and **μ2**.
   - Enter **22** and **22** for **σ10** and **σ20**.

5 **Specify the non-inferiority margin.**
   - Enter **7** for **Non-Inferiority Margin (NIM)**.

6 **Specify the information adjustment for future stages.**
   - Set **Future Stage Information Adjustment** to **Adjust information proportions proportional to original design**.

7 **Specify the boundaries.**
   - Set **Boundaries Used** to **Efficacy with Futility**.
   - Set **Hypothesis Direction** to **Ha: μ1 – μ2 < |NIM|** (Lower values are better).
   - Set **Boundary Specification** to **Spending Function Calculation**.
   - Enter **0.025** for **Alpha**.
   - Set **Alpha Spending Function** to **O'Brien-Fleming Analog**.
   - Leave **Skipped Efficacy Stages** empty.
   - Enter **0.10** for **Beta**.
   - Set **Beta Spending Function** to **Hwang-Shih-DeCani (γ)**.
   - Enter **1.5** for **γ**.
   - Leave **Skipped Futility Stages** empty.
   - Set **Binding or Non-Binding Futility** to **Non-Binding**.
Specify the reports.
- Select the Reports tab.
- Check all of the reports under Reports for Current Stage.
- Leave the Confidence Level at 95%.
- Under Conditional and Predictive Power and Boundary Crossing Probability Parameters, check all three checkboxes. For Custom Means, enter 126 and 124 for $\mu_1$ and $\mu_2$.
- Under Planning Stage (Stage 0) Reports, check the reports Summary using Z Scale and Plots.
- Leave or uncheck all the remaining checkboxes, including those under Past Reports for Previous Stages.

Specify the plots.
- Select the Plots tab.
- Make sure Z-Statistic vs Information checkbox is checked.
- You could add the stage number to the plot by clicking 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.

Run the procedure.
- From the Run menu, select Run Procedure. Alternatively, just click the green Run button.

The following reports and charts will be displayed in the Output window.

**Run Summary Report**

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

<table>
<thead>
<tr>
<th>Item</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Number of Stages (Design):</td>
<td>5</td>
</tr>
<tr>
<td>Current Stage:</td>
<td>3</td>
</tr>
<tr>
<td>Alternative Hypothesis:</td>
<td>$\mu_1 - \mu_2 &lt;</td>
</tr>
<tr>
<td>Non-Inferiority Margin (NIM):</td>
<td>7</td>
</tr>
<tr>
<td>Alpha Spending Function:</td>
<td>O'Brien-Fleming Analog</td>
</tr>
<tr>
<td>Beta Spending Function:</td>
<td>Hwang-Shih-DeCani ($\gamma = 1.5$)</td>
</tr>
<tr>
<td>Futility Boundaries:</td>
<td>Non-Binding</td>
</tr>
<tr>
<td>Alpha:</td>
<td>0.0250</td>
</tr>
<tr>
<td>Maximum Information:</td>
<td>0.2200</td>
</tr>
</tbody>
</table>

**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.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Z-Test Value</th>
<th>Efficacy Boundaries</th>
<th>Futility Boundaries</th>
<th>Information Proportion</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-3.2440</td>
<td>-4.8155</td>
<td>0.1241</td>
<td>0.2049</td>
<td>Continue</td>
</tr>
<tr>
<td>2</td>
<td>-3.0128</td>
<td>-3.9393</td>
<td>-0.5604</td>
<td>0.3919</td>
<td>Continue</td>
</tr>
<tr>
<td>3</td>
<td>-3.3729</td>
<td>-2.6826</td>
<td>-1.1540</td>
<td>0.5986</td>
<td>Crossed Efficacy</td>
</tr>
<tr>
<td>4</td>
<td>-2.2906</td>
<td>-1.5999</td>
<td></td>
<td>0.7993</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>-2.0307</td>
<td>-2.0307</td>
<td></td>
<td>1.0000</td>
<td></td>
</tr>
</tbody>
</table>
Group-Sequential Boundary Plot at Stage 3

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

Maximum Information: 0.2200
Alternative Hypothesis: μ1 - μ2 < [NIM]
Non-Inferiority Margin (NIM): 7
Futility Boundaries: Non-Binding
P-values and P-value boundaries are one-sided values.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Z-Test P-Value</th>
<th>Boundaries Efficacy</th>
<th>Boundaries Futility</th>
<th>Information Proportion</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.00059</td>
<td>0.00000</td>
<td>0.54937</td>
<td>0.2049</td>
<td>Continue</td>
</tr>
<tr>
<td>2</td>
<td>0.00129</td>
<td>0.00034</td>
<td>0.28761</td>
<td>0.3919</td>
<td>Continue</td>
</tr>
<tr>
<td>3</td>
<td>0.00037</td>
<td>0.00365</td>
<td>0.12424</td>
<td>0.5986</td>
<td>Crossed Efficacy</td>
</tr>
<tr>
<td>4</td>
<td>0.01099</td>
<td>0.05481</td>
<td>0.7993</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.02114</td>
<td>0.02114</td>
<td>1.0000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 Mean Difference.

![Table](image)

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.

![Table](image)

Information Report at Stage 3

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

Maximum Information: 0.2200  
Alternative Hypothesis: \( \mu_1 - \mu_2 < |\text{NIM}| \)  
Non-Inferiority Margin (NIM): 7  
Alpha: 0.0250

![Table](image)

* Projected value.
Alpha Spending at Stage 3

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

Target Final Stage Alpha: 0.0250
Spending Function: O'Brien-Fleming Analog

<table>
<thead>
<tr>
<th>Stage</th>
<th>Information Proportion</th>
<th>Alpha Spent this Stage</th>
<th>Cumulative Alpha Spent</th>
<th>Nominal (Boundary) Alpha</th>
<th>Percentage Alpha Spent this Stage</th>
<th>Cumulative Percentage Alpha Spent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.2049</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.000001</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>2</td>
<td>0.3919</td>
<td>0.0003</td>
<td>0.0003</td>
<td>0.000343</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>3</td>
<td>0.5986</td>
<td>0.0034</td>
<td>0.0038</td>
<td>0.003653</td>
<td>13.7</td>
<td>15.1</td>
</tr>
<tr>
<td>4 *</td>
<td>0.7993</td>
<td>0.0084</td>
<td>0.0122</td>
<td>0.010994</td>
<td>33.6</td>
<td>48.7</td>
</tr>
<tr>
<td>5 *</td>
<td>1.0000</td>
<td>0.0128</td>
<td>0.0260</td>
<td>0.021143</td>
<td>51.3</td>
<td>100.0</td>
</tr>
</tbody>
</table>

* projected

Beta Spending for Futility at Stage 3

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

Target Final Stage Beta: 0.1000
Spending Function for Futility: Hwang-Shih-DeCani (γ = 1.5)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Information Proportion</th>
<th>Beta Spent this Stage</th>
<th>Cumulative Beta Spent</th>
<th>Nominal (Boundary) Beta</th>
<th>Percentage Beta Spent this Stage</th>
<th>Cumulative Percentage Beta Spent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.2049</td>
<td>0.0341</td>
<td>0.0341</td>
<td>0.549375</td>
<td>34.1</td>
<td>34.1</td>
</tr>
<tr>
<td>2</td>
<td>0.3919</td>
<td>0.0232</td>
<td>0.0572</td>
<td>0.287611</td>
<td>23.2</td>
<td>57.2</td>
</tr>
<tr>
<td>3</td>
<td>0.5986</td>
<td>0.0191</td>
<td>0.0763</td>
<td>0.124241</td>
<td>19.1</td>
<td>76.3</td>
</tr>
<tr>
<td>4 *</td>
<td>0.7993</td>
<td>0.0136</td>
<td>0.0899</td>
<td>0.054809</td>
<td>13.6</td>
<td>89.9</td>
</tr>
<tr>
<td>5 *</td>
<td>1.0000</td>
<td>0.0101</td>
<td>0.1000</td>
<td>0.021143</td>
<td>10.1</td>
<td>100.0</td>
</tr>
</tbody>
</table>

* 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.

Maximum Information: 0.2200
Information this Stage: 0.1317
Proportion of Maximum Information: 0.5986
Predictive Power: 0.9983

<table>
<thead>
<tr>
<th>δ</th>
<th>Value</th>
<th>Conditional Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Design</td>
<td>0.0000</td>
<td>0.9991</td>
</tr>
<tr>
<td>Data</td>
<td>-2.2937</td>
<td>0.9999</td>
</tr>
<tr>
<td>δ1</td>
<td>2.0000</td>
<td>0.9940</td>
</tr>
</tbody>
</table>

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 $\delta = 0$

Using simulation based on the specified means and standard deviations, this section gives the estimated probabilities of crossing each of the future boundaries. Values given here will vary for each simulation.

<table>
<thead>
<tr>
<th>Stage</th>
<th>$N_1$</th>
<th>$N_2$</th>
<th>Z-Test Value</th>
<th>Efficacy Boundary</th>
<th>Efficacy Probability</th>
<th>Futility Boundary</th>
<th>Futility Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40.00</td>
<td>48.00</td>
<td>-3.2440</td>
<td>-4.8155</td>
<td>0.1241</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>82.00</td>
<td>85.00</td>
<td>-3.0128</td>
<td>-3.3953</td>
<td>-0.5604</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>128.00</td>
<td>127.00</td>
<td>-3.3729</td>
<td>-2.6826</td>
<td>-1.1540</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><em>170.25</em></td>
<td><em>170.25</em></td>
<td>-2.2906</td>
<td>0.9965</td>
<td>-1.5999</td>
<td>0.0000</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><em>213.00</em></td>
<td><em>213.00</em></td>
<td>-2.0307</td>
<td>0.0030</td>
<td>-2.0307</td>
<td>0.0015</td>
<td></td>
</tr>
</tbody>
</table>

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

Boundary Probabilities for $\delta = -2.293738$

This section estimates the probabilities of crossing future boundaries if the current sample means are assumed. Values given here will vary for each simulation.

<table>
<thead>
<tr>
<th>Stage</th>
<th>$N_1$</th>
<th>$N_2$</th>
<th>Z-Test Value</th>
<th>Efficacy Boundary</th>
<th>Efficacy Probability</th>
<th>Futility Boundary</th>
<th>Futility Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40.00</td>
<td>48.00</td>
<td>-3.2440</td>
<td>-4.8155</td>
<td>0.1241</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>82.00</td>
<td>85.00</td>
<td>-3.0128</td>
<td>-3.3953</td>
<td>-0.5604</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>128.00</td>
<td>127.00</td>
<td>-3.3729</td>
<td>-2.6826</td>
<td>-1.1540</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><em>170.25</em></td>
<td><em>170.25</em></td>
<td>-2.2906</td>
<td>1.0000</td>
<td>-1.5999</td>
<td>0.0000</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><em>213.00</em></td>
<td><em>213.00</em></td>
<td>-2.0307</td>
<td>0.0000</td>
<td>-2.0307</td>
<td>0.0000</td>
<td></td>
</tr>
</tbody>
</table>

* Simulation sample size (Non-integer sample sizes were rounded to the next highest integer.)
Boundary Probabilities for $\delta = 2$

This section estimates the probabilities of crossing future boundaries if the difference for the remaining looks is assumed to be 2.

<table>
<thead>
<tr>
<th>Stage</th>
<th>N1</th>
<th>N2</th>
<th>Z-Test Value</th>
<th>Boundary Efficacy</th>
<th>Boundary Probability</th>
<th>Boundary Futility</th>
<th>Futility Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40.00</td>
<td>48.00</td>
<td>-3.2440</td>
<td>-4.8155</td>
<td>0.1241</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>82.00</td>
<td>85.00</td>
<td>-3.0128</td>
<td>-3.3953</td>
<td>-0.5604</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>128.00</td>
<td>127.00</td>
<td>-3.3729</td>
<td>-2.6826</td>
<td>0.9870</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>*170.25</td>
<td>*170.25</td>
<td>-2.2906</td>
<td>-2.2906</td>
<td>-1.5999</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>*213.00</td>
<td>*213.00</td>
<td>-2.0307</td>
<td>-2.0307</td>
<td>0.0000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 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.

Maximum Information: 0.2200
Alternative Hypothesis: $\mu_1 - \mu_2 < |\text{NIM}|$
Non-Inferiority Margin (NIM): 7
Futility Boundaries: Non-Binding

<table>
<thead>
<tr>
<th>Stage</th>
<th>Z-Test Value</th>
<th>Boundaries Efficacy</th>
<th>Boundaries Futility</th>
<th>Information Proportion</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-4.8769</td>
<td>0.1534</td>
<td></td>
<td>0.2000</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-3.3569</td>
<td>0.5982</td>
<td>0.0000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>-2.6803</td>
<td>1.1542</td>
<td>0.6000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>-2.2898</td>
<td>1.6011</td>
<td>0.8000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>-2.0310</td>
<td>2.0310</td>
<td>1.0000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Group-Sequential Boundary Plot at Planning Stage (Stage 0)

This plot shows the projected boundaries at the planning stage.
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.

You may follow along here by making the appropriate entries or load the completed template Example 2 by clicking on Open Example Template from the File menu on the procedure window.

1 Specify the boundaries.
   • Enter 1 2 for Skipped Futility Stages.

2 Run the procedure.
   • From the Run menu, select Run Procedure. Alternatively, just click the green Run button.

The following reports and charts will be displayed in the Output window.

Run Summary Report

The skipped futility stages are now reported.

<table>
<thead>
<tr>
<th>Item</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Number of Stages (Design):</td>
<td>5</td>
</tr>
<tr>
<td>Skipped Futility Stage(s):</td>
<td>1 2</td>
</tr>
<tr>
<td>Current Stage:</td>
<td>3</td>
</tr>
<tr>
<td>Alternative Hypothesis:</td>
<td>( \mu_1 - \mu_2 &lt;</td>
</tr>
<tr>
<td>Non-Inferiority Margin (NIM):</td>
<td>7</td>
</tr>
<tr>
<td>Alpha Spending Function:</td>
<td>O'Brien-Fleming Analog</td>
</tr>
<tr>
<td>Beta Spending Function:</td>
<td>Hwang-Shih-DeCani ((\gamma = 1.5))</td>
</tr>
<tr>
<td>Futility Boundaries:</td>
<td>Non-Binding</td>
</tr>
<tr>
<td>Alpha:</td>
<td>0.0250</td>
</tr>
<tr>
<td>Maximum Information:</td>
<td>0.2200</td>
</tr>
</tbody>
</table>

Z-Values and Boundaries at Stage 3

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

<table>
<thead>
<tr>
<th>Stage</th>
<th>Z-Test Value</th>
<th>Efficacy</th>
<th>Futility</th>
<th>Information Proportion</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-3.2440</td>
<td>-4.8155</td>
<td>0.2049</td>
<td>0.2049</td>
<td>Continue</td>
</tr>
<tr>
<td>2</td>
<td>-3.0128</td>
<td>-3.3953</td>
<td>0.3919</td>
<td>0.3919</td>
<td>Continue</td>
</tr>
<tr>
<td>3</td>
<td>-3.3729</td>
<td>-2.6826</td>
<td>-1.4191</td>
<td>0.5986</td>
<td>Crossed Efficacy</td>
</tr>
<tr>
<td>4</td>
<td>-2.2906</td>
<td>-1.6427</td>
<td>0.5993</td>
<td>0.7993</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>-2.0307</td>
<td>-2.0307</td>
<td>1.0000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Group-Sequential Boundary Plot at Stage 3

The plot now has two futility boundaries skipped.
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.

You may follow along here by making the appropriate entries or load the completed template Example 3 by clicking on Open Example Template from the File menu on the procedure window.

1. Open the BP NI 2 Stages dataset.
   - From the File menu of the NCSS Data window, select Open Example Data.
   - Click on the file BP NI 2 Stages.NCSS.
   - Click Open.

2. Run the procedure.
   - From the Run menu, select Run Procedure. Alternatively, just click the green Run button.

The following reports and charts will be displayed in the Output window.

Run Summary Report

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

<table>
<thead>
<tr>
<th>Item</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Number of Stages (Design)</td>
<td>5</td>
</tr>
<tr>
<td>Current Stage</td>
<td>2</td>
</tr>
<tr>
<td>Alternative Hypothesis: ( \mu_1 - \mu_2 &lt;</td>
<td>NIM</td>
</tr>
<tr>
<td>Non-Inferiority Margin (NIM):</td>
<td>7</td>
</tr>
<tr>
<td>Alpha Spending Function:</td>
<td>O'Brien-Fleming Analog</td>
</tr>
<tr>
<td>Beta Spending Function:</td>
<td>Hwang-Shih-DeCani (( \gamma = 1.5 ))</td>
</tr>
<tr>
<td>Futility Boundaries:</td>
<td>Non-Binding</td>
</tr>
<tr>
<td>Alpha:</td>
<td>0.0250</td>
</tr>
<tr>
<td>Maximum Information:</td>
<td>0.2200</td>
</tr>
</tbody>
</table>

Z-Values and Boundaries at Stage 2

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

<table>
<thead>
<tr>
<th>Stage</th>
<th>Z-Test Value</th>
<th>Efficacy</th>
<th>Futility Proportion</th>
<th>Information Proportion</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-3.2440</td>
<td>-4.8155</td>
<td>0.1245</td>
<td>0.2049</td>
<td>Continue</td>
</tr>
<tr>
<td>2</td>
<td>-3.0128</td>
<td>-3.3953</td>
<td>-0.5598</td>
<td>0.3919</td>
<td>Continue</td>
</tr>
<tr>
<td>3</td>
<td>-2.6932</td>
<td>-1.1403</td>
<td>0.5946</td>
<td>0.5946</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>-2.2931</td>
<td>-1.5957</td>
<td>0.7973</td>
<td>0.7973</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>-2.0300</td>
<td>-2.0300</td>
<td>1.0000</td>
<td>1.0000</td>
<td></td>
</tr>
</tbody>
</table>
**Group-Sequential Boundary Plot at Stage 2**

This plot shows the Z-test values approaching the efficacy boundary side.

![Group-Sequential Plot](image)

**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.

Maximum Information: 0.2200  
Alternative Hypothesis: $\mu_1 - \mu_2 < |NIM|$  
Non-Inferiority Margin (NIM): 7  
Futility Boundaries: Non-Binding  
P-values and P-value boundaries are one-sided values.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Z-Test P-Value</th>
<th>Efficacy Boundaries</th>
<th>Futility Boundaries</th>
<th>Information Proportion</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.00059</td>
<td>0.00000</td>
<td>0.54955</td>
<td>0.2049</td>
<td>Continue</td>
</tr>
<tr>
<td>2</td>
<td>0.00129</td>
<td>0.00034</td>
<td>0.28782</td>
<td>0.3919</td>
<td>Continue</td>
</tr>
<tr>
<td>3</td>
<td>0.00354</td>
<td>0.12707</td>
<td>0.7973</td>
<td>0.5946</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.01092</td>
<td>0.05528</td>
<td>1.0000</td>
<td>0.7973</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.02118</td>
<td>0.02118</td>
<td></td>
<td>1.0000</td>
<td></td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Actual Difference M1 - M2 - NIM</th>
<th>Group Sequential Adjusted Difference</th>
<th>95.0% C.I. of Diff.</th>
<th>C.I. Lower</th>
<th>Upper</th>
<th>Midpoint</th>
<th>Conf. Level Where Upper Boundary Is Zero</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>-10.25968</td>
<td></td>
<td></td>
<td>-27.0507</td>
<td>-5.727014</td>
<td>-16.38885</td>
<td>99.741%</td>
</tr>
</tbody>
</table>

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

Descriptive Statistics up to Stage 2

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

<table>
<thead>
<tr>
<th>Stage</th>
<th>Sample Size</th>
<th>Mean 1</th>
<th>Mean 2</th>
<th>Standard Deviation 1</th>
<th>Standard Deviation 2</th>
<th>Difference</th>
<th>SE(Diff)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40 48</td>
<td>122.45</td>
<td>130.7292</td>
<td>19.04913</td>
<td>28.00436</td>
<td>-8.279166</td>
<td>4.709918</td>
</tr>
<tr>
<td>2</td>
<td>82 85</td>
<td>120.9756</td>
<td>124.2353</td>
<td>19.56816</td>
<td>26.69878</td>
<td>-3.259684</td>
<td>3.405372</td>
</tr>
</tbody>
</table>

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

This section shows that the target sample size for the next stage should be 127 per group.

<table>
<thead>
<tr>
<th>Target Information Proportion</th>
<th>Achieved Information Proportion</th>
<th>Target Information</th>
<th>Achieved Information</th>
<th>N1</th>
<th>N2</th>
<th>σ1</th>
<th>σ2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 0.2000</td>
<td>0.2049</td>
<td>0.0440</td>
<td>0.0451</td>
<td>40.00</td>
<td>48.00</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Stage 2 0.4000</td>
<td>0.3919</td>
<td>0.0880</td>
<td>0.0862</td>
<td>82.00</td>
<td>85.00</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Stage 3 0.6000 *0.5946</td>
<td>0.1320 *0.1308</td>
<td>*126.65</td>
<td>*126.65</td>
<td>*22</td>
<td>*22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 4 0.8000 *0.7973</td>
<td>0.1760 *0.1754</td>
<td>*169.82</td>
<td>*169.82</td>
<td>*22</td>
<td>*22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 5 1.0000 *1.0000</td>
<td>0.2200</td>
<td>*213.00</td>
<td>*213.00</td>
<td>*22</td>
<td>*22</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Projected value.

Alpha Spending at Stage 2

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

| Target Final Stage Alpha: 0.0250 |

<table>
<thead>
<tr>
<th>Nominal Percentage Alpha Spent this Stage</th>
<th>Cumulative Percentage Alpha Spent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 0.0000</td>
<td>0.000001</td>
</tr>
<tr>
<td>Stage 2 0.0003</td>
<td>0.000034</td>
</tr>
<tr>
<td>Stage 3 0.0003</td>
<td>0.000338</td>
</tr>
<tr>
<td>Stage 4 0.0121</td>
<td>0.010920</td>
</tr>
<tr>
<td>Stage 5 0.0250</td>
<td>0.021179</td>
</tr>
</tbody>
</table>

* projected
Beta Spending for Futility at Stage 2

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

<table>
<thead>
<tr>
<th>Stage</th>
<th>Proportion</th>
<th>Beta Spent this Stage</th>
<th>Cumulative Beta Spent</th>
<th>Nominal (Boundary) Beta</th>
<th>Percentage Beta Spent this Stage</th>
<th>Cumulative Percentage Beta Spent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.2049</td>
<td>0.0341</td>
<td>0.0341</td>
<td>0.549551</td>
<td>34.1</td>
<td>34.1</td>
</tr>
<tr>
<td>2</td>
<td>0.3919</td>
<td>0.0232</td>
<td>0.0572</td>
<td>0.287820</td>
<td>23.2</td>
<td>57.2</td>
</tr>
<tr>
<td>3 *</td>
<td>0.5946</td>
<td>0.0187</td>
<td>0.0760</td>
<td>0.127072</td>
<td>18.7</td>
<td>76.0</td>
</tr>
<tr>
<td>4 *</td>
<td>0.7973</td>
<td>0.0138</td>
<td>0.0898</td>
<td>0.055278</td>
<td>13.8</td>
<td>89.8</td>
</tr>
<tr>
<td>5 *</td>
<td>1.0000</td>
<td>0.0102</td>
<td>0.1000</td>
<td>0.021179</td>
<td>10.2</td>
<td>100.0</td>
</tr>
</tbody>
</table>

* projected

Conditional and Predictive Power Report at Stage 2

Conditional power and predictive power are described earlier in the Technical details section. The predictive power does not depend on an assumed difference, as does the conditional power.

<table>
<thead>
<tr>
<th>Name</th>
<th>Value</th>
<th>Conditional Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>0.0000</td>
<td>0.9932</td>
</tr>
<tr>
<td>Data</td>
<td>-3.2597</td>
<td>0.9999</td>
</tr>
<tr>
<td>δ1</td>
<td>2.0000</td>
<td>0.9586</td>
</tr>
</tbody>
</table>

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 $\delta = 0$

Given the data that have already accumulated in the first two stages, and assuming means of 124 and 124 going forward, this report gives the simulation probabilities of crossing each of the future boundaries. The sum of the efficacy boundary probabilities is another estimate of the conditional power.

<table>
<thead>
<tr>
<th>Stage</th>
<th>$N_1$</th>
<th>$N_2$</th>
<th>Z-Test Value</th>
<th>Efficacy Boundary</th>
<th>Futility Boundary</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40.00</td>
<td>48.00</td>
<td>-3.2440</td>
<td>-4.8155</td>
<td>0.1245</td>
</tr>
<tr>
<td>2</td>
<td>82.00</td>
<td>85.00</td>
<td>-3.0128</td>
<td>-3.3953</td>
<td>-0.5598</td>
</tr>
<tr>
<td>3</td>
<td>*126.65</td>
<td>*126.65</td>
<td>-2.6932</td>
<td>-2.6932</td>
<td>0.8560</td>
</tr>
<tr>
<td>4</td>
<td>*169.82</td>
<td>*169.82</td>
<td>-2.2931</td>
<td>-2.2931</td>
<td>0.1155</td>
</tr>
<tr>
<td>5</td>
<td>*213.00</td>
<td>*213.00</td>
<td>-2.0300</td>
<td>-2.0300</td>
<td>0.0210</td>
</tr>
</tbody>
</table>

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

Boundary Probabilities for $\delta = -3.259684$

Given the data that have already accumulated in the first two stages, and assuming means of 120.9756 and 124.2353 going forward, this report gives the simulation probabilities of crossing each of the future boundaries. The sum of the efficacy boundary probabilities is another estimate of the conditional power.

<table>
<thead>
<tr>
<th>Stage</th>
<th>$N_1$</th>
<th>$N_2$</th>
<th>Z-Test Value</th>
<th>Efficacy Boundary</th>
<th>Futility Boundary</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40.00</td>
<td>48.00</td>
<td>-3.2440</td>
<td>-4.8155</td>
<td>0.1245</td>
</tr>
<tr>
<td>2</td>
<td>82.00</td>
<td>85.00</td>
<td>-3.0128</td>
<td>-3.3953</td>
<td>-0.5598</td>
</tr>
<tr>
<td>3</td>
<td>*126.65</td>
<td>*126.65</td>
<td>-2.6932</td>
<td>-2.6932</td>
<td>0.8560</td>
</tr>
<tr>
<td>4</td>
<td>*169.82</td>
<td>*169.82</td>
<td>-2.2931</td>
<td>-2.2931</td>
<td>0.1155</td>
</tr>
<tr>
<td>5</td>
<td>*213.00</td>
<td>*213.00</td>
<td>-2.0300</td>
<td>-2.0300</td>
<td>0.0210</td>
</tr>
</tbody>
</table>

* Simulation sample size (Non-integer sample sizes were rounded to the next highest integer.)
### Boundary Probabilities for $\delta = 2$

Given the data that have already accumulated in the first two stages, and assuming means of 126 and 124 going forward, this report gives the simulation probabilities of crossing each of the future boundaries. The sum of the efficacy boundary probabilities is another estimate of the conditional power.

<table>
<thead>
<tr>
<th>Stage</th>
<th>N1</th>
<th>N2</th>
<th>Z-Test Value</th>
<th>Efficacy Boundary</th>
<th>Efficacy Probability</th>
<th>Futility Boundary</th>
<th>Futility Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40.00</td>
<td>48.00</td>
<td>-3.2440</td>
<td>-4.8155</td>
<td>0.1245</td>
<td>-3.0128</td>
<td>-4.3953</td>
</tr>
<tr>
<td>2</td>
<td>82.00</td>
<td>85.00</td>
<td>-3.0128</td>
<td>-4.8155</td>
<td>0.1245</td>
<td>-3.0128</td>
<td>-4.3953</td>
</tr>
<tr>
<td>3</td>
<td>*126.65</td>
<td>*126.65</td>
<td>-2.6932</td>
<td>-2.6932</td>
<td>0.7345</td>
<td>-1.1403</td>
<td>0.0000</td>
</tr>
<tr>
<td>4</td>
<td>*169.82</td>
<td>*169.82</td>
<td>-2.2931</td>
<td>-2.2931</td>
<td>0.1745</td>
<td>-1.5957</td>
<td>0.0140</td>
</tr>
<tr>
<td>5</td>
<td>*213.00</td>
<td>*213.00</td>
<td>-2.0300</td>
<td>-2.0300</td>
<td>0.0585</td>
<td>-2.0300</td>
<td>0.0540</td>
</tr>
</tbody>
</table>

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