# SAS/STAT® 15.1 User's Guide

# The SEQTEST Procedure

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**SAS/STAT® 15.1 User's Guide**

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# Chapter 108
# The SEQTEST Procedure

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# Overview: SEQTEST Procedure

The purpose of the SEQTEST procedure is to perform interim analyses for clinical trials. Clinical trials are experiments on human beings to demonstrate the efficacy and safety of new drugs or treatments. A simple example is a trial to test the effectiveness of a new drug in humans by comparing the outcomes in a group of patients who receive the new drug with the outcomes in a comparable group of patients who receive a placebo.

A clinical trial is conducted according to a plan called a *protocol*. A protocol details the objectives of the trial, the data collection process, and the analyses of the data. The protocol contains information such as a null hypothesis and an alternative hypothesis, a test statistic, the probability $\alpha$ of a Type I error (incorrectly rejecting the null hypothesis), the probability $\beta$ of a Type II error (incorrectly accepting the null hypothesis), the sample size needed to attain a specified power (probability of correctly rejecting the null hypothesis) of $1 - \beta$ at an alternative reference, and critical values that are associated with the test statistic for hypothesis testing.

In a fixed-sample trial, data about all individuals are first collected and then examined at the end of the study. Most major trials have data safety monitoring boards or data monitoring committees that periodically monitor safety and efficacy data during the trial and recommend that a trial be stopped for safety concerns such as an unacceptable toxicity level. In certain rare situations, the board or committee might even recommend that a trial be stopped for efficacy. In contrast to a fixed-sample trial, a group sequential trial provides for interim analyses before the formal completion of the trial while maintaining the specified overall Type I and Type II error probability levels.

A group sequential trial is most useful in situations where it is important to monitor the trial to prevent unnecessary exposure of patients to an unsafe new drug, or alternatively to a placebo treatment if the new drug shows significant improvement. If a group sequential trial stops early, then it usually requires fewer participants than a corresponding fixed-sample trial.

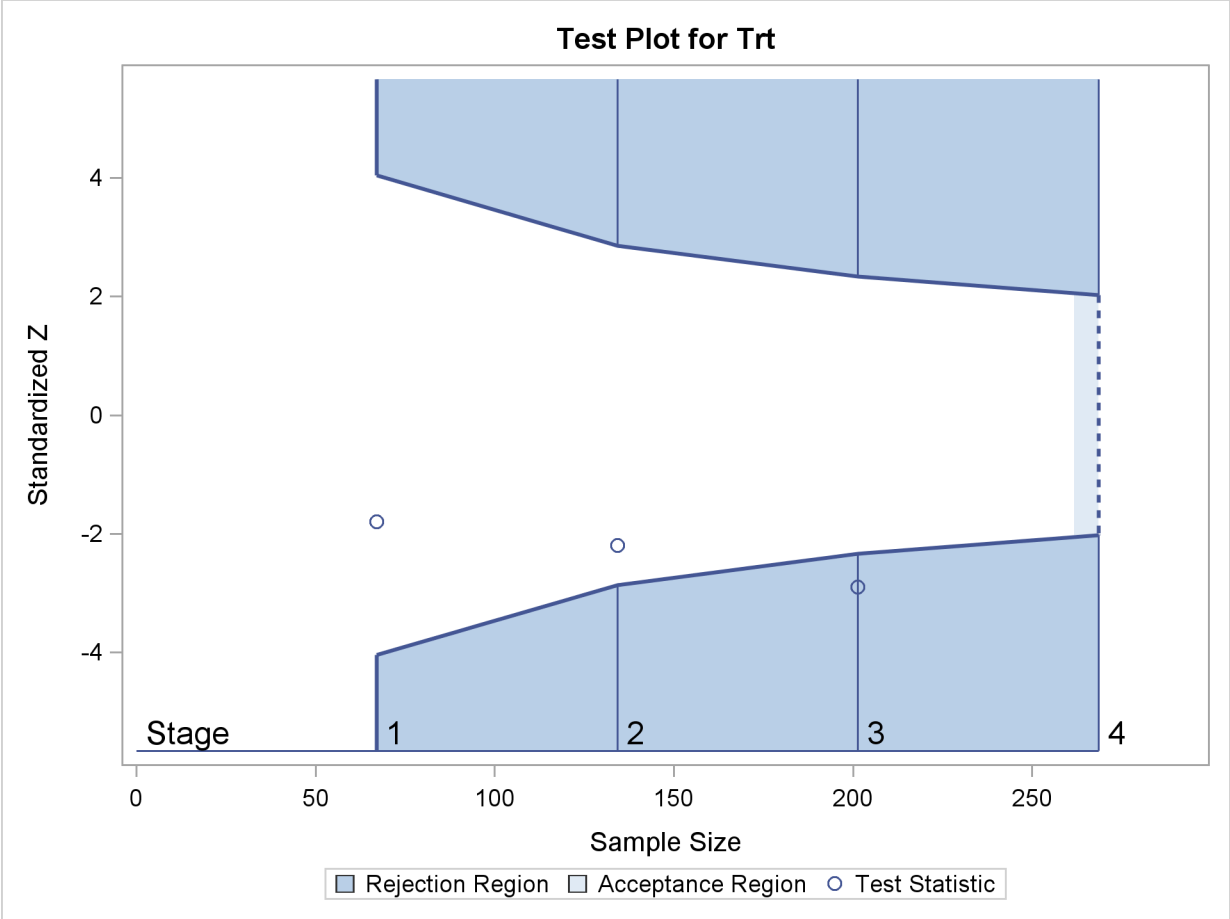
Thus, in most cases, if a group sequential trial stops early for safety of the new treatment, fewer patients will be exposed to the new treatment than in the fixed-sample trial. Also, if a trial stops early for efficacy of the new treatment, the new treatment will be available sooner than it would be in a fixed-sample trial. Furthermore, if a trial stops early, this can also save time and resources.

A group sequential design provides detailed specifications for a group sequential trial. In addition to the usual specification for a fixed-sample design, it provides the total number of stages (the number of interim stages plus a final stage) and a stopping criterion to reject, to accept, or to either reject or accept the null hypothesis at each interim stage. It also provides critical values and the sample size at each stage for the trial.

At each interim stage, the data collected at the current stage in addition to the data collected at previous stages are analyzed, and statistics such as a maximum likelihood test statistic and its associated standard error are computed. The test statistic is then compared with its corresponding critical values at the stage, and the trial is stopped or continued. If a trial continues to the final stage, the null hypothesis is either rejected or accepted. The critical values for each stage are chosen in such a way to maintain the overall $\alpha$ level, the overall $\beta$ level, or both the overall $\alpha$ and $\beta$ levels.

Figure 108.1 shows a two-sided symmetric group sequential trial that stops early to reject the null hypothesis that the parameter Trt is zero.

**Figure 108.1** Sequential Plot for Two-Sided Test




The trial has four stages, which are indicated by vertical lines with accompanying stage numbers. With early stopping to reject the null hypothesis, the lower rejection boundary is constructed by connecting the lower critical values (boundary values) for the stages. Similarly, the upper rejection boundary is constructed by connecting the upper critical values for the stages. The horizontal axis indicates the sample size for the group sequential trial, and the vertical axis indicates the boundary values and test statistics on the standardized $Z$ scale.

At each interim stage, if the standardized $Z$ test statistic falls into a rejection region (the darker shaded areas in Figure 108.1), the trial stops and the null hypothesis is rejected. Otherwise, the trial continues to the next stage. At the final stage (stage 4), the trial is rejected if $Z$ falls into a rejection region. Otherwise, the trial is accepted. In Figure 108.1, the test statistic does not fall into the rejection regions for stages 1 and 2, and so the trial continues to stage 3. At stage 3, the test statistic falls into the rejection region, and the null hypothesis is rejected.

A group sequential trial usually involves six steps:

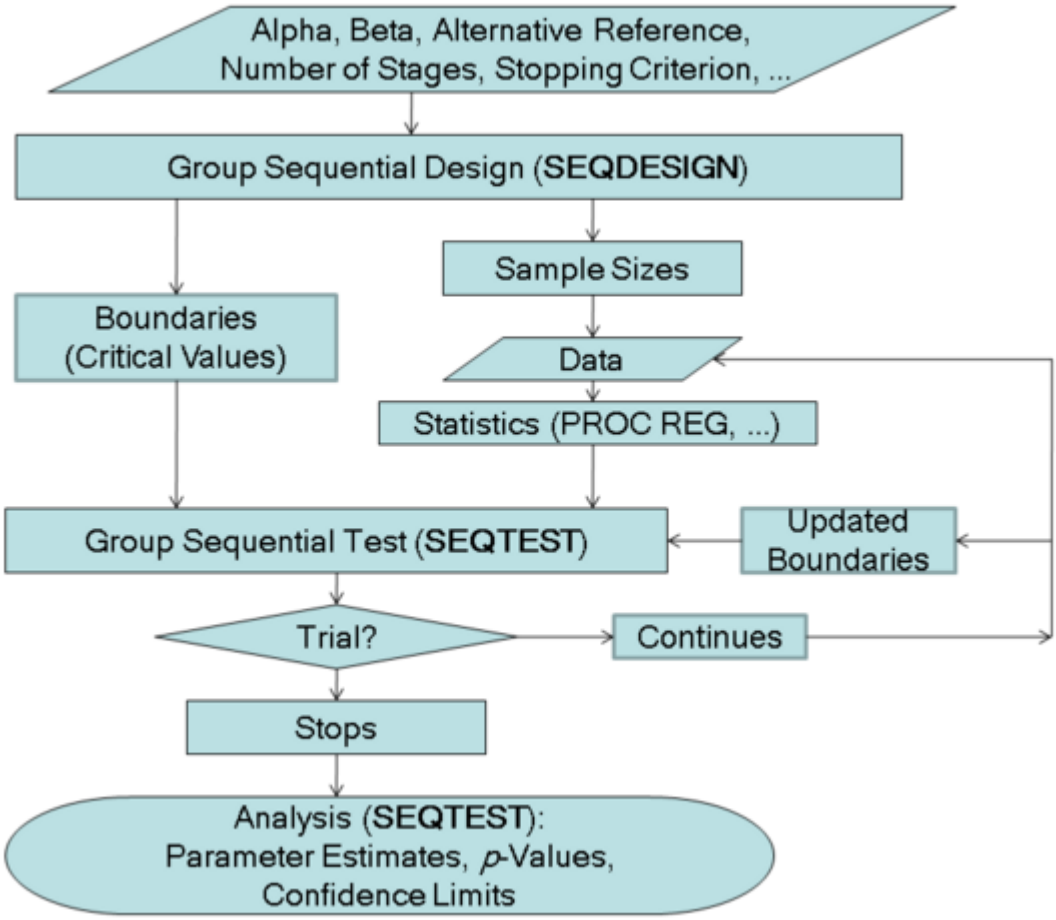
1. You specify the statistical details of the design, including the null and alternative hypotheses, a test statistic for the hypothesis test, the Type I and II error probabilities, a stopping criterion, the total number of stages, and the relative information level at each stage.
2. You compute the boundary values for the trial based on the specifications in Step 1. You also compute the sample size required at each stage for the specified hypothesis test.
3. At each stage, you collect additional data with the required sample sizes. The data available at each stage include the data collected at previous stages in addition to the data collected at the current stage.
4. At each stage, you analyze the available data with a procedure such as the REG procedure, and you compute the test statistic.
5. At each stage, you compare the test statistic with the corresponding boundary values. You stop the trial to reject or accept the hypothesis, or you continue the trial to the next stage. If you continue the trial to the final stage, you either accept or reject the hypothesis.
6. After the trial stops, you compute parameter estimates, confidence limits for the parameter, and a $p$-value for the hypothesis test.

You use the companion SEQDESIGN procedure at Step 2 to compute the boundary values and required sample sizes for the trial. You use the SEQTEST procedure at Step 5 to compare the test statistic with its boundary values. At stage 1, the boundary values are derived by using the boundary information tables created by the SEQDESIGN procedure. These boundary information tables are structured for input to the SEQTEST procedure. At each subsequent stage, the boundary values are derived by using the test information tables created by the SEQTEST procedure at the previous stage. These test information tables are also structured for input to the SEQTEST procedure. You also use the SEQTEST procedure at Step 6 to compute parameter estimates, confidence limits, and $p$-values after the trial stops.

Note that for some clinical trials, the information levels are derived from statistics based on individuals specified in the design plan and might not reach the target maximum information level. For example, if an estimate of the variance is used to compute the required sample size for a group sequential trial, the computed variance at each stage might not be the same as the estimated variance. Thus, instead of specifying the number of individuals in the protocol, the information level can be specified. You can then adjust the sample sizes with the updated variance estimates at interim stages to achieve the target maximum information level for the trial (Jennison and Turnbull 2000, p. 295).

The flowchart in Figure 108.2 summarizes the steps in a typical group sequential trial and the relevant SAS procedures.

**Figure 108.2** Group Sequential Trial




## Features of the SEQTEST Procedure

At each stage, the data are analyzed with a statistical procedure such as the REG procedure, and a test statistic and its associated information level are computed. The information level is the amount of information available about the unknown parameter. For a maximum likelihood statistic, the information level is the inverse of its variance.

At each stage, you use the SEQTEST procedure to compare the test statistic with its boundary values. At stage 1, the boundary values are derived by using the boundary information tables created by the SEQDESIGN procedure. At each subsequent stage, the boundary values are derived by using the test information tables created by the SEQTEST procedure at the previous stage.

If the observed information level does not match the corresponding information level in the BOUNDARY= data set, the SEQTEST procedure modifies the boundary values to adjust for new information levels at the current and subsequent stages. See the section "Boundary Adjustments for Information Levels" on page 9058 for a detailed description of these boundary adjustments.

Either you can specify the test statistic and its information level in the DATA= input data set, or you can specify the test statistic and its associated standard error in the PARMS= input data set. With the PARMS=

input data set, the information level for the test statistic is computed from its standard error. See the section "Input Data Sets" on page 9052 for a detailed description of these input data sets.

At the end of a trial, the parameter estimate is computed. The median unbiased estimate, confidence limits, and $p$-value depend on the specified sample space ordering. A sample space ordering specifies the ordering for test statistics that result in the stopping of a trial. That is, for all the statistics in the rejection region and in acceptance region, the SEQTEST procedure provides three different sample space orderings: the stagewise ordering uses counterclockwise ordering around the continuation region, the LR ordering uses the distance between the observed $Z$ statistic $z$ and its hypothetical value, and the MLE ordering uses the observed maximum likelihood estimate. See the section "Available Sample Space Orderings in a Sequential Test" on page 9065 for a detailed description of these orderings.

## Output from the SEQTEST Procedure

In addition to the adjusted boundary values and test results for the group sequential trial, the SEQTEST procedure also computes the following quantities:

- average sample numbers (as percentages of the corresponding fixed-sample sizes for nonsurvival data or fixed-sample numbers of events for survival data) under various hypothetical references, including the null and alternative references
- stopping probabilities at each stage under various hypothetical references to indicate how likely it is that the trial will stop at that stage
- conditional power given the most recently observed statistic under specified hypothetical references
- predictive power given the most recently observed statistic
- repeated confidence intervals for the parameter from the observed statistic at each stage
- parameter estimate, $p$-value for hypothesis testing, and median and confidence limits for the parameter at the conclusion of a sequential trial

# Getting Started: SEQTEST Procedure

The following example illustrates a clinical study that uses a two-sided O'Brien-Fleming design (O'Brien and Fleming 1979) to stop the trial early for ethical concerns about possible harm or for unexpectedly strong efficacy of the new drug.

Suppose that a pharmaceutical company is conducting a clinical trial to test the efficacy of a new cholesterol-lowering drug. The primary focus is low-density lipoprotein (LDL), the so-called bad cholesterol, which is a risk factor for coronary heart disease. LDL is measured in mg/dl, milligrams per deciliter of blood.

The trial consists of two groups of equally allocated patients with elevated LDL level: an experimental group given the new drug and a placebo control group. Suppose the changes in LDL level after the treatment for patients in the experimental and control groups are normally distributed with means $\mu_e$ and

$\mu_c$, respectively, and have a common variance $\sigma^2$. Then the null hypothesis of no effect for the new drug is $H_0 : \theta = \mu_e - \mu_c = 0$. Also suppose that the alternative reference $\theta = -10$ is the clinically meaningful difference that the trial should detect with a high probability (power), and that a good estimate of the standard deviation for the changes in LDL level is $\hat{\sigma} = 20$.

The following statements invoke the SEQDESIGN procedure and request a four-stage O'Brien-Fleming design for standardized normal test statistics:

```
ods graphics on;
proc seqdesign altref=-10.0;
   TwoSidedOBrienFleming: design nstages=4
                          method=obf
                          ;
   samplesize model=twosamplemean(stddev=20);
   ods output Boundary=Bnd_LDL;
run;
```

The ALTREF= option specifies the alternative reference, and the actual maximum information is derived in the SEQDESIGN procedure.

In the DESIGN statement, the label **TwoSidedOBrienFleming** identifies the design in the output tables. By default (or equivalently if you specify ALT=TWOSIDED and STOP=REJECT), the design has a two-sided alternative hypothesis with early stopping in the interim stages only to reject the null hypothesis. That is, at each interim stage, the trial will either be stopped to reject the null hypothesis or continue to the next stage.

The NSTAGES=4 option in the DESIGN statement specifies the total number of stages in the group sequential trial, including three interim stages and a final stage. In the SEQDESIGN procedure, the null hypothesis for the design is $H_0 : \theta = 0$. By default (or equivalently if you specify ALPHA=0.05 and BETA=0.10), the design has a Type I error probability $\alpha = 0.05$, and a Type II error probability $\beta = 0.10$, which corresponds to a power of $1 - \beta = 0.90$ at the alternative reference $H_1 : \theta = -10$.

For a two-sided design with early stopping to reject the null hypothesis, there are two boundaries for the design: an upper $\alpha$ (rejection) boundary that consists of upper rejection critical values and a lower $\alpha$ boundary that consists of lower rejection critical values. Each boundary is a set of critical values, one from each stage. With the METHOD=OBF option in the DESIGN statement, the O'Brien-Fleming method is used for the two boundaries for the design; see Figure 108.5.

The SAMPLESIZE statement with the MODEL=TWOSAMPLEMEAN option uses the derived maximum information to compute required sample sizes for a two-sample test for mean difference.

The ODS OUTPUT statement with the BOUNDARY=BND_LDL option creates an output data set named BND_LDL which contains the resulting boundary information. At each stage of the trial, data are collected and analyzed with a statistical procedure, and a test statistic and its corresponding information level are computed.

In this example, you can use the REG procedure to compute the maximum likelihood estimate $\hat{\theta}$ for the drug effect and the corresponding standard error for $\hat{\theta}$. At stage 1, you can use the SEQTEST procedure to compare the test statistic with adjusted boundaries that are derived from the boundary information stored in the BOUND_LDL data set. At each subsequent stage, you can use the SEQTEST procedure to compare the test statistic with adjusted boundaries that are derived from the boundary information stored in the test information table that was created by the SEQTEST procedure at the previous stage. The test information tables are structured for input to the SEQTEST procedure.

At each interim stage, the trial will either be stopped to reject the null hypothesis or continue to the next stage. At the final stage, the null hypothesis is either rejected or accepted.

By default (or equivalently if you specify INFO=EQUAL), the SEQDESIGN procedure derives boundary values with equally spaced information levels for all stages—that is, the same information increment between successive stages.

The "Design Information" table in Figure 108.3 displays design specifications and three derived statistics: the maximum information, the average sample number under the null hypothesis (Null Ref ASN), and the average sample number under the alternative hypothesis (Alt Ref ASN). Each statistic is expressed as a percentage of the identical statistic for the corresponding fixed-sample information. The average sample number is the expected sample size (for nonsurvival data) or expected number of events (for survival data). When you specify an alternative reference (in this case, ALTREF=–10), the actual maximum information 0.1074 is also computed. Note that for a symmetric two-sided design, the ALTREF=–10 option implies a lower alternative reference of –10 and an upper alternative reference of 10.

**Figure 108.3** O'Brien-Fleming Design Information

**The SEQDESIGN Procedure**
**Design: TwoSidedOBrienFleming**

| Design Information | |
|---|---|
| **Statistic Distribution** | Normal |
| **Boundary Scale** | Standardized Z |
| **Alternative Hypothesis** | Two-Sided |
| **Early Stop** | Reject Null |
| **Method** | O'Brien-Fleming |
| **Boundary Key** | Both |
| **Alternative Reference** | -10 |
| **Number of Stages** | 4 |
| **Alpha** | 0.05 |
| **Beta** | 0.1 |
| **Power** | 0.9 |
| **Max Information (Percent of Fixed Sample)** | 102.2163 |
| **Max Information** | 0.107403 |
| **Null Ref ASN (Percent of Fixed Sample)** | 101.5728 |
| **Alt Ref ASN (Percent of Fixed Sample)** | 76.7397 |

The "Boundary Information" table in Figure 108.4 displays the information level, the lower and upper alternative references, and the lower and upper boundary values at each stage. By default (or equivalently if you specify INFO=EQUAL), the SEQDESIGN procedure uses equally spaced information levels for all stages.

**Figure 108.4** Boundary Information

| Boundary Information (Standardized Z Scale) Null Reference = 0 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Information Level | | | Alternative Reference | | Boundary Values | |
| | | | | | | Lower | Upper |
| _Stage_ | Proportion | Actual | N | Lower | Upper | Alpha | Alpha |
| 1 | 0.2500 | 0.026851 | 42.96116 | -1.63862 | 1.63862 | -4.04859 | 4.04859 |
| 2 | 0.5000 | 0.053701 | 85.92233 | -2.31736 | 2.31736 | -2.86278 | 2.86278 |
| 3 | 0.7500 | 0.080552 | 128.8835 | -2.83817 | 2.83817 | -2.33745 | 2.33745 |
| 4 | 1.0000 | 0.107403 | 171.8447 | -3.27724 | 3.27724 | -2.02429 | 2.02429 |

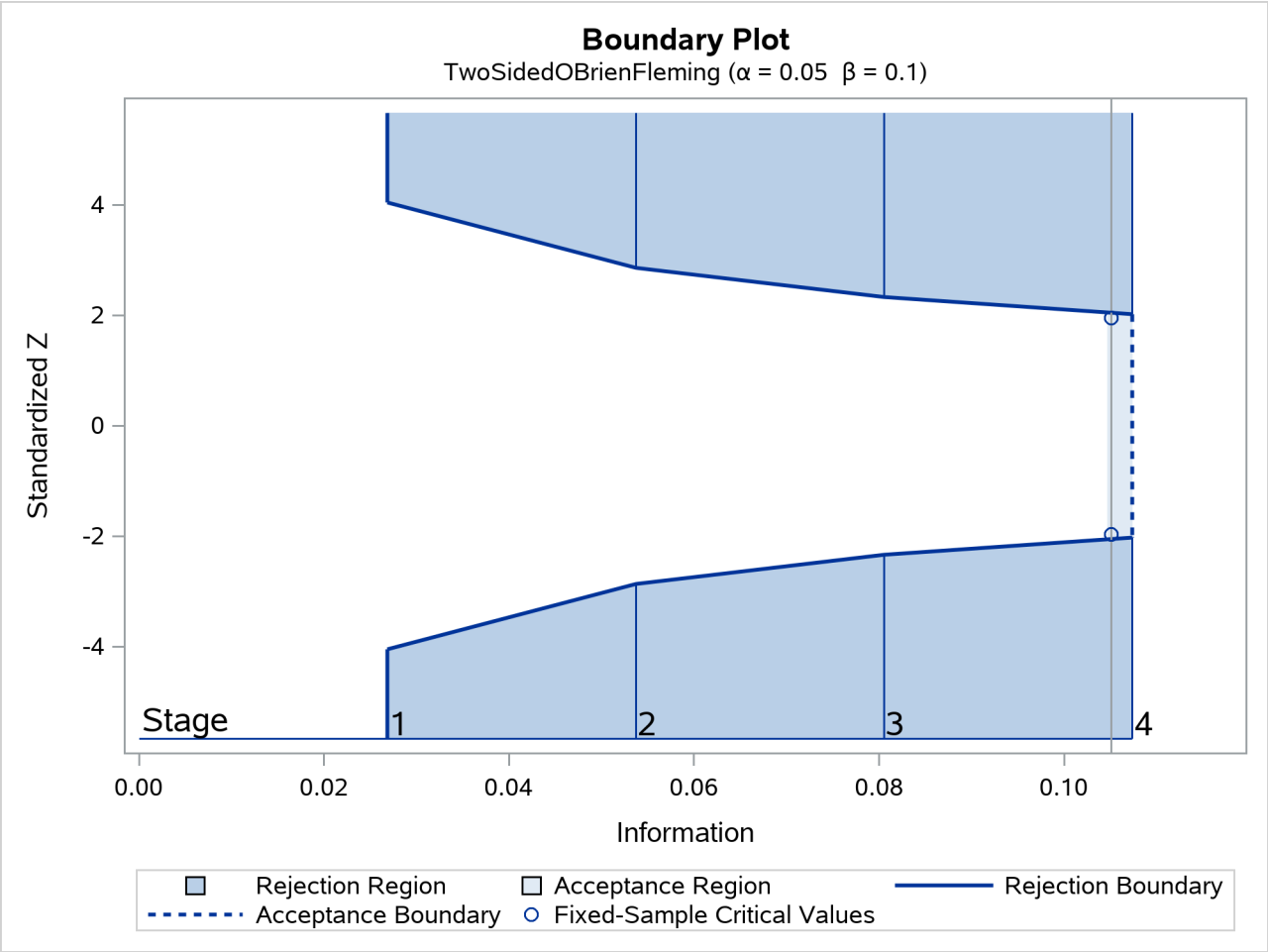
The information proportion is the proportion of maximum information available at each stage. By default (or equivalently if you specify BOUNDARYSCALE=STDZ), the alternative references and boundary values are displayed with the standardized $Z$ statistic scale. The alternative reference in the standardized $Z$ scale at stage $k$ is given by $\theta_1\sqrt{I_k}$, where $\theta_1$ is the alternative reference and $I_k$ is the information available at stage $k$, $k$ = 1, 2, 3, 4.

In this example, a standardized $Z$ statistic is computed by standardizing the parameter estimate of the effect in LDL level. A lower $Z$ test statistic indicates a beneficial effect. Consequently, at each interim stage, if the standardized $Z$ test statistic is less than or equal to the corresponding lower $\alpha$ boundary value, the hypothesis $H_0 : \theta = 0$ is rejected for efficacy. If the test statistic is greater than or equal to the corresponding upper $\alpha$ boundary value, the hypothesis $H_0$ is rejected for harmful effect. Otherwise, the process continues to the next stage. At the final stage (stage 4), the hypothesis $H_0$ is rejected for efficacy if the $Z$ statistic is less than or equal to the corresponding lower $\alpha$ boundary value –2.0243, and the hypothesis $H_0$ is rejected for harmful effect if the $Z$ statistic is greater than or equal to the corresponding upper $\alpha$ boundary value 2.0243. Otherwise, the hypothesis of no significant difference is accepted.

Note that in a typical trial, the actual information levels do not match the information levels specified in the design. Consequently, the SEQTEST procedure modifies the boundary values stored in the BND_LDL data set to adjust for these new information levels.

If ODS Graphics is enabled, a detailed boundary plot with the rejection and acceptance regions is displayed, as shown in Figure 108.5.

**Figure 108.5** O'Brien-Fleming Boundary Plot




This boundary plot displays the boundary values in the "Boundary Information" table in Figure 108.4. The stages are indicated by vertical lines with accompanying stage numbers. The horizontal axis indicates the information levels for the stages. If a test statistic at an interim stage is in the rejection region (shaded area), the trial stops and the null hypothesis is rejected. If the statistic is not in any rejection region, the trial continues to the next stage. The plot also displays critical values for the corresponding fixed-sample design. The symbol "∘" identifies the fixed-sample critical values of –1.96 and 1.96.

When you specify the SAMPLESIZE statement, the maximum information (either explicitly specified or derived in the SEQDESIGN procedure) is used to compute the required sample sizes for the study. The MODEL=TWOSAMPLEMEAN(STDDEV=20) option specifies the test for the difference between two normal means. See the section "Test for the Difference between Two Normal Means" on page 8893 in Chapter 107, "The SEQDESIGN Procedure," for more information about how these required sample sizes are calculated.

The "Sample Size Summary" table in Figure 108.6 displays the parameters for the sample size computation and the resulting maximum and expected sample sizes.

**Figure 108.6** Required Sample Size Summary

| Sample Size Summary | |
|---|---|
| **Test** | Two-Sample Means |
| **Mean Difference** | -10 |
| **Standard Deviation** | 20 |
| **Max Sample Size** | 171.8447 |
| **Expected Sample Size (Null Ref)** | 170.7627 |
| **Expected Sample Size (Alt Ref)** | 129.0137 |

With the derived maximum information 0.1074 and the specified MODEL=TWOSAMPLEMEAN (STDDEV=20) option in the SAMPLESIZE statement, the total sample size in each group is

$$N_a = N_b = 2\,\sigma^2\,I_X = 2 \times 20^2 \times 0.1074 = 85.92$$

The "Sample Sizes (N)" table in Figure 108.7 displays the required sample sizes at each stage for the trial, in both fractional and integer numbers. The derived fractional sample sizes are displayed under the heading "Fractional N." These sample sizes are rounded up to integers under the heading "Ceiling N." By default (or equivalently if you specify WEIGHT=1 in the MODEL=TWOSAMPLEMEAN option), the sample sizes for the two groups are equal for the two-sample test.

**Figure 108.7** Required Sample Sizes

| Sample Sizes (N)<br>Two-Sample Z Test for Mean Difference | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Fractional N | | | | Ceiling N | | | |
| _Stage_ | N | N(Grp 1) | N(Grp 2) | Information | N | N(Grp 1) | N(Grp 2) | Information |
| 1 | 42.96 | 21.48 | 21.48 | 0.0269 | 44 | 22 | 22 | 0.0275 |
| 2 | 85.92 | 42.96 | 42.96 | 0.0537 | 86 | 43 | 43 | 0.0538 |
| 3 | 128.88 | 64.44 | 64.44 | 0.0806 | 130 | 65 | 65 | 0.0812 |
| 4 | 171.84 | 85.92 | 85.92 | 0.1074 | 172 | 86 | 86 | 0.1075 |

In practice, integer sample sizes are used in the trial, and the resulting information levels increase slightly. Thus, each of the two groups needs 22, 43, 65, and 86 patients for the four stages, respectively.

Suppose that 22 patients are available in each group at stage 1 and that their measurements for LDL are saved in the data set LDL_1. Figure 108.8 lists the first 10 observations in the data set LDL_1.

**Figure 108.8** Clinical Trial Data

**First 10 Obs in the Trial Data**

| Obs | Trt | Ldl |
|---|---|---|
| 1 | 0 | 33.33 |
| 2 | 1 | -14.89 |
| 3 | 0 | 15.30 |
| 4 | 1 | 4.71 |
| 5 | 0 | 26.89 |
| 6 | 1 | -48.74 |
| 7 | 0 | -39.35 |
| 8 | 1 | -8.13 |
| 9 | 0 | -8.22 |
| 10 | 1 | 12.35 |

The variable Trt is an indicator variable with value 1 for patients in the treatment group and value 0 for patients in the placebo control group. The variable Ldl is the LDL level of these patients.

The following statements use the REG procedure to estimate the mean treatment difference and its associated standard error at stage 1:

```
proc reg data=LDL_1;
   model Ldl=Trt;
   ods output ParameterEstimates=Parms_LDL1;
run;
```

The following statements create the data set for the mean treatment difference and its associated standard error as a PARMS= data set, which will subsequently serve as an input data set for PROC SEQTEST. Note that all of the variables are required for a PARMS= data set, as described in the section "PARMS= Data Set" on page 9054.

```
data Parms_LDL1;
   set Parms_LDL1;
   if Variable='Trt';
   _Scale_='MLE';
   _Stage_= 1;
   keep _Scale_ _Stage_ Variable Estimate StdErr;
run;

proc print data=Parms_LDL1;
   title 'Statistics Computed at Stage 1';
run;
```

Figure 108.9 displays the statistics computed at stage 1.

**Figure 108.9** Statistics Computed at Stage 1

**Statistics Computed at Stage 1**

| Obs | Variable | Estimate | StdErr | _Scale_ | _Stage_ |
|---|---|---|---|---|---|
| 1 | Trt | -2.52591 | 5.68572 | MLE | 1 |

Since the sample sizes derived are based on the estimated variance at the designing phase, the information level that corresponds to the test statistic at stage 1 is estimated by

$$I_1 = \frac{1}{s_1^2} = \frac{1}{5.686^2} = 0.0309$$

where $s_1$ is the standard error of the treatment estimate.

The following statements invoke the SEQTEST procedure to test for early stopping at stage 1:

```
ods graphics on;
proc seqtest Boundary=Bnd_LDL
             Parms(Testvar=Trt)=Parms_LDL1
             infoadj=prop
             ;
   ods output Test=Test_LDL1;
run;
```

The BOUNDARY= option specifies the input data set that provides the boundary information for the trial at stage 1, which was generated in the SEQDESIGN procedure. The PARMS=PARMS_LDL1 option specifies the input data set PARMS_LDL1 that contains the test statistic and its associated standard error at stage 1, and the TESTVAR=TRT option identifies the test variable TRT in the data set.

By default (or equivalently if you specify BOUNDARYKEY=ALPHA), the maximum information and the Type I error level are maintained. Furthermore, with the INFOADJ=PROP option (which is the default), the information levels at future interim stages (2 and 3) are adjusted proportionally from the levels provided in the BOUNDARY= data set.

The ODS OUTPUT statement with the TEST=TEST_LDL1 option creates an output data set named TEST_LDL1 which contains the updated boundary information for the test at stage 1, and the boundary information that is needed for the group sequential test at the next stage. See the section "Boundary Adjustments for Information Levels" on page 9058 for details.

The "Design Information" table in Figure 108.10 displays design specifications. By default (or equivalently if you specify BOUNDARYKEY=ALPHA), the boundary values are adjusted for the updated information levels to maintain the Type I $\alpha$ level, and the maximum information remains the same as in the BOUNDARY= data set. But the derived Type II error probability $\beta$ and power $1 - \beta$ are slightly different with new information levels. With the updated power $1 - \beta$, the corresponding fixed-sample design is also updated.

**Figure 108.10** Design Information

**The SEQTEST Procedure**

| Design Information | |
|---|---|
| **BOUNDARY Data Set** | WORK.BND_LDL |
| **Data Set** | WORK.PARMS_LDL1 |
| **Statistic Distribution** | Normal |
| **Boundary Scale** | Standardized Z |
| **Alternative Hypothesis** | Two-Sided |
| **Early Stop** | Reject Null |
| **Number of Stages** | 4 |
| **Alpha** | 0.05 |
| **Beta** | 0.10074 |
| **Power** | 0.89926 |
| **Max Information (Percent of Fixed Sample)** | 102.4815 |
| **Max Information** | 0.10740291 |
| **Null Ref ASN (Percent of Fixed Sample)** | 101.7765 |
| **Alt Ref ASN (Percent of Fixed Sample)** | 75.4928 |

The "Test Information" table in Figure 108.11 displays the boundary values for the test statistic. By default (or equivalently if you specify BOUNDARYSCALE=STDZ), these statistics are displayed with the standardized $Z$ scale. With the INFOADJ=PROP option (which is the default), information levels at future interim stages are derived proportionally from the corresponding levels provided in the BOUNDARY= data set.

**Figure 108.11** Sequential Tests

**Test Information (Standardized Z Scale)**
**Null Reference = 0**

| | Information Level | | Alternative Reference | | Boundary Values | | Test Trt | |
|---|---|---|---|---|---|---|---|---|
| _Stage_ | Proportion | Actual | Lower | Upper | Lower Alpha | Upper Alpha | Estimate | Action |
| 1 | 0.2880 | 0.030934 | -1.75879 | 1.75879 | -3.39532 | 3.39532 | -0.44426 | Continue |
| 2 | 0.5253 | 0.056423 | -2.37536 | 2.37536 | -2.77374 | 2.77374 | . | |
| 3 | 0.7627 | 0.081913 | -2.86205 | 2.86205 | -2.32412 | 2.32412 | . | |
| 4 | 1.0000 | 0.107403 | -3.27724 | 3.27724 | -2.03147 | 2.03147 | . | |

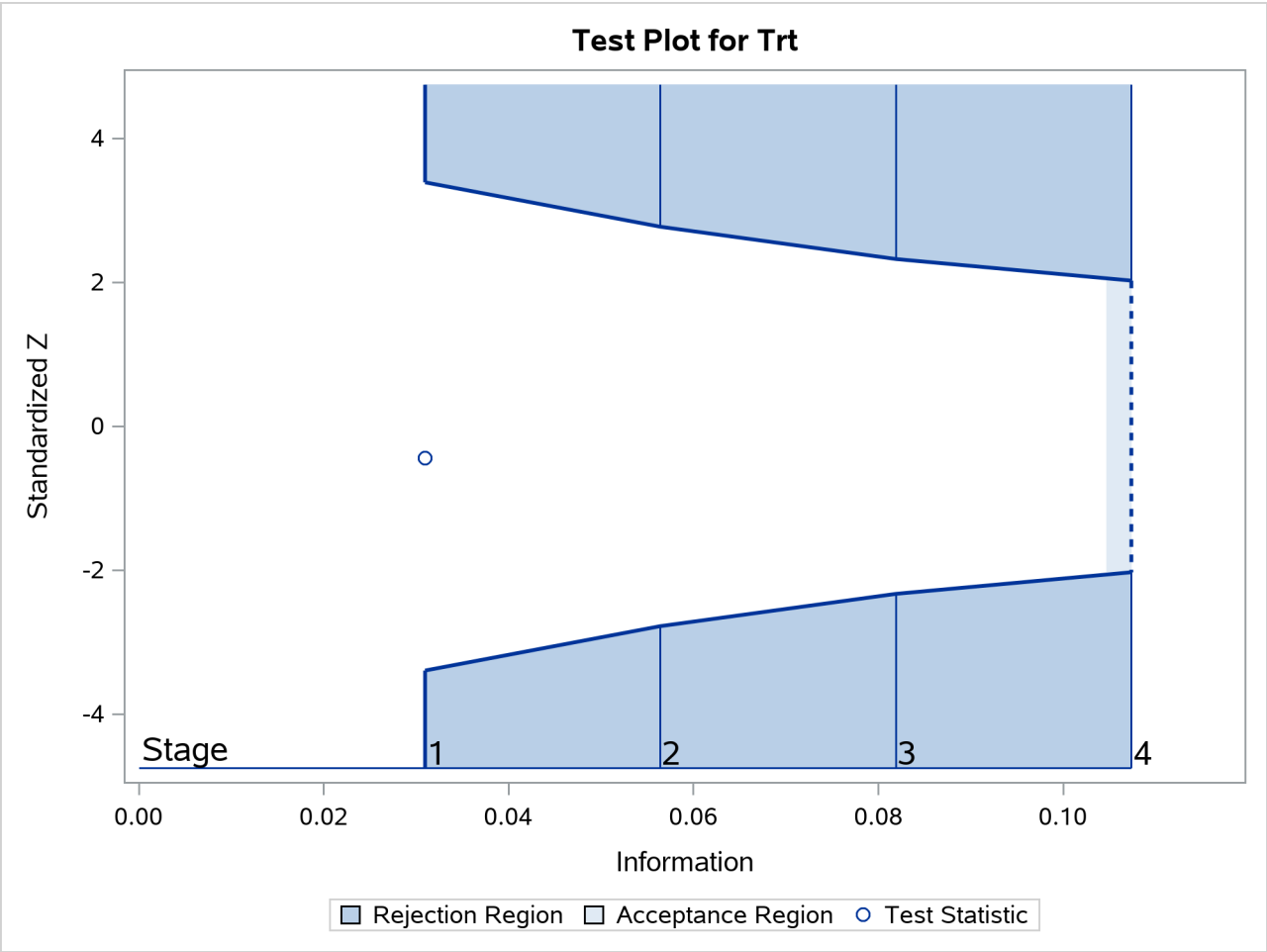
At stage 1, the standardized $Z$ statistic –0.44426 is between the lower and upper $\alpha$ boundary values, and so the trial continues to the next stage. With the observed information level at stage 1, $I_1 = 0.0309$ (which is not substantially different from the target information level at stage 1), the trial continues to the next stage without adjustment of the sample size according to the study plan.

If an observed information level is different from its target level at an interim stage, the sample sizes at future stages can be adjusted to achieve the target maximum information level according to the study plan. That is, a study plan might modify the final sample size to achieve the target maximum information level if the observed information level is different from its target level by a specified amount at the interim stage. For example, if the variance estimate is used to compute the required sample size of a two-sample $Z$ test for mean difference, the study plan might use the current variance estimate to update the required sample size for the trial (Jennison and Turnbull 2000, p. 295).

See the section "Test for the Difference between Two Normal Means" on page 8893 in Chapter 107, "The SEQDESIGN Procedure," for more information about how to compute the sample size from the variance estimate.

If ODS Graphics is enabled, a detailed test plot with the rejection and acceptance regions is displayed, as shown in Figure 108.12. This plot displays the boundary values in the "Test Information" table in Figure 108.11. The stages are indicated by vertical lines with accompanying stage numbers. The horizontal axis indicates the information levels for the stages. As expected, the test statistic is in the continuation region between the lower and upper $\alpha$ boundaries.

**Figure 108.12** Sequential Test Plot




The following statements use the REG procedure with the data available at the first two stages to estimate the mean treatment difference and its associated standard error at stage 2:

```
proc reg data=LDL_2;
   model Ldl=Trt;
   ods output ParameterEstimates=Parms_LDL2;
run;
```

The following statements create and display (in Figure 108.13) the data set for the mean treatment difference and its associated standard error:

```
data Parms_LDL2;
   set Parms_LDL2;
   if Variable='Trt';
   _Scale_='MLE';
   _Stage_= 2;
   keep _Scale_ _Stage_ Variable Estimate StdErr;
run;

proc print data=Parms_LDL2;
   title 'Statistics Computed at Stage 2';
run;
```

**Figure 108.13** Statistics Computed at Stage 2

**Statistics Computed at Stage 2**

| Obs | Variable | Estimate | StdErr | _Scale_ | _Stage_ |
|---|---|---|---|---|---|
| 1 | Trt | -8.37628 | 4.24405 | MLE | 2 |

Using the standard error for the treatment estimate available at stage 2, the information level that corresponds to the test statistic at stage 2 is estimated by

$$I_2 = \frac{1}{s_2^2} = \frac{1}{4.244^2} = 0.0555$$

where $s_2$ is the standard error of the treatment estimate at stage 2.

The following statements invoke the SEQTEST procedure to test for early stopping at stage 2:

```
proc seqtest Boundary=Test_LDL1
             Parms(Testvar=Trt)=Parms_LDL2
             infoadj=prop
             ;
   ods output Test=Test_LDL2;
run;
```

The BOUNDARY= option specifies the input data set that provides the boundary information for the trial at stage 2, which was generated by the SEQTEST procedure at the previous stage. The PARMS= option specifies the input data set that contains the test statistic and its associated standard error at stage 2, and the TESTVAR= option identifies the test variable in the data set.

The ODS OUTPUT statement with the TEST=TEST_LDL2 option creates an output data set named TEST_LDL2 which contains the updated boundary information for the test at stage 2. The data set also provides the boundary information that is needed for the group sequential test at the next stage.

The "Test Information" table in Figure 108.14 displays the boundary values for the test statistic with the default standardized $Z$ scale

**Figure 108.14** Sequential Tests

**The SEQTEST Procedure**

| Test Information (Standardized Z Scale) Null Reference = 0 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Information Level | | Alternative Reference | | Boundary Values | | Test Trt | |
| _Stage_ | Proportion | Actual | Lower | Upper | Lower Alpha | Upper Alpha | Estimate | Action |
| 1 | 0.2880 | 0.030934 | -1.75879 | 1.75879 | -3.39532 | 3.39532 | -0.44426 | Continue |
| 2 | 0.5169 | 0.055519 | -2.35624 | 2.35624 | -2.78456 | 2.78456 | -1.97365 | Continue |
| 3 | 0.7585 | 0.081461 | -2.85413 | 2.85413 | -2.32908 | 2.32908 | . | |
| 4 | 1.0000 | 0.107403 | -3.27724 | 3.27724 | -2.03097 | 2.03097 | . | |

At stage 2, the standardized test statistic, $z = -8.37628/4.24405 = -1.97365$, is between its corresponding lower and upper $\alpha$ boundary values. Therefore, the trial continues to the next stage.

The following statements use the REG procedure with the data available at the first three stages to estimate the mean treatment difference and its associated standard error at stage 3:

```
proc reg data=LDL_3;
   model Ldl=Trt;
   ods output ParameterEstimates=Parms_LDL3;
run;
```

The following statements create and display (in Figure 108.15) the data set for the mean treatment difference and its associated standard error:

```
data Parms_LDL3;
   set Parms_LDL3;
   if Variable='Trt';
   _Scale_='MLE';
   _Stage_= 3;
   keep _Scale_ _Stage_ Variable Estimate StdErr;
run;

proc print data=Parms_LDL3;
   title 'Statistics Computed at Stage 3';
run;
```

**Figure 108.15** Statistics Computed at Stage 3

**Statistics Computed at Stage 3**

| Obs | Variable | Estimate | StdErr | _Scale_ | _Stage_ |
|---|---|---|---|---|---|
| 1 | Trt | -9.21369 | 3.42149 | MLE | 3 |

The following statements invoke the SEQTEST procedure to test for early stopping at stage 3:

```
ods graphics on;
proc seqtest Boundary=Test_LDL2
             Parms(Testvar=Trt)=Parms_LDL3
             infoadj=prop
             ;
   ods output Test=Test_LDL3;
run;
```

The BOUNDARY= option specifies the input data set that provides the boundary information for the trial at stage 3, which was generated by the SEQTEST procedure at the previous stage. The PARMS= option specifies the input data set that contains the test statistic and its associated standard error at stage 3, and the TESTVAR= option identifies the test variable in the data set.

The ODS OUTPUT statement with the TEST=TEST_LDL3 option creates an output data set named TEST_LDL3 which contains the updated boundary information for the test at stage 3. The data set also provides the boundary information that is needed for the group sequential test at the next stage.

The "Test Information" table in Figure 108.16 displays the boundary values for the test statistic with the default standardized $Z$ scale.

**Figure 108.16** Sequential Tests

**The SEQTEST Procedure**

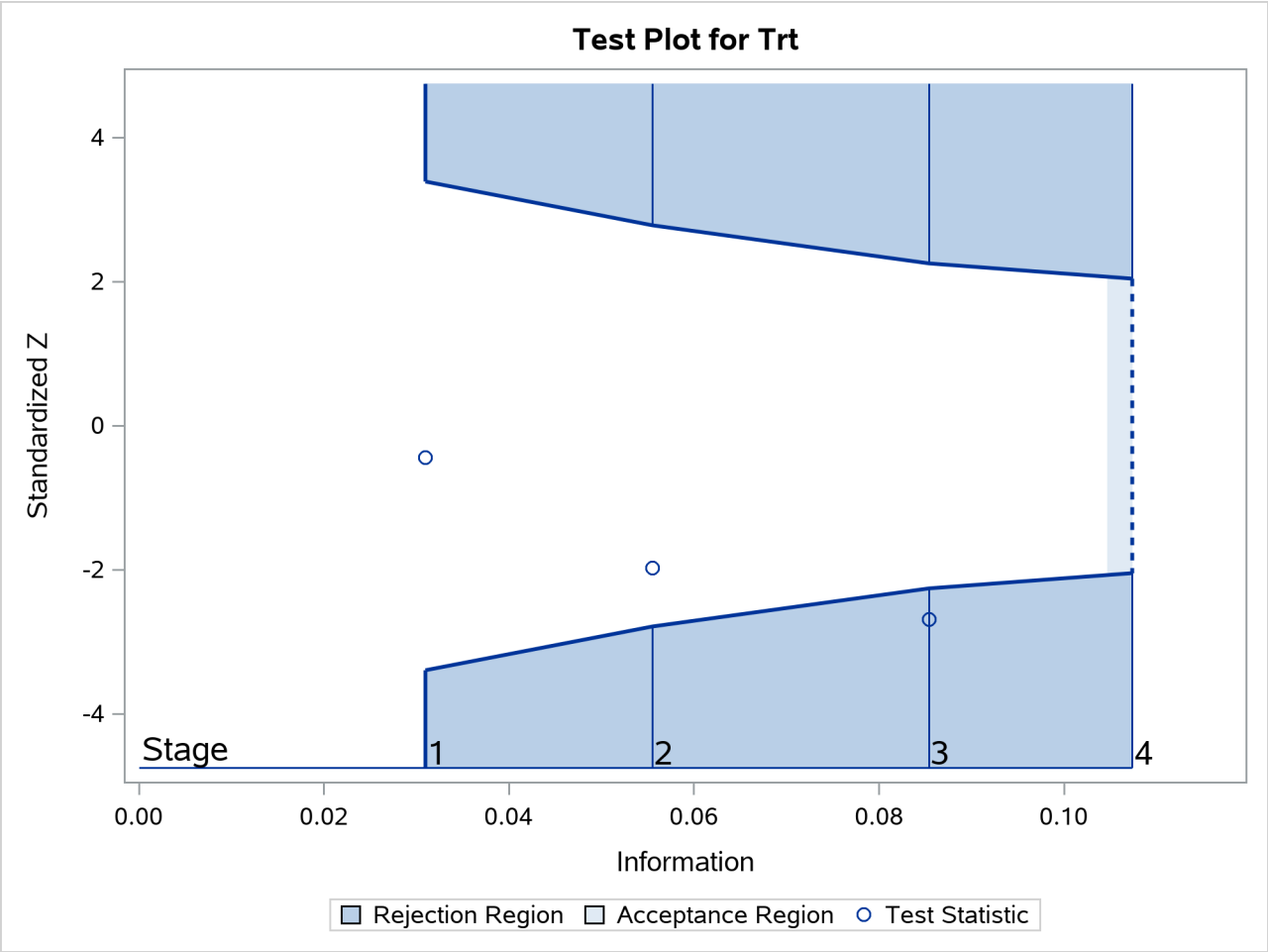
**Test Information (Standardized Z Scale)**
**Null Reference = 0**

| | Information Level | | Alternative Reference | | Boundary Values | | Test | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Lower | Upper | Trt | |
| _Stage_ | Proportion | Actual | Lower | Upper | Alpha | Alpha | Estimate | Action |
| 1 | 0.2880 | 0.030934 | -1.75879 | 1.75879 | -3.39532 | 3.39532 | -0.44426 | Continue |
| 2 | 0.5169 | 0.055519 | -2.35624 | 2.35624 | -2.78456 | 2.78456 | -1.97365 | Continue |
| 3 | 0.7953 | 0.085422 | -2.92271 | 2.92271 | -2.25480 | 2.25480 | -2.69289 | Reject Null |
| 4 | 1.0000 | 0.107403 | -3.27724 | 3.27724 | -2.04573 | 2.04573 | . | |

The sequential test stops at stage 3 to reject the null hypothesis for the lower alternative because the test statistic –2.69289 is less than the corresponding upper $\alpha$ boundary –2.25480. That is, the test demonstrates significant beneficial effect for the new drug.

The "Test Plot" displays boundary values for the design and the test statistic at the first three stages, as shown in Figure 108.17. It shows that the test statistic is in the "Rejection Region" below the lower $\alpha$ boundary at stage 3.

**Figure 108.17** Sequential Test Plot




When a trial stops, the "Parameter Estimates" table in Figure 108.18 displays the stopping stage, parameter estimate, unbiased median estimate, confidence limits, and $p$-value under the null hypothesis $H_0 : \theta = 0$. As expected, the $p$-value 0.0108 is significant at the two-sided $\alpha$ level, $\alpha = 0.05$, and the confidence interval does not contain the value zero. The $p$-value, unbiased median estimate, and confidence limits depend on the ordering of the sample space $(k, z)$, where $k$ is the stage number and $z$ is the standardized $Z$ statistic. See the section "Analysis after a Sequential Test" on page 9065 for a detailed description of these statistics.

**Figure 108.18** Parameter Estimates

**Parameter Estimates**
**Stagewise Ordering**

| Parameter | Stopping Stage | MLE | p-Value for H0:Parm=0 | Median Estimate | 95% Confidence Limits | |
|---|---|---|---|---|---|---|
| Trt | 3 | -9.213692 | 0.0108 | -9.022891 | -15.79845 | -2.13138 |

# Syntax: SEQTEST Procedure

The following statement is available in the SEQTEST procedure:

**PROC SEQTEST** < *options* > **;**

## PROC SEQTEST Statement

The PROC SEQTEST statement invokes the SEQTEST procedure. Table 108.1 summarizes the *options* available in the PROC SEQTEST statement.

**Table 108.1** Summary of PROC SEQTEST Options

| Option | Description |
|---|---|
| **Input Data Sets** | |
| BOUNDARY= | Specifies the data set for boundary information |
| DATA= | Specifies the data set for parameter estimates and information levels |
| PARMS= | Specifies the data set for parameter estimates and standard errors |
| **Boundaries** | |
| BETABOUNDARY= | Specifies whether the $\beta$ boundary is used in the computation of the Type I error level $\alpha$ |
| BETAOVERLAP= | Checks for overlapping of the lower and upper $\beta$ boundaries at the current and subsequent interim stages in a two-sided design |
| BOUNDARYKEY= | Specifies the boundary key to maintain Type I and II error probability levels |
| BOUNDARYSCALE= | Specifies the boundary scale |
| ERRSPENDADJ= | Specifies error spending methods for boundary adjustments |
| ERRSPENDMIN= | Specifies minimum error spending values for the boundaries |
| INFOADJ= | Specifies whether information levels at future interim stages should be adjusted |
| NSTAGES= | Specifies the number of stages |
| **Test Statistics** | |
| DATA( INFOVAR= ) | Specifies the information variable in the DATA= data set |
| DATA( TESTVAR= ) | Specifies the test variable in the DATA= data set |
| PARMS( INFOVAR= ) | Specifies the information variable in the PARMS= data set |
| PARMS( TESTVAR= ) | Specifies the test variable in the PARMS= data set |
| ***p*-Values and Confidence Intervals** | |
| CIALPHA= | Specifies the significance levels for the confidence interval |
| CITYPE= | Specifies the types of confidence interval |
| ORDER= | Specifies the ordering of the sample space used to derive the *p*-values and confidence limits |
| **Table Output** | |
| CONDPOWER | Displays conditional powers |
| ERRSPEND | Displays the cumulative error spending at each stage |

**Table 108.1** *continued*

| Option | Description |
|---|---|
| PREDPOWER | Displays the predictive powers |
| PSS | Displays the powers and expected sample sizes |
| RCI | Displays the repeated confidence intervals |
| STOPPROB | Displays the expected cumulative stopping probabilities |
| **Graphics Output** | |
| PLOTS=ASN | Displays the expected sample numbers plot |
| PLOTS=CONDPOWER | Displays the conditional powers plot |
| PLOTS=ERRSPEND | Displays the error spending plot |
| PLOTS=POWER | Displays the powers plot |
| PLOTS=RCI | Displays the repeated confidence intervals plot |
| PLOTS=TEST | Displays the boundary plot with test statistics |

The BOUNDARY= option provides the information for the design and is required in the PROC SEQTEST statement. By default, the SEQTEST procedure displays tables of design information and test information. If ODS Graphics is enabled, the procedure also displays a sequential test plot.

The following *options* can be used in the PROC SEQTEST statement. They are listed in alphabetical order.

**BETABOUNDARY=BINDING | NONBINDING**

specifies whether the $\beta$ boundary is used in the computation of the Type I error level $\alpha$. The BETABOUNDARY=BINDING option computes the Type I error probability with the $\beta$ (acceptance) boundary, and the BETABOUNDARY=NONBINDING suboption computes the Type I error probability without the $\beta$ boundary (Zhu, Ni, and Yao 2011, pp. 132–133). For a detailed description of nonbinding acceptance boundary, see the section "Acceptance ($\boldsymbol{\beta}$) Boundary" on page 8877 in Chapter 107, "The SEQDESIGN Procedure." The default is BETABOUNDARY=BINDING.

**BETAOVERLAP=ADJUST | NOADJUST**

**OVERLAP=ADJUST | NOADJUST**

specifies whether to check for overlapping of the lower and upper $\beta$ boundaries for the two corresponding one-sided tests at the current and subsequent interim stages. This option applies to two-sided designs with early stopping to accept $H_0$, or to either accept or reject $H_0$. This type of overlapping might result from a small $\beta$ spending at an interim stage. When you specify BETAOVERLAP=ADJUST, the procedure checks for this type of overlapping at the current and subsequent interim stages. If such overlapping is found, the $\beta$ boundaries for the two-sided design at that stage are set to missing, and the $\beta$ spending values at subsequent stages are adjusted, as described in the section "Boundary Adjustments for Overlapping Lower and Upper $\boldsymbol{\beta}$ Boundaries" on page 9061.

You can specify BETAOVERLAP=NOADJUST to request that no adjustment be made. The default is BETAOVERLAP=ADJUST.

**BOUNDARY=***SAS-data-set*

names the required SAS data set that contains the design boundary information. At stage 1, the data set is usually created from the "Boundary Information" table created by the SEQDESIGN procedure. At each subsequent stage, the data set is usually created from the "Test Information" table created by the SEQTEST procedure at the previous stage. The data set includes the variables _Scale_ for the

boundary scale, _Stop_ for the stopping criterion, and _ALT_ for the type of alternative hypothesis. It also includes _Stage_ for the stage number, Info_Prop for the information proportion, and a set of the boundary variables from Bound_LA, Bound_LB, Bound_UB, and Bound_UA for boundary values at each stage.

The data set might also include _Info_ for the actual information level, NObs for the number of observation, and Events for the number of events required at each stage.

**BOUNDARYKEY=ALPHA | BETA | BOTH**

specifies the boundary key to be maintained in the boundary adjustments. The BOUNDARYKEY=ALPHA option maintains the Type I $\alpha$ level and derives the Type II error probability, and the BOUNDARYKEY=BETA option maintains the Type II $\beta$ level and derives the Type I error probability. The BOUNDARYKEY=BOTH option maintains both $\alpha$ and $\beta$ levels simultaneously by deriving a new maximum information. The default is BOUNDARYKEY=ALPHA.

**BOUNDARYSCALE=MLE | SCORE | STDZ | PVALUE**

**BSCALE=MLE | SCORE | STDZ | PVALUE**

specifies the boundary scale to be displayed in the output boundary table and plot. The BOUNDARYSCALE=MLE, BOUNDARYSCALE=SCORE, BOUNDARYSCALE=STDZ, and BOUNDARYSCALE=PVALUE options correspond to the boundary with the maximum likelihood estimator scale, score statistic scale, standardized normal $Z$ scale, and $p$-value scale, respectively. The default is BOUNDARYSCALE=STDZ.

With the BOUNDARYSCALE=MLE or BOUNDARYSCALE=SCORE option, either the MAXINFO= option must be specified or the _Info_ variable must be in the BOUNDARY= data set to provide the necessary information level at each stage to derive the boundary values. Usually, these values are obtained from analysis output in SAS procedures.

Note that for a two-sided design, the $p$-value scale displays the one-sided fixed-sample $p$-value under the null hypothesis with a lower alternative hypothesis.

**CIALPHA=$\alpha$ <( <LOWER=$\alpha_l$> <UPPER=$\alpha_u$> )>**

specifies the significance levels for the confidence interval, where $0 < \alpha < 1$, $0 < \alpha_l < 0.5$, and $0 < \alpha_u < 0.5$. The default is CIALPHA= 0.05.

For a lower confidence interval (CITYPE=LOWER), the CIALPHA=$\alpha$ option produces a $(1 - \alpha)$ lower confidence interval. For an upper confidence interval (CITYPE=UPPER), the CIALPHA=$\alpha$ option produces a $(1 - \alpha)$ upper confidence interval. The LOWER= and UPPER= suboptions are applicable only for a two-sided confidence interval (CITYPE=TWOSIDED). The LOWER= suboption specifies the lower significance level $\alpha_l$ and the upper significance level $\alpha_u = 1 - \alpha_l$. The UPPER= suboption specifies the upper significance level $\alpha_u$ and the lower significance level $\alpha_l = 1 - \alpha_u$. If both LOWER= and UPPER= suboptions are not specified, $\alpha_l = \alpha_u = \alpha/2$. The significance levels $\alpha_l$ and $\alpha_u$ are then used for the $(1 - \alpha_l)$ lower confidence limit and $(1 - \alpha_u)$ upper confidence limit, respectively.

**CITYPE=LOWER | UPPER | TWOSIDED**

specifies the type of confidence interval. The CITYPE=LOWER, CITYPE=UPPER, and CITYPE=TWOSIDED options correspond to the lower confidence interval, upper confidence interval, and two-sided confidence interval, respectively. The default is CITYPE=LOWER for the design with an upper alternative, CITYPE=UPPER for the design with a lower alternative, and CITYPE=TWOSIDED for the design with a two-sided alternative.

**DATA < ( TESTVAR=***variable* | **INFOVAR=***variable* **) >=***SAS-data-set*

names the SAS data set that contains the test statistic and its associated information level for the stage. The *SAS-data-set* includes the stage variable _Stage_. You can also specify the following options within parentheses after the DATA keyword:

**TESTVAR=***variable*

identifies the test variable in the *SAS-data-set*. If you specify this option, the data set also includes the scale variable _Scale_ for the test statistic. Usually, these test variable values are obtained from analysis output in SAS procedures.

**INFOVAR=***variable*

identifies the information variable in the *SAS-data-set* to either identify or derive the information levels. If you specify this option, the following information variables apply:

- _Info_ uses _Info_ for the information levels.
- Events uses Events for the numbers of events to derive the information levels.
- NObs uses NObs for the numbers of observations to derive the information levels.
- None uses the information levels in the BOUNDARY= data set.

If you do not specify the INFOVAR= option, PROC SEQTEST uses _Info_ (if it exists) in the *SAS-data-set* for the information levels. Otherwise, the procedure uses NObs to derive information levels from the numbers of observation or uses Events to derive information levels from the numbers of events. If these variables are not in the *SAS-data-set*, the information levels in the BOUNDARY= data set are used. See Example 108.4 for an illustration of the INFOVAR=NObs option.

**ERRSPENDADJ=***method*

**ERRSPENDADJ(***boundary***)=***method*

**BOUNDARYADJ=***method*

**BOUNDARYADJ(***boundary***)=***method*

specifies methods to compute the error spending values at the current and future interim stages for the boundaries. This option is applicable only if the observed information level at the current stage does not match the value provided in the BOUNDARY= data set. These error spending values are then used to derive the updated boundary values. The default is ERRSPENDADJ=ERRLINE. Note that the information levels at future interim stages are determined by the INFOADJ= option.

The following options specify available error spending methods for boundary adjustment:

**NONE**

specifies that the cumulative error spending at each interim stage not be changed, even if the corresponding information level has been changed.

**ERRLINE**

specifies the linear interpolation method for the adjustment.

**ERRFUNCGAMMA < ( GAMMA=** $\gamma$ **) >**

specifies the gamma function method for the adjustment. The GAMMA= suboption specifies the $\gamma$ parameter in the function, where $\gamma \leq 3$. The default is GAMMA=–2.

**ERRFUNCOBF**
specifies the approximate O'Brien-Fleming cumulative error spending function for the adjustment.

**ERRFUNCPOC**
specifies the approximate Pocock cumulative error spending function for the adjustment.

**ERRFUNCPOW < ( RHO=** $\rho$ **) >**
specifies the power function method for the adjustment. The RHO= suboption specifies the power parameter $\rho$ in the function, where $\rho \geq 0.25$. The default is RHO=2.

See the section "Boundary Adjustments for Information Levels" on page 9058 for a detailed description of the available error spending methods for boundary adjustment in the SEQTEST procedure.

If an error spending method for boundary adjustments is used for all boundaries in a group sequential test, you can use the ERRSPENDADJ=*method* option to specify the method. Otherwise, you can use the following ERRSPENDADJ(*boundary*)=*method* options to specify different methods for the boundaries.

**ERRSPENDADJ(ALPHA)=***method*
**ERRSPENDADJ(REJECT)=***method*
**BOUNDARYADJ(ALPHA)=***method*
**BOUNDARYADJ(REJECT)=***method*
specifies the adjustment method for the $\alpha$ (rejection) boundary of a one-sided design or the lower and upper $\alpha$ boundaries of a two-sided design.

**ERRSPENDADJ(LOWERALPHA)=***method*
**ERRSPENDADJ(LOWERREJECT)=***method*
**BOUNDARYADJ(LOWERALPHA)=***method*
**BOUNDARYADJ(LOWERREJECT)=***method*
specifies the adjustment method for the lower $\alpha$ boundary of a two-sided design.

**ERRSPENDADJ(UPPERALPHA)=***method*
**ERRSPENDADJ(UPPERREJECT)=***method*
**BOUNDARYADJ(UPPERALPHA)=***method*
**BOUNDARYADJ(UPPERREJECT)=***method*
specifies the adjustment method for the upper $\alpha$ boundary of a two-sided design.

**ERRSPENDADJ(BETA)=***method*
**ERRSPENDADJ(ACCEPT)=***method*
**BOUNDARYADJ(BETA)=***method*
**BOUNDARYADJ(ACCEPT)=***method*
specifies the adjustment method for the $\beta$ (acceptance) boundary of a one-sided design or the lower and upper $\beta$ boundaries of a two-sided design.

**ERRSPENDADJ(LOWERBETA)=***method*
**ERRSPENDADJ(LOWERACCEPT)=***method*
**BOUNDARYADJ(LOWERBETA)=***method*
**BOUNDARYADJ(LOWERACCEPT)=***method*
specifies the adjustment method for the lower $\beta$ boundary of a two-sided design.

**ERRSPENDADJ(UPPERBETA)=***method*
**ERRSPENDADJ(UPPERACCEPT)=***method*
**BOUNDARYADJ(UPPERBETA)=***method*
**BOUNDARYADJ(UPPERACCEPT)=***method*
specifies the adjustment method for the upper $\beta$ boundary of a two-sided design.

**ERRSPENDMIN=***numbers*
**ERRSPENDMIN(***boundary***)=***numbers*
specifies the minimum error spending values at the current observed and future interim stages for the boundaries specified in the BOUNDARYKEY= option. The default is ERRSPENDMIN=0.

If a set of numbers is used for each boundary in the design, you can use the ERRSPENDMIN=*numbers* option. Otherwise, you can use the following ERRSPENDMIN(*boundary*)=*numbers* options to specify different sets of minimum error spending values for the boundaries. For a boundary, the error spending value at stage 1 is identical to its nominal $p$-value.

**ERRSPENDMIN(ALPHA)=***numbers*
**ERRSPENDMIN(REJECT)=***numbers*
specifies the minimum error spending values for the $\alpha$ boundary of a one-sided design or the lower and upper $\alpha$ boundaries of a two-sided design.

**ERRSPENDMIN(LOWERALPHA)=***numbers*
**ERRSPENDMIN(LOWERREJECT)=***numbers*
specifies the minimum error spending values for the lower $\alpha$ boundary of a two-sided design.

**ERRSPENDMIN(UPPERALPHA)=***numbers*
**ERRSPENDMIN(UPPERREJECT)=***numbers*
specifies the minimum error spending values for the upper $\alpha$ boundary of a two-sided design.

**ERRSPENDMIN(BETA)=***numbers*
**ERRSPENDMIN(ACCEPT)=***numbers*
specifies the minimum error spending values for the $\beta$ boundary of a one-sided design or the lower and upper $\beta$ boundaries of a two-sided design.

**ERRSPENDMIN(LOWERBETA)=***numbers*
**ERRSPENDMIN(LOWERACCEPT)=***numbers*
specifies the minimum error spending values for the lower $\beta$ boundary of a two-sided design.

**ERRSPENDMIN(UPPERBETA)=***numbers*
**ERRSPENDMIN(UPPERACCEPT)=***numbers*
specifies the minimum error spending values for the upper $\beta$ boundary of a two-sided design.

**INFOADJ=NONE | PROP**

specifies whether information levels at future interim stages are to be adjusted. If you specify INFOADJ=NONE, no adjustment is made, and the information levels are preserved at the levels provided in the BOUNDARY= data set. If you specify INFOADJ=PROP (which is the default), the information levels are adjusted proportionally from the levels provided in the BOUNDARY= data set. The section "Information Level Adjustments at Future Stages" on page 9058 describes how the adjustments are computed.

Note that if you specify BOUNDARYKEY=BOTH, the INFOADJ=NONE option is not applicable, and the INFOADJ=PROP option is used to adjusted the information levels at future stages proportionally from the levels provided in the BOUNDARY= data set to maintain both $\alpha$ and $\beta$ levels.

**NSTAGES=***number*

specifies the number of stages for the clinical trial. The default is the number derived from the BOUNDARY= data set.

The specified NSTAGES= number might or might not be the same as the number derived in the BOUNDARY= data set. You can use the NSTAGES= option to set the next stage as the final stage to compute the conditional power, as described in the section "Conditional Power Approach" on page 9062.

**ORDER=LR | MLE | STAGEWISE**

specifies the ordering of the sample space $(k, z)$, where $k$ is the stage number and $z$ is the observed standardized $Z$ statistic. The ordering is used to derive the $p$-values for the observed $(k, z)$ statistic and to create unbiased median estimate and confidence limits from the statistic. The ORDER=LR option specifies the LR ordering that compares the distances between observed standardized $Z$ statistics and their corresponding hypothetical values, the ORDER=MLE option specifies the MLE ordering that compares values in the MLE scale, and the ORDER=STAGEWISE specifies the stagewise ordering that uses counterclockwise ordering around the continuation region. The default is ORDER=STAGEWISE. See the section "Available Sample Space Orderings in a Sequential Test" on page 9065 for a detailed description of these sample space orderings.

**PARMS < ( TESTVAR=***variable* **| INFOVAR=***variable* **) >=***SAS-data-set*

names the SAS data set that contains the parameter estimate and its associated standard error for the stage. The *SAS-data-set* includes the stage variable _Stage_. You can also specify the following *options* within parentheses after the PARMS keyword:

**TESTVAR=***variable*

identifies the test variable in the *SAS-data-set*. If you specify this option, the *SAS-data-set* also includes the Parameter, Effect, Variable, or Parm variable that contains the *variable*. In addition, the *SAS-data-set* also includes the test statistic Estimate, the standard error of the estimate StdErr, and the test statistic scale variable _Scale_. Usually, these test variable values are obtained from analysis output in SAS procedures.

**INFOVAR=***variable*

identifies the information variable in the *SAS-data-set* to either identify or derive the information levels. If you specify this option, the following information variables apply:

- Events uses Events for the numbers of events to derive the information levels.
- NObs uses NObs for the numbers of observations to derive the information levels.

- None uses the information levels in the BOUNDARY= data set.
- StdErr uses StdErr to derive the information levels.

If you do not specify the INFOVAR= option, PROC SEQTEST uses StdErr (if it exists) in the *SAS-data-set* to derive the information levels. Otherwise, the procedure uses NObs to derive information levels from the numbers of observation or uses Events to derive information levels from the numbers of events. If these variables are not in the *SAS-data-set*, the information levels in the BOUNDARY= data set are used.

## Table Output Options

You can specify the following *options* in the PROC SEQTEST statement to display additional table output. They are listed in alphabetical order.

**CONDPOWER < ( *options* ) >**

displays conditional powers given the most recently observed statistic under specified hypothetical references.

You can specify the following *options*:

**CREF=** $c_1 < c_2 \ldots >$

specifies the hypothetical references, where $c_i \geq 0$. For a one-sided test, the powers are derived under the hypothetical references $\theta = \hat{\theta}$ and $\theta = c_i\theta_1$, where $\hat{\theta}$ is the observed statistic, $\theta_1$ is the alternative reference, and $c_i$ are the values specified in the CREF= option. For a two-sided test, the powers are derived under hypothetical references $\theta = \hat{\theta}$, $\theta = c_i\theta_{1l}$, and $\theta = c_i\theta_{1u}$, where $\theta_{1l}$ is the lower alternative reference and $\theta_{1u}$ is the upper alternative reference. The default is CREF= 0 0.5 1.0 1.5.

**TYPE=ALLSTAGES | FINALSTAGE**

specifies the probability to be computed for the conditional power. Two types of conditional power can be computed: TYPE=ALLSTAGES computes the conditional power as the total probability of rejecting the null hypothesis at all future stages given the observed statistic, and TYPE=FINALSTAGE computes the conditional power as the probability that the test statistic at the final stage would exceed the rejection critical value given the observed statistic. The default is TYPE=ALLSTAGES.

If interim stages exist between the current stage and the final stage, the conditional power that is computed when TYPE=FINALSTAGE is not the conditional probability to reject the null hypothesis $H_0$. In this case, you can set the next stage as the final stage, and the resulting conditional power is the conditional probability to reject $H_0$.

**ERRSPEND**

displays the error spending at each stage for each sequential boundary.

**PREDPOWER**

displays predictive powers given the most recently observed statistic. The predictive power is the posterior probability that the test statistic at the final stage would exceed the rejection critical value given the observed statistic and a prior distribution of the hypothetical reference. A noninformative prior is used in the procedure.

**PSS < ( CREF=** $c_1 < c_2 \ldots >$ **) >**

displays powers and expected sample sizes under various hypothetical references, where $c_i \geq 0$.

For a one-sided design with the null reference $\theta_0 = 0$, the power and expected sample sizes under hypotheses $\theta = c_i\ \theta_1$ are displayed, where $\theta_1$ is the alternative reference and $c_i$ are the values specified in the CREF= option.

For a two-sided design, the power and expected sample sizes under hypotheses $\theta = c_i \theta_{1l}$ and $\theta = c_i \theta_{1u}$ are displayed, where $\theta_{1l}$ and $\theta_{1u}$ are the lower and upper alternative references, respectively. The default is CREF= 0 0.5 1.0 1.5.

Note that for a symmetric two-sided design, only the power and expected sample sizes under hypotheses $\theta = c_i\ \theta_{1u}$ are derived.

**RCI**

displays repeated confidence intervals for the parameter from the observed statistic at each stage. Repeated confidence intervals include both rejection and acceptance confidence intervals.

With the STOP=REJECT or STOP=BOTH option, rejection confidence limits can be derived, and the null hypothesis $H_0 : \theta = 0$ is rejected if the lower rejection confidence limit is greater than 0 or the upper rejection confidence limit is less than 0.

With the STOP=ACCEPT or STOP=BOTH option, acceptance confidence limits can be derived, and the null hypothesis is accepted with alternative hypotheses $H_{1l} : \theta = \theta_{1l}$ and $H_{1u} : \theta = \theta_{1u}$ if the upper acceptance confidence limit is less than $\theta_{1u}$ and the lower acceptance confidence limit is greater than $\theta_{1l}$.

**STOPPROB < ( CREF=** $c_1 < c_2 \ldots >$ **) >**

displays expected cumulative stopping probabilities under various hypothetical references, where $c_i \geq 0$.

For a one-sided design, expected cumulative stopping probabilities at each stage under hypotheses $\theta = c_i\ \theta_1$ are displayed, where $\theta_1$ is the alternative reference and $c_i$ are the values specified in the CREF= option.

For a two-sided design, expected cumulative stopping probabilities at each stage under hypotheses $\theta = c_i \theta_{1l}$ and $\theta = c_i \theta_{1u}$ are displayed, where $\theta_{1l}$ and $\theta_{1u}$ are the lower and upper alternative references, respectively. Note that for a symmetric two-sided design, only expected cumulative stopping probabilities under hypotheses $\theta = c_i\ \theta_{1u}$ are derived. The default is CREF= 0 0.5 1.0 1.5.

## Graphics Output Options

The following *options* can be used in the PROC SEQTEST statement to display plots with ODS Graphics. They are listed in alphabetical order.

**PLOTS < ( ONLY ) > < =** *plot-request* **>**

**PLOTS < ( ONLY ) > < = (** *plot-request* **< . . .** *plot-request* **> ) >**

specifies options that control the details of the plots. The default is PLOTS=TEST. The global plot option ONLY suppresses the default plots and displays only plots specifically requested.

ODS Graphics must be enabled before plots can be requested. For example:

```
ods graphics on;
proc seqtest Boundary=Bnd_LDL
             Parms(Testvar=Trt)=Parms_LDL1
             Plots=(test errspend);
run;
```

For more information about enabling and disabling ODS Graphics, see the section "Enabling and Disabling ODS Graphics" on page 623 in Chapter 21, "Statistical Graphics Using ODS."

The *plot-request-options* include the following.

**ALL**

produces all appropriate plots.

**ASN < ( CREF=** $c_1 < c_2 \ldots >$ **) >**

displays a plot of the average sample numbers (expected sample sizes for nonsurvival data or expected number of events for survival data) under various hypothetical references, where $c_i \geq 0$.

For a one-sided design, expected sample numbers under hypotheses $\theta = c_i\,\theta_1$ are displayed, where $\theta_1$ is the alternative reference and $c_i$ are the values specified in the CREF= option.

For a two-sided design, expected sample numbers under hypotheses $\theta = c_i\theta_{1l}$ and $\theta = c_i\theta_{1u}$ are displayed, where $\theta_{1l}$ and $\theta_{1u}$ are the lower and upper alternative references, respectively. Note that for a symmetric two-sided design, only the average sample numbers under hypotheses $\theta = c_i\,\theta_{1u}$ are derived. The default is CREF= 0 to 1.5 by 0.01.

**CONDPOWER < (** *options* **) >**

displays a plot of conditional powers given the most recently observed statistic under specified hypothetical references.

You can specify the following *options*:

**CREF=** $c_1 < c_2 \ldots >$

specifies the hypothetical references, where $c_i \geq 0$. For a one-sided test, the powers are derived under hypothetical references $\theta = \hat{\theta}$ and $\theta = c_i\theta_1$, where $\hat{\theta}$ is the observed statistic, $\theta_1$ is the alternative reference, and $c_i$ are the values specified in the CREF= option. For a two-sided test, the powers are derived under hypothetical references $\theta = \hat{\theta}$, $\theta = c_i\theta_{1l}$, and $\theta = c_i\theta_{1u}$, where $\theta_{1l}$ is the lower alternative reference and $\theta_{1u}$ is the upper alternative reference. The default is CREF= 0 to 1.5 by 0.01.

**TYPE=ALLSTAGES | FINALSTAGE**

specifies the probability to be computed for the conditional power. Two types of conditional power can be computed: TYPE=ALLSTAGES computes the conditional power as the total probability of rejecting the null hypothesis at all future stages given the observed statistic, and TYPE=FINALSTAGE computes the conditional power as the probability that the test statistic at the final stage would exceed the rejection critical value given the observed statistic. The default is TYPE=ALLSTAGES.

**ERRSPEND < ( HSCALE=INFO | STAGE ) >**
displays a plot of the error spending for all sequential boundaries in the designs simultaneously. You can display the information level (HSCALE=INFO) or the stage number (HSCALE=STAGE) on the horizontal axis. With HSCALE=INFO, the information fractions are used in the plot. The default is HSCALE=STAGE.

**NONE**
suppresses all plots.

**POWER < ( CREF=** $c_1 < c_2 \ldots >$ **) >**
displays a plot of the power curves under various hypothetical references, where $c_i \geq 0$.

For a one-sided design, powers under hypotheses $\theta = c_i\,\theta_1$ are displayed, where $\theta_1$ is the alternative reference and $c_i$ are the values specified in the CREF= option.

For a two-sided design, powers under hypotheses $\theta = c_i\theta_{1l}$ and $\theta = c_i\theta_{1u}$ are displayed, where $\theta_{1l}$ and $\theta_{1u}$ are the lower and upper alternative references, respectively. Note that for a symmetric two-sided design, only powers under hypotheses $\theta = c_i\,\theta_{1u}$ are derived. The default is CREF= 0 to 1.5 by 0.01.

**RCI**
displays a plot of repeated confidence intervals. Repeated confidence intervals include both rejection and acceptance confidence intervals.

With the STOP=REJECT or STOP=BOTH option, rejection confidence limits can be derived and the null hypothesis $H_0 : \theta = 0$ is rejected if the lower rejection confidence limit is greater than 0 or the upper rejection confidence limit is less than 0.

With the STOP=ACCEPT or STOP=BOTH option, acceptance confidence limits can be derived and the null hypothesis is accepted with alternative hypotheses $H_{1l} : \theta = \theta_{1l}$ and $H_{1u} : \theta = \theta_{1u}$ if the upper acceptance confidence limit is less than $\theta_{1u}$ and the lower acceptance confidence limit is greater than $\theta_{1l}$.

**TEST < ( HSCALE=INFO | SAMPLESIZE ) >**
displays a plot of the sequential boundaries and test variables. Either the information level (HSCALE=INFO) or the sample size (HSCALE=SAMPLESIZE) is displayed on the horizontal axis. The HSCALE=SAMPLESIZE option is applicable only if the sample size information is available in both the input BOUNDARY= data set and input DATA= data set. The stage number for each stage is displayed inside the plot. The default is HSCALE=INFO.

# Details: SEQTEST Procedure

## Input Data Sets

The BOUNDARY= data set option is required, and if neither the DATA= nor the PARMS= data set option is specified, the procedure derives statistics such as Type I and Type II error probabilities from the BOUNDARY= data set. The resulting boundaries are displayed with the scale specified in the BOUNDARYSCALE= option.

## BOUNDARY= Data Set

The BOUNDARY= data set provides the boundary information for the sequential test. At stage 1, the data set is usually created with an ODS OUTPUT statement from the "Boundary Information" table created by the SEQDESIGN procedure. At each subsequent stage, the data set is usually created with an ODS OUTPUT statement from the "Test Information" table that was created by the SEQTEST procedure at the previous stage. See the section "Getting Started: SEQTEST Procedure" on page 9028 for an illustration of the BOUNDARY= data set option.

The BOUNDARY= data set contains the following variables:

- _Scale_, the boundary scale, with the value MLE for the maximum likelihood estimate, STDZ for the standardized Z, SCORE for the score statistic, or PVALUE for the nominal $p$-value. Note that for a two-sided design, the nominal $p$-value is the one-sided fixed-sample $p$-value under the null hypothesis with a lower alternative hypothesis.
- _Stop_, the stopping criterion, with the value REJECT for rejecting the null hypothesis $H_0$, ACCEPT for accepting $H_0$, or BOTH for both rejecting and accepting $H_0$
- _ALT_, the type of alternative hypothesis, with the value UPPER for an upper alternative, LOWER for a lower alternative, or TWOSIDED for a two-sided alternative
- _Stage_, the stage number
- the boundary variables, a subset of Bound_LA for lower $\alpha$ boundary, Bound_LB for lower $\beta$ boundary, Bound_UB for upper $\beta$ boundary, and Bound_UA for upper $\alpha$ boundary
- AltRef_L, the lower alternative reference, if ALT=LOWER or ALT=TWOSIDED
- AltRef_U, the upper alternative reference, if ALT=UPPER or ALT=TWOSIDED
- _InfoProp_, the information proportion at each stage

Optionally, the BOUNDARY= data set also contains the following variables:

- _Info_, the information level at each stage
- NObs, the required number of observations for nonsurvival data at each stage
- Events, the required number of events for survival data at each stage
- Parameter, the variable specified in the DATA(TESTVAR=) or PARMS(TESTVAR=) option
- Estimate, the parameter estimate

If the BOUNDARY= data set contains the variable Parameter for the test variable that is specified in the TESTVAR= option, and the variable Estimate for the test statistics, then these test statistics are also displayed in the output test information table and output test plot.

## DATA= Data Set

The DATA= data set provides the test variable information for the current stage of the trial. Such data sets are usually created with an ODS OUTPUT statement by using a procedure such as PROC MEANS. See "Example 108.4: Testing a Binomial Proportion" on page 9112 for an illustration of the DATA= data set option.

The DATA= data set includes the following variables:

- _Stage_, the stage number
- _Scale_, the scale for the test statistic, with the value MLE for the maximum likelihood estimate, STDZ for the standardized Z, SCORE for the score statistic, or PVALUE for the nominal $p$-value
- _Info_, the information level
- NObs, the number of observations for nonsurvival data at each stage
- Events, the number of events for survival data at each stage
- test variable, specified in the TESTVAR= option, contains the test variable value in the scale specified in the _Scale_ variable

With the specified DATA= data set, PROC SEQTEST derives boundary values from the information levels in the _Info_ variable. If the data set does not include the _Info_ variable, then the information levels are derived from the NObs or Events variable in the DATA= data set if that variable is also in the input BOUNDARY= data set. That is, the information level at stage $k$ is computed as $I_k^* = I_k \times (n_k^*/n_k)$, where $I_k$ and $n_k$ are the information level and sample size, respectively, at stage $k$ in the BOUNDARY= data set and $n_k^*$ is the sample size at stage $k$ in the DATA= data set. Otherwise, the information levels from the BOUNDARY= data set are used.

If the TESTVAR= option is specified, the DATA= data set must also include the test variable for the test statistic and _Scale_ variable for the corresponding scale. Note that for a two-sided design, the nominal $p$-value is the one-sided fixed-sample $p$-value under the null hypothesis with a lower alternative hypothesis.

## PARMS= Data Set

The PARMS= data set provides a parameter estimate and associated standard error for the current stage of the trial. Such data sets are usually created with an ODS OUTPUT statement by using procedures such as the GENMOD, GLM, LOGISTIC, and REG procedures. See the section "Getting Started: SEQTEST Procedure" on page 9028 for an illustration of the PARMS= data set option.

The PARMS= data set includes the following variables:

- _Stage_, the stage number
- _Scale_, the scale for the test statistic, with the value MLE for the maximum likelihood estimate, STDZ for the standardized Z, SCORE for the score statistic, or PVALUE for the nominal $p$-value
- Parameter, Effect, Variable, or Parm, which contains the variable specified in the TESTVAR= option
- Estimate, the parameter estimate

- StdErr, standard error of the parameter estimate
- NObs, the number of observations for nonsurvival data at each stage
- Events, the number of events for survival data at each stage

With the specified PARMS= data set, the information level is derived from the StdErr variable. For a score statistic, the information level $I_k$ is the variance of the statistic, $\hat{s}_k^2$, where $\hat{s}_k$ is the standard error in the StdErr variable. Otherwise, the information level is the inverse of the variance of the statistic, $\hat{s}_k^{-2}$. If the data set does not include the StdErr variable, the information levels derived from the BOUNDARY= data set are used.

If the data set does not include the StdErr variable, then the information levels are derived from the NObs or Events variable in the PARMS= data set if that variable is also in the input BOUNDARY= data set. That is, the information level at stage $k$ is computed as $I_k^* = I_k \times (n_k^*/n_k)$, where $I_k$ and $n_k$ are the information level and sample size, respectively, at stage $k$ in the BOUNDARY= data set and $n_k^*$ is the sample size at stage $k$ in the PARMS= data set. Otherwise, the information levels from the BOUNDARY= data set are used.

If the TESTVAR= option is specified, the PARMS= data set also includes the variable Parameter, Effect, Variable, or Parm for the test variable, Estimate for the test statistic, and _Scale_ variable for the corresponding scale. Note that for a two-sided design, the nominal $p$-value is the one-sided fixed-sample $p$-value under the null hypothesis with a lower alternative hypothesis.

## Boundary Variables

The boundaries created in group sequential trials depend on the type of the alternative hypothesis and the early stopping criterion. Table 108.2 shows the boundaries created with various design specifications.

**Table 108.2** Boundary Variables

| Specifications | | Boundary Variables | | | |
|---|---|---|---|---|---|
| | | Lower | | Upper | |
| **Alternative Hypothesis** | **Early Stopping** | **Alpha** | **Beta** | **Beta** | **Alpha** |
| Lower | Accept $H_0$ | | X | | |
| | Reject $H_0$ | X | | | |
| | Accept/Reject $H_0$ | X | X | | |
| Upper | Accept $H_0$ | | | X | |
| | Reject $H_0$ | | | | X |
| | Accept/Reject $H_0$ | | | X | X |
| Two-sided | Accept $H_0$ | | X | X | |
| | Reject $H_0$ | X | | | X |
| | Accept/Reject $H_0$ | X | X | X | X |

Up to four different boundaries can be generated in a group sequential design:

- the upper $\alpha$ boundary, used to reject the null hypothesis in favor of an upper alternative hypothesis
- the upper $\beta$ boundary, used to accept the null hypothesis with an upper alternative hypothesis
- the lower $\beta$ boundary, used to accept the null hypothesis with a lower alternative hypothesis
- the lower $\alpha$ boundary, used to reject the null hypothesis in favor of a lower alternative hypothesis

For a two-sided design, the null hypothesis is accepted only if both the null hypothesis is accepted with an upper alternative hypothesis and the null hypothesis is accepted with a lower alternative hypothesis.

For a one-sided design with a lower alternative, only the lower boundaries are created. Similarly, for a one-sided design with an upper alternative, only the upper boundaries are created. For example, Figure 108.19 shows the boundary plot for a one-sided test with an upper alternative.

**Figure 108.19** Boundary Plot for One-Sided Test

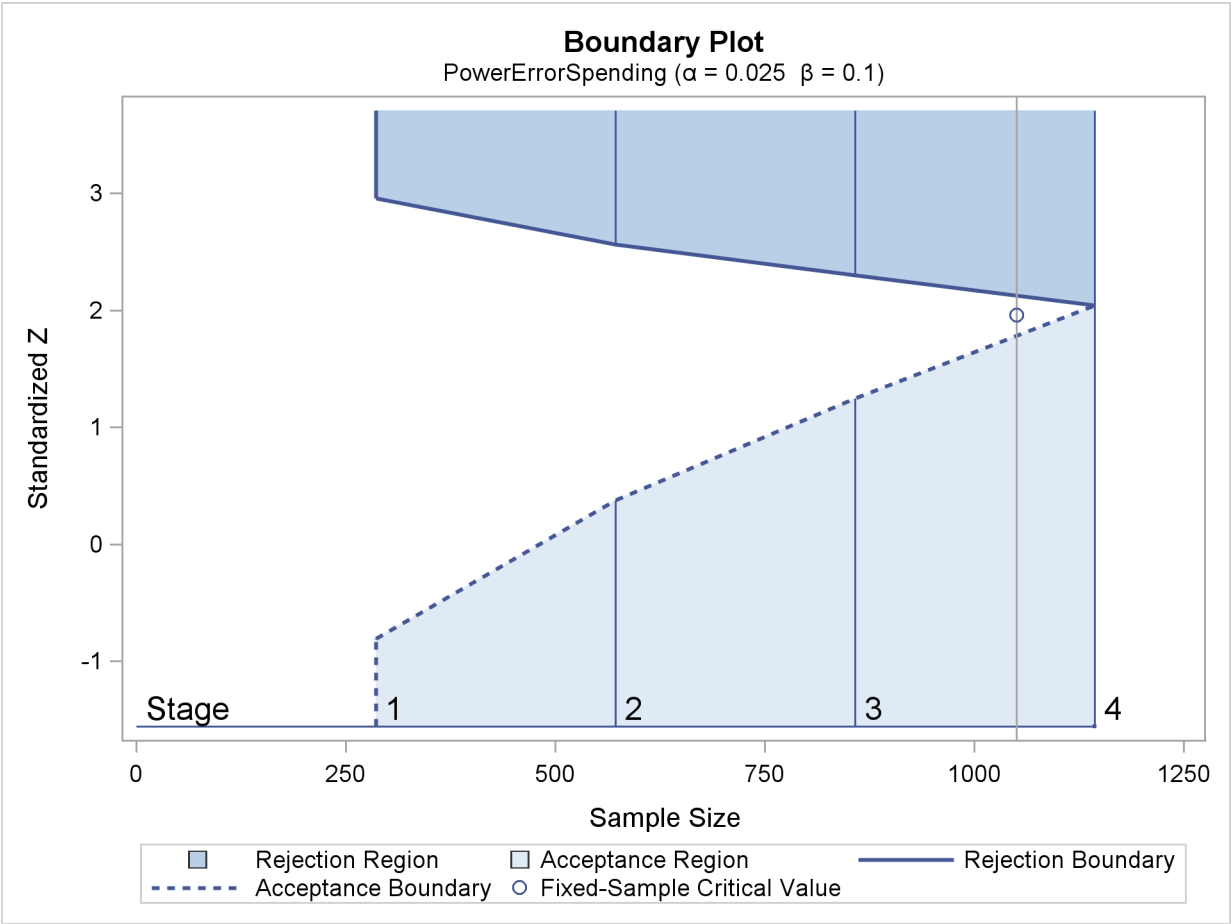



Figure 108.19 corresponds to a one-sided sequential design with early stopping to reject or accept the null hypothesis. For a sequential test with early stopping only to reject the null hypothesis, there are no acceptance boundary values at interim stages. The acceptance boundary value and its associated acceptance region are

displayed only at the final stage. Similarly, for a sequential test with early stopping only to accept the null hypothesis, there are no rejection boundary values at interim stages. The rejection boundary value and its associated rejection region are displayed only at the final stage.

For a two-sided design, both the lower and upper boundaries are created. For a design with early stopping to reject the null hypothesis, $\alpha$ boundaries are created. Similarly, for a design with early stopping to accept the null hypothesis, $\beta$ boundaries are created. For a design with early stopping to accept or reject the null hypothesis, both the $\alpha$ and $\beta$ boundaries are created.

For example, Figure 108.20 shows the boundary plot for a two-sided test.

**Figure 108.20** Boundary Plot for Two-Sided Test

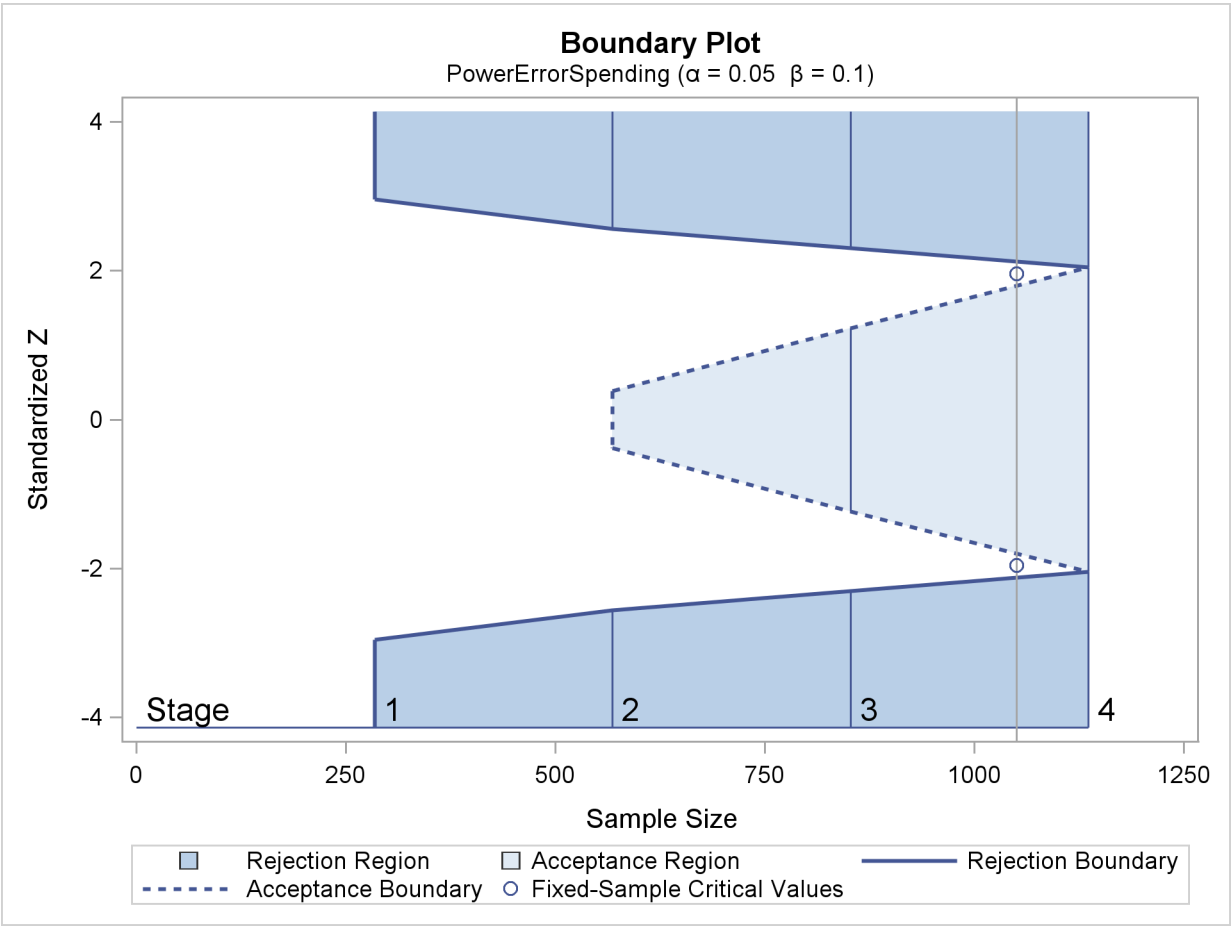



Figure 108.20 corresponds to a two-sided sequential design with early stopping to reject or accept the null hypothesis. For a sequential test with early stopping only to reject the null hypothesis, there are no acceptance boundary values at interim stages. The acceptance boundary value and its associated acceptance region are displayed only at the final stage. Similarly, for a sequential test with early stopping only to accept the null hypothesis, there are no rejection boundary values at interim stages. The rejection boundary value and its associated rejection region are displayed only at the final stage.

## Information Level Adjustments at Future Stages

In a group sequential clinical trial, the information level for the observed test statistic at the current stage generally does not match the corresponding information level in the BOUNDARY= data set. By default (or equivalently if you specify INFOADJ=PROP), the SEQTEST procedure accommodates the observed information level by adjusting the information levels at future interim stages. The adjustment of information levels depends on the boundary key to be maintained in the boundary adjustments, which in turn is determined by the BOUNDARYKEY= option.

If you specify BOUNDARYKEY=ALPHA (which is the default) or BOUNDARYKEY=BETA, the maximum information level (the information level at the final stage) provided in the BOUNDARY= data set is maintained. In this case, if an observed information level at the current stage is different from the level provided in the BOUNDARY= data set, you can use the INFOADJ= option to determine whether the information levels at subsequent interim stages are to be adjusted. Specifying INFOADJ=NONE preserves the levels provided in the BOUNDARY= data set without adjustment. Specifying INFOADJ=PROP proportionally adjusts the levels provided in the BOUNDARY= data set as follows.

Denote the information level at stage $k$ for the $K$-stage design that is stored in the BOUNDARY= data set by $I_k$, $k = 1, 2, \ldots, K$. Also denote the information level that corresponds to the test statistic at an interim stage $k_0$ by $I'_{k_0}$, $1 \le k_0 \le (K-1)$. Then for the updated design, the information level at stage $k$, $k = k_0 + 1, \ldots, (K-1)$, is computed as

$$I'_k = I'_{k_0} + (I_K - I'_{k_0}) \frac{I_k - I_{k_0}}{I_K - I_{k_0}}$$

Note that if $I'_{k_0} \ge I_K$, the information level at stage $k_0$ reaches the maximum information level in the design, the trial stops at stage $k_0$, and no future information levels are derived.

If you specify BOUNDARYKEY=BOTH, the maximum information level for the trial is not necessarily the same as the maximum information level saved in the BOUNDARY= data set. In this case, the INFOADJ=NONE option is not applicable, and the INFOADJ=PROP option is used to proportionally adjust the information levels at future interim stages with the updated maximum information $I'_K$. That is, with an updated $I'_K$, the information level at a future interim stage $k$ is computed as

$$I'_k = I'_{k_0} + (I'_K - I'_{k_0}) \frac{I_k - I_{k_0}}{I_K - I_{k_0}}$$

## Boundary Adjustments for Information Levels

In a group sequential clinical trial, if the information level for the observed test statistic does not match the corresponding information level in the BOUNDARY= data set, the INFOADJ=PROP option (which is the default) can be used to modify information levels at future stages to accommodate this observed information level. With the adjusted information levels, the ERRSPENDADJ= option provides various methods to compute error spending values at the current and future interim stages. These error spending values are then used to derive boundary values in the SEQTEST procedure. See the section "Error Spending Methods" on page 8875 in Chapter 107, "The SEQDESIGN Procedure," for more information about how to use these error spending values to derive boundary values.

The ERRSPENDADJ=NONE option keeps the error spending the same at each stage. The ERRSPENDADJ=ERRLINE option uses a linear interpolation on the cumulative error spending in the design stored in the BOUNDARY= data set to derive the error spending for each unmatched information level (Kittelson and Emerson 1999, p. 882). That is, the cumulative error spending for an information level $I$ is computed as

$$e(I) = \begin{cases} e_1 \left(\frac{I}{I_1}\right) & \text{if } I < I_1 \\ e_j + (\alpha_{j+1} - \alpha_j) \left(\frac{I - I_j}{I_{j+1} - I_j}\right) & \text{if } I_j \le I < I_{j+1} \\ e_K & \text{if } I \ge I_K \end{cases}$$

where $e_1, e_2, \ldots, e_K$ are the cumulative errors at the $K$ stages of the design that is stored in the BOUNDARY= data set.

The ERRSPENDADJ=ERRFUNCPOC option uses Pocock-type cumulative error spending function (Lan and DeMets 1983):

$$E(t) = \begin{cases} 1 & \text{if } t \ge 1 \\ \log(1 + (e-1)t) & \text{if } 0 < t < 1 \\ 0 & \text{otherwise} \end{cases}$$

With an error level of $\alpha$ or $\beta$, the cumulative error spending for an information level $I$ is $e(I) = \alpha\, E(I/I_K)$ or $e(I) = \beta\, E(I/I_K)$.

The ERRSPENDADJ=ERRFUNCOBF option uses O'Brien-Fleming-type cumulative error spending function (Lan and DeMets 1983):

$$E(t; a) = \begin{cases} 1 & \text{if } t \ge 1 \\ \frac{1}{a}\, 2\,(1 - \Phi(\frac{z_{(1-a/2)}}{\sqrt{t}})) & \text{if } 0 < t < 1 \\ 0 & \text{otherwise} \end{cases}$$

where $a$ is either $\alpha$ for the $\alpha$ spending function or $\beta$ for the $\beta$ spending function, and $\Phi$ is the cumulative distribution function of the standardized $Z$ statistic. That is, with an error level of $\alpha$ or $\beta$, the cumulative error spending for an information level $I$ is $e(I) = \alpha\, E(I/I_K; \alpha)$ or $e(I) = \beta\, E(I/I_K; \beta)$.

The ERRSPENDADJ=ERRFUNCGAMMA option uses gamma cumulative error spending function (Hwang, Shih, and DeCani 1990):

$$E(t; \gamma) = \begin{cases} 1 & \text{if } t \ge 1 \\ \frac{1-e^{-\gamma t}}{1-e^{-\gamma}} & \text{if } 0 < t < 1, \gamma \ne 0 \\ t & \text{if } 0 < t < 1, \gamma = 0 \\ 0 & \text{otherwise} \end{cases}$$

where $\gamma$ is the parameter $\gamma$ specified in the GAMMA= option. That is, with an error level of $\alpha$ or $\beta$, the cumulative error spending for an information level $I$ is $e(I) = \alpha\, E(I/I_K; \gamma)$ or $e(I) = \beta\, E(I/I_K; \gamma)$.

The ERRSPENDADJ=ERRFUNCPOW option uses power cumulative error spending function (Jennison and Turnbull 2000, p. 148):

$$E(t; \rho) = \begin{cases} 1 & \text{if } t \ge 1 \\ t^{\rho} & \text{if } 0 < t < 1 \\ 0 & \text{otherwise} \end{cases}$$

where $\rho$ is the power parameter specified in the RHO= suboption. With an error level of $\alpha$ or $\beta$, the cumulative error spending for an information level $I$ is $e(I) = \alpha\, E(I/I_K; \rho)$ or $e(I) = \beta\, E(I/I_K; \rho)$.

If the BOUNDARYKEY=BOTH option is specified, the maximum information required for the trial might not be the same as the maximum information level stored in the BOUNDARY= data set. In this case, the information levels at future stages are adjusted proportionally, and the same error spending values that were computed based on the maximum information level stored in the BOUNDARY= data set are used to derive boundary values for the trial.

If an error spending function is used to create boundaries for the design in the SEQDESIGN procedure, then in order to better maintain the design features throughout the group sequential trial, the same error spending function to create boundaries for the design in the SEQDESIGN procedure should be used to modify boundaries in the SEQTEST procedure at each subsequent stage.

## Boundary Adjustments for Minimum Error Spending

In a group sequential clinical trial, boundary values created from a design such as an O'Brien-Fleming design might be too conservative in early stages. Thus the trial is unlikely to stop in early stages. Lan and DeMets (1983, p. 662) suggest truncating boundary values to a number such as 3.5 for the trial to have a reasonable probability of stopping at early stages. Instead of truncating boundary values by a specified number, the ERRSPENDMIN= option provides individual minimum error spending at each interim stage to stop the trial early.

For a $K$-stage trial, denote the derived cumulative error spending at stage $k$ after adjusting for information levels by $e_k, k = 1, 2, \ldots, K$. Also denote the specified minimum error spending at interim stage $k$ by $\epsilon_k, k = 1, 2, \ldots, K-1$. Then the cumulative error spending at stage 1 is $e'_1 = \max(e_1,\ \epsilon_1)$. If $e_1 < e'_1$, the error spending values at subsequent interim stages are adjusted proportionally by

$$e'_j = e'_1 + \frac{e_j - e_1}{e_K - e_1}\,(e_K - e'_1)$$

for $j = 2, \ldots, K-1$.

The process is repeated at each subsequent interim stage. That is, at stage $k, k = 2, \ldots, K-1$, denote the updated cumulative $\beta$ spending at stage $j$ by $e_j,\ j = k, k+1, \ldots, K$. Then the cumulative error spending at stage $k$ is $e'_k = \max(e_k,\ e'_{k-1} + \epsilon_k)$. If $e_k < e'_k$, the error spending values at subsequent interim stages are adjusted proportionally by

$$e'_j = e'_k + \frac{e_j - e_k}{e_K - e_k}\,(e_K - e'_k)$$

for $j = k+1, \ldots, K-1$.

Note that the ERRSPENDMIN= option is applicable only to the boundaries specified in the BOUNDARYKEY= option. That is, the ERRSPENDMIN= option is applicable to the $\alpha$ boundaries with BOUNDARYKEY=ALPHA or BOUNDARYKEY=BOTH, and it is applicable to the $\beta$ boundaries with BOUNDARYKEY=BETA or BOUNDARYKEY=BOTH.

## Boundary Adjustments for Overlapping Lower and Upper $\beta$ Boundaries

In the SEQTEST procedure, the $\alpha$ and $\beta$ spending values at the stages are used to derive the boundary values for the trial. For a two-sided design with early stopping to accept $H_0$, or to either reject or accept $H_0$, a zero $\beta$ spending at an interim stage sets the $\beta$ boundary values to missing. A small $\beta$ spending at the current or subsequent interim stage might result in overlapping of the lower and upper $\beta$ boundaries for the two corresponding one-sided tests. Specifically, this form of overlapping occurs at an interim stage $k$ if the upper $\beta$ boundary value that is derived from the one-sided test for the upper alternative is less than the lower $\beta$ boundary value that is derived from the one-sided test for the lower alternative (Kittelson and Emerson 1999, pp. 881–882; Rudser and Emerson 2007, p. 6). You can use the BETAOVERLAP= option to specify how this type of overlapping is to be handled.

If BETAOVERLAP=ADJUST (which is the default) is specified, the procedure derives the boundary values for the two-sided design and then checks for overlapping of the two one-sided $\beta$ boundaries at the current and subsequent interim stages. If overlapping occurs at a particular stage, the $\beta$ boundary values for the two-sided design are set to missing (so the trial does not stop to accept the null hypothesis at this stage), and the $\beta$ spending values at subsequent stages are adjusted proportionally as follows.

If the $\beta$ boundary values are set to missing at stage $k$ in a $K$-stage trial, the adjusted $\beta$ spending value at stage $k$, $e'_k$, is updated for these missing $\beta$ boundary values, and then the $\beta$ spending values at subsequent stages are adjusted proportionally by

$$e'_j = e'_k + \frac{e_j - e_k}{e_K - e_k}\,(e_K - e'_k)$$

for $j = k+1, \ldots, K$, where $e_j$ and $e'_j$ are cumulative $\beta$ spending values at stage $j$ before and after the adjustment, respectively.

After all these adjusted $\beta$ spending values are computed, the boundary values are then further modified for these adjusted $\beta$ spending values.

If you specify BETAOVERLAP=NOADJUST, no adjustment is made when overlapping of one-sided $\beta$ boundaries occurs.

## Stochastic Curtailment

Lan, Simon, and Halperin (1982) introduce stochastic curtailment to stop a trial if, given current data, it is likely to predict the outcome of the trial with high probability. That is, a trial can be stopped to reject the null hypothesis $H_0$ if, given current data in the analyses, the conditional probability of rejecting $H_0$ under $H_0$ at the end of the trial is greater than $\gamma$, where the constant $\gamma$ should be between 0.5 and 1 and values of 0.8 or 0.9 are recommended (Jennison and Turnbull 2000, p. 206). Similarly, a trial can be stopped to accept the null hypothesis $H_0$ if, given current data in the analyses, the conditional probability of rejecting $H_0$ under the alternative hypothesis $H_1$ at the end of the trial is less than $\gamma$.

The following two approaches for stochastic curtailment are available in the SEQTEST procedures: conditional power approach and predictive power approach. For each approach, the derived group sequential test is used as the reference test for rejection.

## Conditional Power Approach

In the SEQTEST procedure, you can compute two types of conditional power as described in the following sections:

### TYPE=ALLSTAGES

The default TYPE=ALLSTAGES suboption in the CONDPOWER and PLOT=CONDPOWER options computes the conditional power at an interim stage $k$ as the total probability of rejecting the null hypothesis at all future stages given the observed statistic (Zhu, Ni, and Yao 2011, pp. 131–132).

For a one-sided test with an upper alternative, the conditional power at an interim stage $k$ is given by

$$\begin{aligned} p_{ku}(\theta) &= P_\theta(z_{k+1} > a_{k+1} \mid z_k, \theta) \\ &+ P_\theta(b_{k+1} \le z_{k+1} < a_{k+1}, z_{k+2} > a_{k+2} \mid z_k, \theta) \\ &+ \ldots \\ &+ P_\theta(b_j \le z_j < a_j, j = k+1, \ldots, K-1, z_K > a_K \mid z_k, \theta) \end{aligned}$$

where $z_k$ is the observed statistic and $\theta$ is the hypothetical reference. The conditional power for a one-sided test with a lower alternative is similarly derived.

For a two-sided test, the conditional power for the upper alternative is given by

$$\begin{aligned} p_{ku}(\theta) &= P_\theta(z_{k+1} > a_{k+1} \mid z_k, \theta) \\ &+ P_\theta(_a_{k+1} < z_{k+1} \le _b_{k+1} \text{ or } b_{k+1} \le z_{k+1} < a_{k+1}, z_{k+2} > a_{k+2} \mid z_k, \theta) \\ &+ \ldots \\ &+ {}_\theta(_a_j < z_j \le _b_j \text{ or } b_j \le z_j < a_j, j = k+1, \ldots, K-1, z_K > a_K \mid z_k, \theta) \end{aligned}$$

The conditional power for the lower alternative is similarly derived.

### TYPE=FINALSTAGE

The TYPE=FINALSTAGE suboption in the CONDPOWER and PLOT=CONDPOWER options computes the conditional power at an interim stage $k$ as the probability that the test statistic at the final stage (stage $K$) would exceed the rejection critical value given the observed statistic (Jennison and Turnbull 2000, p. 207).

The conditional distribution of $Z_K$ given the observed statistic $z_k$ at the $k$th stage and the hypothetical reference $\theta$ is

$$Z_K \mid (z_k, \theta) \sim N\left( z_k \ \Pi_k^{\frac{1}{2}} + \theta \ I_X^{\frac{1}{2}} (1 - \Pi_k) \, , \ 1 - \Pi_k \right)$$

where $\Pi_k = I_k / I_X$ is the fraction of information at the $k$th stage.

The power for the upper alternative, $\text{prob}(\, Z_K > a_K \mid z_k, \theta)$, is then given by

$$p_{ku}(\theta) = \Phi\left( (1 - \Pi_k)^{-\frac{1}{2}} \, (z_k \, \Pi_k^{\frac{1}{2}} - a_K) \ + \ \theta \, I_X^{\frac{1}{2}} \, (1 - \Pi_k)^{\frac{1}{2}} \right)$$

where $\Phi$ is the cumulative distribution function of the standardized $Z$ statistic and $a_K$ is the upper critical value at the final stage.

Similarly, the power for the lower alternative, $\text{prob}(Z_K < a_K \mid z_k, \theta)$, is

$$p_{kl}(\theta) = 1 - \Phi\left((1-\Pi_k)^{-\frac{1}{2}}\,(z_k\,\Pi_k^{\frac{1}{2}} - a_K) \;+\; \theta\, I_X^{\frac{1}{2}}\,(1-\Pi_k)^{\frac{1}{2}}\right)$$

where $a_K$ is the lower critical value at the final stage.

If $\theta = \hat{\theta}_k = z_k I_k^{-\frac{1}{2}}$, the maximum likelihood estimate at stage $k$, the powers for the upper and lower alternatives can be simplified:

$$p_{ku}(\theta) = \Phi\left((1-\Pi_k)^{-\frac{1}{2}}\;(z_k\,\Pi_k^{-\frac{1}{2}} - a_K)\right)$$

$$p_{kl}(\theta) = 1 - \Phi\left((1-\Pi_k)^{-\frac{1}{2}}\;(z_k\,\Pi_k^{-\frac{1}{2}} - a_K)\right)$$

If there exist interim stages between the $k$th stage and the final stage, $k < K-1$, the conditional power computed with TYPE=FINALSTAGE is not the conditional probability to reject the null hypothesis $H_0$. In this case, you can set the next stage as the final stage, and the conditional power is the conditional probability of rejecting $H_0$.

A special case of the conditional power is the futility index (Ware, Muller, and Braunwald 1985). It is 1 minus the conditional power under $H_1 : \theta = \theta_1$:

$$1 - p_{ku}(\theta_1) \;\text{ or }\; 1 - p_{kl}(\theta_1)$$

That is, it is the probability of accepting the null hypothesis under the alternative hypothesis given current data. A high futility index indicates a small probability of success (rejecting $H_0$) given the current data.

## Predictive Power Approach

The conditional power depends on the specified reference $\theta$, which might be supported by the current data (Jennison and Turnbull 2000, p. 210). An alternative is to use the predictive power (Herson 1979), which is a weighted average of the conditional power over values of $\theta$. Without prior knowledge about $\theta$, then with $\hat{\theta} = z_k/\sqrt{I_k}$, the maximum likelihood estimate at stage $k$, the posterior distribution for $\theta$ (Jennison and Turnbull 2000, p. 211) is

$$\theta \mid Z_K \sim N\left(\frac{z_k}{\sqrt{I_k}},\; \frac{1}{I_k}\right)$$

Thus, the predictive power at stage $k$ for the upper and lower alternatives can be derived as

$$p_{ku} = 1 - \Phi\left((1-\Pi_k)^{-\frac{1}{2}}\;(a_K\,\Pi_k^{\frac{1}{2}} - z_k)\right)$$

$$p_{kl} = \Phi\left((1-\Pi_k)^{-\frac{1}{2}}\;(a_K\,\Pi_k^{\frac{1}{2}} - z_k)\right)$$

where $a_K$ and $a_K$ are the upper and lower critical values at the final stage.

## Repeated Confidence Intervals

In a group sequential test, repeated confidence intervals for a parameter $\theta$ are defined as a sequence of intervals $(\hat{\theta}_{kl}, \hat{\theta}_{ku})$, $k = 1, 2, \ldots, K$, for which a simultaneous coverage probability is maintained (Jennison and Turnbull 2000, p. 189). That is, a $(1 - \alpha)$ sequence of repeated confidence intervals has

$$\text{Prob}(\hat{\theta}_{kl} \leq \theta \leq \hat{\theta}_{ku}) = 1 - \alpha$$

These confidence limits $\hat{\theta}_{kl}$ and $\hat{\theta}_{ku}$ can be created from observed statistic and boundary values at each stage.

### Two-Sided Repeated Confidence Intervals

Two sequences of repeated confidence intervals can be derived for a two-sided test. One is a $(1 - \alpha_l - \alpha_u)$ rejection repeated confidence intervals $(\hat{\theta}_{kl}(\alpha), \hat{\theta}_{ku}(\alpha))$, $k = 1, 2, \ldots, K$, and the other is a $(1 - \beta_l - \beta_u)$ acceptance repeated confidence intervals $(\hat{\theta}_{kl}(\beta), \hat{\theta}_{ku}(\beta))$, $k = 1, 2, \ldots, K$, where $\alpha_l$ and $\alpha_u$ are the lower and upper Type I error probabilities for the test and $\beta_l$ and $\beta_u$ are the lower and upper Type II error probabilities for the test (Jennison and Turnbull 2000, p. 196).

The rejection lower and upper repeated confidence limits at stage $k$ are

$$\hat{\theta}_{kl}(\alpha) = \hat{\theta}_k - \frac{a_k}{\sqrt{I_k}} \qquad \hat{\theta}_{ku}(\alpha) = \hat{\theta}_k - \frac{a_k}{\sqrt{I_k}}$$

The hypothesis is rejected for upper alternative if the lower limit $\hat{\theta}_{kl}(\alpha) > \theta_{0u}$ and is rejected for lower alternative if the upper limit $\hat{\theta}_{ku}(\alpha) < \theta_{0l}$. That is, the hypothesis is rejected if both $\theta_{0l}$ and $\theta_{0u}$ are not in a rejection repeated confidence interval $(\hat{\theta}_{kl}(\alpha), \hat{\theta}_{ku}(\alpha))$.

The acceptance lower and upper repeated confidence limits at stage $k$ are

$$\hat{\theta}_{kl}(\beta) = \hat{\theta}_k + \left(\theta_{1l} - \frac{b_k}{\sqrt{I_k}}\right) \qquad \hat{\theta}_{ku}(\beta) = \hat{\theta}_k + \left(\theta_{1u} - \frac{b_k}{\sqrt{I_k}}\right)$$

The hypothesis is accepted if the lower limit $\hat{\theta}_{kl}(\beta) > \theta_{1l}$ and the upper limit $\hat{\theta}_{ku}(\beta) < \theta_{1u}$. That is, a repeated confidence interval is contained in the interval $(\theta_{1l}, \theta_{1u})$.

### One-Sided Repeated Confidence Intervals

Like the two-sided repeated confidence intervals, two sequences of repeated confidence intervals can be derived for a one-sided test. Suppose the one-sided test has an upper alternative $\theta_{1u}$. Then one sequence of repeated confidence intervals is a $(1 - \alpha_u)$ rejection repeated confidence intervals $(\hat{\theta}_{kl}(\alpha), \infty)$, $k = 1, 2, \ldots, K$, and the other is a $(1 - \beta_u)$ acceptance repeated confidence intervals $(-\infty, \hat{\theta}_{ku}(\beta))$, $k = 1, 2, \ldots, K$, where $\alpha_u$ and $\beta_u$ are the upper Type I and Type II error probabilities for the test. Thus, a sequence of repeated confidence intervals with confidence level greater than or equal to $(1 - \alpha_u - \beta_u)$ is given by $(\hat{\theta}_{kl}(\alpha), \hat{\theta}_{ku}(\beta))$.

The rejection lower repeated confidence limit and the acceptance upper repeated confidence limit at stage $k$ are

$$\hat{\theta}_{kl}(\alpha) = \hat{\theta}_k - \left(\frac{a_k}{\sqrt{I_k}} - \theta_{0u}\right) \qquad \hat{\theta}_{ku}(\beta) = \hat{\theta}_k + \left(\theta_{1u} - \frac{b_k}{\sqrt{I_k}}\right)$$

The hypothesis is rejected if the lower limit $\hat{\theta}_{kl}(\alpha) > \theta_{0u}$. and it is accepted if the upper limit $\hat{\theta}_{ku}(\beta) < \theta_{1u}$.

## Analysis after a Sequential Test

At the end of a trial, the hypothesis is either rejected or accepted. But the $p$-value, median, and confidence limits depend on the ordering the sample space $(k, z)$, where $k$ is the stage number and $z$ is the standardized $Z$ statistic.

Following the notations used in Jennison and Turnbull (2000, pp. 179–180), $(k', z') \succ (k, z)$ if $(k', z')$ has a higher order or more extreme than $(k, z)$. Then for a given ordering, the $p$-value, median, and confidence limits associated with the observed statistics $(k, z)$ can be derived.

### *p*-value

With the observed pair of statistics $(k_0, z_0)$ when the trial is stopped, a one-sided upper $p$-value is computed as

$$\text{Prob}\{\, (k, z) \succeq (k_0, z_0) \,\}$$

A one-sided lower $p$-value is computed as

$$\text{Prob}\{\, (k, z) \preceq (k_0, z_0) \,\}$$

A two-sided $p$-value is twice the smaller of the lower and upper $p$-values.

### Median Unbiased Estimate

With the observed pair $(k_0, z_0)$, a median unbiased estimate $\theta_m$ is computed from

$$\text{Prob}\{\, (k, z) \succeq (k_0, z_0) \mid \theta_m \,\} = 0.50$$

### Confidence Limits

With the observed pair $(k_0, z_0)$, a lower $(1 - \alpha_l)$ confidence limit for $\theta$, $\theta_l$, is computed from

$$\text{Prob}\{\, (k, z) \succeq (k_0, z_0) \mid \theta_l \,\} = \alpha_l$$

Similarly, an upper $(1 - \alpha_u)$ confidence limit for $\theta$, $\theta_u$, is computed from

$$\text{Prob}\{\, (k, z) \preceq (k_0, z_0) \mid \theta_u \,\} = \alpha_u$$

## Available Sample Space Orderings in a Sequential Test

At the end of a trial, the hypothesis is either rejected or accepted. Denote the stage number and the statistic at the end of a trial by a pair of statistics $(k, z)$, where $k$ is the stage number and $z$ is the standardized $Z$ statistic. Then an ordering on the sample space $(k, z)$ is needed to derive the $p$-value, median, and confidence limits associated with the observed statistics $(k^*, z^*)$.

The SEQTEST procedure provides the stagewise, LR, and MLE orderings. See Jennison and Turnbull (2000, pp. 179–187) for a detailed description and comparison of these orderings.

## Stagewise Ordering

If the continuation regions of a design are intervals, the stagewise ordering (Fairbanks and Madsen 1982; Tsiatis, Rosner, and Mehta 1984; Jennison and Turnbull 2000, pp. 179–180) uses counter-clockwise ordering around the continuation region to compute the $p$-value, unbiased median estimate, and confidence limits. This ordering depends on the stopping region, stopping stage, and standardized statistic at the stopping stage. But it does not depend on information levels beyond the observed stage. For a one-sided design with an upper alternative, $(k', z') \succ (k, z)$ if one of the following criteria holds:

- $k' = k$ and $z' > z$
- $k' < k$ and $z' \geq a_{k'}$, the upper $\alpha$ boundary at stage $k'$
- $k' > k$ and $z < b_k$, the upper $\beta$ boundary at stage $k$

Similar criteria can be derived for a one-sided design with a lower alternative.

For a two-sided design with early stopping to reject the null hypothesis, $(k', z') \succ (k, z)$ if one of the following criteria holds:

- $k' = k$ and $z' > z$
- $k' < k$ and $z' \geq a_{k'}$, the upper $\alpha$ boundary at stage $k'$
- $k' > k$ and $z \leq _a_k$, the lower $\alpha$ boundary at stage $k$

Note that the stagewise ordering is not applicable for two-sided designs with early stopping to accept $H_0$ or to either accept or reject $H_0$, which might have two disjoint continuous intervals at each interim stage.

For a two-sided design with early stopping either to reject or to accept the null hypothesis, $(k', z') \succ (k, z)$ if one of the following criteria holds:

- $z' \geq a_{k'}$ and $z < b_k$
- $z' > _b_{k'}$ and $z \leq _a_k$

That is, each value in the continuation region is less extreme than each value in the upper rejection region and more extreme than each value in the lower rejection region. Then, combining with the ordering defined for a two-sided design with early stopping to reject the null hypothesis, the $p$-value, median, and confidence limits can be derived for the observed statistics in the lower or upper rejection region.

Thus, if the stagewise ordering is specified in the SEQTEST procedure for a two-sided design with early stopping to either reject or accept the null hypothesis, the stagewise ordering is used to derive these statistics only if the observed statistics is in the lower or upper rejection region. Otherwise, the LR ordering is used.

### LR Ordering

The LR ordering (Chang 1989) depends on the observed standardized $Z$ statistic $z$, information levels, and a specified hypothetical reference. For the LR ordering under a given hypothesis $H : \theta = \theta_g$, $(k', z') \succ (k, z)$ if

$$(z' - \theta_g \sqrt{I_{k'}}) \ > \ (z - \theta_g \sqrt{I_k})$$

Under the null hypothesis $H_0 : \theta = 0$, it reduces to

$$z' > z$$

and can be used to derive statistics under $H_0$, such as $p$-values.

The LR ordering is applicable to all designs if all information levels are available. But depending on the boundary shape, some observed statistics $(k, z)$ in the rejection region might be less extreme than the statistics in the acceptance region. That is, the $p$-value for observed statistics in the rejection region might be greater than the significance level.

### MLE Ordering

The MLE ordering (Emerson and Fleming 1990) depends only on the observed maximum likelihood estimate. $(k', z') \succ (k, z)$ if

$$\frac{z'}{\sqrt{I_{k'}}} > \frac{z}{\sqrt{I_k}}$$

The MLE ordering is applicable to all designs if all information levels are available.

## Applicable Tests and Sample Size Computation

The SEQDESIGN procedure assumes that the data are from a multivariate normal distribution and the sequence of the standardized test statistics $\{Z_1, Z_2, \ldots, Z_K\}$ have the following canonical joint distribution:

- $Z_k \sim N\left(\theta\sqrt{I_k},\ 1\right)$
- $\mathrm{Cov}(Z_{k_1}, Z_{k_2}) = \sqrt{I_{k_1}/I_{k_2}} \quad , \quad 1 \le k_1 \le k_2 \le K$

where $K$ is the total number of stages and $I_k$ is the information available at stage $k$.

If the data are not from a normal distribution such as binomial distribution, then it is assumed that the test statistic is computed from a large sample such that the statistic has an approximately normal distribution.

In a clinical trial, the sample size required depends on the Type I error probability $\alpha$, reference improvement $\theta_1$, power $1 - \beta$, and variance of the response variable. Given a null hypothesis $H_0 : \theta = 0$ with an upper alternative hypothesis $H_1 : \theta = \theta_1$, the information required for a fixed-sample test is given by

$$I_0 = \frac{(\Phi^{-1}(1-\alpha) + \Phi^{-1}(1-\beta))^2}{\theta_1^2}$$

where the parameter $\theta$ depends on the test specified in the clinical trial. For example, if you are comparing two binomial populations $H_0 : \theta = 0$, then $\theta = p_t - p_c$ is the difference between two proportions if the proportion difference statistic is used, and $\theta = \log\left(\frac{p_t(1-p_c)}{p_c(1-p_t)}\right)$, the log odds ratio for the two proportions if the log odds ratio statistic is used.

If the maximum likelihood estimate $\hat{\theta}$ from the likelihood function can be derived, then the asymptotic variance for $\hat{\theta}$ is $\mathrm{Var}(\hat{\theta}) = 1/I$, where $I$ is Fisher's information for $\theta$.

The resulting statistic $\hat{\theta}$ corresponds to the MLE scale as specified in the BOUNDARYSCALE=MLE option in the PROC SEQDESIGN statement, $\hat{\theta}\sqrt{I}$ corresponds to the standardized $Z$ scale (BOUNDARYSCALE=STDZ), and $\hat{\theta}I$ corresponds to the score scale (BOUNDARYSCALE=SCORE).

Alternatively, if the score statistic is derived, it can also be used as the test statistic and its asymptotic variance is given by Fisher's information.

For a group sequential trial, the maximum information $I_X$ is derived in the SEQDESIGN procedure by using the specified $\alpha$, $\beta$, and $\theta_1$. With the maximum information

$$I_X = \frac{1}{\mathrm{Var}(\hat{\theta})}$$

the sample size required for a specified test statistic in the trial can be evaluated or estimated from the known or estimated variance of the response variable. Note that different designs might produce different maximum information levels for the same hypothesis, and this in turn might require a different number of observations for the trial.

With a specified test statistic, the required sample sizes at the stages can be computed. These tests include commonly used tests for normal means, binomial proportions, and survival distributions. See the section "Sample Size Computation" on page 8883 in Chapter 107, "The SEQDESIGN Procedure," for more information about these tests.

## Table Output

The SEQTEST procedure displays the "Design Information" and "Test Information" tables by default.

### Conditional Power

The "Conditional Power Information" table displays the following information under a hypothetical reference:

- stopping stage
- MLE, observed maximum likelihood estimate
- conditional power under the hypothetical reference

For a one-sided test, the power are derived under hypothetical references $\theta = \hat{\theta}$ and $\theta = c_i\theta_1$, where $\hat{\theta}$ is the observed statistic, $\theta_1$ is the alternative reference, and $c_i$ are the values specified in the CREF= option. For a two-sided test, the power are derived under the hypothetical references $\theta = \hat{\theta}$, $\theta = c_i\theta_{1l}$, and $\theta = c_i\theta_{1u}$, where $\theta_{1l}$ is the lower alternative reference and $\theta_{1u}$ is the upper alternative reference. The default is CREF= 0 0.5 1.0 1.5.

## Design Information

The "Design Information" table displays the design specifications and derived statistics. The derived Max Information (Percent Fixed-Sample) is the maximum information for the sequential design in percentage of the corresponding fixed-sample information.

The Null Ref ASN (Percent Fixed-Sample) is the average sample size required under the null hypothesis for the group sequential design in percentage of the corresponding fixed-sample design. Similarly, the Alt Ref ASN (Percent Fixed-Sample) is the average sample size required under the alternative reference for the group sequential design in percentage of the corresponding fixed-sample design.

## Error Spending Information

The "Error Spending Information" table displays the following information at each stage:

- proportion of information
- actual information level, if the maximum information is either specified or derived
- cumulative error spending for each boundary

## Parameter Estimates

The "Parameter Estimates" table displays the following information at the conclusion of a sequential trial:

- stopping stage
- parameter estimate
- median and confidence limits based on the specified ordering
- $p$-value for the hypothesis $H_0$ based on the specified ordering

## Powers and Expected Sample Sizes

The "Powers and Expected Sample Sizes" table displays the following information under each of the specified hypothetical references $\theta = c_i\theta_1$, where $\theta_1$ is the alternative reference and $c_i$ are values specified in the CREF= option.

- coefficient $c_i$ for the hypothetical references. The value $c_i = 0$ corresponds to the null hypothesis and $c_i = 1$ corresponds to the alternative hypothesis
- power
- expected sample size, as percentage of fixed-sample size

For a one-sided design, the power and expected sample sizes under the hypothetical references $\theta = c_i \theta_1$ are displayed.

For a two-sided symmetric design, the power and expected sample sizes under each of the hypothetical references $\theta = c_i \theta_{1u}$ are displayed, where $\theta_{1u}$ is the upper alternative reference.

For a two-sided asymmetric design, the power and expected sample sizes under each of the hypothetical references $\theta = c_i \theta_{1l}$ and $\theta = c_i \theta_{1u}$ are displayed, where $\theta_{1l}$ and $\theta_{1u}$ are the lower and upper alternative references, respectively.

For a two-sided design, the power is the probability of correctly rejecting the null hypothesis for the correct alternative. Thus, under the null hypothesis, the displayed power corresponds to a one-sided Type I error probability level—that is, the lower $\alpha$ level or the upper $\alpha$ level.

The expected sample size as a percentage of the corresponding fixed-sample design is

$$100 \times \frac{\sum_{k=1}^{K} p_k \, I_k}{I_0}$$

where $p_k$ is the stopping probability at stage $k$, $\sum_{k=1}^{K} p_k \, I_k$ is the expected information level, and $I_0$ is the information level for the fixed-sample design.

## Predictive Power

The "Predictive Power Information" table displays the following information:

- stopping stage
- MLE, observed maximum likelihood estimate
- predictive power

## Repeated Confidence Intervals

The "Repeated Confidence Intervals" table displays the following information for the observed statistic at each stage:

- information level
- parameter estimate
- rejection confidence limits. The null hypothesis is rejected for the upper alternative if the lower rejection confidence limit is greater than the null parameter value. Similarly, the null hypothesis is rejected for the lower alternative if the upper rejection confidence limit is less than the null parameter value.
- acceptance confidence limits. The upper alternative hypothesis is rejected if the upper acceptance confidence limit is less than the upper alternative value. Similarly, the lower alternative hypothesis is rejected if the lower acceptance confidence limit is greater than the upper alternative value. For a two-sided design, if both upper and lower alternative hypothesis are rejected, the null hypothesis is accepted.

## Stopping Probabilities

The "Expected Cumulative Stopping Probabilities" table displays the following information under each of the specified hypothetical references $\theta = c_i \theta_1$, where $c_i$ are values specified in the CREF= option, and $\theta_1$ is the alternative reference:

- coefficient $c_i$ for the hypothetical references. The value $c_i = 0$ corresponds to the null hypothesis, and $c_i = 1$ corresponds to the alternative hypothesis
- expected stopping stage
- source of the stopping probability: reject $H_0$ (with STOP=REJECT or STOP=BOTH), accept $H_0$ (with STOP=ACCEPT or STOP=BOTH), or either reject or accept $H_0$ (with STOP=BOTH)
- expected cumulative stopping probabilities at each stage

For a one-sided design, the expected cumulative stopping probabilities under the hypothetical references $\theta = c_i \theta_1$ are displayed.

For a two-sided design, the expected cumulative stopping probabilities under each of the hypothetical references $\theta = c_i \theta_{1l}$ and $\theta = c_i \theta_{1u}$ are displayed, where $\theta_{1l}$ and $\theta_{1u}$ are the lower and upper alternative references, respectively.

Note that for a symmetric two-sided design, only the expected cumulative stopping probabilities under the hypothetical references $\theta = c_i \theta_{1u}$ are derived.

The expected stopping stage is given by $k_0 + d$ and is derived from the expected information level

$$\sum_{k=1}^{K} p_k \, I_k = I_{k_0} + d \, (I_{(k_0+1)} - I_{k_0})$$

where $p_k$ is the stopping probability at stage $k$ and $0 \leq d < 1$.

For equally spaced information levels, the expected stopping stage is reduced to the weighted average

$$\sum_{k=1}^{K} p_k \, k$$

## Test Information

The "Test Information" table displays the following information at each stage:

- proportion of information
- actual information level, if the maximum information is available from the input BOUNDARY= data set
- alternative references with the specified statistic scale. If a $p$-value scale is specified, the standardized $Z$ scale is used.
- boundary values with the specified statistic scale to reject or accept the null hypothesis

Note that implicitly, the test information table also contains variables for the boundary scale, stopping criterion, and type of alternative hypothesis. That is, if an ODS statement is used to save the table, the data set also contains the variables _Scale_ for the boundary scale, _Stop_ for the stopping criterion, and _ALT_ for the type of alternative hypothesis.

If the test variable is specified, the table also displays the following:

- test statistic
- resulting action of test statistic: continue to the next stage, accept the null hypothesis $H_0$, or reject $H_0$

## ODS Table Names

PROC SEQTEST assigns a name to each table it creates. You must use these names to reference tables when using the Output Delivery System (ODS). These names are listed in Table 108.3. For more information about ODS, see Chapter 20, "Using the Output Delivery System."

**Table 108.3** ODS Tables Produced by PROC SEQTEST

| ODS Table Name | Description | Option |
|---|---|---|
| CondPower | Conditional power | CONDPOWER |
| Design | Design information | |
| ErrSpend | Error spending | ERRSPEND |
| ParameterEstimates | Parameter estimates | DATA( TESTVAR= ) or PARMS( TESTVAR= ) |
| PowerSampleSize | Power and expected sample sizes | PSS |
| PredPower | Predictive power | PREDPOWER |
| RepeatedCI | Repeated confidence intervals | RCI |
| StopProb | Stopping probabilities | STOPPROB |
| Test | Test statistics and boundary values | |

## Graphics Output

This section describes the use of ODS for creating graphics with the SEQTEST procedure. To request these graphs, ODS Graphics must be enabled and you must specify the associated graphics options in the PROC SEQTEST statement. For more information about ODS Graphics, see Chapter 21, "Statistical Graphics Using ODS."

### Sequential ASN Plot

The PLOTS=ASN option displays the average sample numbers (expected sample sizes for nonsurvival data or expected numbers of events for survival data) under various hypothetical references. The average sample

numbers are connected for each design, and these connected curves for all designs are displayed in the "Sequential ASN Plot" graph.

For a one-sided design, average sample numbers under the hypothetical references $\theta = c_i\theta_1$ are displayed, where $c_i$ are the values specified in the CREF= option and $\theta_1$ is the alternative reference. The horizontal axis displays the $c_i$ values of these hypothetical references.

For a two-sided design, average sample numbers under each of the hypothetical references $\theta = c_i\theta_{1l}$ and $\theta = c_i\theta_{1u}$ are displayed, where $\theta_{1l}$ and $\theta_{1u}$ are the lower and upper alternative references, respectively. The horizontal axis displays $-c_i$ values for lower hypothetical references $\theta = c_i\theta_{1l}$ and $c_i$ values for upper hypothetical references $\theta = c_i\theta_{1u}$. Note that for a symmetric two-sided design, only average sample numbers under the hypothetical references $\theta = c_i\theta_{1u}$ are derived.

If the trial stops after the sequential test, the hypothetical reference corresponding to the test statistic is also indicated in the plot.

## Conditional Power Plot

The PLOTS=CONDPOWER option displays the conditional powers given the observed statistic under various hypothetical references. These powers are connected and are displayed in the "Conditional Power Plot" graph.

For a one-sided test, the power are derived under the hypothetical references $\theta = \hat{\theta}$ and $\theta = c_i\theta_1$, where $\hat{\theta}$ is the observed statistic, $\theta_1$ is the alternative reference, and $c_i$ are the values specified in the CREF= option. The horizontal axis displays these $c_i$ values for hypothetical references.

For a two-sided test, the power are derived under hypothetical references $\theta = \hat{\theta}$, $\theta = c_i\theta_{1l}$, and $\theta = c_i\theta_{1u}$, where $\theta_{1l}$ is the lower alternative reference and $\theta_{1u}$ is the upper alternative reference. The horizontal axis displays $-c_i$ values for hypothetical references $\theta = c_i\theta_{1l}$ and $c_i$ values for hypothetical references $\theta = c_i\theta_{1u}$.

If the trial stops after the sequential test, the hypothetical reference corresponding to the test statistic is also indicated in the plot.

## Sequential Error Spending Plot

The PLOTS=ERRSPEND option displays the cumulative error spending at each stage on each boundary in the "Sequential Error Spending Plot" graph. A legend table uses the design labels to identify the curves for the corresponding design in the plot.

## Sequential Power Plot

The PLOTS=POWER option displays the powers under various hypothetical references. The powers are connected for each design, and these connected curves for all designs are displayed in the "Sequential Power Plot" graph.

For a one-sided design, powers under hypothetical references $\theta = c_i\theta_1$ are displayed, where $c_i$ are the values specified in the CREF= option and $\theta_1$ is the alternative reference. The horizontal axis displays the $c_i$ values of these hypothetical references.

For a two-sided design, powers under hypothetical references $\theta = c_i\theta_{1l}$ and $\theta = c_i\theta_{1u}$ are displayed, where $\theta_{1l}$ and $\theta_{1u}$ are the lower and upper alternative references, respectively. The horizontal axis displays $-c_i$ values for lower hypothetical references $\theta = c_i\theta_{1l}$ and $c_i$ values for upper hypothetical references $\theta = c_i\theta_{1u}$.

Note that for a symmetric two-sided design, only powers under hypothetical references $\theta = c_i \theta_{1u}$ are derived.

If the trial stops after the sequential test, the hypothetical reference corresponding to the test statistic is also indicated in the plot.

### Repeated Confidence Intervals Plot

The PLOTS=RCI option displays repeated confidence intervals at each stage given the observed statistic at that stage. These repeated confidence intervals are displayed in the "Repeated Confidence Intervals Plot" graph.

### Sequential Test Plot

The PLOTS=TEST option displays boundary values and test statistics in the "Test Plot" graph. The boundary values are connected for each boundary, and both the stage number and the information level at each stage are displayed. The legend table identifies the acceptance and rejection regions in the plot.

## ODS Graphics

Statistical procedures use ODS Graphics to create graphs as part of their output. ODS Graphics is described in detail in Chapter 21, "Statistical Graphics Using ODS."

Before you create graphs, ODS Graphics must be enabled (for example, by specifying the ODS GRAPHICS ON statement). For more information about enabling and disabling ODS Graphics, see the section "Enabling and Disabling ODS Graphics" on page 623 in Chapter 21, "Statistical Graphics Using ODS."

The overall appearance of graphs is controlled by ODS styles. Styles and other aspects of using ODS Graphics are discussed in the section "A Primer on ODS Statistical Graphics" on page 622 in Chapter 21, "Statistical Graphics Using ODS."

PROC SEQTEST assigns a name to each graph it creates. You can use these names to reference the graphs when using ODS. To request these graphs, ODS Graphics must be enabled and you must specify the *options* indicated in Table 108.4.

**Table 108.4** Graphs Produced by PROC SEQTEST

| ODS Graph Name | Plot Description | Option |
|---|---|---|
| AsnPlot | Average sample numbers | PLOTS=ASN |
| CondPowerPlot | Conditional power curves | PLOTS=CONDPOWER |
| ErrSpendPlot | Error spending | PLOTS=ERRSPEND |
| PowerPlot | Power curves | PLOTS=POWER |
| RepeatedCIPlot | Repeated confidence intervals | PLOTS=RCI |
| TestPlot | Boundary values and test statistics | PLOTS=TEST |

# Examples: SEQTEST Procedure

The following examples perform group sequential tests with various designs and test statistics.

Four statistic scales are available for the input boundary values, the input test statistic, and the displayed test information in the SEQTEST procedure. These are the maximum likelihood estimator scale, score statistic scale, standardized normal $Z$ scale, and $p$-value scale. There is a unique one-to-one transformation between any two of the scales, and you can use different scales for the input boundary values and input test statistic. These boundary values and test statistic are displayed with the scale specified in the BOUNDARYSCALE= option in the SEQTEST procedure.

## Example 108.1: Testing the Difference between Two Proportions

This example demonstrates group sequential tests that use an O'Brien-Fleming group sequential design. A clinic is studying the effect of vitamin C supplements in treating flu symptoms. The study consists of patients in the clinic who have exhibited the first sign of flu symptoms within the last 24 hours. These patients are randomly assigned to either the control group (which receives placebo pills) or the treatment group (which receives large doses of vitamin C supplements). At the end of a five-day period, the flu symptoms of each patient are recorded.

Suppose that you know from past experience that flu symptoms disappear in five days for 60% of patients who experience flu symptoms. The clinic would like to detect a 75% symptom disappearance with a high probability. A test that compares the proportions directly specifies the null hypothesis $H_0 : \theta = p_t - p_c = 0$ with a one-sided alternative $H_1 : \theta > 0$ and a power of 0.90 at $H_1 : \theta = 0.15$, where $p_t$ and $p_c$ are the proportions of symptom disappearance in the treatment group and control group, respectively.

The following statements invoke the SEQDESIGN procedure and request a four-stage group sequential design by using an O'Brien-Fleming method for normally distributed data. The design uses a one-sided alternative hypothesis with early stopping either to accept or reject the null hypothesis $H_0$. The BOUNDARYSCALE=MLE option uses the MLE scale to display statistics in the boundary table and boundary plots.

```
ods graphics on;
proc seqdesign altref=0.15
               boundaryscale=mle
               ;
   OBrienFleming: design method=obf
                         nstages=4
                         alt=upper
                         stop=both
                         alpha=0.025
                         ;
   samplesize model=twosamplefreq(nullprop=0.6 test=prop);
   ods output Boundary=Bnd_Count;
run;
```

The ODS OUTPUT statement with the BOUNDARY=BND_COUNT option creates an output data set named BND_COUNT which contains the resulting boundary information for the subsequent sequential tests.

The "Design Information" table in Output 108.1.1 displays design specifications. With the specified alternative hypothesis $H_1 : \theta = 0.15$, the maximum information is derived to achieve a power of 0.90 at $H_1$. The derived fixed-sample information ratio 1.0767 is the maximum information needed for a group sequential design relative to its corresponding fixed-sample design.

**Output 108.1.1** O'Brien-Fleming Design Information

**The SEQDESIGN Procedure**
**Design: OBrienFleming**

| Design Information | |
|---|---|
| **Statistic Distribution** | Normal |
| **Boundary Scale** | MLE |
| **Alternative Hypothesis** | Upper |
| **Early Stop** | Accept/Reject Null |
| **Method** | O'Brien-Fleming |
| **Boundary Key** | Both |
| **Alternative Reference** | 0.15 |
| **Number of Stages** | 4 |
| **Alpha** | 0.025 |
| **Beta** | 0.1 |
| **Power** | 0.9 |
| **Max Information (Percent of Fixed Sample)** | 107.6741 |
| **Max Information** | 502.8343 |
| **Null Ref ASN (Percent of Fixed Sample)** | 61.12891 |
| **Alt Ref ASN (Percent of Fixed Sample)** | 75.89782 |

The "Boundary Information" table in Output 108.1.2 displays the information level, alternative reference, and boundary values at each stage. With the BOUNDARYSCALE=MLE option, the SEQDESIGN procedure displays the output boundaries with the maximum likelihood estimator scale.

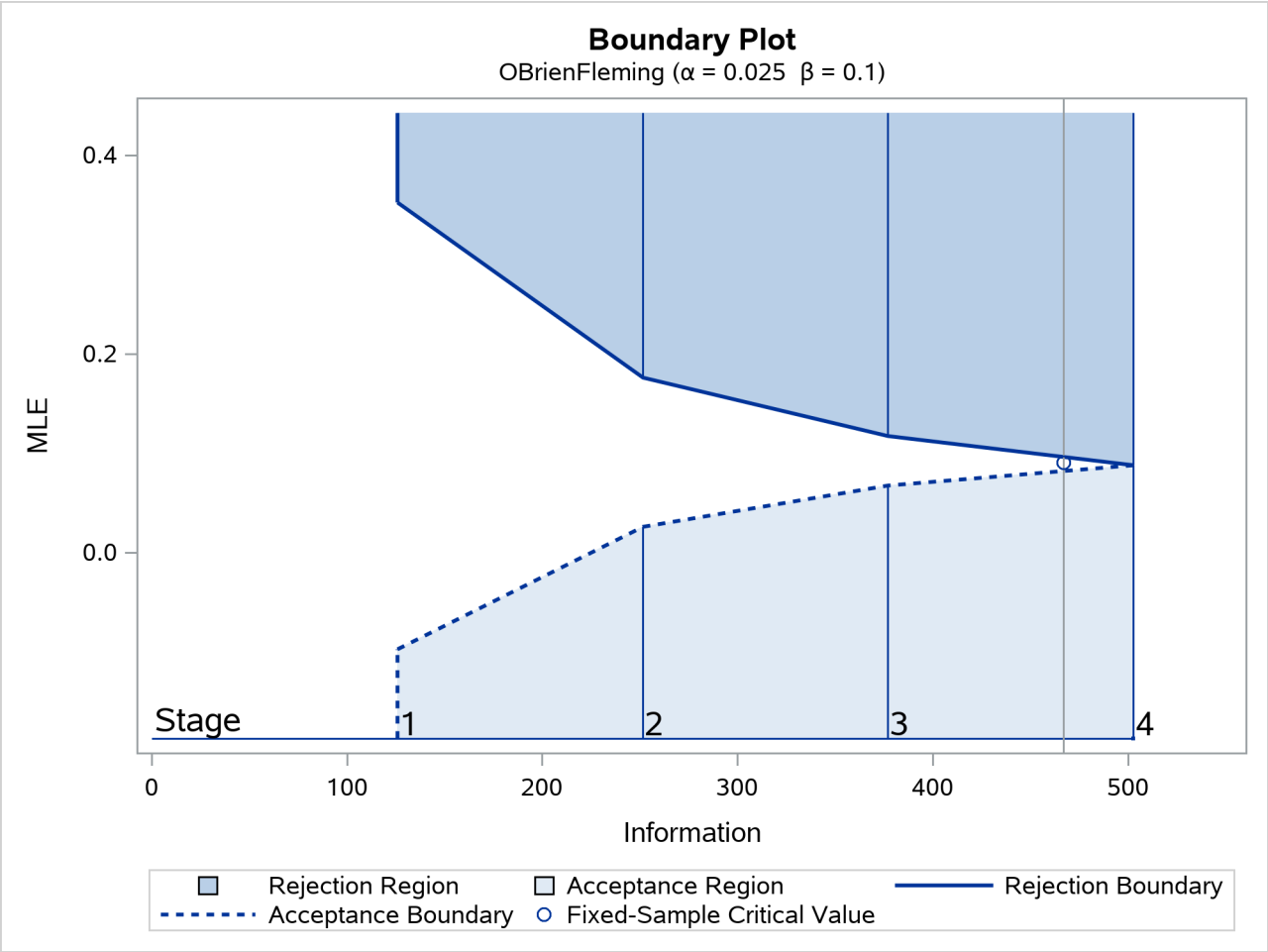
**Output 108.1.2** O'Brien-Fleming Boundary Information

**Boundary Information (MLE Scale)**
**Null Reference = 0**

| | Information Level | | | Alternative Reference | Boundary Values | |
|---|---|---|---|---|---|---|
| | | | | | Upper | |
| _Stage_ | Proportion | Actual | N | Upper | Beta | Alpha |
| 1 | 0.2500 | 125.7086 | 107.4808 | 0.15000 | -0.09709 | 0.35291 |
| 2 | 0.5000 | 251.4171 | 214.9617 | 0.15000 | 0.02645 | 0.17645 |
| 3 | 0.7500 | 377.1257 | 322.4425 | 0.15000 | 0.06764 | 0.11764 |
| 4 | 1.0000 | 502.8343 | 429.9233 | 0.15000 | 0.08823 | 0.08823 |

With ODS Graphics enabled, a detailed boundary plot with the rejection and acceptance regions is displayed, as shown in Output 108.1.3. The horizontal axis indicates the information levels for the design. The stages are indicated by vertical lines with accompanying stage numbers. If the test statistic at a stage is in a rejection region, the trial stops and the hypothesis is rejected. If the test statistic is in an acceptance region, then the trial also stops and the hypothesis is accepted. If the statistic is not in a rejection or an acceptance region, the trial continues to the next stage.

**Output 108.1.3** O'Brien-Fleming Boundary Plot




The boundary plot also displays the information level and critical value for the corresponding fixed-sample design. The solid and dashed lines at the fixed-sample information level correspond to the rejection and acceptance lines, respectively.

With the SAMPLESIZE statement, the maximum information is used to derive the required sample size for the study. The "Sample Size Summary" table in Output 108.1.4 displays parameters for the sample size computation.

**Output 108.1.4** Required Sample Size Summary

| Sample Size Summary | |
|---|---|
| **Test** | Two-Sample Proportions |
| **Null Proportion** | 0.6 |
| **Proportion (Group A)** | 0.75 |
| **Test Statistic** | Z for Proportion |
| **Reference Proportions** | Alt Ref |
| **Max Sample Size** | 429.9233 |
| **Expected Sample Size (Null Ref)** | 244.0768 |
| **Expected Sample Size (Alt Ref)** | 303.0464 |

With the derived maximum information and the specified MODEL= option in the SAMPLESIZE statement, the total sample size in each group for testing the difference between two proportions under the alternative hypothesis is

$$N_1 = N_2 = (p_{1c}\,(1 - p_{1c}) + p_{1t}\,(1 - p_{1t}))\ I_X$$

where $p_{1c} = 0.6$ and $p_{1t} = p_{1c} + \theta_1 = 0.75$. By default (or equivalently if you specify REF=PROP in the MODEL=TWOSAMPLEFREQ option), the required sample sizes are computed under the alternative hypothesis. See the section "Test for the Difference between Two Binomial Proportions" on page 8895 in Chapter 107, "The SEQDESIGN Procedure," for more information about these parameters.

The "Sample Sizes (N)" table in Output 108.1.5 displays the required sample sizes at each stage, in both fractional and integer numbers. The derived sample sizes under the heading Fractional N which correspond to the design are not integers. These sample sizes are rounded up to integers under the heading Ceiling N. In practice, integer sample sizes are used, and the information levels increase slightly. Thus, 54, 108, 162, and 215 patients are needed in each group for the four stages, respectively.

**Output 108.1.5** Required Sample Sizes

**Sample Sizes (N)**
**Two-Sample Z Test for Proportion Difference**

| | Fractional N | | | | Ceiling N | | | |
|---|---|---|---|---|---|---|---|---|
| _Stage_ | N | N(Grp 1) | N(Grp 2) | Information | N | N(Grp 1) | N(Grp 2) | Information |
| 1 | 107.48 | 53.74 | 53.74 | 125.7 | 108 | 54 | 54 | 126.3 |
| 2 | 214.96 | 107.48 | 107.48 | 251.4 | 216 | 108 | 108 | 252.6 |
| 3 | 322.44 | 161.22 | 161.22 | 377.1 | 324 | 162 | 162 | 378.9 |
| 4 | 429.92 | 214.96 | 214.96 | 502.8 | 430 | 215 | 215 | 502.9 |

Suppose the trial follows the study plan, and 54 patients are available in each group at stage 1. The data set count_1 contains these 108 patients. Output 108.1.6 lists the first 10 observations of the data set.

**Output 108.1.6** Clinical Trial Data

**First 10 Obs in the Trial Data**

| Obs | Trt | Resp |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 1 | 1 |
| 3 | 0 | 1 |
| 4 | 1 | 0 |
| 5 | 0 | 0 |
| 6 | 1 | 0 |
| 7 | 0 | 0 |
| 8 | 1 | 1 |
| 9 | 0 | 1 |
| 10 | 1 | 0 |

The Trt variable is a grouping variable with value 0 for a patient in the placebo control group and value 1 for a patient in the treatment group who is given vitamin C supplements. The Resp variable is an indicator variable with value 1 for a patient without flu symptoms after five days and value 0 for a patient with flu symptoms after five days.

The following statements use the GENMOD procedure to estimate the treatment effect at stage 1:

```
proc genmod data=count_1;
   model Resp= Trt;
   ods output ParameterEstimates=Parms_Count1;
run;
```

Output 108.1.7 displays the treatment effect at stage 1.

**Output 108.1.7** Stage 1 Treatment Difference

**The GENMOD Procedure**

**Analysis Of Maximum Likelihood Parameter Estimates**

| Parameter | DF | Estimate | Standard Error | Wald 95% Confidence Limits | | Wald Chi-Square | Pr > ChiSq |
|---|---|---|---|---|---|---|---|
| **Intercept** | 1 | 0.6296 | 0.0627 | 0.5066 | 0.7526 | 100.68 | <.0001 |
| **Trt** | 1 | 0.1111 | 0.0887 | -0.0628 | 0.2850 | 1.57 | 0.2105 |
| **Scale** | 1 | 0.4611 | 0.0314 | 0.4035 | 0.5269 | | |

**Note:** The scale parameter was estimated by maximum likelihood.

The test statistic is $\hat{\theta}_1 = \hat{p}_t - \hat{p}_c = 0.1111$, and its associated standard error is

$$\sqrt{\mathrm{Var}(\hat{\theta}_1)} = \sqrt{\frac{\hat{p}_c(1-\hat{p}_c)}{54} + \frac{\hat{p}_t(1-\hat{p}_t)}{54}} = 0.0887$$

The following statements create and display (in Output 108.1.8) the data set that contains the parameter estimate at stage 1, $\hat{\theta}_1 = 0.1111$, and its associated standard error $\sqrt{\mathrm{Var}(\hat{\theta}_1)} = 0.0887$ which are used in the SEQTEST procedure:

```
data Parms_Count1;
   set Parms_Count1;
   if Parameter='Trt';
   _Scale_='MLE';
   _Stage_= 1;
   keep _Scale_ _Stage_ Parameter Estimate StdErr;
run;

proc print data=Parms_Count1;
   title 'Statistics Computed at Stage 1';
run;
```

**Output 108.1.8** Statistics Computed at Stage 1

**Statistics Computed at Stage 1**

| Obs | Parameter | Estimate | StdErr | _Scale_ | _Stage_ |
|---|---|---|---|---|---|
| **1** | Trt | 0.1111 | 0.0887 | MLE | 1 |

The initial required sample sizes are derived with the proportions $p_c = 0.6$ and $p_t = 0.75$. If the observed proportions are different from these assumed values, or if the number of available patients is different from the study plan in one of the stages, then the information level that corresponds to the test statistic is estimated from

$$I_k = \frac{1}{\mathrm{Var}(\hat{\theta}_k)}$$

The following statements invoke the SEQTEST procedure and test for early stopping at stage 1:

```
ods graphics on;
proc seqtest Boundary=Bnd_Count
             Parms(Testvar=Trt)=Parms_Count1
             infoadj=none
             errspendmin=0.001
             boundaryscale=mle
             errspend
             plots=errspend
             ;
   ods output Test=Test_Count1;
run;
```

The BOUNDARY= option specifies the input data set that provides the boundary information for the trial at stage 1, which was generated in the SEQDESIGN procedure. The PARMS=PARMS_COUNT1 option specifies the input data set PARMS_COUNT1 that contains the test statistic and its associated standard error at stage 1, and the TESTVAR=TRT option identifies the test variable TRT in the data set. The INFOADJ=NONE option maintains the information levels at future interim stages (2 and 3) as provided in the BOUNDARY= data set. The BOUNDARYSCALE=MLE option displays the output boundaries in terms of the MLE scale.

The O'Brien-Fleming design is conservative in early stages and might not be desirable in a clinical trial. The ERRSPENDMIN=0.001 option specifies the minimum error spending at each stage to be 0.001, and it might increase the corresponding nominal $p$-value in early stages for the trial. The BOUNDARYSCALE=MLE option uses the MLE scale to display test statistics in the boundary table and boundary plots.

The ODS OUTPUT statement with the TEST=TEST_COUNT1 option creates an output data set named TEST_COUNT1 which contains the updated boundary information for the test at stage 1. The data set also provides the boundary information that is needed for the group sequential test at the next stage.

The "Design Information" table in Output 108.1.9 displays design specifications. The derived statistics, such as the overall $\alpha$ and $\beta$ levels, are derived from the specified maximum information and boundary values in the BOUNDARY= data set. Note that with a minor change in the information level at stage 1, the power also changes slightly from the design provided in the BOUNDARY= data set.

**Output 108.1.9** Design Information

**The SEQTEST Procedure**

| Design Information | |
|---|---|
| **BOUNDARY Data Set** | WORK.BND_COUNT |
| **Data Set** | WORK.PARMS_COUNT1 |
| **Statistic Distribution** | Normal |
| **Boundary Scale** | MLE |
| **Alternative Hypothesis** | Upper |
| **Early Stop** | Accept/Reject Null |
| **Number of Stages** | 4 |
| **Alpha** | 0.025 |
| **Beta** | 0.10147 |
| **Power** | 0.89853 |
| **Max Information (Percent of Fixed Sample)** | 108.2301 |
| **Max Information** | 502.834283 |
| **Null Ref ASN (Percent of Fixed Sample)** | 61.09917 |
| **Alt Ref ASN (Percent of Fixed Sample)** | 73.9745 |

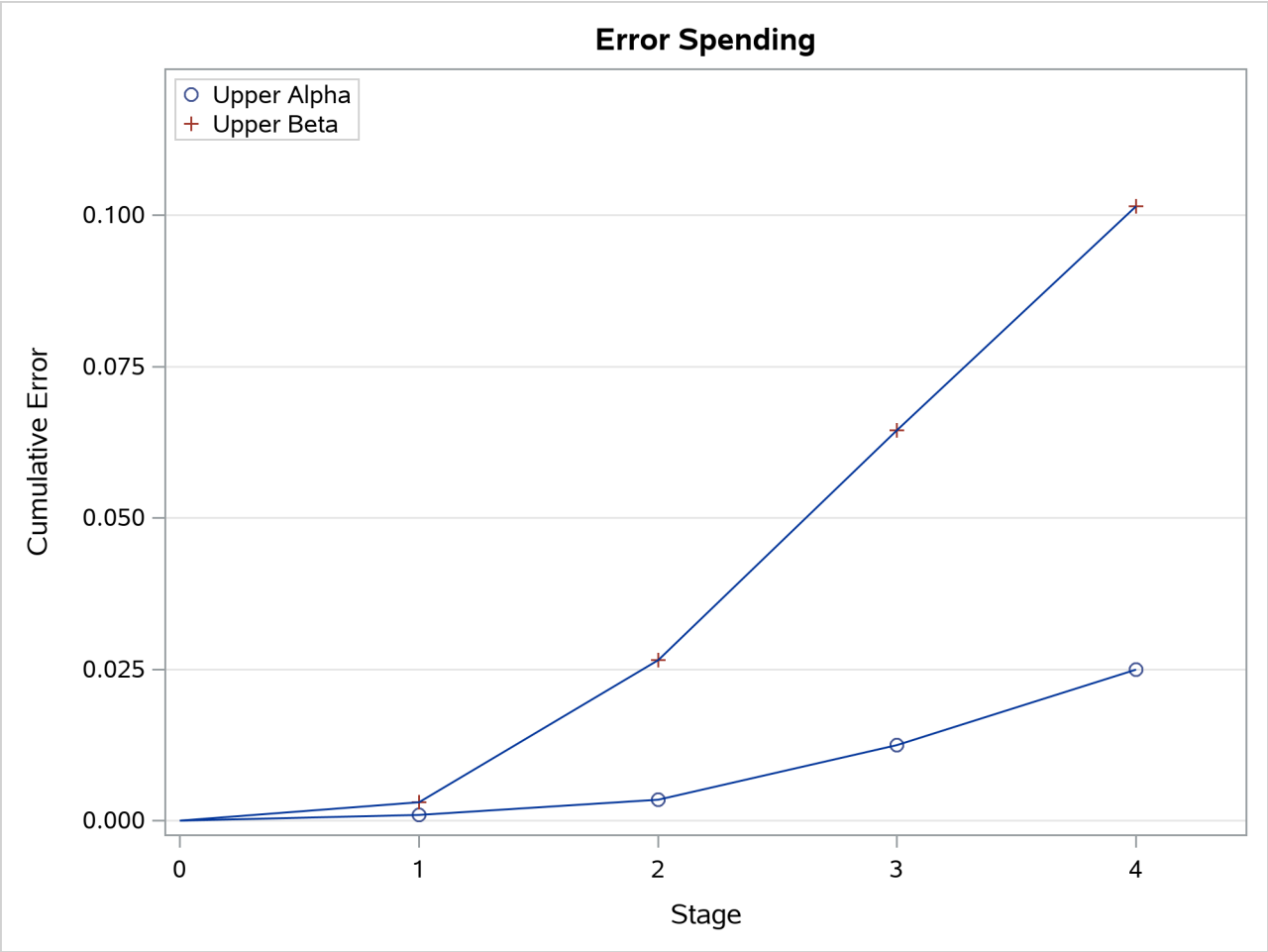
With the ERRSPEND option, the "Error Spending Information" table in Output 108.1.10 displays cumulative error spending at each stage for each boundary. By default (or equivalently if you specify BOUNDARYKEY=ALPHA), the Type I error level $\alpha = 0.025$ is maintained. Furthermore, with the ERRSPENDMIN=0.001 option, the $\alpha$ spending at each stage is greater than or equal to 0.001.

**Output 108.1.10** Error Spending Information

| Error Spending Information | | | | |
|---|---|---|---|---|
| | | | Cumulative Error Spending | |
| | Information Level | | Upper | |
| _Stage_ | Proportion | Actual | Beta | Alpha |
| 1 | 0.2525 | 126.9871 | 0.00308 | 0.00100 |
| 2 | 0.5000 | 251.4171 | 0.02653 | 0.00343 |
| 3 | 0.7500 | 377.1257 | 0.06456 | 0.01254 |
| 4 | 1.0000 | 502.8343 | 0.10147 | 0.02500 |

With the PLOTS=ERRSPEND option, the procedure displays a plot of error spending for each boundary, as shown in Output 108.1.11. The error spending values in the "Error Spending Information" table in Output 108.1.10 are displayed in the plot.

**Output 108.1.11** Error Spending Plot




The "Test Information" table in Output 108.1.12 displays the boundary values for the design, test statistic, and resulting action at each stage. With the BOUNDARYSCALE=MLE option, the maximum likelihood estimator scale is used for the test statistic and boundary values. The table shows that the test statistic 0.1111 is between the upper $\alpha$ and $\beta$ boundaries, so the trial continues to the next stage.

**Output 108.1.12** Sequential Test

**Test Information (MLE Scale)**
**Null Reference = 0**

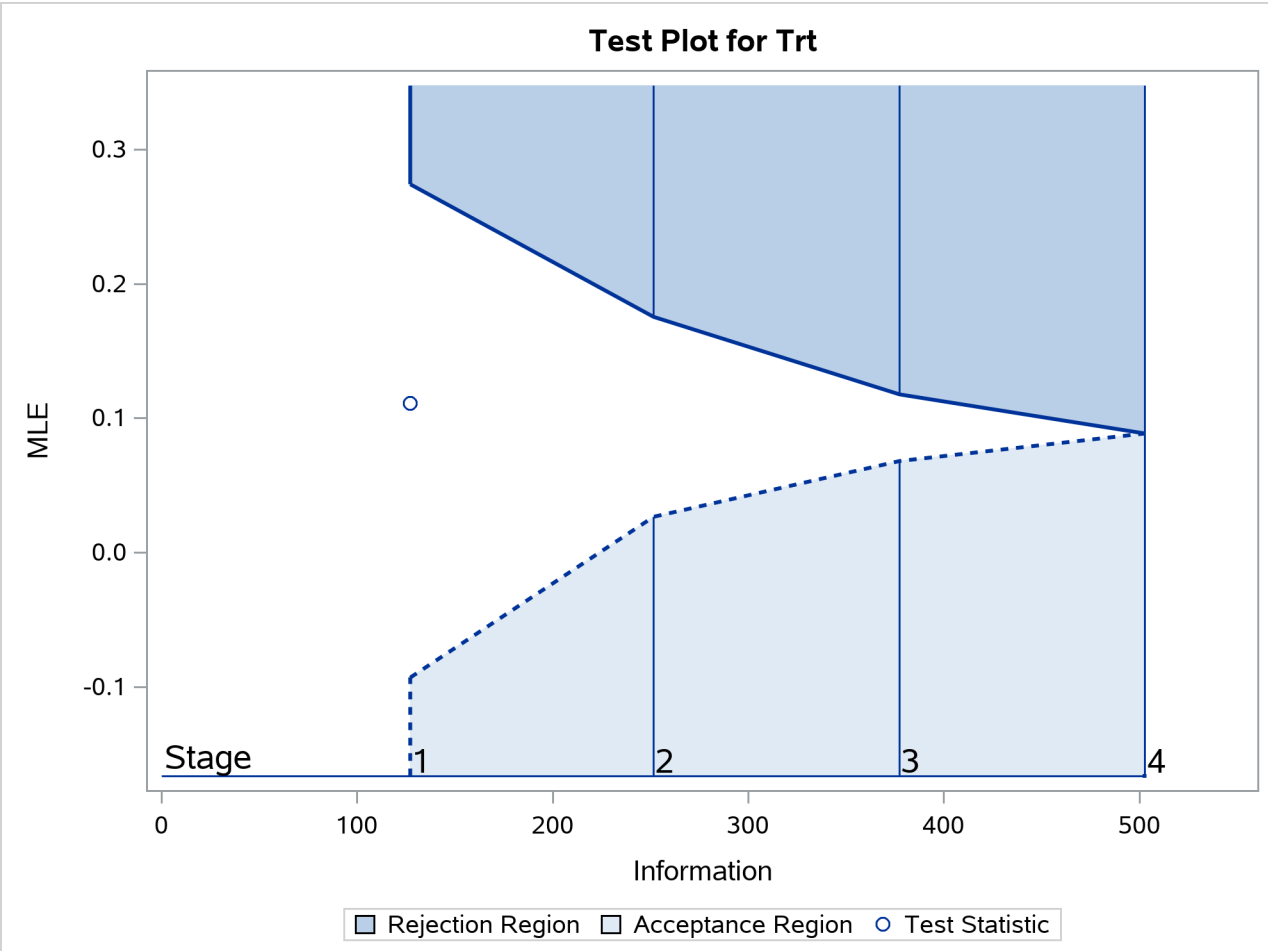
| | Information Level | | Alternative Reference | Boundary Values | | Test | |
|---|---|---|---|---|---|---|---|
| | | | | Upper | | Trt | |
| _Stage_ | Proportion | Actual | Upper | Beta | Alpha | Estimate | Action |
| 1 | 0.2525 | 126.9871 | 0.15000 | -0.09306 | 0.27423 | 0.11111 | Continue |
| 2 | 0.5000 | 251.4171 | 0.15000 | 0.02674 | 0.17527 | . | |
| 3 | 0.7500 | 377.1257 | 0.15000 | 0.06805 | 0.11792 | . | |
| 4 | 1.0000 | 502.8343 | 0.15000 | 0.08875 | 0.08875 | . | |

The information level at stage 1 is derived from the standard error,

$$I_1 = \frac{1}{\mathrm{Var}(\hat{\theta}_1)} = \frac{1}{(\mathrm{s.e.}(\hat{\theta}_1))^2} = 126.987$$

By default (or equivalently if you specify PLOTS=TEST), the "Test Plot" graph displays boundary values of the design and the test statistic at stage 1, as shown in Output 108.1.13. It also shows that the observed statistic is in the continuation region.

**Output 108.1.13** Sequential Test Plot




The observed information level at stage 1, $I_1 = 126.987$, is slightly larger than the target information level at the design. If an observed information level in the study is substantially different from its target level in the design, then the sample sizes should be adjusted in the subsequent stages to achieve the target information levels.

Suppose the trial continues to the next stage, and 108 patients are available in each group at stage 2. The data set COUNT_2 contains these 216 patients.

The following statements use the GENMOD procedure to estimate the treatment effect at stage 2:

```
proc genmod data=Count_2;
   model Resp= Trt;
   ods output ParameterEstimates=Parms_Count2;
run;
```

The following statements create the parameter estimate at stage 2, $\hat{\theta}_2 = \hat{p}_2 - \hat{p}_1 = 0.1759$, and its associated standard error $\sqrt{\mathrm{Var}(\hat{\theta}_2)} = 0.0623$ into a test data set:

```
data Parms_Count2;
   set Parms_Count2;
   if Parameter='Trt';
   _Scale_='MLE';
   _Stage_= 2;
   keep _Scale_ _Stage_ Parameter Estimate StdErr;
run;

proc print data=Parms_Count2;
   title 'Statistics Computed at Stage 2';
run;
```

Output 108.1.14 displays the test statistics at stage 2.

**Output 108.1.14** Statistics Computed at Stage 2

**Statistics Computed at Stage 2**

| Obs | Parameter | Estimate | StdErr | _Scale_ | _Stage_ |
|---|---|---|---|---|---|
| 1 | Trt | 0.1759 | 0.0623 | MLE | 2 |

The following statements invoke the SEQTEST procedure and test for early stopping at stage 2:

```
ods graphics on;
proc seqtest Boundary=Test_Count1
             Parms(Testvar=Trt)=Parms_Count2
             infoadj=none
             boundaryscale=mle
             ;
   ods output Test=Test_Count2;
run;
```

The BOUNDARY= option specifies the input data set that provides the boundary information for the trial at stage 2, which was generated by the SEQTEST procedure at the previous stage. The PARMS= option specifies the input data set that contains the test statistic and its associated standard error at stage 2, and the TESTVAR= option identifies the test variable in the data set.

The ODS OUTPUT statement with the TEST=TEST_COUNT2 option creates an output data set named TEST_COUNT2 which contains the updated boundary information for the test at stage 2. The data set also provides the boundary information that is needed for the group sequential test at the next stage.

The "Test Information" table in Output 108.1.15 displays the boundary values, test statistic, and resulting action at each stage. The table shows that the test statistic 0.17593 is larger than the corresponding upper alpha boundary value, so the trial stops to reject the hypothesis.

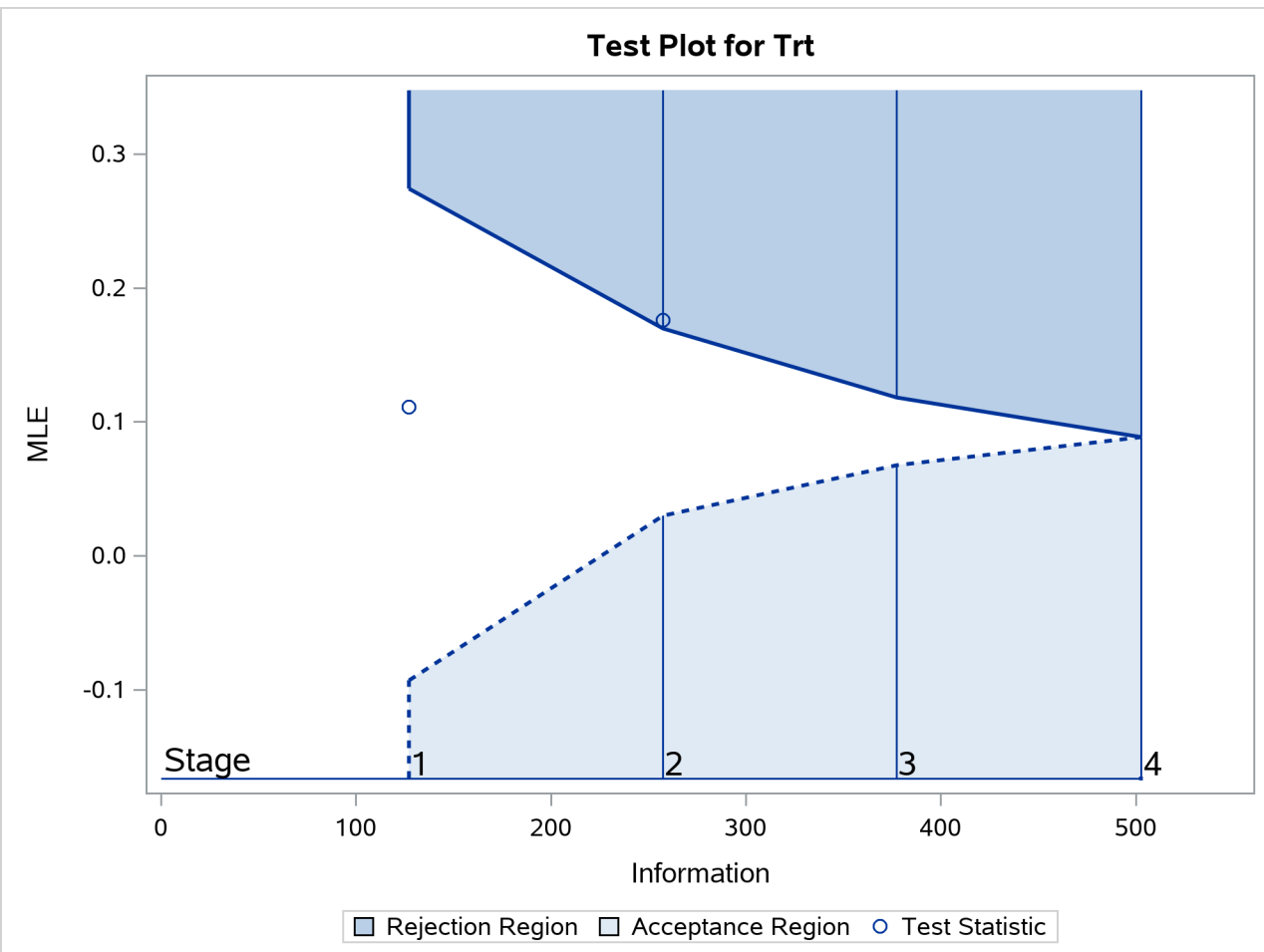
**Output 108.1.15** Sequential Test

**The SEQTEST Procedure**

| Test Information (MLE Scale) Null Reference = 0 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Information Level | | Alternative Reference | Boundary Values | | Test Trt | |
| _Stage_ | Proportion | Actual | Upper | Upper Beta | Alpha | Estimate | Action |
| 1 | 0.2525 | 126.9871 | 0.15000 | -0.09306 | 0.27423 | 0.11111 | Continue |
| 2 | 0.5122 | 257.5571 | 0.15000 | 0.03019 | 0.17001 | 0.17593 | Reject Null |
| 3 | 0.7500 | 377.1257 | 0.15000 | 0.06783 | 0.11826 | . | |
| 4 | 1.0000 | 502.8343 | 0.15000 | 0.08878 | 0.08878 | . | |

With ODS Graphics enabled, the "Test Plot" is displayed, as shown in Output 108.1.16. The plot displays boundary values of the design and the test statistics at the first two stages. As expected, the test statistic at stage 2 is in the "Upper Rejection Region" above the upper alpha boundary.

**Output 108.1.16** Sequential Test Plot



After a trial is stopped, the "Parameter Estimates" table in Output 108.1.17 displays the stopping stage and the maximum likelihood estimate of the parameter. It also displays the $p$-value, median estimate, and confidence limits for the parameter that correspond to the observed statistic by using the specified sample space ordering.

**Output 108.1.17** Parameter Estimates

| Parameter Estimates Stagewise Ordering | | | | | |
|---|---|---|---|---|---|
| Parameter | Stopping Stage | MLE | p-Value for H0:Parm=0 | Median Estimate | Lower 95% CL |
| Trt | 2 | 0.175926 | 0.0031 | 0.174462 | 0.07059 |

The MLE statistic at the stopping stage is the maximum likelihood estimate of the parameter and is biased. The computation of $p$-value, unbiased median estimate, and confidence limits depends on the ordering of the sample space $(k, z)$, where $k$ is the stage number and $z$ is the observed standardized $Z$ statistic. By default (or equivalently if you specify ORDER=STAGEWISE), the stagewise ordering that uses counterclockwise ordering around the continuation region is used to compute the $p$-value, unbiased median estimate, and confidence limits. As expected, the $p$-value is less than 0.025, and the confidence interval does not contain the null reference zero. With the stagewise ordering, the $p$-value is computed as

$$P_{\theta=0}\left(Z_1 > a_1\right) + P_{\theta=0}\left(Z_2 > z_2 \mid b_1 < Z_1 < a_1\right)$$

where $z_2$ is the observed standardized $Z$ statistic at stage 2, $Z_1$ is the standardized normal variate at stage 1, $Z_2$ is the standardized normal variate at stage 2, and $a_1$ and $b_1$ are the stage 1 upper rejection and acceptance boundary values, respectively.

See the section "Available Sample Space Orderings in a Sequential Test" on page 9065 for a detailed description of the stagewise ordering.

## Example 108.2: Testing an Effect in a Regression Model

This example demonstrates a two-sided group sequential test that uses an error spending design with early stopping to reject the null hypothesis. A study is conducted to examine the effects of Age (years), Weight (kg), RunTime (time in minutes to run 1.5 miles), RunPulse (heart rate while running), and MaxPulse (maximum heart rate recorded while running) on Oxygen (oxygen intake rate, ml per kg body weight per minute). The primary interest is whether oxygen intake rate is associated with weight.

The hypothesis is tested using the following linear model:

$$\text{Oxygen} = \text{Age} + \text{Weight} + \text{RunTime} + \text{RunPulse} + \text{MaxPulse}$$

The null hypothesis is $H_0 : \beta_w = 0$, where $\beta_w$ is the regression parameter for the variable Weight. Suppose that $\beta_w = 0.10$ is the reference improvement that should be detected at a 0.90 level. Then the maximum information $I_X$ can be derived in the SEQDESIGN procedure.

Following the derivations in the section "Test for a Parameter in the Regression Model" on page 8901 in Chapter 107, "The SEQDESIGN Procedure," the required sample size can be derived from

$$N = I_X \, \frac{\sigma_y^2}{(1 - r_x^2)\,\sigma_x^2}$$

where $\sigma_y^2$ is the variance of the response variable in the regression model, $r_x^2$ is the proportion of variance of Weight explained by other covariates, and $\sigma_x^2$ is the variance of Weight.

Further suppose that from past experience, $\sigma_y^2 = 5$, $r_x^2 = 0.10$, and $\sigma_x^2 = 64$. Then the required sample size can be derived using the SAMPLESIZE statement in the SEQDESIGN procedure.

The following statements invoke the SEQDESIGN procedure and request a three-stage group sequential design for normally distributed data to test the null hypothesis of a regression parameter $H_0 : \beta_w = 0$ against the alternative $H_1 : \beta_w \neq 0$:

```
ods graphics on;
proc seqdesign altref=0.10;
   OBFErrorFunction: design method=errfuncobf
                           nstages=3
                           info=cum(2 3 4)
                           ;
   samplesize model=reg(variance=5 xvariance=64 xrsquare=0.10);
   ods output Boundary=Bnd_Fit;
run;
```

By default (or equivalently if you specify ALPHA=0.05 and BETA=0.10), the procedure uses a Type I error probability 0.05 and a Type II error probability 0.10. The ALTREF=0.10 option specifies a power of $1 - \beta = 0.90$ at the alternative hypothesis $H_1 : \beta_w = \pm 0.10$. The INFO=CUM(2 3 4) option specifies that the study perform the first interim analysis with information proportion $2/4 = 0.5$—that is, after half of the total observations are collected.

The ODS OUTPUT statement with the BOUNDARY=BND_FIT option creates an output data set named BND_FIT which contains the resulting boundary information for the subsequent sequential tests.

The "Design Information" table in Output 108.2.1 displays design specifications and derived statistics. Since the alternative reference is specified, the maximum information is derived.

**Output 108.2.1** Design Information

**The SEQDESIGN Procedure**
**Design: OBFErrorFunction**

| Design Information | |
|---|---|
| **Statistic Distribution** | Normal |
| **Boundary Scale** | Standardized Z |
| **Alternative Hypothesis** | Two-Sided |
| **Early Stop** | Reject Null |
| **Method** | Error Spending |
| **Boundary Key** | Both |
| **Alternative Reference** | 0.1 |
| **Number of Stages** | 3 |
| **Alpha** | 0.05 |
| **Beta** | 0.1 |
| **Power** | 0.9 |
| **Max Information (Percent of Fixed Sample)** | 101.8276 |
| **Max Information** | 1069.948 |
| **Null Ref ASN (Percent of Fixed Sample)** | 101.2587 |
| **Alt Ref ASN (Percent of Fixed Sample)** | 77.81586 |

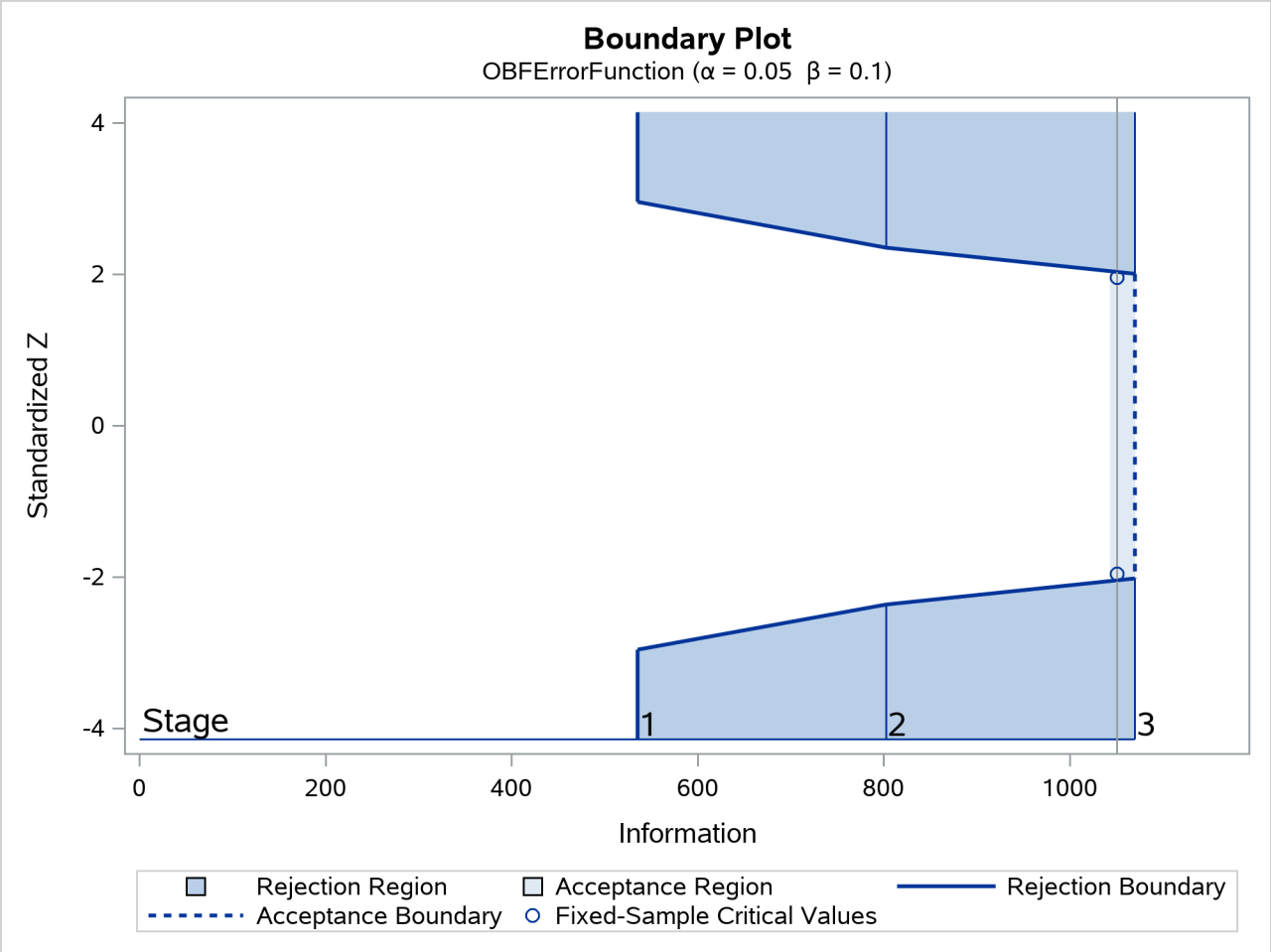
The "Boundary Information" table in Output 108.2.2 displays information level, alternative reference, and boundary values at each stage.

**Output 108.2.2** Boundary Information

| Boundary Information (Standardized Z Scale) Null Reference = 0 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Information Level | | | Alternative Reference | | Boundary Values | |
| _Stage_ | Proportion | Actual | N | Lower | Upper | Lower Alpha | Upper Alpha |
| 1 | 0.5000 | 534.9738 | 46.43869 | -2.31295 | 2.31295 | -2.96259 | 2.96259 |
| 2 | 0.7500 | 802.4606 | 69.65804 | -2.83277 | 2.83277 | -2.35902 | 2.35902 |
| 3 | 1.0000 | 1069.948 | 92.87739 | -3.27101 | 3.27101 | -2.01409 | 2.01409 |

With ODS Graphics enabled, a detailed boundary plot with the rejection and acceptance regions is displayed, as shown in Output 108.2.3. The boundary plot also displays the information level and critical value for the corresponding fixed-sample design. This design has characteristics of an O'Brien-Fleming design; the probability for early stopping is low, and the maximum information and critical values at the final stage are similar to those of the corresponding fixed-sample design.

**Output 108.2.3** Boundary Plot



With the MODEL=REG option in the SAMPLESIZE statement, the "Sample Size Summary" table in Output 108.2.4 displays the parameters for the sample size computation.

**Output 108.2.4** Required Sample Size Summary

| Sample Size Summary | |
|---|---|
| **Test** | Reg Parameter |
| **Parameter** | 0.1 |
| **Variance** | 5 |
| **X Variance** | 64 |
| **R Square (X)** | 0.1 |
| **Max Sample Size** | 92.87739 |
| **Expected Sample Size (Null Ref)** | 92.35845 |
| **Expected Sample Size (Alt Ref)** | 70.97617 |

The "Sample Sizes" table in Output 108.2.5 displays the required sample sizes for the group sequential clinical trial.

**Output 108.2.5** Required Sample Sizes

| Sample Sizes (N)<br>Z Test for Regression Parameter | | | | |
|---|---|---|---|---|
| | Fractional N | | Ceiling N | |
| _Stage_ | N | Information | N | Information |
| 1 | 46.44 | 535.0 | 47 | 541.4 |
| 2 | 69.66 | 802.5 | 70 | 806.4 |
| 3 | 92.88 | 1069.9 | 93 | 1071.4 |

Thus, 47, 70, and 93 individuals are needed in stages 1, 2, and 3, respectively. Since the sample sizes are derived from estimated values of $\sigma_y^2$, $r_x^2$, and $\sigma_x^2$, the actual information levels might not achieve the target information levels. Thus, instead of specifying sample sizes in the protocol, you can specify the maximum information levels. Then if an actual information level is much less than the target level, you can increase the sample sizes for the remaining stages to achieve the desired information levels and power.

Suppose that 47 individuals are available at stage 1. Output 108.2.6 lists the first 10 observations of the trial data.

**Output 108.2.6** Clinical Trial Data

**First 10 Obs in the Trial Data**

| Obs | Oxygen | Age | Weight | RunTime | RunPulse | MaxPulse |
|---|---|---|---|---|---|---|
| 1 | 54.5521 | 44 | 87.7676 | 11.6949 | 178.435 | 181.607 |
| 2 | 52.2821 | 40 | 75.4853 | 9.8872 | 184.433 | 183.667 |
| 3 | 62.1871 | 44 | 89.0638 | 8.7950 | 155.540 | 167.108 |
| 4 | 65.3269 | 42 | 67.7310 | 8.4577 | 162.926 | 173.877 |
| 5 | 59.9809 | 37 | 93.1902 | 9.3228 | 179.033 | 180.144 |
| 6 | 52.5588 | 47 | 75.9044 | 12.0385 | 177.753 | 175.033 |
| 7 | 51.7838 | 40 | 73.5422 | 11.6607 | 175.838 | 178.140 |
| 8 | 57.0024 | 43 | 81.2861 | 11.2219 | 160.963 | 171.770 |
| 9 | 48.0775 | 44 | 85.2290 | 13.1789 | 173.722 | 176.548 |
| 10 | 68.3357 | 38 | 80.2490 | 8.5066 | 171.824 | 184.011 |

The following statements use the REG procedure to estimate the slope $\beta_w$ and its associated standard error at stage 1:

```
proc reg data=Fit_1;
   model Oxygen=Age Weight RunTime RunPulse MaxPulse;
   ods output ParameterEstimates=Parms_Fit1;
run;
```

The following statements create and display (in Output 108.2.7) the input data set that contains slope $\beta_w$ and its associated standard error for the SEQTEST procedure:

```
data Parms_Fit1;
   set Parms_Fit1;
   if Variable='Weight';
   _Scale_='MLE';
   _Stage_= 1;
   keep _Scale_ _Stage_ Variable Estimate StdErr;
run;

proc print data=Parms_Fit1;
   title 'Statistics Computed at Stage 1';
run;
```

**Output 108.2.7** Statistics Computed at Stage 1

**Statistics Computed at Stage 1**

| Obs | Variable | Estimate | StdErr | _Scale_ | _Stage_ |
|---|---|---|---|---|---|
| 1 | Weight | 0.03772 | 0.04345 | MLE | 1 |

The following statements invoke the SEQTEST procedure to test for early stopping at stage 1:

```
ods graphics on;
proc seqtest Boundary=Bnd_Fit
             Parms(Testvar=Weight)=Parms_Fit1
             infoadj=prop
             errspendadj=errfuncobf
```

```
                order=lr
                stopprob
                ;
      ods output Test=Test_Fit1;
   run;
```

The BOUNDARY= option specifies the input data set that provides the boundary information for the trial at stage 1 (this data set was generated in the SEQDESIGN procedure). Recall that these boundary values were derived for the information levels specified with the INFO=CUM(2 3 4) option in the SEQDESIGN procedure. The PARMS=PARMS_FIT1 option specifies the input data set PARMS_FIT1 that contains the test statistic and its associated standard error at stage 1, and the TESTVAR=WEIGHT option identifies the test variable WEIGHT in the data set.

If the computed information level for stage 1 is not the same as the value provided in the BOUNDARY= data set, the INFOADJ=PROP option (which is the default) proportionally adjusts the information levels at future interim stages from the levels provided in the BOUNDARY= data set. The ORDER=LR option uses the LR ordering to derive the $p$-value, the unbiased median estimate, and the confidence limits for the regression slope estimate. The ERRSPENDADJ=ERRFUNCOBF option adjusts the boundaries with the updated error spending values generated from an O'Brien-Fleming-type cumulative error spending function.

The ODS OUTPUT statement with the TEST=TEST_FIT1 option creates an output data set named TEST_FIT1 which contains the updated boundary information for the test at stage 1. The adjustment is needed because the observed information level is different from the information level in the BOUNDARY= data set. The data set TEST_FIT1 also provides the boundary information that is needed for the group sequential test at the next stage.

The "Design Information" table in Output 108.2.8 displays the design specifications. By default (or equivalently if you specify BOUNDARYKEY=ALPHA), the boundary values are modified for the new information levels to maintain the Type I $\alpha$ level. The maximum information remains the same as in the BOUNDARY= data set, but the derived Type II error probability $\beta$ and power $1 - \beta$ are different because of the new information level.

**Output 108.2.8** Design Information

**The SEQTEST Procedure**

| Design Information | |
|---|---|
| **BOUNDARY Data Set** | WORK.BND_FIT |
| **Data Set** | WORK.PARMS_FIT1 |
| **Statistic Distribution** | Normal |
| **Boundary Scale** | Standardized Z |
| **Alternative Hypothesis** | Two-Sided |
| **Early Stop** | Reject Null |
| **Number of Stages** | 3 |
| **Alpha** | 0.05 |
| **Beta** | 0.09994 |
| **Power** | 0.90006 |
| **Max Information (Percent of Fixed Sample)** | 101.8057 |
| **Max Information** | 1069.94751 |
| **Null Ref ASN (Percent of Fixed Sample)** | 101.2416 |
| **Alt Ref ASN (Percent of Fixed Sample)** | 77.87607 |

With the STOPPROB option, the "Expected Cumulative Stopping Probabilities" table in Output 108.2.9 displays the expected stopping stage and cumulative stopping probability to reject the null hypothesis at each stage under various hypothetical references $\theta = c_i\theta_1$, where $\theta_1$ is the alternative reference and $c_i = 0, 0.5, 1, 1.5$ by default. You can specify other values for $c_i$ with the CREF= option.

**Output 108.2.9** Stopping Probabilities

Expected Cumulative Stopping Probabilities
Reference = CRef * (Alt Reference)

| CRef | Expected Stopping Stage | Source | Stopping Probabilities Stage_1 | Stage_2 | Stage_3 |
|---|---|---|---|---|---|
| 0.0000 | 2.978 | Reject Null | 0.00289 | 0.01906 | 0.05000 |
| 0.5000 | 2.792 | Reject Null | 0.03373 | 0.17443 | 0.36566 |
| 1.0000 | 2.069 | Reject Null | 0.24884 | 0.68206 | 0.90006 |
| 1.5000 | 1.348 | Reject Null | 0.68172 | 0.97032 | 0.99820 |

The "Test Information" table in Output 108.2.10 displays the boundary values for the test statistic. By default (or equivalently if you specify BOUNDARYSCALE=STDZ), these statistics are displayed with the standardized $Z$ scale. The information level at stage 1 is derived from the standard error $s_1$ in the PARMS= data set,

$$I_1 = \frac{1}{s_1^2} = \frac{1}{0.043453^2} = 529.62$$

**Output 108.2.10** Sequential Tests

Test Information (Standardized Z Scale)
Null Reference = 0

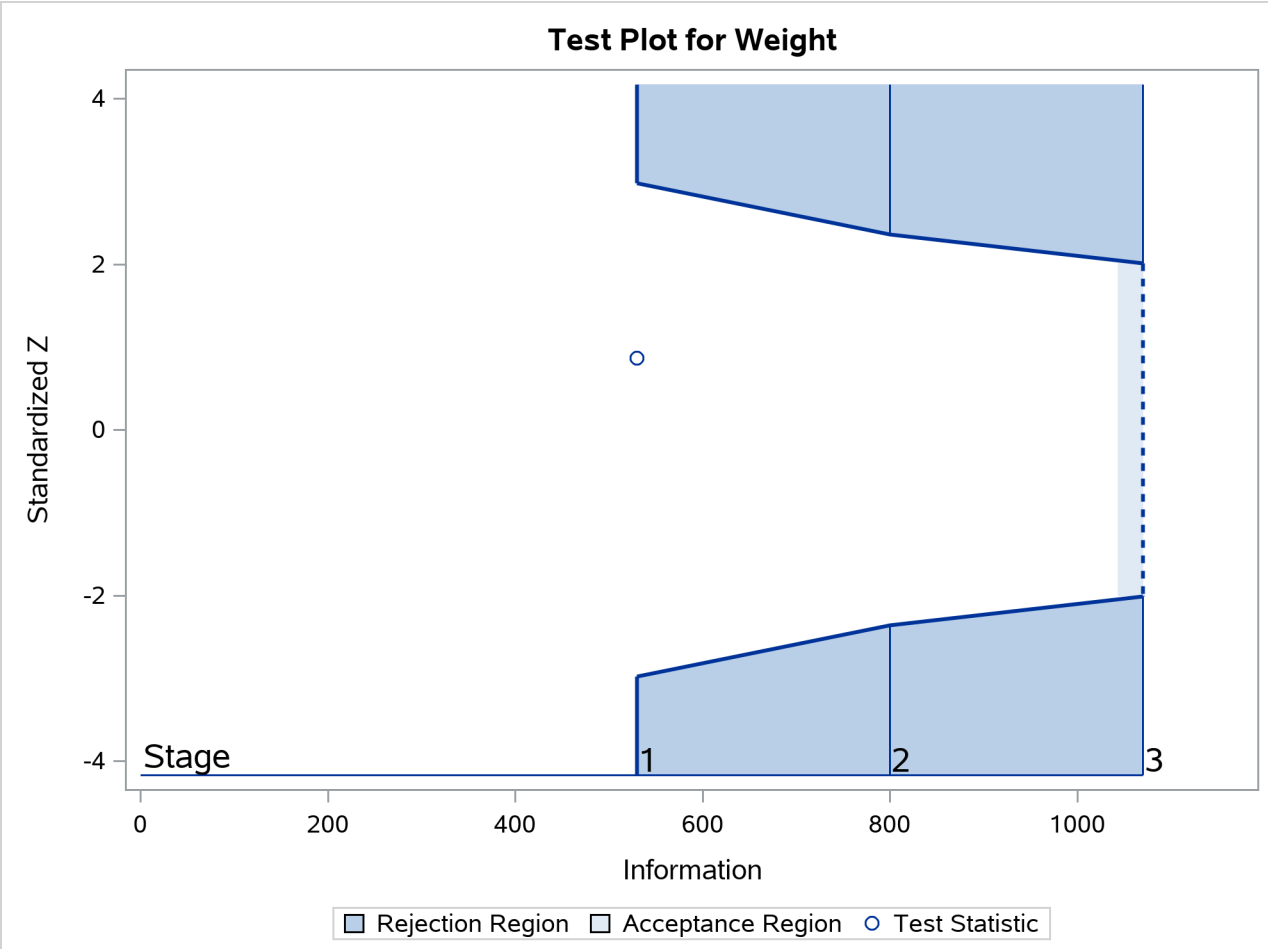
| _Stage_ | Information Level Proportion | Actual | Alternative Reference Lower | Upper | Boundary Values Lower Alpha | Upper Alpha | Test Weight Estimate | Action |
|---|---|---|---|---|---|---|---|---|
| 1 | 0.4950 | 529.6232 | -2.30135 | 2.30135 | -2.97951 | 2.97951 | 0.86798 | Continue |
| 2 | 0.7475 | 799.7853 | -2.82805 | 2.82805 | -2.36291 | 2.36291 | . | |
| 3 | 1.0000 | 1069.948 | -3.27101 | 3.27101 | -2.01336 | 2.01336 | . | |

With the INFOADJ=PROP option (which is the default), the information level at stage 2 is derived proportionally from the observed information at stage 1 and the information levels in the BOUNDARY= data set. See the section "Boundary Adjustments for Information Levels" on page 9058 for details about how the adjusted information levels are computed.

At stage 1, the standardized $Z$ statistic 0.86798 is between the lower $\alpha$ boundary –2.97951 and the upper $\alpha$ boundary 2.97951, so the trial continues to the next stage.

With ODS Graphics enabled, a boundary plot with test statistics is displayed, as shown in Output 108.2.11. As expected, the test statistic is in the continuation region between the lower and upper $\alpha$ boundaries.

**Output 108.2.11** Sequential Test Plot




The following statements use the REG procedure to estimate the slope $\beta_w$ and its associated standard error at stage 2:

```
proc reg data=Fit_2;
   model Oxygen=Age Weight RunTime RunPulse MaxPulse;
   ods output ParameterEstimates=Parms_Fit2;
run;
```

Note that the data set Fit_2 contains both the data from stage 1 and the data from stage 2.

The following statements create and display (in Output 108.2.12) the input data set that contains slope $\beta_w$ and its associated standard error at stage 2 for the SEQTEST procedure:

```
data Parms_Fit2;
   set Parms_Fit2;
   if Variable='Weight';
   _Scale_='MLE';
   _Stage_= 2;
   keep _Scale_ _Stage_ Variable Estimate StdErr;
run;
```

```
proc print data=Parms_Fit2;
   title 'Statistics Computed at Stage 2';
run;
```

**Output 108.2.12** Statistics Computed at Stage 2

**Statistics Computed at Stage 2**

| Obs | Variable | Estimate | StdErr | _Scale_ | _Stage_ |
|---|---|---|---|---|---|
| 1 | Weight | 0.02932 | 0.03520 | MLE | 2 |

The following statements invoke the SEQTEST procedure to test for early stopping at stage 2:

```
proc seqtest Boundary=Test_Fit1
             Parms(Testvar=Weight)=Parms_Fit2
             infoadj=prop
             errspendadj=errfuncobf
             order=lr
             ;
   ods output Test=Test_Fit2;
run;
```

The BOUNDARY= option specifies the input data set that provides the boundary information for the trial at stage 2, which was generated by the SEQTEST procedure at the previous stage. The PARMS= option specifies the input data set that contains the test statistic and its associated standard error at stage 2, and the TESTVAR= option identifies the test variable in the data set.

The ODS OUTPUT statement with the TEST=TEST_FIT2 option creates an output data set named TEST_FIT2 which contains the updated boundary information for the test at stage 2. The data set also provides the boundary information that is needed for the group sequential test at the next stage.

Since the data set PARMS_FIT2 does not contain the test information at stage 1, the information level at stage 1 in the TEST_FIT1 data set is used to generate boundary values for the test at stage 2.

Following the process at stage 1, the slope estimate is also between its corresponding lower and upper $\alpha$ boundary values, so the trial continues to the next stage.

The following statements use the REG procedure to estimate the slope $\beta_w$ and its associated standard error at the final stage:

```
proc reg data=Fit_3;
   model Oxygen=Age Weight RunTime RunPulse MaxPulse;
   ods output ParameterEstimates=Parms_Fit3;
run;
```

The following statements create the input data set that contains slope $\beta_w$ and its associated standard error at stage 3 for the SEQTEST procedure:

```
data Parms_Fit3;
   set Parms_Fit3;
   if Variable='Weight';
   _Scale_='MLE';
   _Stage_= 3;
   keep _Scale_ _Stage_ Variable Estimate StdErr;
run;
```

The following statements print (in Output 108.2.13) the test statistics at stage 3:

```
proc print data=Parms_Fit3;
   title 'Statistics Computed at Stage 3';
run;
```

**Output 108.2.13** Statistics Computed at Stage 3

**Statistics Computed at Stage 3**

| Obs | Variable | Estimate | StdErr | _Scale_ | _Stage_ |
|---|---|---|---|---|---|
| 1 | Weight | 0.02189 | 0.03028 | MLE | 3 |

The following statements invoke the SEQTEST procedure to test the hypothesis:

```
ods graphics on;
proc seqtest Boundary=Test_Fit2
             Parms(testvar=Weight)=Parms_Fit3
             errspendadj=errfuncobf
             order=lr
             pss
             plots=(asn power)
             ;
   ods output Test=Test_Fit3;
run;
```

The BOUNDARY= option specifies the input data set that provides the boundary information for the trial at stage 3, which was generated by the SEQTEST procedure at the previous stage. The PARMS= option specifies the input data set that contains the test statistic and its associated standard error at stage 3, and the TESTVAR= option identifies the test variable in the data set.

The ODS OUTPUT statement with the TEST=TEST_FIT3 option creates an output data set named TEST_FIT3 which contains the updated boundary information for the test at stage 3.

The "Design Information" table in Output 108.2.14 displays design specifications. By default (or equivalently if you specify BOUNDARYKEY=ALPHA), the boundary values are modified for the new information levels to maintain the Type I $\alpha$ level.

**Output 108.2.14** Design Information

**The SEQTEST Procedure**

| Design Information | |
|---|---|
| **BOUNDARY Data Set** | WORK.TEST_FIT2 |
| **Data Set** | WORK.PARMS_FIT3 |
| **Statistic Distribution** | Normal |
| **Boundary Scale** | Standardized Z |
| **Alternative Hypothesis** | Two-Sided |
| **Early Stop** | Reject Null |
| **Number of Stages** | 3 |
| **Alpha** | 0.05 |
| **Beta** | 0.09514 |
| **Power** | 0.90486 |
| **Max Information (Percent of Fixed Sample)** | 102.0102 |
| **Max Information** | 1090.63724 |
| **Null Ref ASN (Percent of Fixed Sample)** | 101.4122 |
| **Alt Ref ASN (Percent of Fixed Sample)** | 77.22139 |

The maximum information is derived from the standard error associated with the slope estimate at the final stage and is larger than the target level. The derived Type II error probability $\beta$ and power $1 - \beta$ are different because of the new information levels.

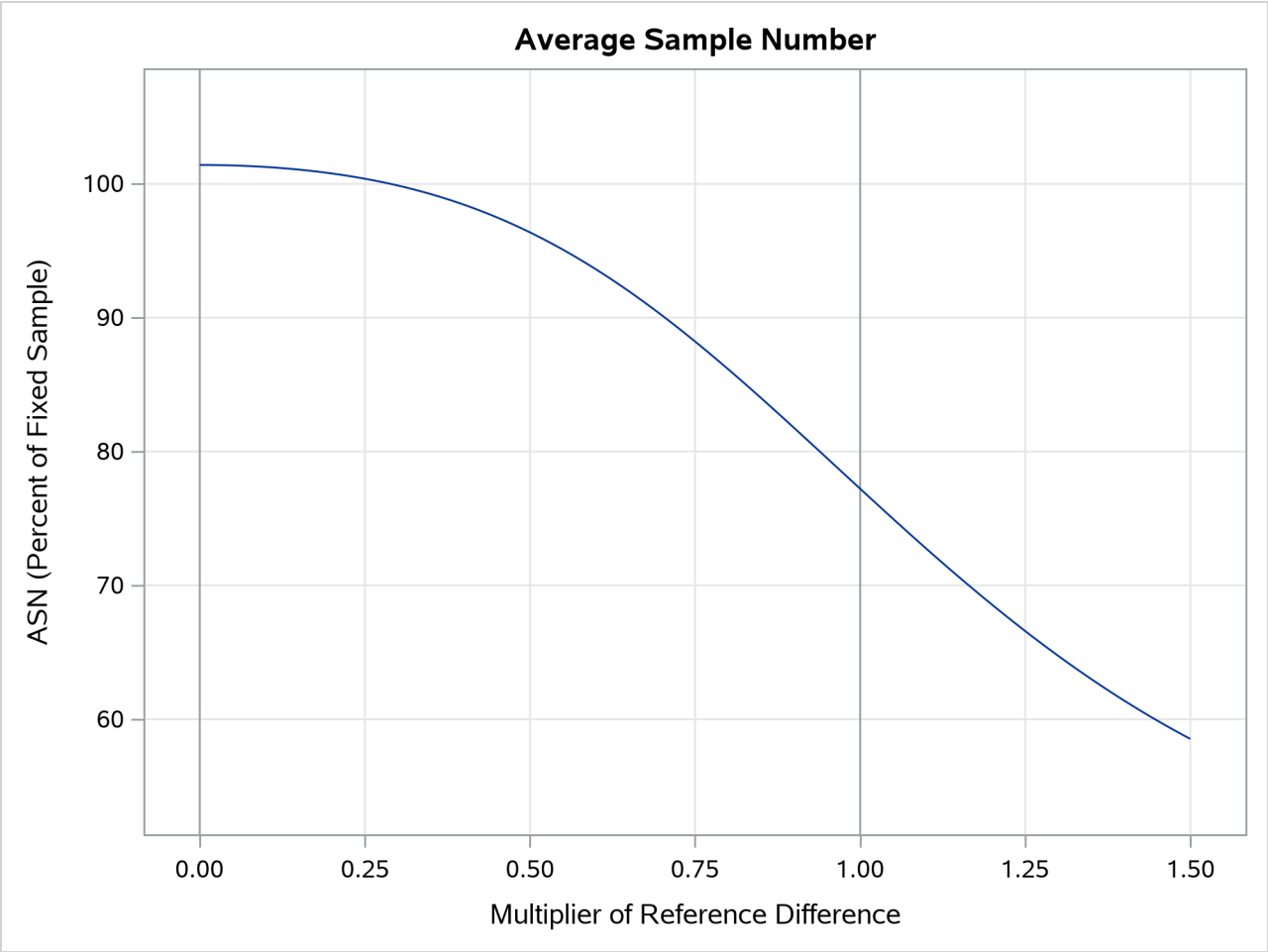
With the PSS option, the "Power and Expected Sample Sizes" table in Output 108.2.15 displays powers and expected mean sample sizes under various hypothetical references $\theta = c_i \theta_1$, where $\theta_1$ is the alternative reference and $c_i = 0, 0.5, 1, 1.5$ by default. You can specify the $c_i$ values with the CREF= option.

**Output 108.2.15** Power and Expected Sample Size Information

| Powers and Expected Sample Sizes<br>Reference = CRef * (Alt Reference) | | |
|---|---|---|
| | | **Sample Size** |
| **CRef** | **Power** | **Percent Fixed-Sample** |
| 0.0000 | 0.02500 | 101.4122 |
| 0.5000 | 0.37046 | 96.3754 |
| 1.0000 | 0.90486 | 77.2214 |
| 1.5000 | 0.99844 | 58.5301 |

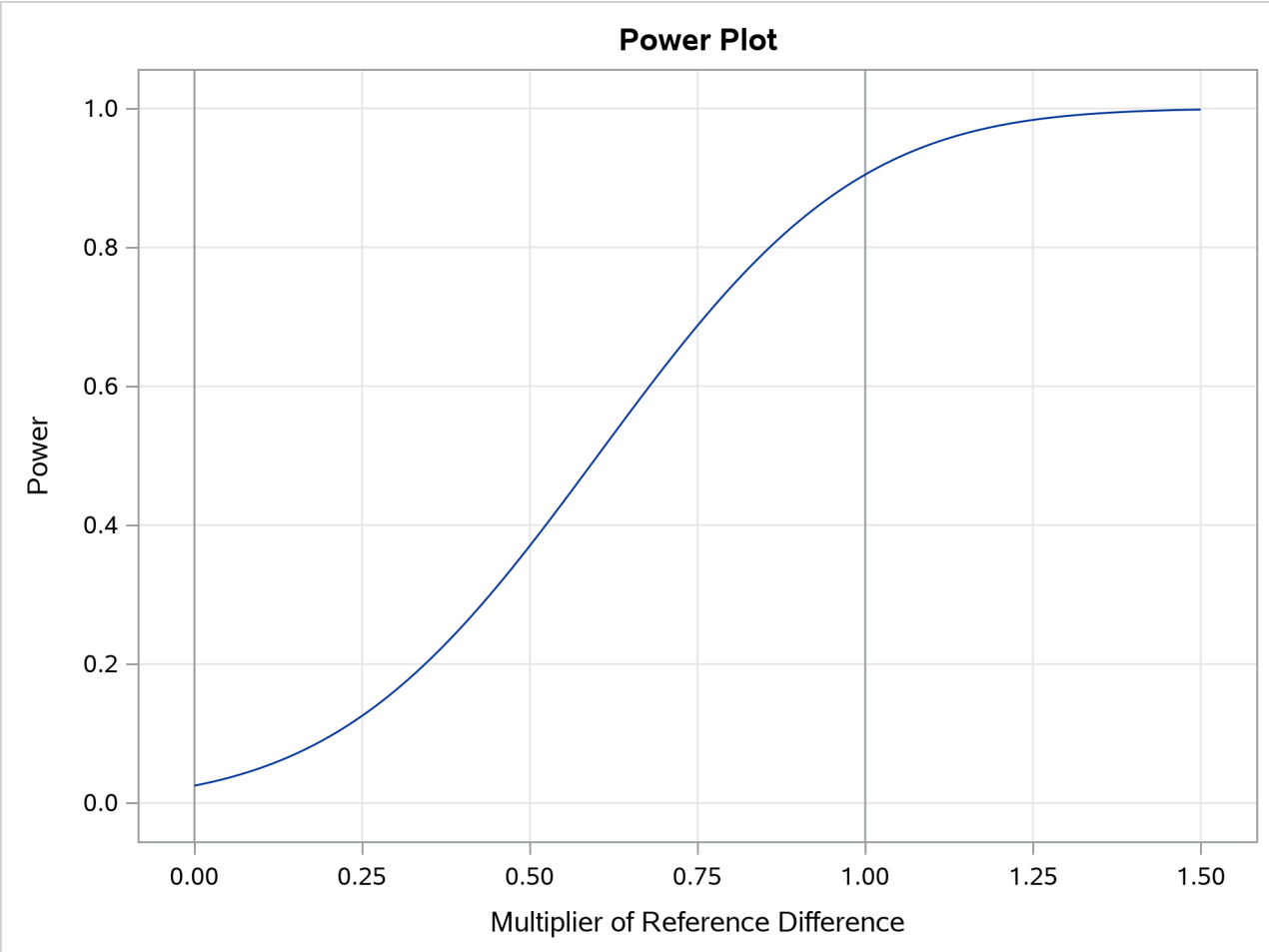
With the PLOTS=ASN option, the procedure displays a plot of expected sample sizes under various hypothetical references, as shown in Output 108.2.16. By default, expected sample sizes under the hypotheses $\theta = c_i\ \theta_1$, $c_i = 0, 0.01, 0.02, \ldots, 1.50$, are displayed, where $\theta_1$ is the alternative reference.

**Output 108.2.16** ASN Plot




With the PLOTS=POWER option, the procedure displays a plot of powers under various hypothetical references, as shown in Output 108.2.17. By default, powers under hypothetical references $\theta = c_i\ \theta_1$ are displayed, where $c_i = 0, 0.01, 0.02, \ldots, 1.50$ by default. You can specify $c_i$ values with the CREF= option. The $c_i$ values are displayed on the horizontal axis.

**Output 108.2.17** Power Plot




Under the null hypothesis, $c_i = 0$, the power is 0.025, which is the upper Type I error probability. Under the alternative hypothesis, $c_i = 1$, the power is 0.90486, which is one minus the Type II error probability.

The "Test Information" table in Output 108.2.18 displays the boundary values for the test statistic with the default standardized $Z$ scale. The information level at the current stage is derived from the standard error for the current stage in the PARMS= data set. At stage 3, the standardized slope estimate 0.72284 is still between the lower and upper $\alpha$ boundary values. Since it is the final stage, the trial stops to accept the null hypothesis that the variable Weight has no effect on the oxygen intake rate after adjusting for other covariates.

**Output 108.2.18** Sequential Tests

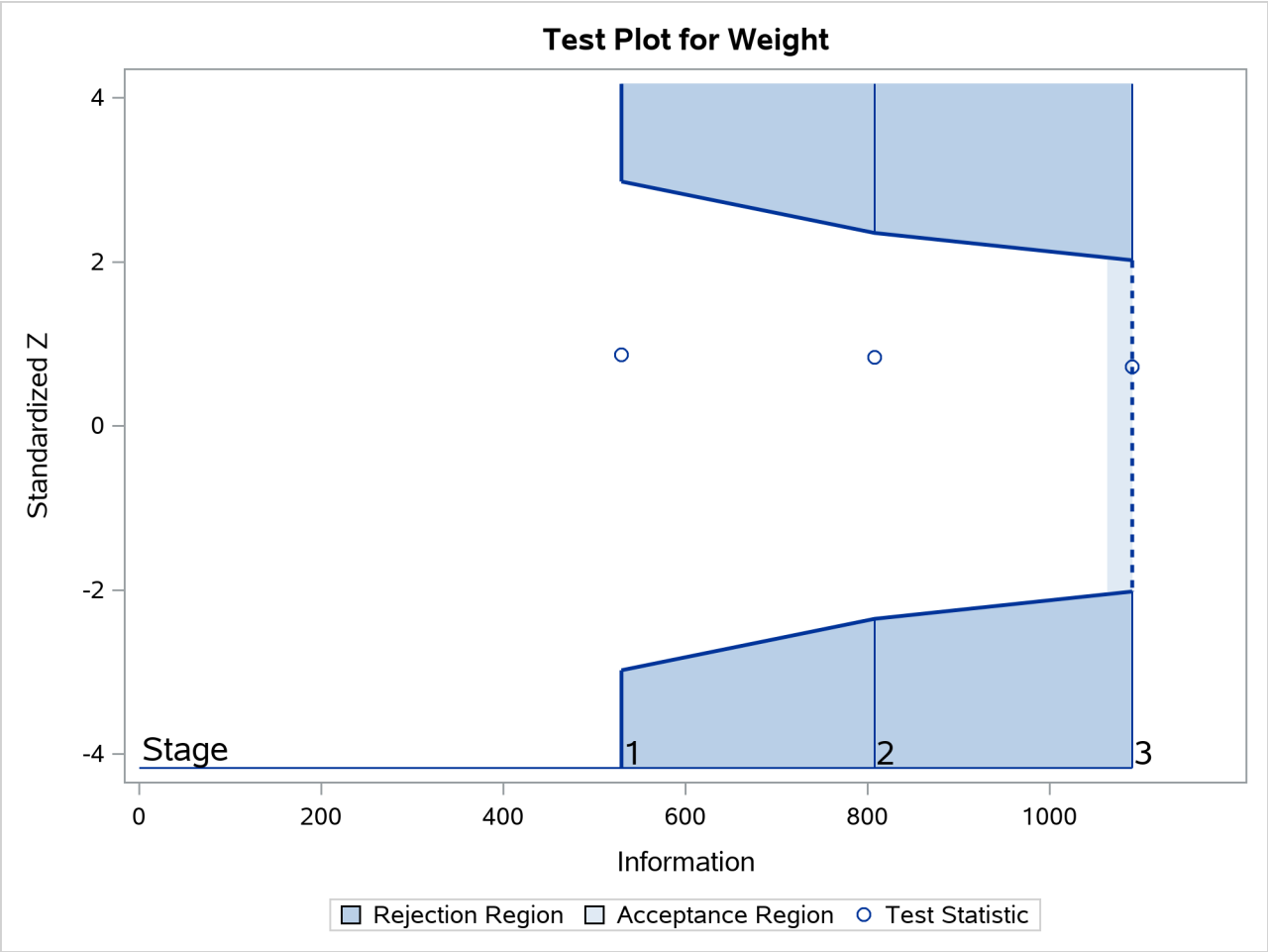
**Test Information (Standardized Z Scale)**
**Null Reference = 0**

| | Information Level | | Alternative Reference | | Boundary Values | | Test | |
|---|---|---|---|---|---|---|---|---|
| _Stage_ | Proportion | Actual | Lower | Upper | Lower Alpha | Upper Alpha | Weight Estimate | Action |
| 1 | 0.4856 | 529.6232 | -2.30135 | 2.30135 | -2.97951 | 2.97951 | 0.86798 | Continue |
| 2 | 0.7401 | 807.1954 | -2.84112 | 2.84112 | -2.34945 | 2.34945 | 0.83305 | Continue |
| 3 | 1.0000 | 1090.637 | -3.30248 | 3.30248 | -2.01885 | 2.01885 | 0.72284 | Accept Null |

Since the data set FIT_3 contains the test information only at stage 3, the information levels at previous stages in the TEST_FIT2 data set are used to generate boundary values for the test.

With ODS Graphics enabled, a boundary plot with test statistics is displayed, as shown in Output 108.2.19. As expected, the test statistic is in the acceptance region between the lower and upper $\alpha$ boundaries at the final stage.

**Output 108.2.19** Sequential Test Plot




After a trial is stopped, the "Parameter Estimates" table in Output 108.2.20 displays the stopping stage, parameter estimate, unbiased median estimate, confidence limits, and the $p$-value under the null hypothesis $H_0 : \beta_w = 0$.

**Output 108.2.20** Parameter Estimates

**Parameter Estimates**
**LR Ordering**

| Parameter | Stopping Stage | MLE | p-Value for H0:Parm=0 | Median Estimate | 95% Confidence Limits | |
|---|---|---|---|---|---|---|
| **Weight** | 3 | 0.021888 | 0.4699 | 0.021884 | -0.03747 | 0.08123 |

As expected, the $p$-value 0.4699 is not significant at the $\alpha = 0.05$ level, and the confidence interval does contain the value zero. The $p$-value, unbiased median estimate, and confidence limits depend on the ordering of the sample space $(k, z)$, where $k$ is the stage number and $z$ is the standardized $Z$ statistic. With the specified LR ordering, the $p$-values are computed with the ordering $(k', z') \succ (k, z)$ if $z' > z$. See the section "Available Sample Space Orderings in a Sequential Test" on page 9065 for a detailed description of the LR ordering.

## Example 108.3: Testing an Effect with Early Stopping to Accept $H_0$

This example demonstrates a two-sided group sequential test that uses an error spending design with early stopping to accept the null hypothesis $H_0$. The example is similar to Example 108.2 but with early stopping to accept $H_0$.

A study is conducted to examine the effects of Age (years), Weight (kg), RunTime (time in minutes to run 1.5 miles), RunPulse (heart rate while running), and MaxPulse (maximum heart rate recorded while running) on Oxygen (oxygen intake rate, ml per kg body weight per minute). The primary interest is whether oxygen intake rate is associated with weight.

The hypothesis is tested using the following linear model:

$$\text{Oxygen} = \text{Age} + \text{Weight} + \text{RunTime} + \text{RunPulse} + \text{MaxPulse}$$

The null hypothesis is $H_0 : \beta_w = 0$, where $\beta_w$ is the regression parameter for the variable Weight. Suppose that $\beta_w = 0.10$ is the reference improvement that should be detected at a 0.90 level. Then the maximum information $I_X$ can be derived in the SEQDESIGN procedure.

Following the derivations in the section "Test for a Parameter in the Regression Model" on page 8901 in Chapter 107, "The SEQDESIGN Procedure," the required sample size can be derived from

$$N = I_X \frac{\sigma_y^2}{(1 - r_x^2)\,\sigma_x^2}$$

where $\sigma_y^2$ is the variance of the response variable in the regression model, $r_x^2$ is the proportion of variance of Weight explained by other covariates, and $\sigma_x^2$ is the variance of Weight.

Further suppose that from past experience, $\sigma_y^2 = 5$, $r_x^2 = 0.10$, and $\sigma_x^2 = 64$. Then the required sample size can be derived using the SAMPLESIZE statement in the SEQDESIGN procedure.

The following statements invoke the SEQDESIGN procedure and request a three-stage group sequential design for normally distributed data to test the null hypothesis of a regression parameter $H_0 : \beta_w = 0$ against the alternative $H_1 : \beta_w \neq 0$:

```
ods graphics on;
proc seqdesign altref=0.10;
   OBFErrorFunction: design method=errfuncgamma
                            stop=accept
                            nstages=3
                            info=cum(2 3 4);

   samplesize model=reg( variance=5 xvariance=64 xrsquare=0.10);
   ods output Boundary=Bnd_Fit;
run;
```

By default (or equivalently if you specify ALPHA=0.05 and BETA=0.10), the procedure uses a Type I error probability 0.05 and a Type II error probability 0.10. The ALTREF=0.10 option specifies a power of $1 - \beta = 0.90$ at the alternative hypothesis $H_1 : \beta_w = \pm 0.10$. The INFO=CUM(2 3 4) option specifies that the study perform the first interim analysis with information proportion $2/4 = 0.5$—that is, after half of the total observations are collected.

The ODS OUTPUT statement with the BOUNDARY=BND_FIT option creates an output data set named BND_FIT which contains the resulting boundary information for the subsequent sequential tests.

The "Design Information" table in Output 108.3.1 displays design specifications and derived statistics. Since the alternative reference is specified, the maximum information is derived.

**Output 108.3.1** Error Spending Design Information

**The SEQDESIGN Procedure**
**Design: OBFErrorFunction**

| Design Information | |
|---|---|
| **Statistic Distribution** | Normal |
| **Boundary Scale** | Standardized Z |
| **Alternative Hypothesis** | Two-Sided |
| **Early Stop** | Accept Null |
| **Method** | Error Spending |
| **Boundary Key** | Both |
| **Alternative Reference** | 0.1 |
| **Number of Stages** | 3 |
| **Alpha** | 0.05 |
| **Beta** | 0.1 |
| **Power** | 0.9 |
| **Max Information (Percent of Fixed Sample)** | 103.9245 |
| **Max Information** | 1091.972 |
| **Null Ref ASN (Percent of Fixed Sample)** | 75.00521 |
| **Alt Ref ASN (Percent of Fixed Sample)** | 101.8099 |

The "Boundary Information" table in Output 108.3.2 displays information level, alternative reference, and boundary values at each stage.

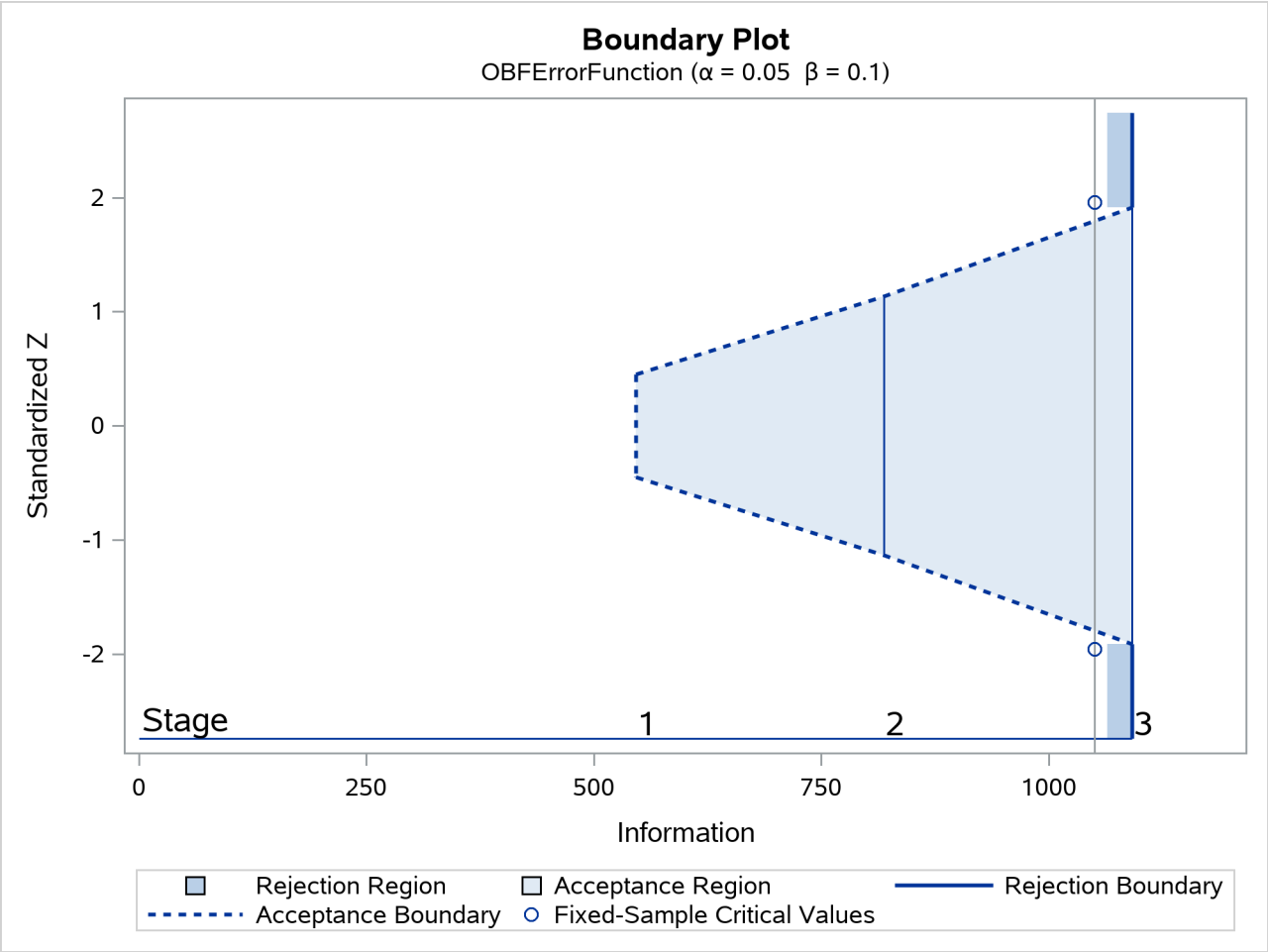
**Output 108.3.2** Boundary Information

**Boundary Information (Standardized Z Scale)**
**Null Reference = 0**

| | Information Level | | | Alternative Reference | | Boundary Values | |
|---|---|---|---|---|---|---|---|
| _Stage_ | Proportion | Actual | N | Lower | Upper | Lower Beta | Upper Beta |
| 1 | 0.5000 | 545.9862 | 47.39463 | -2.33663 | 2.33663 | -0.44937 | 0.44937 |
| 2 | 0.7500 | 818.9792 | 71.09195 | -2.86178 | 2.86178 | -1.13583 | 1.13583 |
| 3 | 1.0000 | 1091.972 | 94.78926 | -3.30450 | 3.30450 | -1.91428 | 1.91428 |

With ODS Graphics enabled, a detailed boundary plot with the rejection and acceptance regions is displayed, as shown in Output 108.3.3. The boundary plot also displays the information level and critical value for the corresponding fixed-sample design.

**Output 108.3.3** Boundary Plot




With the MODEL=REG option in the SAMPLESIZE statement, the "Sample Size Summary" table in Output 108.3.4 displays the parameters for the sample size computation.

**Output 108.3.4** Required Sample Size Summary

| Sample Size Summary | |
|---|---|
| **Test** | Reg Parameter |
| **Parameter** | 0.1 |
| **Variance** | 5 |
| **X Variance** | 64 |
| **R Square (X)** | 0.1 |
| **Max Sample Size** | 94.78926 |
| **Expected Sample Size (Null Ref)** | 68.41207 |
| **Expected Sample Size (Alt Ref)** | 92.86057 |

The "Sample Sizes" table in Output 108.3.5 displays the required sample sizes for the group sequential clinical trial.

**Output 108.3.5** Required Sample Sizes

| Sample Sizes (N) Z Test for Regression Parameter | | | | |
|---|---|---|---|---|
| | Fractional N | | Ceiling N | |
| _Stage_ | N | Information | N | Information |
| 1 | 47.39 | 546.0 | 48 | 553.0 |
| 2 | 71.09 | 819.0 | 72 | 829.4 |
| 3 | 94.79 | 1092.0 | 95 | 1094.4 |

Thus, 48, 72, and 95 individuals are needed in stages 1, 2, and 3, respectively. Since the sample sizes are derived from estimated values of $\sigma_y^2$, $r_x^2$, and $\sigma_x^2$, the actual information levels might not achieve the target information levels. Thus, instead of specifying sample sizes in the protocol, you can specify the maximum information levels. Then if an actual information level is much less than the target level, you can increase the sample sizes for the remaining stages to achieve the desired information levels and power.

Suppose that 48 individuals are available at stage 1. Output 108.3.6 lists the first 10 observations of the trial data.

**Output 108.3.6** Clinical Trial Data

**First 10 Obs in the Trial Data**

| Obs | Oxygen | Age | Weight | RunTime | RunPulse | MaxPulse |
|---|---|---|---|---|---|---|
| 1 | 54.5521 | 44 | 87.7676 | 11.6949 | 178.435 | 181.607 |
| 2 | 52.2821 | 40 | 75.4853 | 9.8872 | 184.433 | 183.667 |
| 3 | 62.1871 | 44 | 89.0638 | 8.7950 | 155.540 | 167.108 |
| 4 | 65.3269 | 42 | 67.7310 | 8.4577 | 162.926 | 173.877 |
| 5 | 59.9809 | 37 | 93.1902 | 9.3228 | 179.033 | 180.144 |
| 6 | 52.5588 | 47 | 75.9044 | 12.0385 | 177.753 | 175.033 |
| 7 | 51.7838 | 40 | 73.5422 | 11.6607 | 175.838 | 178.140 |
| 8 | 57.0024 | 43 | 81.2861 | 11.2219 | 160.963 | 171.770 |
| 9 | 48.0775 | 44 | 85.2290 | 13.1789 | 173.722 | 176.548 |
| 10 | 68.3357 | 38 | 80.2490 | 8.5066 | 171.824 | 184.011 |

The following statements use the REG procedure to estimate the slope $\beta_w$ and its associated standard error at stage 1:

```
proc reg data=Fit_1;
   model Oxygen=Age Weight RunTime RunPulse MaxPulse;
   ods output ParameterEstimates=Parms_Fit1;
run;
```

The following statements create and display (in Output 108.3.7) the input data set that contains slope $\beta_w$ and its associated standard error for the SEQTEST procedure:

```
data Parms_Fit1;
   set Parms_Fit1;
   if Variable='Weight';
   _Scale_='MLE';
   _Stage_= 1;
   keep _Scale_ _Stage_ Variable Estimate StdErr;
run;
```

```
proc print data=Parms_Fit1;
   title 'Statistics Computed at Stage 1';
run;
```

**Output 108.3.7** Statistics Computed at Stage 1

**Statistics Computed at Stage 1**

| Obs | Variable | Estimate | StdErr | _Scale_ | _Stage_ |
|---|---|---|---|---|---|
| 1 | Weight | 0.04660 | 0.04308 | MLE | 1 |

The following statements invoke the SEQTEST procedure to test for early stopping at stage 1:

```
ods graphics on;
proc seqtest Boundary=Bnd_Fit
             Parms(testvar=Weight)=Parms_Fit1
             infoadj=none
             errspendadj=errfuncgamma
             stopprob
             order=lr
             ;
   ods output Test=Test_Fit1;
run;
```

The BOUNDARY= option specifies the input data set that provides the boundary information for the trial at stage 1, which was generated in the SEQDESIGN procedure. The PARMS=PARMS_FIT1 option specifies the input data set PARMS_FIT1 that contains the test statistic and its associated standard error at stage 1, and the TESTVAR=WEIGHT option identifies the test variable WEIGHT in the data set. The INFOADJ=NONE option maintains the information level for stage 2 at the value provided in the BOUNDARY= data set.

The ORDER=LR option uses the LR ordering to derive the $p$-value, the unbiased median estimate, and the confidence limits for the regression slope estimate. The ERRSPENDADJ=ERRFUNCGAMMA option adjusts the boundaries with the updated error spending values generated from a gamma cumulative error spending function.

The ODS OUTPUT statement with the TEST=TEST_FIT1 option creates an output data set named TEST_FIT1 which contains the updated boundary information for the test at stage 1. The data set also provides the boundary information that is needed for the group sequential test at the next stage.

The "Design Information" table in Output 108.3.8 displays the design specifications. By default (or equivalently if you specify BOUNDARYKEY=ALPHA), the boundary values are modified for the new information levels to maintain the Type I $\alpha$ level. The maximum information remains the same as in the BOUNDARY= data set, but the derived Type II error probability $\beta$ and power $1 - \beta$ are different because of the new information level.

**Output 108.3.8** Design Information

**The SEQTEST Procedure**

| Design Information | |
|---|---|
| **BOUNDARY Data Set** | WORK.BND_FIT |
| **Data Set** | WORK.PARMS_FIT1 |
| **Statistic Distribution** | Normal |
| **Boundary Scale** | Standardized Z |
| **Alternative Hypothesis** | Two-Sided |
| **Early Stop** | Accept Null |
| **Number of Stages** | 3 |
| **Alpha** | 0.05 |
| **Beta** | 0.10007 |
| **Power** | 0.89993 |
| **Max Information (Percent of Fixed Sample)** | 103.9498 |
| **Max Information** | 1091.97232 |
| **Null Ref ASN (Percent of Fixed Sample)** | 75.15846 |
| **Alt Ref ASN (Percent of Fixed Sample)** | 101.8296 |

With the STOPPROB option, the "Expected Cumulative Stopping Probabilities" table in Output 108.3.9 displays the expected stopping stage and the cumulative stopping probability of accepting the null hypothesis at each stage under various hypothetical references $\theta = c_i\theta_1$, where $\theta_1$ is the alternative reference and $c_i = 0, 0.5, 1, 1.5$ by default. You can specify other values for $c_i$ with the CREF= option.

**Output 108.3.9** Stopping Probabilities

**Expected Cumulative Stopping Probabilities**
**Reference = CRef * (Alt Reference)**

| | | | Stopping Probabilities | | |
|---|---|---|---|---|---|
| **CRef** | **Expected Stopping Stage** | **Source** | **Stage_1** | **Stage_2** | **Stage_3** |
| 0.0000 | 1.895 | Accept Null | 0.33304 | 0.76607 | 0.95000 |
| 0.5000 | 2.409 | Accept Null | 0.17680 | 0.40947 | 0.62828 |
| 1.0000 | 2.918 | Accept Null | 0.02636 | 0.05453 | 0.10007 |
| 1.5000 | 2.997 | Accept Null | 0.00109 | 0.00166 | 0.00242 |

The "Test Information" table in Output 108.3.10 displays the boundary values for the test statistic. By default (or equivalently if you specify BOUNDARYSCALE=STDZ), these statistics are displayed with the standardized $Z$ scale. The information level at stage 1 is derived from the standard error $s_1$ in the PARMS= data set,

$$I_1 = \frac{1}{s_1^2} = \frac{1}{0.04308^2} = 538.8$$

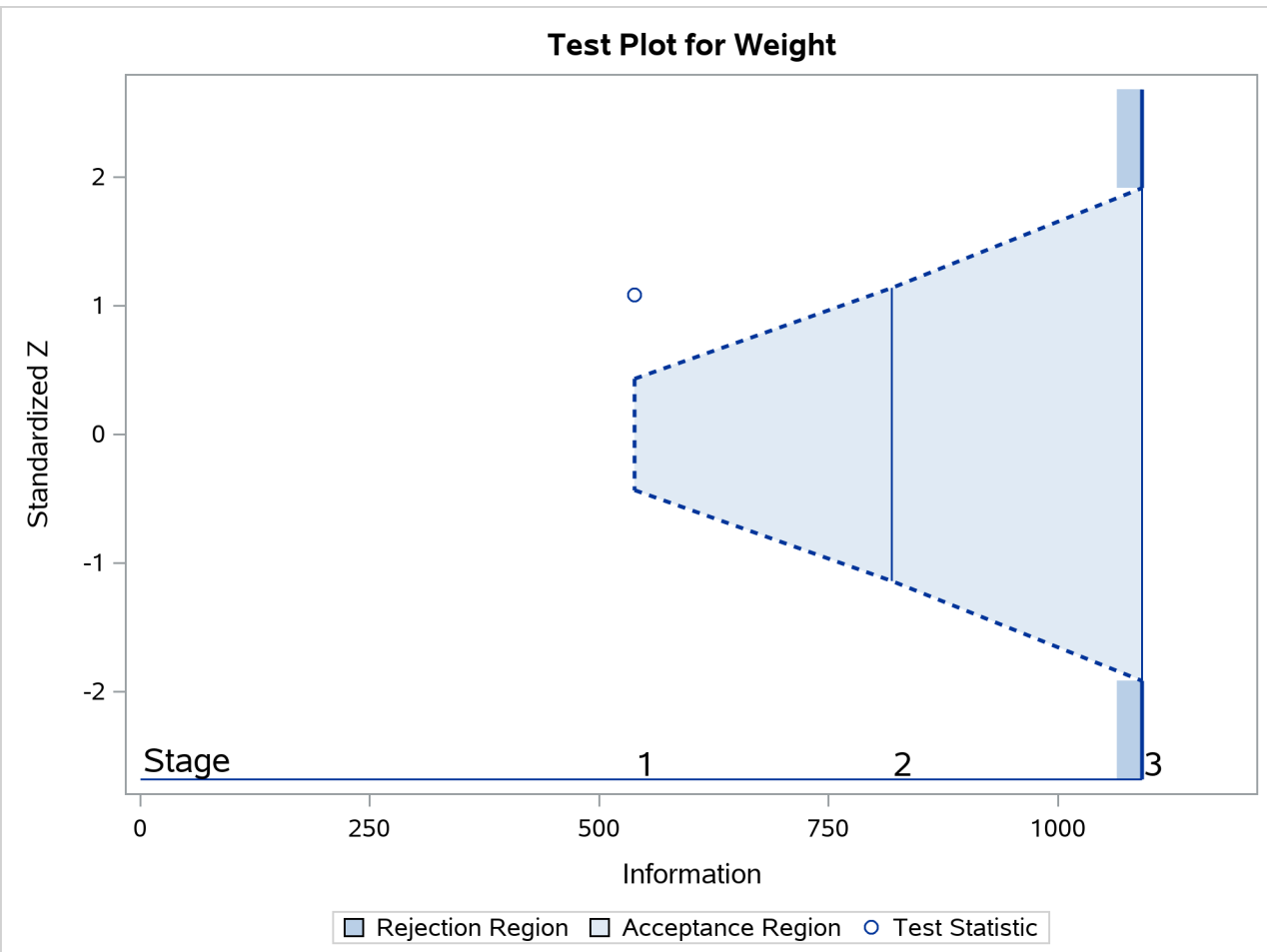
**Output 108.3.10** Sequential Tests

| Test Information (Standardized Z Scale) Null Reference = 0 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Information Level | | Alternative Reference | | Boundary Values | | Test Weight | |
| _Stage_ | Proportion | Actual | Lower | Upper | Lower Beta | Upper Beta | Estimate | Action |
| 1 | 0.4934 | 538.7887 | -2.32118 | 2.32118 | -0.43033 | 0.43033 | 1.08174 | Continue |
| 2 | 0.7500 | 818.9792 | -2.86178 | 2.86178 | -1.13623 | 1.13623 | . | |
| 3 | 1.0000 | 1091.972 | -3.30450 | 3.30450 | -1.91431 | 1.91431 | . | |

At stage 1, the standardized $Z$ statistic 1.08174 is greater than the upper $\beta$ boundary 0.43033, so the trial continues to the next stage.

With ODS Graphics enabled, a boundary plot with test statistics is displayed, as shown in Output 108.3.11. As expected, the test statistic is in the continuation region.

**Output 108.3.11** Sequential Test Plot



The following statements use the REG procedure to estimate the slope $\beta_w$ and its associated standard error at stage 2:

```
proc reg data=Fit_2;
   model Oxygen=Age Weight RunTime RunPulse MaxPulse;
   ods output ParameterEstimates=Parms_Fit2;
run;
```

Note that the data set Fit_2 contains both the data from stage 1 and the data from stage 2,

The following statements create and display (in Output 108.3.12) the input data set that contains slope $\beta_w$ and its associated standard error at stage 2 for the SEQTEST procedure:

```
data Parms_Fit2;
   set Parms_Fit2;
   if Variable='Weight';
   _Scale_='MLE';
   _Stage_= 2;
   keep _Scale_ _Stage_ Variable Estimate StdErr;
run;


proc print data=Parms_Fit2;
   title 'Statistics Computed at Stage 2';
run;
```

**Output 108.3.12** Statistics Computed at Stage 2

**Statistics Computed at Stage 2**

| Obs | Variable | Estimate | StdErr | _Scale_ | _Stage_ |
|---|---|---|---|---|---|
| 1 | Weight | 0.02925 | 0.03490 | MLE | 2 |

The following statements invoke the SEQTEST procedure to test for early stopping at stage 2:

```
ods graphics on;
proc seqtest Boundary=Test_Fit1
             Parms(testvar=Weight)=Parms_Fit2
             errspendadj=errfuncgamma
             order=lr
             pss
             plots=(asn power)
             ;
   ods output Test=Test_Fit2;
run;
```

The BOUNDARY= option specifies the input data set that provides the boundary information for the trial at stage 2, which was generated by the SEQTEST procedure at the previous stage. The PARMS= option specifies the input data set that contains the test statistic and its associated standard error at stage 2, and the TESTVAR= option identifies the test variable in the data set.

Since the data set PARMS_FIT2 does not contain the test information at stage 1, the information level at stage 1 in the TEST_FIT1 data set is used to generate boundary values for the test.

The ORDER=LR option uses the LR ordering to derive the $p$-value, unbiased median estimate, and confidence limits for the regression slope estimate.

The ODS OUTPUT statement with the TEST=TEST_FIT2 option creates an output data set named TEST_FIT2 which contains the updated boundary information for the test at stage 2. The data set also provides the boundary information that is needed for the group sequential test at the next stage.

The "Design Information" table in Output 108.3.13 displays design specifications. By default (or equivalently if you specify BOUNDARYKEY=ALPHA), the boundary values are modified for the new information levels to maintain the Type I $\alpha$ level.

**Output 108.3.13** Design Information

**The SEQTEST Procedure**

| Design Information | |
|---|---|
| **BOUNDARY Data Set** | WORK.TEST_FIT1 |
| **Data Set** | WORK.PARMS_FIT2 |
| **Statistic Distribution** | Normal |
| **Boundary Scale** | Standardized Z |
| **Alternative Hypothesis** | Two-Sided |
| **Early Stop** | Accept Null |
| **Number of Stages** | 3 |
| **Alpha** | 0.05 |
| **Beta** | 0.10009 |
| **Power** | 0.89991 |
| **Max Information (Percent of Fixed Sample)** | 103.9566 |
| **Max Information** | 1091.97232 |
| **Null Ref ASN (Percent of Fixed Sample)** | 75.18254 |
| **Alt Ref ASN (Percent of Fixed Sample)** | 101.8349 |

The derived Type II error probability $\beta$ and power $1 - \beta$ are different because of the new information levels.

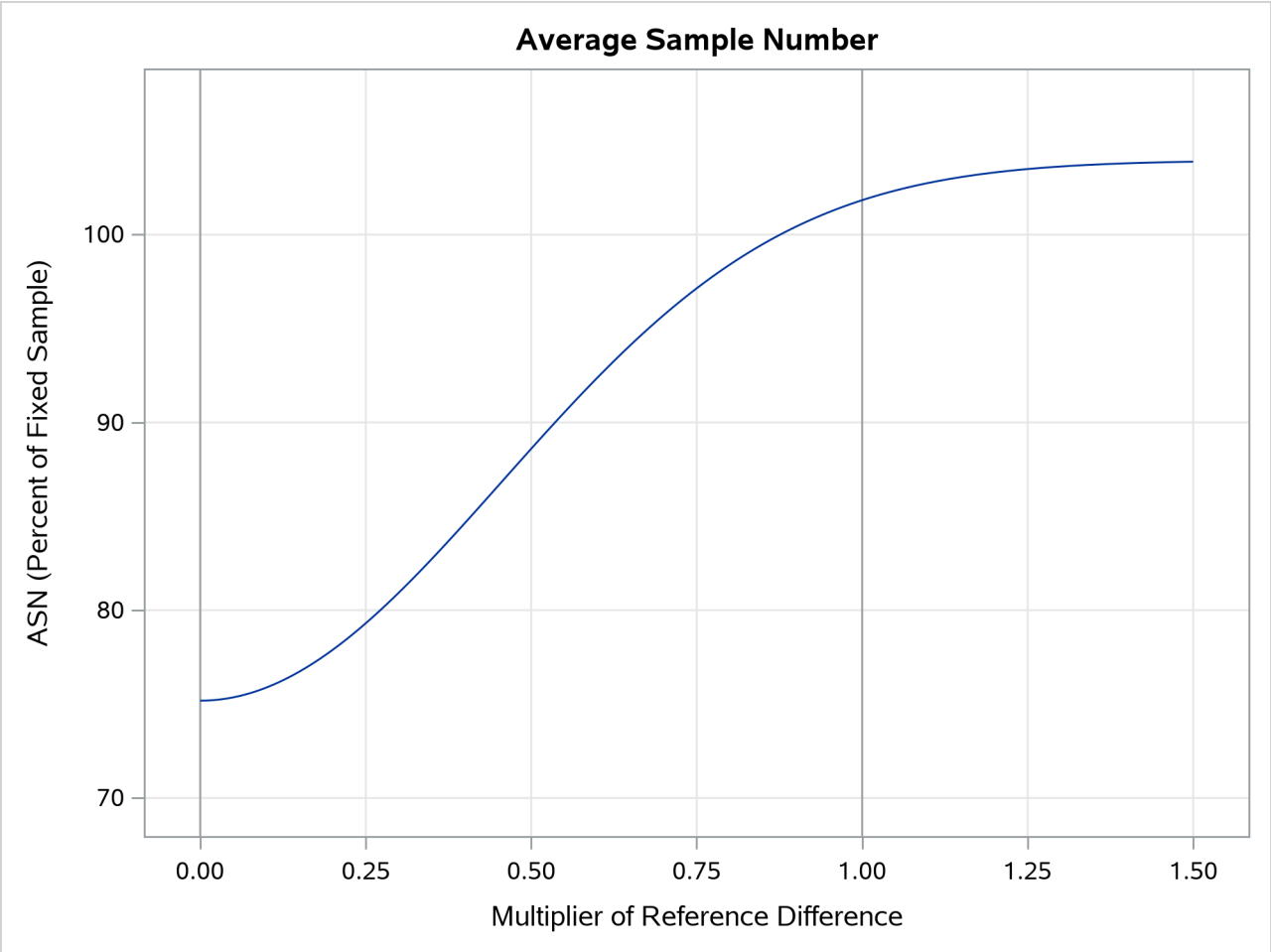
With the PSS option, the "Power and Expected Sample Sizes" table in Output 108.3.14 displays powers and expected mean sample sizes under various hypothetical references $\theta = c_i\theta_1$, where $\theta_1$ is the alternative reference and $c_i = 0, 0.5, 1, 1.5$ are the default values in the CREF= option.

**Output 108.3.14** Power and Expected Sample Size Information

| Powers and Expected Sample Sizes<br>Reference = CRef * (Alt Reference) | | |
|---|---|---|
| | | Sample Size |
| CRef | Power | Percent Fixed-Sample |
| 0.0000 | 0.02500 | 75.1825 |
| 0.5000 | 0.37154 | 88.5975 |
| 1.0000 | 0.89991 | 101.8349 |
| 1.5000 | 0.99758 | 103.8843 |

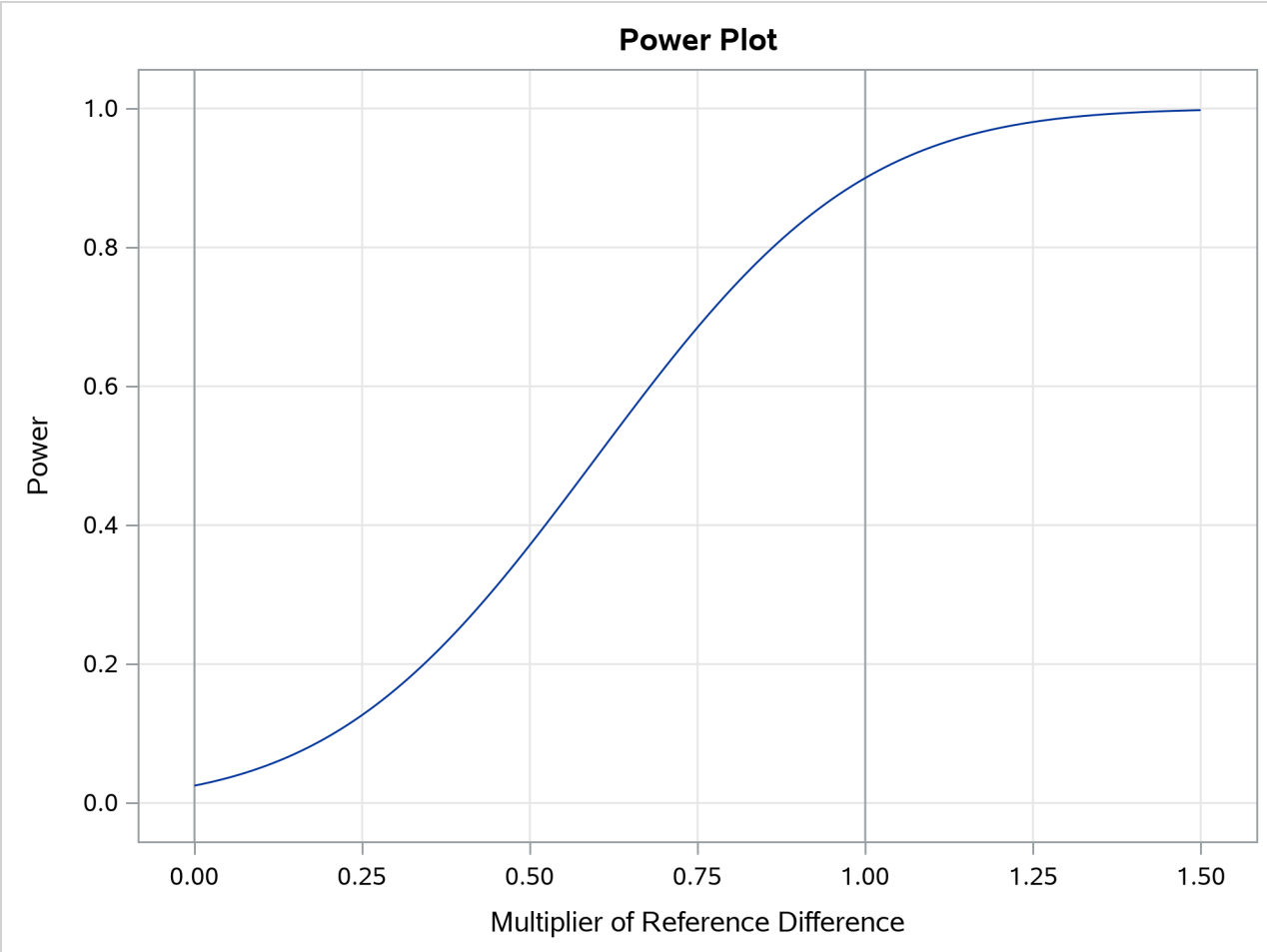
With the PLOTS=ASN option, the procedure displays a plot of expected sample sizes under various hypothetical references, as shown in Output 108.3.15. By default, expected sample sizes under the hypotheses $\theta = c_i\,\theta_1$, $c_i = 0, 0.01, 0.02, \ldots, 1.50$, are displayed, where $\theta_1$ is the alternative reference.

**Output 108.3.15** ASN Plot




With the PLOTS=POWER option, the procedure displays a plot of the power curves under various hypothetical references for all designs simultaneously, as shown in Output 108.3.16. By default, powers under hypothetical references $\theta = c_i\,\theta_1$ are displayed, where $c_i = 0, 0.01, 0.02, \ldots, 1.50$ by default. You can specify $c_i$ values with the CREF= option. The $c_i$ values are displayed on the horizontal axis.

**Output 108.3.16** Power Plot




Under the null hypothesis, $c_i = 0$, the power is 0.025, which is the upper Type I error probability. Under the alternative hypothesis, $c_i = 1$, the power is 0.89991, which is one minus the Type II error probability, as displayed in the "Design Information" table in Output 108.3.13.

The "Test Information" table in Output 108.3.17 displays the boundary values for the test statistic with the default standardized $Z$ scale. At stage 2, the standardized slope estimate 0.83805 is between the lower and upper $\beta$ boundary values. The trial stops to accept the null hypothesis that the variable Weight has no effect on the oxygen intake rate after adjusting for other covariates.

**Output 108.3.17** Sequential Tests

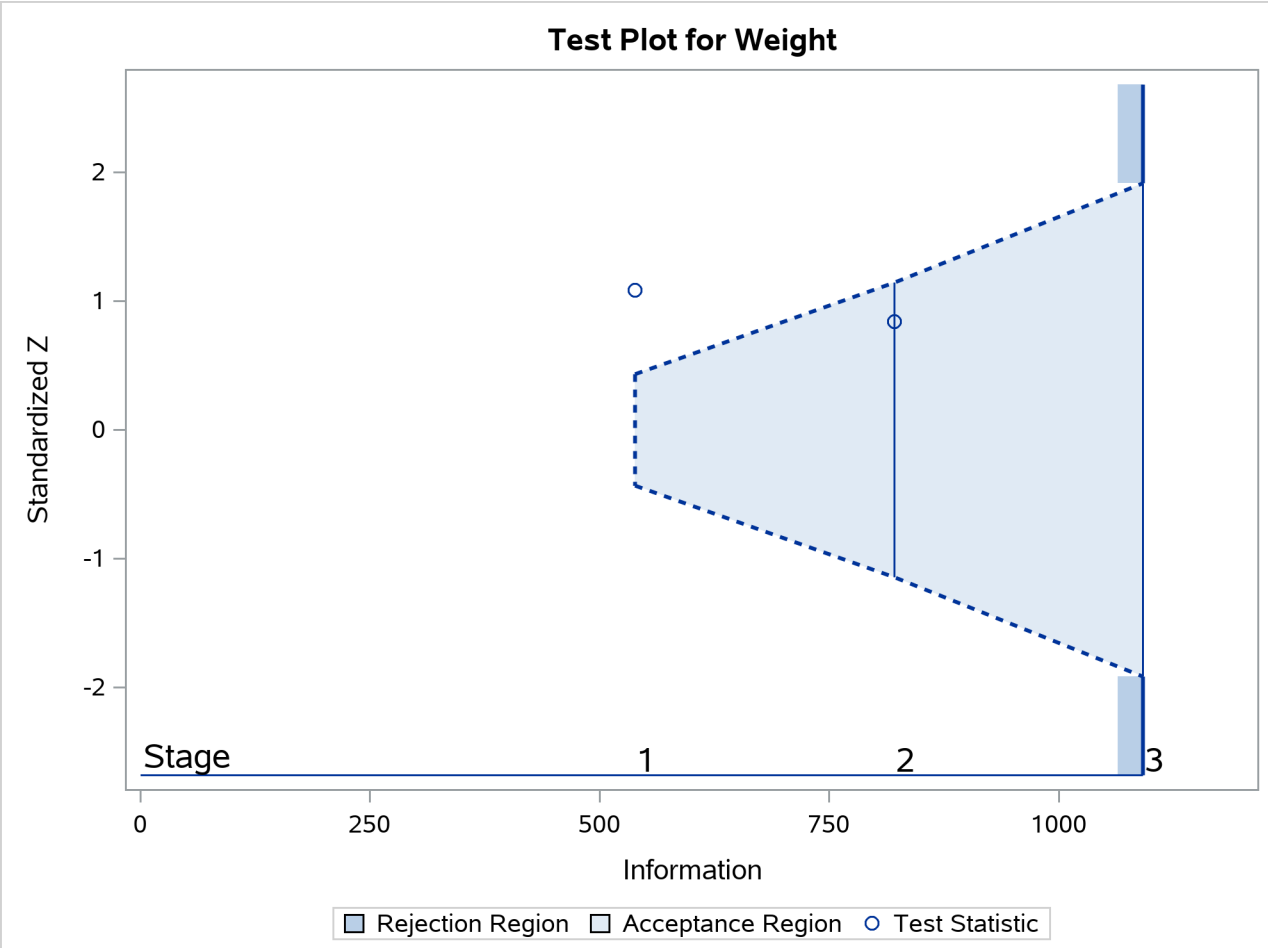
**Test Information (Standardized Z Scale)**
**Null Reference = 0**

| | Information Level | | Alternative Reference | | Boundary Values | | Test Weight | |
|---|---|---|---|---|---|---|---|---|
| _Stage_ | Proportion | Actual | Lower | Upper | Lower Beta | Upper Beta | Estimate | Action |
| 1 | 0.4934 | 538.7887 | -2.32118 | 2.32118 | -0.43033 | 0.43033 | 1.08174 | Continue |
| 2 | 0.7517 | 820.8509 | -2.86505 | 2.86505 | -1.14239 | 1.14239 | 0.83805 | Accept Null |
| 3 | 1.0000 | 1091.972 | -3.30450 | 3.30450 | -1.91408 | 1.91408 | . | |

Since the data set PARMS_FIT2 contains the test information only at stage 2, the information level at stage 1 in the TEST_FIT1 data set is used to generate boundary values for the test.

With ODS Graphics enabled, a boundary plot with test statistics is displayed, as shown in Output 108.3.18. As expected, the test statistic is in the acceptance region between the lower and upper $\alpha$ boundaries at the final stage.

**Output 108.3.18** Sequential Test Plot




After a trial is stopped, the "Parameter Estimates" table in Output 108.3.19 displays the stopping stage, parameter estimate, unbiased median estimate, confidence limits, and the $p$-value under the null hypothesis $H_0 : \beta_w = 0$. As expected, the $p$-value 0.3056 is not significant at the $\alpha = 0.05$ level, and the confidence interval does contain the value zero. The $p$-value, unbiased median estimate, and confidence limits depend on the ordering of the sample space $(k, z)$, where $k$ is the stage number and $z$ is the standardized $Z$ statistic. With the specified LR ordering, the $p$-values are computed with the ordering $(k', z') \succ (k, z)$ if $z' > z$. See the section "Available Sample Space Orderings in a Sequential Test" on page 9065 for a detailed description of the LR ordering.

**Output 108.3.19** Parameter Estimates

| Parameter Estimates LR Ordering | | | | | | |
|---|---|---|---|---|---|---|
| Parameter | Stopping Stage | MLE | p-Value for H0:Parm=0 | Median Estimate | 95% Confidence Limits | |
| Weight | 2 | 0.029251 | 0.3056 | 0.037080 | -0.03368 | 0.10532 |

## Example 108.4: Testing a Binomial Proportion

This example tests a binomial proportion by using a four-stage group sequential design. Suppose a supermarket is developing a new store-brand coffee. From past studies, the positive response for the current store-brand coffee from customers is around 60%. The store is interested in whether the new brand has a better positive response than the current brand.

A power family method is used for the group sequential trial with the null hypothesis $H_0 : p = p_0 = 0.60$ and a one-sided upper alternative with a power of 0.80 at $H_1 : p = 0.70$. To accommodate the zero null reference that is assumed in the SEQDESIGN procedure, an equivalent hypothesis $H_0 : \theta = 0$ with $H_1 : \theta = 0.10$ is used, where $\theta = p - p_0$. The following statements request a power family method with early stopping to reject the null hypothesis:

```
ods graphics on;
proc seqdesign altref=0.10
               boundaryscale=mle
               ;
   PowerFamily: design method=pow
                       nstages=4
                       alt=upper
                       beta=0.20
                       ;
   samplesize model(ceiladjdesign=include)=onesamplefreq( nullprop=0.6);
   ods output AdjustedBoundary=Bnd_Prop;
run;
```

The NULLPROP= option in the SAMPLESIZE statement specifies $p_0 = 0.60$ for the sample size computation. When BOUNDARYSCALE=MLE in the PROC SEQTEST statement, the procedure displays the output boundaries in terms of the maximum likelihood estimates.

When CEILADJDESIGN=INCLUDE in the SAMPLESIZE statement, the table also displays the ceiling-adjusted design information. When you specify ADJUSTEDBOUNDARY=BND_PROP in the ODS OUTPUT statement, PROC SEQTEST creates an output data set named BND_PROP, which contains the resulting ceiling-adjusted design boundary information for the subsequent sequential tests.

The "Design Information" table in Output 108.4.1 displays design specifications and derived statistics. With the specified alternative reference $\theta_1 = p_1 - p_0 = 0.7 - 0.6 = 0.1$, the maximum information 670.38 is also derived.

**Output 108.4.1** Design Information

**The SEQDESIGN Procedure**
**Design: PowerFamily**

| Design Information | |
|---|---|
| **Statistic Distribution** | Normal |
| **Boundary Scale** | MLE |
| **Alternative Hypothesis** | Upper |
| **Early Stop** | Reject Null |
| **Method** | Power Family |
| **Boundary Key** | Both |
| **Alternative Reference** | 0.1 |
| **Number of Stages** | 4 |
| **Alpha** | 0.05 |
| **Beta** | 0.2 |
| **Power** | 0.8 |
| **Max Information (Percent of Fixed Sample)** | 108.4306 |
| **Max Information** | 670.3782 |
| **Null Ref ASN (Percent of Fixed Sample)** | 106.9276 |
| **Alt Ref ASN (Percent of Fixed Sample)** | 78.51072 |
| **Adj Design Alpha** | 0.05 |
| **Adj Design Beta** | 0.19951 |
| **Adj Design Power** | 0.80049 |
| **Adj Design Max Information (Percent of Fixed Sample)** | 108.4461 |
| **Adj Design Max Information** | 671.4286 |
| **Adj Design Null Ref ASN (Percent of Fixed Sample)** | 106.9406 |
| **Adj Design Alt Ref ASN (Percent of Fixed Sample)** | 78.42926 |

The "Boundary Information" table in Output 108.4.2 displays the information level, alternative reference, and boundary values at each stage. With the STOP=REJECT option, only the rejection boundary values are displayed.

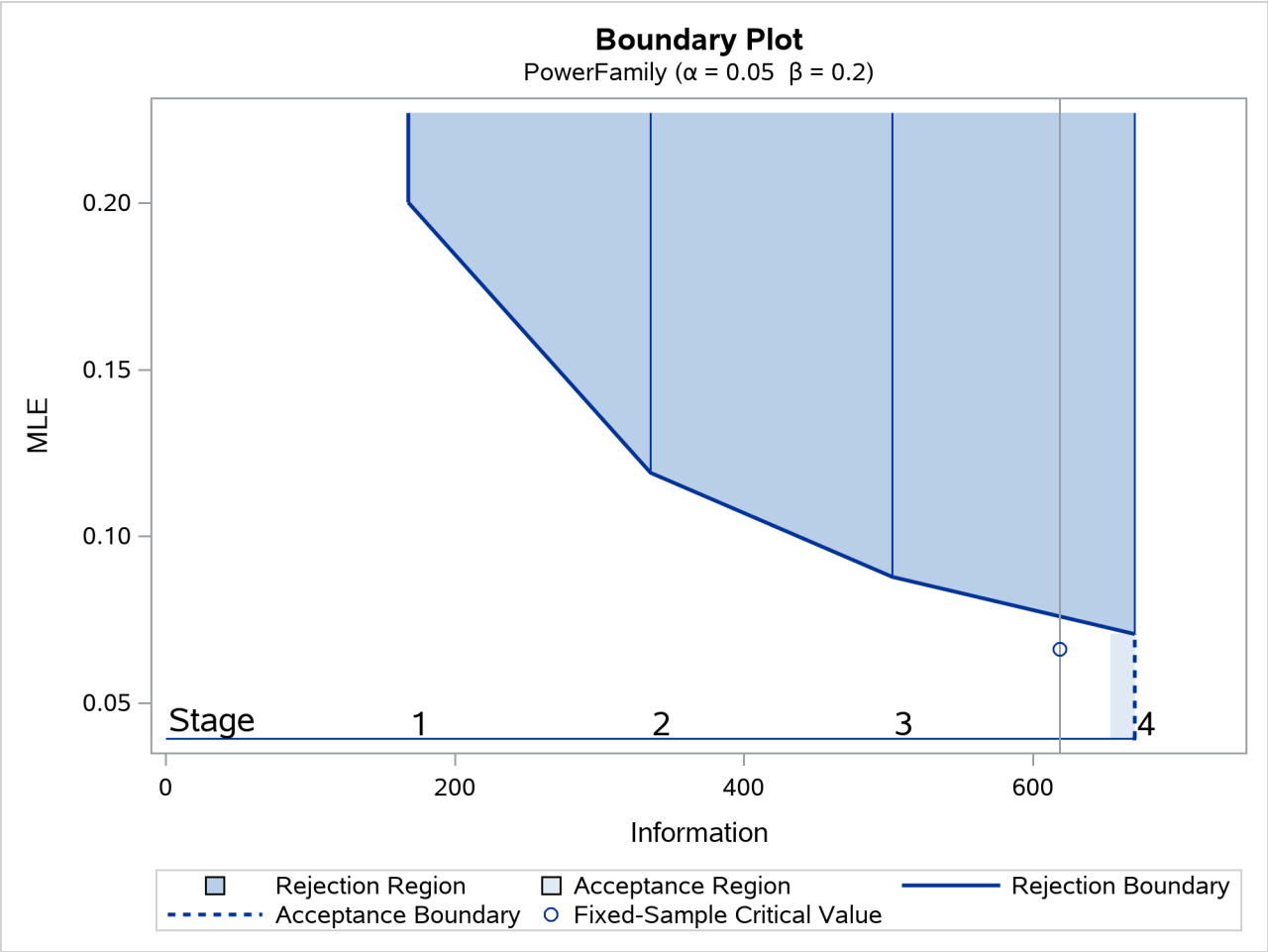
**Output 108.4.2** Boundary Information

**Boundary Information (MLE Scale)**
**Null Reference = 0**

| | Information Level | | | Alternative Reference | Boundary Values |
|---|---|---|---|---|---|
| _Stage_ | Proportion | Actual | N | Upper | Upper Alpha |
| 1 | 0.2500 | 167.5945 | 35.19485 | 0.10000 | 0.20018 |
| 2 | 0.5000 | 335.1891 | 70.38971 | 0.10000 | 0.11903 |
| 3 | 0.7500 | 502.7836 | 105.5846 | 0.10000 | 0.08782 |
| 4 | 1.0000 | 670.3782 | 140.7794 | 0.10000 | 0.07077 |

With ODS Graphics enabled, a detailed boundary plot with the rejection and acceptance regions is displayed, as shown in Output 108.4.3.

**Output 108.4.3** Boundary Plot




With the MODEL=ONESAMPLEFREQ option in the SAMPLESIZE statement, the "Sample Size Summary" table in Output 108.4.4 displays the parameters for the sample size computation.

**Output 108.4.4** Required Sample Size Summary

| Sample Size Summary | |
|---|---|
| **Test** | One-Sample Proportion |
| **Null Proportion** | 0.6 |
| **Proportion** | 0.7 |
| **Test Statistic** | Z for Proportion |
| **Reference Proportion** | Alt Ref |
| **Max Sample Size** | 140.7794 |
| **Expected Sample Size (Null Ref)** | 138.828 |
| **Expected Sample Size (Alt Ref)** | 101.9333 |

The "Sample Sizes" table in Output 108.4.5 displays the required sample sizes for the group sequential clinical trial.

**Output 108.4.5** Required Sample Sizes

| Sample Sizes (N) One-Sample Z Test for Proportion | | | | |
|---|---|---|---|---|
| | Fractional N | | Ceiling N | |
| _Stage_ | N | Information | N | Information |
| 1 | 35.19 | 167.6 | 36 | 171.4 |
| 2 | 70.39 | 335.2 | 71 | 338.1 |
| 3 | 105.58 | 502.8 | 106 | 504.8 |
| 4 | 140.78 | 670.4 | 141 | 671.4 |

When you specify CEILADJDESIGN=INCLUDE in the SAMPLESIZE statement, the "Ceiling-Adjusted Design Boundary Information" table in Output 108.4.6 displays the boundary information for the ceiling-adjusted design.

**Output 108.4.6** Ceiling-Adjusted Design Boundary Information

| Ceiling-Adjusted Design Boundary Information (MLE Scale) Null Reference = 0 | | | | | |
|---|---|---|---|---|---|
| | | | | Alternative | Boundary Values |
| | Information Level | | | Reference | Upper |
| _Stage_ | Proportion | Actual | N | Upper | Alpha |
| 1 | 0.2553 | 171.4286 | 36 | 0.10000 | 0.19696 |
| 2 | 0.5035 | 338.0952 | 71 | 0.10000 | 0.11835 |
| 3 | 0.7518 | 504.7619 | 106 | 0.10000 | 0.08763 |
| 4 | 1.0000 | 671.4286 | 141 | 0.10000 | 0.07075 |

Thus, 36 customers are needed at stage 1, and 35 new customers are needed at each of the remaining stages. Suppose that 36 customers are available at stage 1. Output 108.4.6 lists the 10 observations in the data set count_1.

**Output 108.4.7** Clinical Trial Data

**First 10 Obs in the Trial Data**

| Obs | Resp |
|---|---|
| **1** | 1 |
| **2** | 1 |
| **3** | 0 |
| **4** | 0 |
| **5** | 1 |
| **6** | 1 |
| **7** | 0 |
| **8** | 1 |
| **9** | 1 |
| **10** | 1 |

The Resp variable is an indicator variable with a value of 1 for a customer with a positive response and a value of 0 for a customer without a positive response.

The following statements use the MEANS procedure to compute the mean response at stage 1:

```
proc means data=Prop_1;
   var Resp;
   ods output Summary=Data_Prop1;
run;
```

The following statements create and display (in Output 108.4.8) the data set for the centered mean positive response, $\hat{p} - p_0$:

```
data Data_Prop1;
   set Data_Prop1;
   _Scale_='MLE';
   _Stage_= 1;
   NObs= Resp_N;
   PDiff= Resp_Mean - 0.6;
   keep _Scale_ _Stage_ NObs PDiff;
run;
proc print data=Data_Prop1;
   title 'Statistics Computed at Stage 1';
run;
```

**Output 108.4.8** Statistics Computed at Stage 1

**Statistics Computed at Stage 1**

| Obs | _Scale_ | _Stage_ | NObs | PDiff |
|---|---|---|---|---|
| 1 | MLE | 1 | 36 | -0.016667 |

The following statements invoke the SEQTEST procedure to test for early stopping at stage 1:

```
ods graphics on;
proc seqtest Boundary=Bnd_Prop
             Data(Testvar=PDiff Infovar=NObs)=Data_Prop1
             infoadj=prop
             boundarykey=both
             boundaryscale=mle
             ;
   ods output Test=Test_Prop1;
run;
```

The BOUNDARY= option specifies the input data set that provides the boundary information for the trial at stage 1, which was generated in the SEQDESIGN procedure. The DATA=DATA_PROP1 option specifies the input data set DATA_PROP1, which contains the test statistic and its associated sample size at stage 1. The TESTVAR=PDIFF option identifies the test variable PDIFF, and the INFOVAR=NOBS option uses the variable NOBS for the number of observations to derive the information level.

If the computed information level for stage 1 is not the same as the value provided in the BOUNDARY= data set, the INFOADJ=PROP option (which is the default) proportionally adjusts the information levels at future interim stages from the levels provided in the BOUNDARY= data set. The BOUNDARYKEY=BOTH option maintains both the $\alpha$ and $\beta$ levels. The BOUNDARYSCALE=MLE option displays the output boundaries in terms of the MLE scale.

The ODS OUTPUT statement with the TEST=TEST_PROP1 option creates an output data set named TEST_PROP1 which contains the updated boundary information for the test at stage 1. The data set also provides the boundary information that is needed for the group sequential test at the next stage.

The "Design Information" table in Output 108.4.9 displays design specifications. With the specified BOUNDARYKEY=BOTH option, the information levels and boundary values at future stages are modified to maintain both the $\alpha$ and $\beta$ levels.

**Output 108.4.9** Design Information

**The SEQTEST Procedure**

| Design Information | |
|---|---|
| **BOUNDARY Data Set** | WORK.BND_PROP |
| **Data Set** | WORK.DATA_PROP1 |
| **Statistic Distribution** | Normal |
| **Boundary Scale** | MLE |
| **Alternative Hypothesis** | Upper |
| **Early Stop** | Reject Null |
| **Number of Stages** | 4 |
| **Alpha** | 0.05 |
| **Beta** | 0.19951 |
| **Power** | 0.80049 |
| **Max Information (Percent of Fixed Sample)** | 108.4461 |
| **Max Information** | 671.428589 |
| **Null Ref ASN (Percent of Fixed Sample)** | 106.9406 |
| **Alt Ref ASN (Percent of Fixed Sample)** | 78.42929 |

The "Test Information" table in Output 108.4.10 displays the boundary values for the test statistic with the specified MLE scale.

**Output 108.4.10** Sequential Tests

**Test Information (MLE Scale)**
**Null Reference = 0**

| | Information Level | | | Alternative Reference | Boundary Values Upper | | Test PDiff | |
|---|---|---|---|---|---|---|---|---|
| _Stage_ | Proportion | Actual | N | Upper | Alpha | Estimate | Action |
| 1 | 0.2553 | 171.4286 | 36 | 0.10000 | 0.19696 | -0.01667 | Continue |
| 2 | 0.5035 | 338.0952 | 71 | 0.10000 | 0.11835 | . | |
| 3 | 0.7518 | 504.7619 | 106 | 0.10000 | 0.08763 | . | |
| 4 | 1.0000 | 671.4286 | 141 | 0.10000 | 0.07075 | . | |

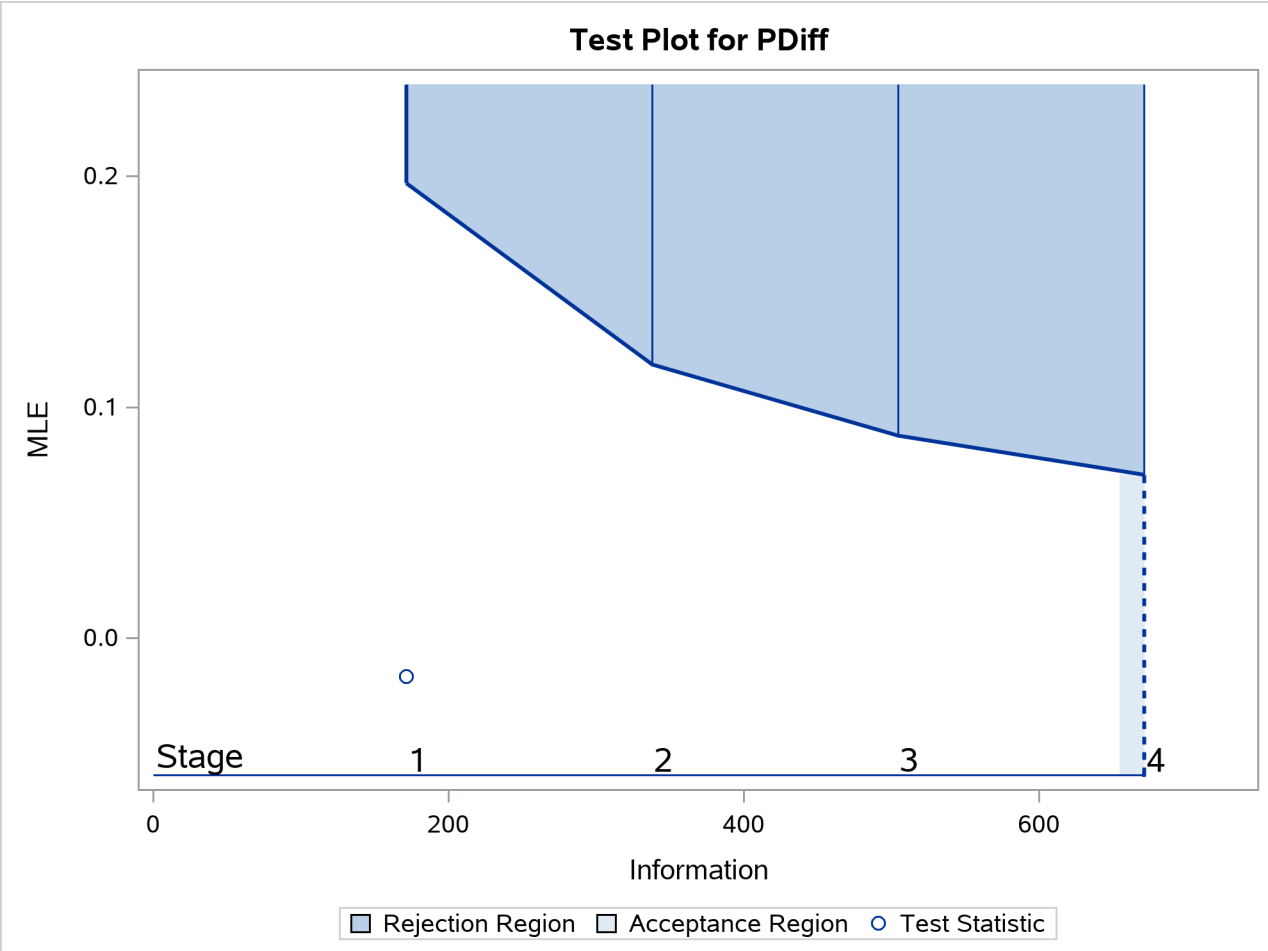
When you specify INFOVAR=NOBS in the DATA= option in the PROC SEQTEST statement, the information level at stage 1 is computed as $I_1^* = I_1 \times (n_1^*/n_1)$, where $I_1$ and $n_1$ are the information level and sample size, respectively, at stage 1 in the BOUNDARY= data set, and where $n_1^* = 36$ is the available sample size at stage 1. Because $n_1^* = n_1$, the information level at stage 1 is not changed.

With INFOADJ=PROP (which is the default) in the PROC SEQTEST statement, the information levels at interim stages 2 and 3 are derived proportionally from the information levels in the BOUNDARY= data set.

At stage 1, the statistic $\hat{\theta} = \hat{p} - p_0 = 0.58333 - 0.6 = -0.01667$ is less than the upper $\alpha$ boundary value 0.19696, so the trial continues to the next stage.

When ODS Graphics is enabled, a boundary plot with the rejection and acceptance regions is displayed, as shown in Output 108.4.11. As expected, the test statistic is in the continuation region.

**Output 108.4.11** Sequential Test Plot




The following statements use the MEANS procedure to compute the mean response at stage 2:

```
proc means data=Prop_2;
   var Resp;
   ods output Summary=Data_Prop2;
run;
```

The following statements create and display (in Output 108.4.12) the data set for the centered mean positive response ($\hat{p} - p_0$) at stage 2:

```
data Data_Prop2;
   set Data_Prop2;
   _Scale_='MLE';
   _Stage_= 2;
   NObs= Resp_N;
```

```
   PDiff= Resp_Mean - 0.6;
   keep _Scale_ _Stage_ NObs PDiff;
run;

proc print data=Data_Prop2;
   title 'Statistics Computed at Stage 2';
run;
```

**Output 108.4.12** Statistics Computed at Stage 2

**Statistics Computed at Stage 2**

| Obs | _Scale_ | _Stage_ | NObs | PDiff |
|---|---|---|---|---|
| 1 | MLE | 2 | 71 | -0.064789 |

The following statements invoke the SEQTEST procedure to test for early stopping at stage 2:

```
ods graphics on;
proc seqtest Boundary=Test_Prop1
             Data(Testvar=PDiff Infovar=NObs)=Data_Prop2
             infoadj=prop
             boundarykey=both
             boundaryscale=mle
             condpower(cref=1)
             predpower
             plots=condpower
             ;
   ods output test=Test_Prop2;
run;
```

The BOUNDARY= option specifies the input data set that provides the boundary information for the trial at stage 2, which was generated by the SEQTEST procedure at the previous stage. The DATA= option specifies the input data set that contains the test statistic and its associated sample size at stage 2, and the TESTVAR= option identifies the test variable in the data set.

The ODS OUTPUT statement with the TEST=TEST_PROP2 option creates an output data set named TEST_PROP2 which contains the updated boundary information for the test at stage 2. The data set also provides the boundary information that is needed for the group sequential test at the next stage.

The CONDPOWER(CREF=1) option requests the conditional power with the observed statistic under the alternative hypothesis, in addition to the conditional power under the hypothetical reference $\theta = \hat{\theta}$, the MLE estimate. The PREDPOWER option requests the noninformative predictive power with the observed statistic.

The "Test Information" table in Output 108.4.13 displays the boundary values for the test statistic with the specified MLE scale. The test statistic $\hat{\theta} = -0.06479$ is less than the corresponding upper $\alpha$ boundary 0.11835, so the sequential test does not stop at stage 2 to reject the null hypothesis.

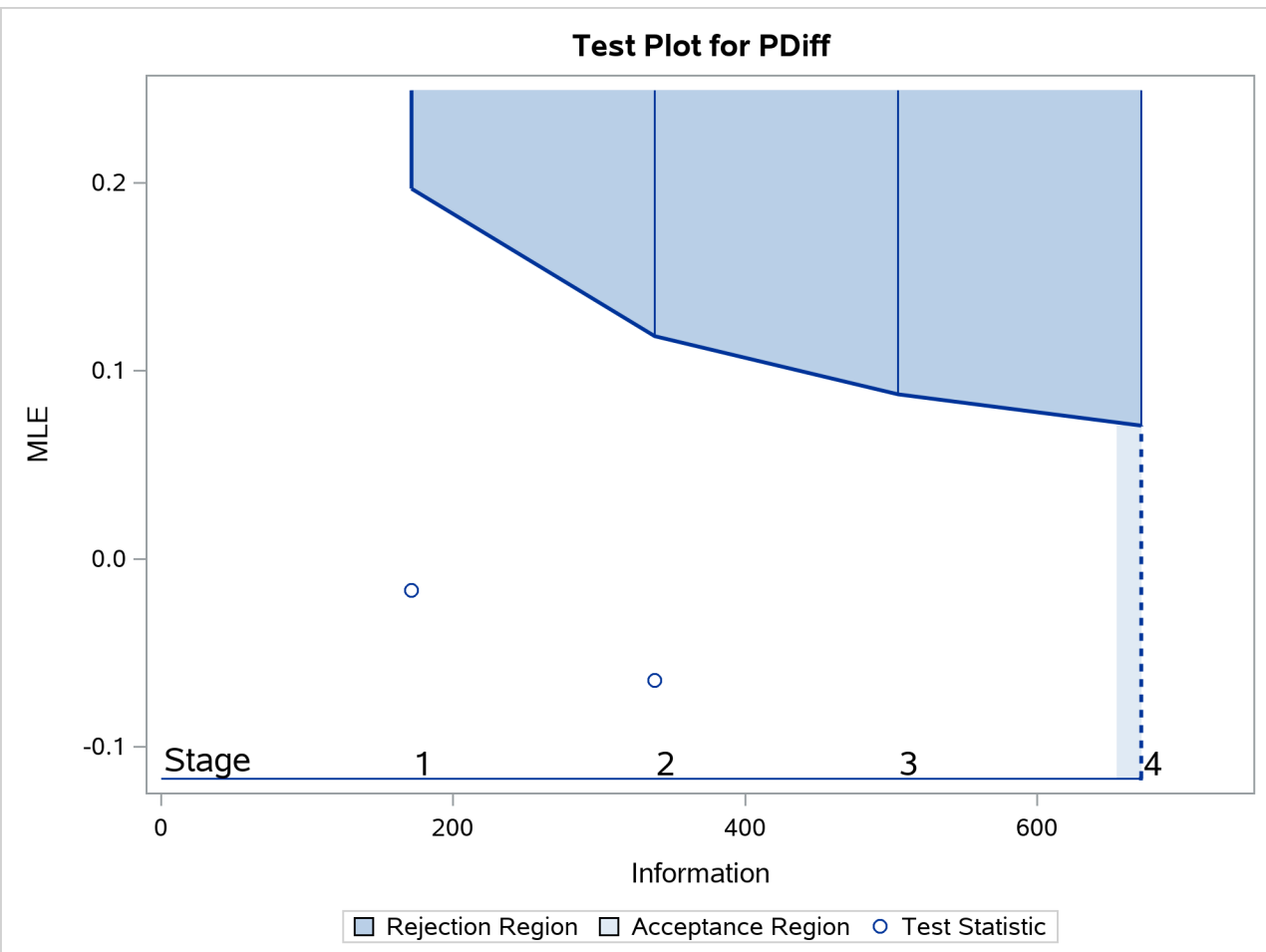
**Output 108.4.13** Sequential Tests

**The SEQTEST Procedure**

| Test Information (MLE Scale) Null Reference = 0 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Information Level | | | Alternative Reference | Boundary Values Upper | Test PDiff | |
| _Stage_ | Proportion | Actual | N | Upper | Alpha | Estimate | Action |
| 1 | 0.2553 | 171.4286 | 36 | 0.10000 | 0.19696 | -0.01667 | Continue |
| 2 | 0.5035 | 338.0952 | 71 | 0.10000 | 0.11835 | -0.06479 | Continue |
| 3 | 0.7518 | 504.7619 | 106 | 0.10000 | 0.08763 | . | |
| 4 | 1.0000 | 671.4285 | 141 | 0.10000 | 0.07075 | . | |

With ODS Graphics enabled, the "Test Plot" displays boundary values of the design and the test statistic, as shown in Output 108.4.14. It also shows that the test statistic is in the "Continuation Region" below the upper $\alpha$ boundary value at stage 2.

**Output 108.4.14** Sequential Test Plot



The "Conditional Power Information" table in Output 108.4.15 displays conditional powers given the observed statistic under hypothetical references $\theta = \hat{\theta}$, the maximum likelihood estimate, and $\theta = \theta_1$. The constant $c$ under CRef for the MLE is derived from $\hat{\theta} = c\theta_1$; that is, $c = \hat{\theta}/\theta_1 = -0.06479/0.1 = -0.6479$.

**Output 108.4.15** Conditional Power

**Conditional Power Information**
**Reference = CRef * (Alt Reference)**

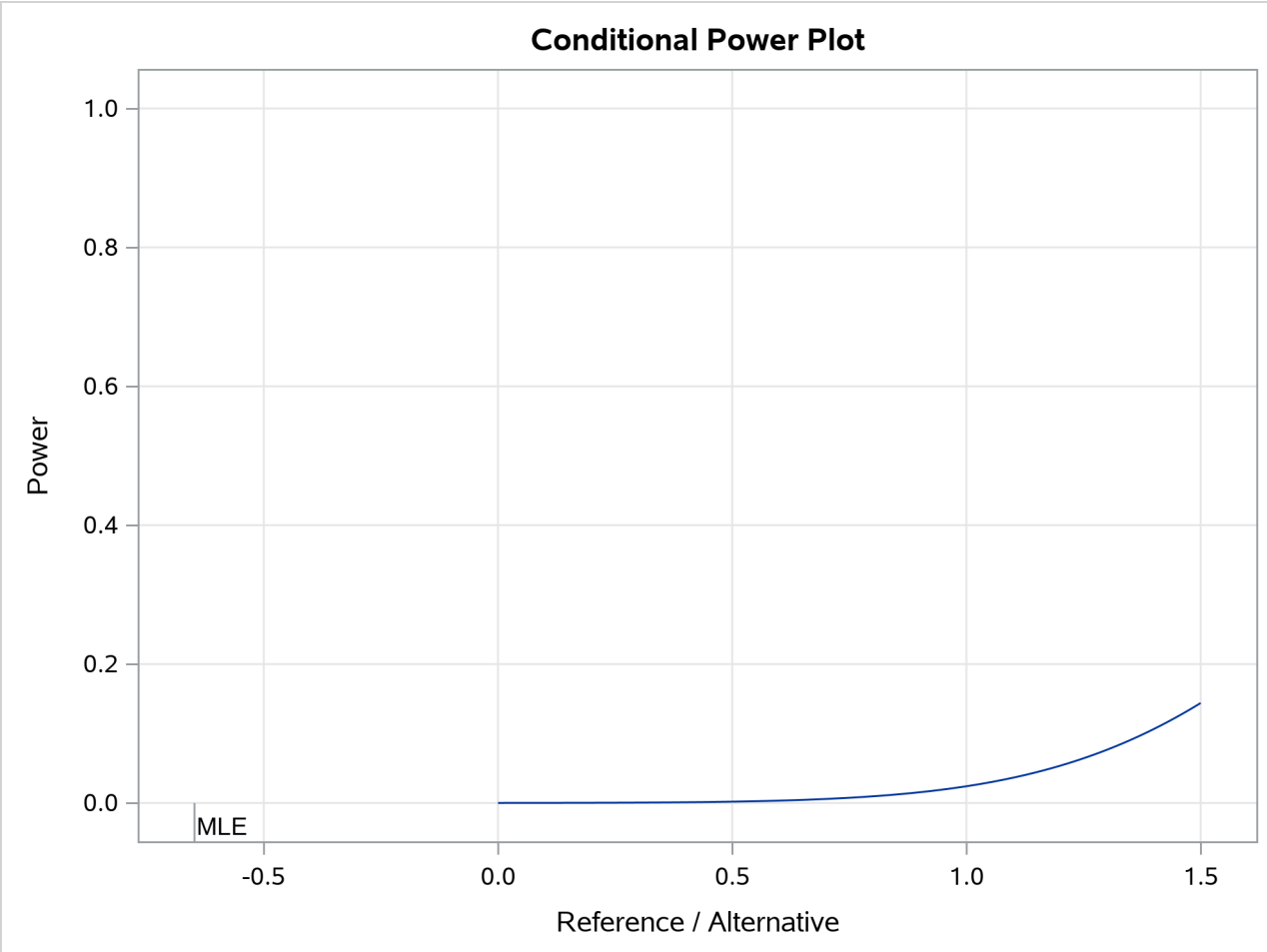
| Stopping Stage | Reference MLE | Reference Ref | Reference CRef | Conditional Power |
|---|---|---|---|---|
| 2 | -0.06479 | MLE | -0.6479 | 0.00000 |
| 2 | -0.06479 | Alternative | 1.0000 | 0.02410 |

The conditional power is the probability of rejecting the null hypothesis under these hypothetical references given the observed statistic $\hat{\theta} = -0.06479$. The table in Output 108.4.14 shows a weak conditional power of 0.0241 under the alternative hypothesis.

With the default TYPE=ALLSTAGES suboption in the CONDPOWER option, the conditional power at the interim stage 2 is the probability that the test statistic would exceed the rejection critical value at all future stages given the observed statistic $\hat{\theta} = -0.06479$.

The "Conditional Power Plot" displays conditional powers given the observed statistic under various hypothetical references, as shown in Output 108.4.16. These references include $\theta = \hat{\theta}$, the maximum likelihood estimate, and $\theta = c_i\theta_1$, where $\theta_1$ is the alternative reference and $c_i = 0, 0.01, \ldots, 1.50$ are constants that are specified in the CREF= option. Output 108.4.16 shows that the conditional power increases as $c_i$ increases.

**Output 108.4.16** Conditional Power Plot




The predictive power is the probability to reject the null hypothesis under the posterior distribution with a noninformative prior given the observed statistic $\hat{\theta} = -0.06479$. The "Predictive Power Information" table in Output 108.4.17 indicates that the predictive power at $\hat{\theta} = -0.06479$ is 0.0002.

**Output 108.4.17** Predictive Power

| Predictive Power Information | | |
|---|---|---|
| Stopping Stage | MLE | Predictive Power |
| 2 | -0.06479 | 0.00020 |

With a predictive power 0.0002 and a conditional power of 0.0241 under $H_1$, the supermarket decides to stop the trial and accept the null hypothesis. That is, the positive response for the new store-brand coffee is not better than that for the current store-brand coffee.

The following statements invoke the SEQTEST procedure to test for early stopping at stage 2. The NSTAGES=3 option sets the next stage as the final stage (stage 3), and the BOUNDARYKEY=BOTH option derives the information level at stage 3 that maintain both Type I and Type II error probability levels. The CONDPOWER(CREF=1) option requests the conditional power with the observed statistic under the

alternative hypothesis, in addition to the conditional power under the hypothetical reference $\theta = \hat{\theta}$, the MLE estimate.

```
proc seqtest Boundary=Test_Prop1
             Data(Testvar=PDiff Infovar=NObs)=Data_Prop2
             nstages=3
             boundarykey=both
             boundaryscale=mle
             condpower(cref=1)
             ;
run;
```

The "Test Information" table in Output 108.4.18 displays the boundary values for the test statistic with the specified MLE scale, assuming that the next stage is the final stage.

**Output 108.4.18** Sequential Tests

**The SEQTEST Procedure**

**Test Information (MLE Scale)**
**Null Reference = 0**

| | Information Level | | | Alternative Reference | Boundary Values Upper | | Test PDiff | |
|---|---|---|---|---|---|---|---|---|
| _Stage_ | Proportion | Actual | N | Upper | Alpha | Estimate | Action |
| 1 | 0.2642 | 171.4286 | 36 | 0.10000 | 0.19696 | -0.01667 | Continue |
| 2 | 0.5211 | 338.0952 | 71 | 0.10000 | 0.11835 | -0.06479 | Continue |
| 3 | 1.0000 | 648.8122 | 136.2506 | 0.10000 | 0.06825 | . | |

The "Conditional Power Information" table in Output 108.4.19 displays conditional powers given the observed statistic, assuming that the next stage is the final stage.

**Output 108.4.19** Conditional Power

**Conditional Power Information**
**Reference = CRef * (Alt Reference)**

| Stopping Stage | Reference MLE | Ref | CRef | Conditional Power |
|---|---|---|---|---|
| 2 | -0.06479 | MLE | -0.6479 | 0.00000 |
| 2 | -0.06479 | Alternative | 1.0000 | 0.02318 |

The conditional power is the probability of rejecting the null hypothesis under these hypothetical references given the observed statistic $\hat{\theta} = -0.06479$. The table in Output 108.4.19 also shows a weak conditional power of 0.02318 under the alternative hypothesis.

## Example 108.5: Comparing Two Proportions with a Log Odds Ratio Test

This example compares two binomial proportions by using a log odds ratio statistic in a five-stage group sequential test. A clinic is studying the effect of vitamin C supplements in treating flu symptoms. The study consists of patients in the clinic who exhibit the first sign of flu symptoms within the last 24 hours. These

patients are randomly assigned to either the control group (which receives placebo pills) or the treatment group (which receives large doses of vitamin C supplements). At the end of a five-day period, the flu symptoms of each patient are recorded.

Suppose that you know from past experience that flu symptoms disappear in five days for 60% of patients who experience flu symptoms. The clinic would like to detect a 70% symptom disappearance with a high probability. A test that compares the proportions directly specifies the null hypothesis $H_0 : \theta = p_t - p_c = 0$ with a one-sided alternative $H_1 : \theta > 0$ and a power of 0.90 at $H_1 : \theta = 0.10$, where $p_t$ and $p_c$ are the proportions of symptom disappearance in the treatment group and control group, respectively. An alternative trial tests an equivalent hypothesis by using the log odds ratio statistics:

$$\theta = \log\left(\frac{(\frac{p_t}{1-p_t})}{(\frac{p_c}{1-p_c})}\right)$$

Then the null hypothesis is $H_0 : \theta = \theta_0 = 0$ and the alternative hypothesis is

$$H_1 : \theta = \theta_1 = \log\left(\frac{(\frac{0.70}{0.30})}{(\frac{0.6}{0.4})}\right) = 0.441833$$

The following statements invoke the SEQDESIGN procedure and request a five-stage group sequential design by using an error spending function method for normally distributed statistics. The design uses a two-sided alternative hypothesis with early stopping to reject the null hypothesis $H_0$.

```
ods graphics on;
proc seqdesign altref=0.441833
               boundaryscale=mle
               ;
   OneSidedErrorSpending: design method=errfuncpow
                                 nstages=5
                                 alt=upper
                                 stop=accept
                                 alpha=0.025;
   samplesize model=twosamplefreq( nullprop=0.6 test=logor);
   ods output Boundary=Bnd_CSup;
run;
```

The ODS OUTPUT statement with the BOUNDARY=BND_CSUP option creates an output data set named BND_CSUP which contains the resulting boundary information for the subsequent sequential tests.

The “Design Information” table in Output 108.5.1 displays design specifications and derived statistics. With the specified alternative reference, the maximum information 56.30934 is derived.

**Output 108.5.1** Design Information

**The SEQDESIGN Procedure**
**Design: OneSidedErrorSpending**

| Design Information | |
|---|---|
| **Statistic Distribution** | Normal |
| **Boundary Scale** | MLE |
| **Alternative Hypothesis** | Upper |
| **Early Stop** | Accept Null |
| **Method** | Error Spending |
| **Boundary Key** | Both |
| **Alternative Reference** | 0.441833 |
| **Number of Stages** | 5 |
| **Alpha** | 0.025 |
| **Beta** | 0.1 |
| **Power** | 0.9 |
| **Max Information (Percent of Fixed Sample)** | 104.6166 |
| **Max Information** | 56.30934 |
| **Null Ref ASN (Percent of Fixed Sample)** | 57.21399 |
| **Alt Ref ASN (Percent of Fixed Sample)** | 102.1058 |

The "Boundary Information" table in Output 108.5.2 displays information level, alternative reference, and boundary values at each stage. With the specified BOUNDARYSCALE=MLE option, the procedure displays the output boundaries in terms of the MLE scale.

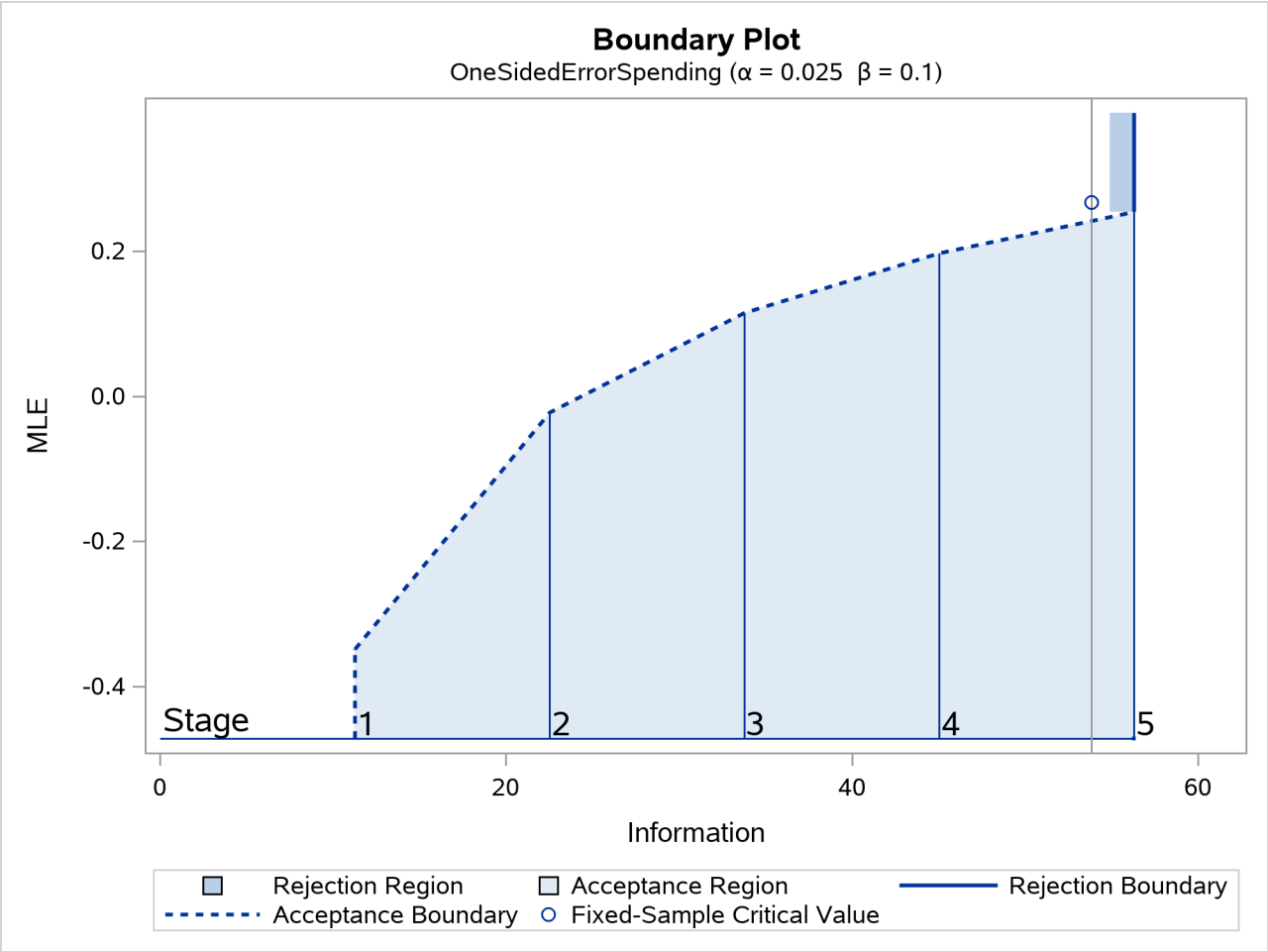
**Output 108.5.2** Boundary Information

**Boundary Information (MLE Scale)**
**Null Reference = 0**

| | Information Level | | | Alternative Reference | Boundary Values |
|---|---|---|---|---|---|
| _Stage_ | Proportion | Actual | N | Upper | Upper Beta |
| 1 | 0.2000 | 11.26187 | 201.1048 | 0.44183 | -0.34844 |
| 2 | 0.4000 | 22.52374 | 402.2096 | 0.44183 | -0.02262 |
| 3 | 0.6000 | 33.7856 | 603.3144 | 0.44183 | 0.11527 |
| 4 | 0.8000 | 45.04747 | 804.4192 | 0.44183 | 0.19708 |
| 5 | 1.0000 | 56.30934 | 1005.524 | 0.44183 | 0.25345 |

With ODS Graphics enabled, a detailed boundary plot with the rejection and acceptance regions is displayed, as shown in Output 108.5.3.

**Output 108.5.3** Boundary Plot




With the SAMPLESIZE statement, the "Sample Size Summary" table in Output 108.5.4 displays the parameters for the sample size computation.

**Output 108.5.4** Sample Size Summary

| Sample Size Summary | |
|---|---|
| **Test** | Two-Sample Proportions |
| **Null Proportion** | 0.6 |
| **Proportion (Group A)** | 0.7 |
| **Test Statistic** | Log Odds Ratio |
| **Reference Proportions** | Alt Ref |
| **Max Sample Size** | 1005.524 |
| **Expected Sample Size (Null Ref)** | 549.9132 |
| **Expected Sample Size (Alt Ref)** | 981.3914 |

The "Sample Sizes" table in Output 108.5.5 displays the required sample sizes for the group sequential clinical trial.

**Output 108.5.5** Required Sample Sizes

| Sample Sizes (N) Two-Sample Log Odds Ratio Test for Proportion Difference | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Fractional N | | | | Ceiling N | | | |
| _Stage_ | N | N(Grp 1) | N(Grp 2) | Information | N | N(Grp 1) | N(Grp 2) | Information |
| 1 | 201.10 | 100.55 | 100.55 | 11.2619 | 202 | 101 | 101 | 11.3120 |
| 2 | 402.21 | 201.10 | 201.10 | 22.5237 | 404 | 202 | 202 | 22.6240 |
| 3 | 603.31 | 301.66 | 301.66 | 33.7856 | 604 | 302 | 302 | 33.8240 |
| 4 | 804.42 | 402.21 | 402.21 | 45.0475 | 806 | 403 | 403 | 45.1360 |
| 5 | 1005.52 | 502.76 | 502.76 | 56.3093 | 1006 | 503 | 503 | 56.3360 |

Thus, 101 new patients are needed in each group at stages 1, 2, and 4, and 100 new patients are needed in each group at stages 3 and 5. Suppose that 101 patients are available in each group at stage 1. Output 108.5.6 lists the 10 observations in the data set count_1.

**Output 108.5.6** Clinical Trial Data

**First 10 Obs in the Trial Data**

| Obs | TrtGrp | Resp |
|---|---|---|
| 1 | Control | 1 |
| 2 | C_Sup | 0 |
| 3 | Control | 0 |
| 4 | C_Sup | 1 |
| 5 | Control | 1 |
| 6 | C_Sup | 1 |
| 7 | Control | 1 |
| 8 | C_Sup | 0 |
| 9 | Control | 0 |
| 10 | C_Sup | 1 |

The TrtGrp variable is a grouping variable with the value Control for a patient in the placebo control group and the value C_Sup for a patient in the treatment group who receives vitamin C supplements. The Resp variable is an indicator variable with the value 1 for a patient without flu symptoms after five days and the value 0 for a patient with flu symptoms after five days.

The following statements use the LOGISTIC procedure to compute the log odds ratio statistic and its associated standard error at stage 1:

```
proc logistic data=CSup_1 descending;
   class TrtGrp / param=ref;
   model Resp= TrtGrp;
   ods output ParameterEstimates=Parms_CSup1;
run;
```

The DESCENDING option is used to reverse the order for the response levels, so the LOGISTIC procedure is modeling the probability that Resp = 1.

The following statements create and display (in Output 108.5.7) the data set for the log odds ratio statistic and its associated standard error:

```
data Parms_CSup1;
   set Parms_CSup1;
   if Variable='TrtGrp' and ClassVal0='C_Sup';
   _Scale_='MLE';
   _Stage_= 1;
   keep _Scale_ _Stage_ Variable Estimate StdErr;
run;

proc print data=Parms_CSup1;
   title 'Statistics Computed at Stage 1';
run;
```

**Output 108.5.7** Statistics Computed at Stage 1

**Statistics Computed at Stage 1**

| Obs | Variable | Estimate | StdErr | _Scale_ | _Stage_ |
|---|---|---|---|---|---|
| 1 | TrtGrp | 0.3247 | 0.2856 | MLE | 1 |

The following statements invoke the SEQTEST procedure to test for early stopping at stage 1:

```
ods graphics on;
proc seqtest Boundary=Bnd_CSup
             Parms(Testvar=TrtGrp)=Parms_CSup1
             infoadj=prop
             errspendadj=errfuncpow
             boundarykey=both
             boundaryscale=mle
             ;
   ods output test=Test_CSup1;
run;
```

The BOUNDARY= option specifies the input data set that provides the boundary information for the trial at stage 1, which was generated in the SEQDESIGN procedure. The PARMS=PARMS_CSUP1 option specifies the input data set PARMS_CSUP1 that contains the test statistic and its associated standard error at stage 1, and the TESTVAR=TRTGRP option identifies the test variable TRTGRP in the data set.

If the computed information level for stage 1 is not the same as the value provided in the BOUNDARY= data set, the INFOADJ=PROP option (which is the default) proportionally adjusts the information levels at future interim stages from the levels provided in the BOUNDARY= data set. The ERRSPENDADJ=ERRFUNCPOW option adjusts the boundaries with the updated error spending values generated from the power error spending function. The BOUNDARYKEY=BOTH option maintains both the $\alpha$ and $\beta$ levels. The BOUNDARYSCALE=MLE option displays the output boundaries in terms of the MLE scale.

The ODS OUTPUT statement with the TEST=TEST_CSUP1 option creates an output data set named TEST_CSUP1 which contains the updated boundary information for the test at stage 1. The data set also provides the boundary information that is needed for the group sequential test at the next stage.

The "Design Information" table in Output 108.5.8 displays design specifications. With the specified BOUNDARYKEY=BOTH option, the information levels and boundary values at future stages are modified to maintain both the $\alpha$ and $\beta$ levels.

**Output 108.5.8** Design Information

**The SEQTEST Procedure**

| Design Information | |
|---|---|
| **BOUNDARY Data Set** | WORK.BND_CSUP |
| **Data Set** | WORK.PARMS_CSUP1 |
| **Statistic Distribution** | Normal |
| **Boundary Scale** | MLE |
| **Alternative Hypothesis** | Upper |
| **Early Stop** | Accept Null |
| **Number of Stages** | 5 |
| **Alpha** | 0.025 |
| **Beta** | 0.1 |
| **Power** | 0.9 |
| **Max Information (Percent of Fixed Sample)** | 104.6673 |
| **Max Information** | 56.3361718 |
| **Null Ref ASN (Percent of Fixed Sample)** | 57.02894 |
| **Alt Ref ASN (Percent of Fixed Sample)** | 102.1369 |

The "Test Information" table in Output 108.5.9 displays the boundary values for the test statistic with the specified MLE scale. With the INFOADJ=PROP option (which is the default), the information levels at future interim stages are derived proportionally from the observed information at stage 1 and the information levels in the BOUNDARY= data set.

Since the information level at stage 1 is derived from the PARMS= data set and other information levels are not specified, equal increments are used at remaining stages. At stage 1, the MLE statistic 0.32474 is greater than the corresponding upper $\beta$ boundary value –0.29906, so the sequential test continues to the next stage.

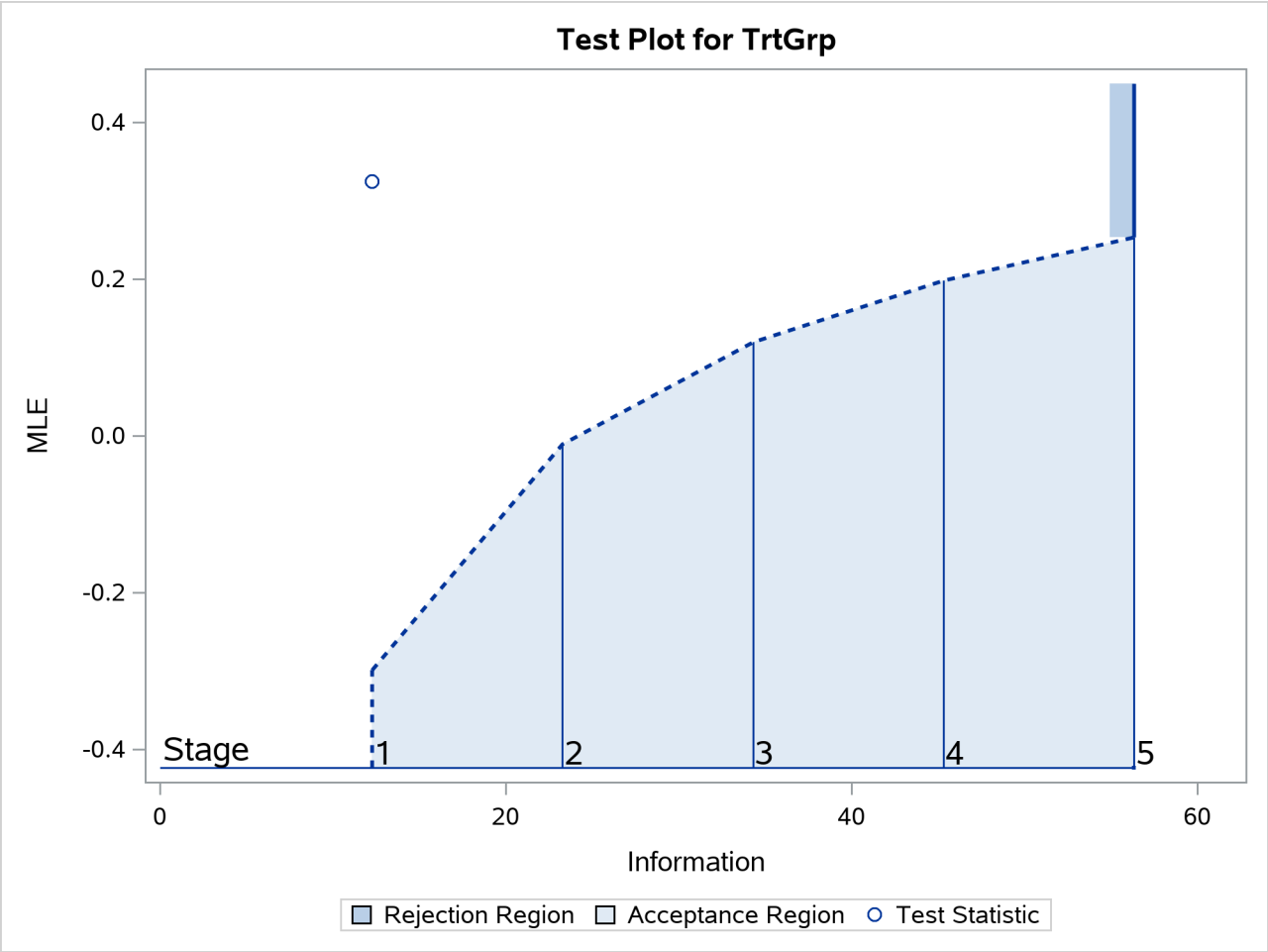
**Output 108.5.9** Sequential Tests

**Test Information (MLE Scale)**
**Null Reference = 0**

| | Information Level | | Alternative Reference | Boundary Values Upper | Test TrtGrp | |
|---|---|---|---|---|---|---|
| _Stage_ | Proportion | Actual | Upper | Beta | Estimate | Action |
| 1 | 0.2176 | 12.26014 | 0.44183 | -0.29906 | 0.32474 | Continue |
| 2 | 0.4132 | 23.27914 | 0.44183 | -0.01067 | . | |
| 3 | 0.6088 | 34.29815 | 0.44183 | 0.11942 | . | |
| 4 | 0.8044 | 45.31716 | 0.44183 | 0.19829 | . | |
| 5 | 1.0000 | 56.33617 | 0.44183 | 0.25325 | . | |

With ODS Graphics enabled, a boundary plot with the boundary values and test statistics is displayed, as shown in Output 108.5.10. As expected, the test statistic is in the continuation region.

**Output 108.5.10** Sequential Test Plot




The following statements use the LOGISTIC procedure to compute the log odds ratio statistic and its associated standard error at stage 2:

```
proc logistic data=CSup_2 descending;
   class TrtGrp / param=ref;
   model Resp= TrtGrp;
   ods output ParameterEstimates=Parms_CSup2;
run;
```

The following statements create and display (in Output 108.5.11) the data set for the mean positive response and its associated standard error at stage 2:

```
data Parms_CSup2;
   set Parms_CSup2;
   if Variable='TrtGrp' and ClassVal0='C_Sup';
   _Scale_='MLE';
   _Stage_= 2;
   keep _Scale_ _Stage_ Variable Estimate StdErr;
run;
proc print data=Parms_CSup2;
   title 'Statistics Computed at Stage 2';
run;
```

**Output 108.5.11** Statistics Computed at Stage 2

**Statistics Computed at Stage 2**

| Obs | Variable | Estimate | StdErr | _Scale_ | _Stage_ |
|---|---|---|---|---|---|
| 1 | TrtGrp | 0.2356 | 0.2073 | MLE | 2 |

The following statements invoke the SEQTEST procedure to test for early stopping at stage 2:

```
proc seqtest Boundary=Test_CSup1
             Parms( testvar=TrtGrp)=Parms_CSup2
             infoadj=prop
             errspendadj=errfuncpow
             boundarykey=both
             boundaryscale=mle
             ;
   ods output Test=Test_CSup2;
run;
```

The BOUNDARY= option specifies the input data set that provides the boundary information for the trial at stage 2, which was generated by the SEQTEST procedure at the previous stage. The PARMS= option specifies the input data set that contains the test statistic and its associated standard error at stage 2, and the TESTVAR= option identifies the test variable in the data set.

The ODS OUTPUT statement with the TEST=CSUP_LDL2 option creates an output data set named CSUP_LDL2 which contains the updated boundary information for the test at stage 2. The data set also provides the boundary information that is needed for the group sequential test at the next stage.

The "Test Information" table in Output 108.5.12 displays the boundary values for the test statistic with the specified MLE scale. The test statistic 0.2356 is greater than the corresponding upper $\beta$ boundary value –0.01068, so the sequential test continues to the next stage.

**Output 108.5.12** Sequential Tests

**The SEQTEST Procedure**

| Test Information (MLE Scale) Null Reference = 0 | | | | | | |
|---|---|---|---|---|---|---|
| | Information Level | | Alternative Reference | Boundary Values Upper | Test TrtGrp | |
| _Stage_ | Proportion | Actual | Upper | Beta | Estimate | Action |
| 1 | 0.2176 | 12.26014 | 0.44183 | -0.29906 | 0.32474 | Continue |
| 2 | 0.4132 | 23.27916 | 0.44183 | -0.01068 | 0.23560 | Continue |
| 3 | 0.6088 | 34.29799 | 0.44183 | 0.11942 | . | |
| 4 | 0.8044 | 45.31681 | 0.44183 | 0.19829 | . | |
| 5 | 1.0000 | 56.33563 | 0.44183 | 0.25325 | . | |

Similar results are found at stages 3 and stage 4, so the trial continues to the final stage. The following statements use the LOGISTIC procedure to compute the log odds ratio statistic and its associated standard error at stage 5:

```
proc logistic data=CSup_5 descending;
   class TrtGrp / param=ref;
   model Resp= TrtGrp;
   ods output ParameterEstimates=Parms_CSup5;
run;
```

The following statements create and display (in Output 108.5.13) the data set for the log odds ratio statistic and its associated standard error at stage 5:

```
data Parms_CSup5;
   set Parms_CSup5;
   if Variable='TrtGrp' and ClassVal0='C_Sup';
   _Scale_='MLE';
   _Stage_= 5;
   keep _Scale_ _Stage_ Variable Estimate StdErr;
run;

proc print data=Parms_CSup5;
   title 'Statistics Computed at Stage 5';
run;
```

**Output 108.5.13** Statistics Computed at Stage 5

**Statistics Computed at Stage 5**

| Obs | Variable | Estimate | StdErr | _Scale_ | _Stage_ |
|---|---|---|---|---|---|
| 1 | TrtGrp | 0.2043 | 0.1334 | MLE | 5 |

The following statements invoke the SEQTEST procedure to test for the hypothesis at stage 5:

```
ods graphics on;
proc seqtest Boundary=Test_CSup4
             Parms( testvar=TrtGrp)=Parms_CSup5
             errspendadj=errfuncpow
             boundaryscale=mle
             cialpha=.025
             rci
             plots=rci
             ;
run;
```

The BOUNDARY= option specifies the input data set that provides the boundary information for the trial at stage 5, which was generated by the SEQTEST procedure at the previous stage. The PARMS= option specifies the input data set that contains the test statistic and its associated standard error at stage 5, and the TESTVAR= option identifies the test variable in the data set. By default (or equivalently if you specify BOUNDARYKEY=ALPHA), the boundary value at stage 5 is derived to maintain the $\alpha$ level.

The "Test Information" table in Output 108.5.14 displays the boundary values for the test statistic with the specified MLE scale. The test statistic 0.2043 is less than the corresponding upper $\beta$ boundary 0.25375, so the sequential test stops to accept the null hypothesis. That is, there is no reduction in duration of symptoms for the group receiving vitamin C supplements.

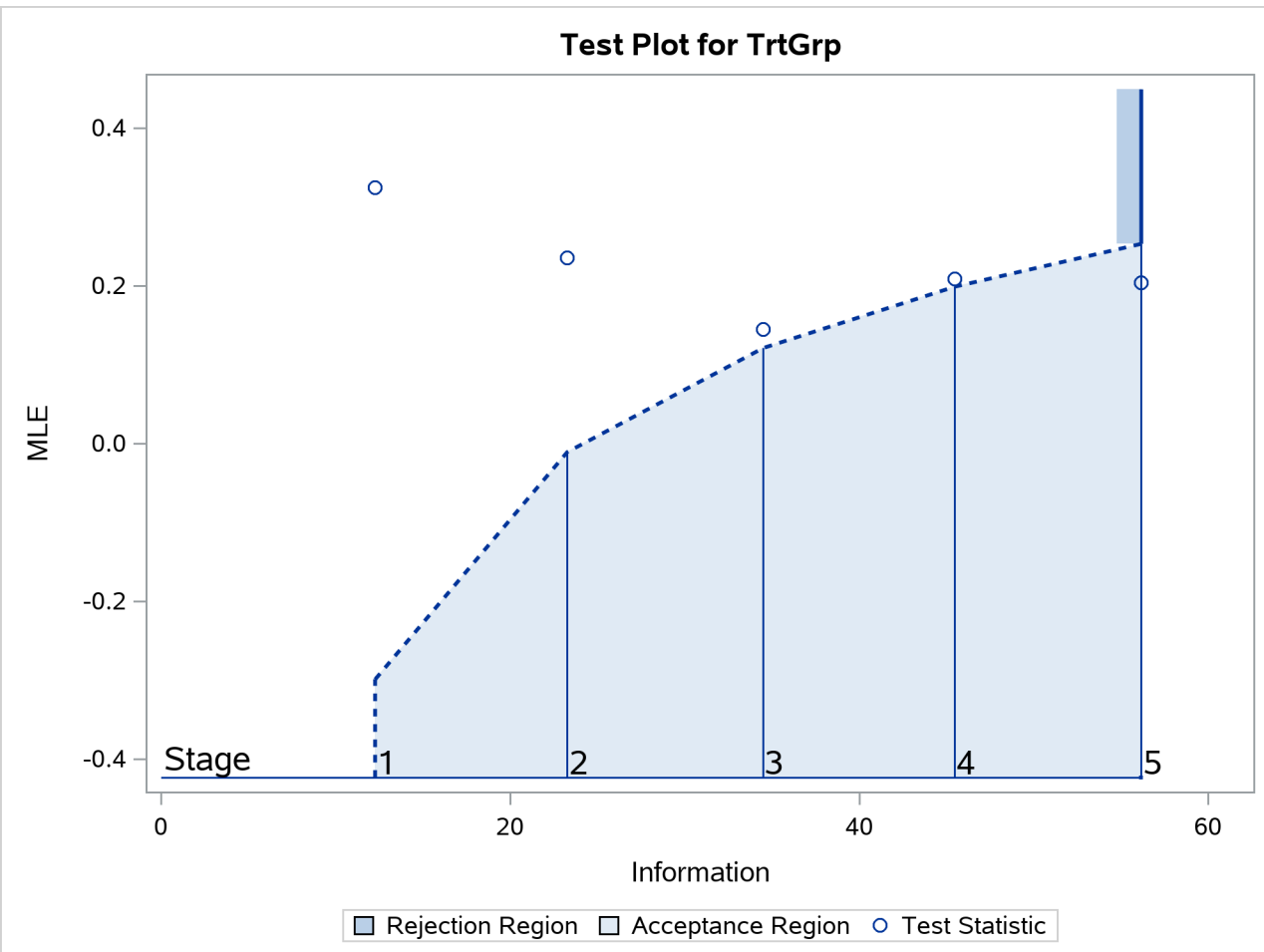
**Output 108.5.14** Sequential Tests

**The SEQTEST Procedure**

| | Test Information (MLE Scale) Null Reference = 0 | | | | | |
|---|---|---|---|---|---|---|
| | Information Level | | Alternative Reference | Boundary Values Upper | Test TrtGrp | |
| _Stage_ | Proportion | Actual | Upper | Beta | Estimate | Action |
| 1 | 0.2183 | 12.26014 | 0.44183 | -0.29906 | 0.32474 | Continue |
| 2 | 0.4145 | 23.27916 | 0.44183 | -0.01068 | 0.23560 | Continue |
| 3 | 0.6141 | 34.48793 | 0.44183 | 0.12134 | 0.14482 | Continue |
| 4 | 0.8092 | 45.44685 | 0.44183 | 0.19899 | 0.20855 | Continue |
| 5 | 1.0000 | 56.16068 | 0.44183 | 0.25375 | 0.20430 | Accept Null |

The "Test Plot" displays boundary values of the design and the test statistics, as shown in Output 108.5.15. It also shows that the test statistic is in the "Acceptance Region" at the final stage.

**Output 108.5.15** Sequential Test Plot



After a trial is stopped, the "Parameter Estimates" table in Output 108.5.16 displays the stopping stage, parameter estimate, unbiased median estimate, confidence limits, and the $p$-value under the null hypothesis $H_0 : \theta = 0$. As expected, the $p$-value 0.0456 is not significant at $\alpha = 0.025$ level and the lower 97.5% confidence limit is less than the value $\theta_0 = 0$. The $p$-value, unbiased median estimate, and confidence limits depend on the ordering of the sample space $(k, z)$, where $k$ is the stage number and $z$ is the standardized $Z$ statistic.

**Output 108.5.16** Parameter Estimates

| Parameter Estimates Stagewise Ordering | | | | | |
|---|---|---|---|---|---|
| Parameter | Stopping Stage | MLE | p-Value for H0:Parm=0 | Median Estimate | Lower 97.5% CL |
| TrtGrp | 5 | 0.204303 | 0.0456 | 0.234494 | -0.03712 |

Since the test is accepted at stage 5, the $p$-value computed by using the default stagewise ordering can be expressed as

$$\alpha_u = P_{\theta=0}\left(z_5 < Z_5 \mid b_k < Z_k, k < 5\right)$$

where $z_5 = 1.53105$ is the test statistic at stage 5, $Z_k$ is a standardized normal variate at stage $k$, and $b_k$ is the upper $\beta$ boundary value in the standardized $Z$ scale at stage $k, k = 1, 2, \ldots, 5$.

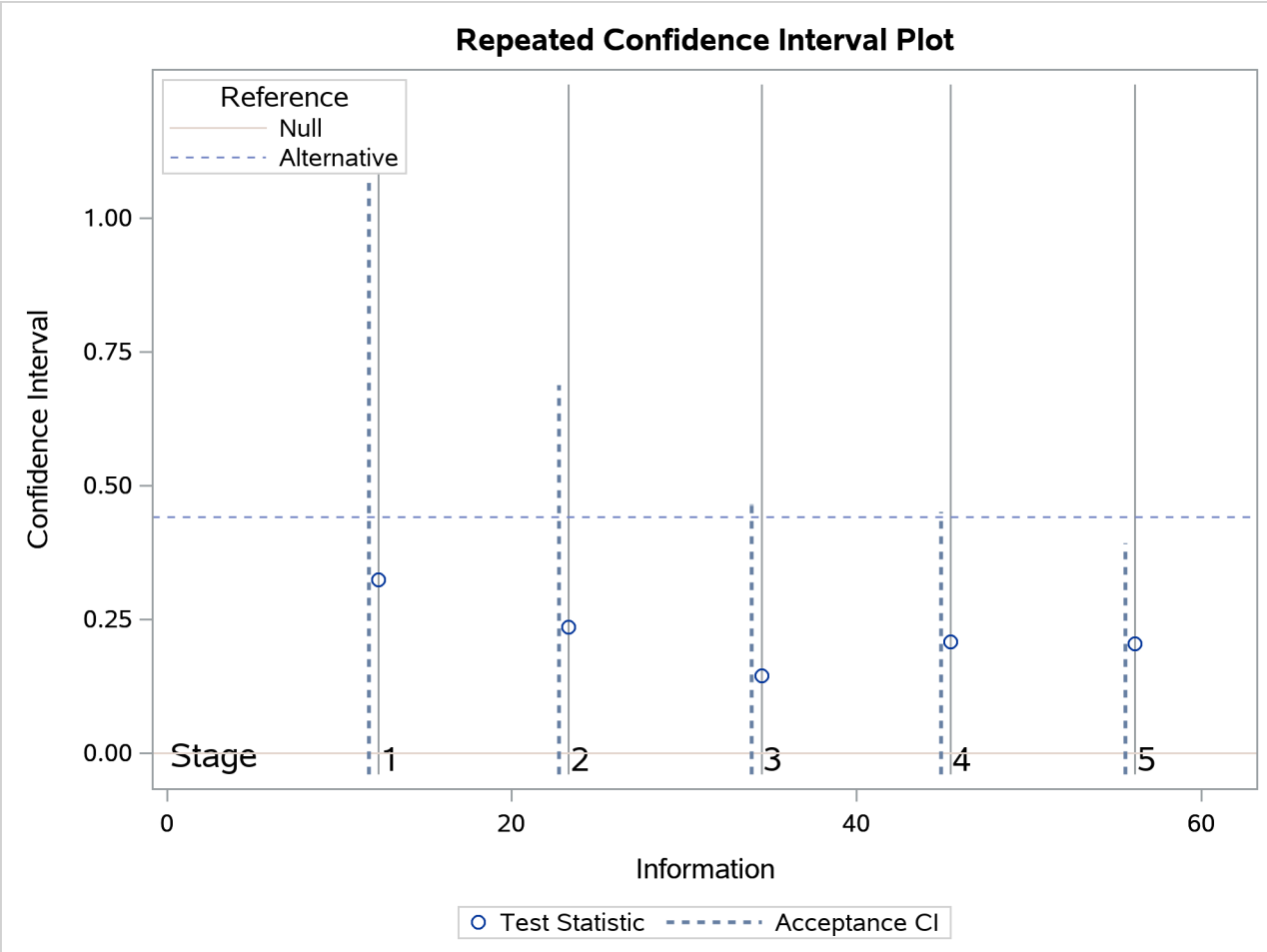
With the RCI option, the "Repeated Confidence Intervals" table in Output 108.5.17 displays repeated confidence intervals for the parameter. For a one-sided test with an upper alternative hypothesis, since the upper acceptance repeated confidence limit 0.3924 at the final stage is less than the alternative reference 0.441833, the null hypothesis is accepted.

**Output 108.5.17** Repeated Confidence Intervals

| Repeated Confidence Intervals | | | |
|---|---|---|---|
| | | | Acceptance Boundary |
| _Stage_ | Information Level | Parameter Estimate | Upper 89.94% CL |
| 1 | 12.2601 | 0.32474 | 1.0656 |
| 2 | 23.2792 | 0.23560 | 0.6881 |
| 3 | 34.4879 | 0.14482 | 0.4653 |
| 4 | 45.4468 | 0.20855 | 0.4514 |
| 5 | 56.1607 | 0.20430 | 0.3924 |

With the PLOTS=RCI option, the "Repeated Confidence Intervals Plot" displays repeated confidence intervals for the parameter, as shown in Output 108.5.18. It shows that the upper acceptance repeated confidence limit at the final stage is less than the alternative reference 0.441833. This implies that the study accepts the null hypothesis at the final stage.

**Output 108.5.18** Repeated Confidence Intervals Plot




## Example 108.6: Comparing Two Survival Distributions with a Log-Rank Test

This example requests a log-rank test that compares two survival distributions for the treatment effect (Jennison and Turnbull 2000, pp. 77–79; Whitehead 1997, pp. 36–39).

A clinic is studying the effect of a new cancer treatment. The study consists of mice exposed to a carcinogen and randomized to either the control group or the treatment group. The event of interest is the death from cancer induced by the carcinogen, and the response is the time from randomization to death.

Following the derivations in the section "Test for Two Survival Distributions with a Log-Rank Test" on page 8899 in Chapter 107, "The SEQDESIGN Procedure," the hypothesis $H_0 : \theta = -\log(\lambda) = 0$ with an alternative hypothesis $H_1 : \theta = \theta_1 > 0$ can be used, where $\lambda$ is the hazard ratio between the treatment group and control group.

Suppose that from past experience, the median survival time for the control group is $t_0 = 20$ weeks, and the study would like to detect a $t_1 = 40$ weeks median survival time with a 80% power in the trial. Assuming exponential survival functions for the two groups, the hazard rates can be computed from

$$S_j(t_j) = e^{-h_j t_j} = \frac{1}{2}$$

where $j = 0, 1$.

Thus, with $h_0 = 0.03466$ and $h_1 = 0.01733$, the hazard ratio $\lambda_1 = h_1/h_0 = 1/2$ and the alternative hypothesis is

$$\theta_1 = -\log(\lambda_1) = -\log(\frac{1}{2}) = 0.69315$$

The following statements invoke the SEQDESIGN procedure and request a four-stage group sequential design for normally distributed data. The design uses a one-sided alternative hypothesis with early stopping to reject and to accept the null hypothesis $H_0$. Whitehead's triangular method is used to derive the boundaries.

```
ods graphics on;
proc seqdesign boundaryscale=score
               ;
   OneSidedWhitehead: design method=whitehead
                             nstages=4
                             boundarykey=alpha
                             alt=upper  stop=both
                             beta=0.20;
   samplesize model=twosamplesurvival
                     ( nullhazard=0.03466
                       hazard=0.01733
                       accrate=10);
run;
```

A Whitehead method creates boundaries that approximately satisfy the Type I and Type II error probability level specification. The BOUNDARYKEY=ALPHA option is used to adjust the boundary value at the last stage and to meet the specified Type I probability level.

The specified ACCRATE=10 option indicates that 10 mice will be accrued each week and the resulting minimum and maximum accrual times are displayed. With the BOUNDARYSCALE=SCORE option, the procedure displays the output boundaries with the score statistics.

The "Design Information" table in Output 108.6.1 displays design specifications and derived statistics.

**Output 108.6.1** Design Information

**The SEQDESIGN Procedure**
**Design: OneSidedWhitehead**

| Design Information | |
|---|---|
| **Statistic Distribution** | Normal |
| **Boundary Scale** | Score |
| **Alternative Hypothesis** | Upper |
| **Early Stop** | Accept/Reject Null |
| **Method** | Whitehead |
| **Boundary Key** | Alpha |
| **Alternative Reference** | 0.693147 |
| **Number of Stages** | 4 |
| **Alpha** | 0.05 |
| **Beta** | 0.20044 |
| **Power** | 0.79956 |
| **Max Information (Percent of Fixed Sample)** | 129.9894 |
| **Max Information** | 16.70638 |
| **Null Ref ASN (Percent of Fixed Sample)** | 62.6302 |
| **Alt Ref ASN (Percent of Fixed Sample)** | 74.00064 |

The "Boundary Information" table in Output 108.6.2 displays the information level, alternative reference, and boundary values at each stage.

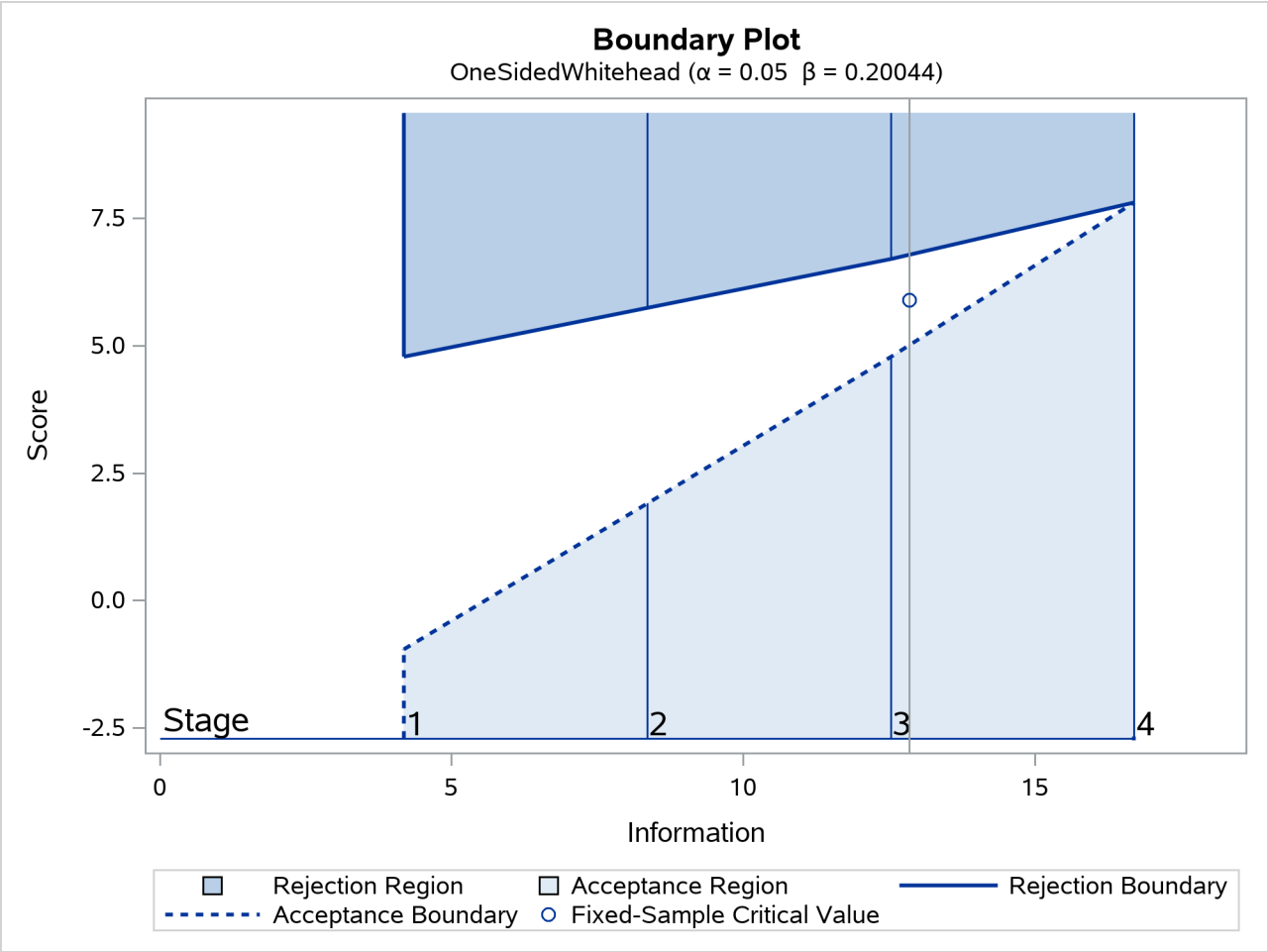
**Output 108.6.2** Boundary Information

**Boundary Information (Score Scale)**
**Null Reference = 0**

| | Information Level | | | Alternative Reference | Boundary Values Upper | |
|---|---|---|---|---|---|---|
| _Stage_ | Proportion | Actual | Events | Upper | Beta | Alpha |
| 1 | 0.2500 | 4.176595 | 16.70638 | 2.89500 | -0.95755 | 4.78775 |
| 2 | 0.5000 | 8.35319 | 33.41276 | 5.78999 | 1.91510 | 5.74529 |
| 3 | 0.7500 | 12.52979 | 50.11914 | 8.68499 | 4.78775 | 6.70284 |
| 4 | 1.0000 | 16.70638 | 66.82552 | 11.57998 | 7.81300 | 7.81300 |

With ODS Graphics enabled, a detailed boundary plot with the rejection and acceptance regions is displayed, as shown in Output 108.6.3.

**Output 108.6.3** Boundary Plot




With the MODEL=TWOSAMPLESURVIVAL option in the SAMPLESIZE statement, the "Sample Size Summary" table in Output 108.6.4 displays the parameters for the sample size computation.

**Output 108.6.4** Required Sample Size Summary

| Sample Size Summary | |
|---|---|
| **Test** | Two-Sample Survival |
| **Null Hazard Rate** | 0.03466 |
| **Hazard Rate (Group A)** | 0.01733 |
| **Hazard Rate (Group B)** | 0.03466 |
| **Hazard Ratio** | 0.5 |
| **log(Hazard Ratio)** | -0.69315 |
| **Reference Hazards** | Alt Ref |
| **Accrual** | Uniform |
| **Accrual Rate** | 10 |
| **Min Accrual Time** | 6.682552 |
| **Min Sample Size** | 66.82552 |
| **Max Accrual Time** | 25.40111 |
| **Max Sample Size** | 254.0111 |
| **Max Number of Events** | 66.82552 |

With a minimum accrual time of 6.6826 weeks and a maximum accrual time of 25.401 weeks, an accrual time of 20 weeks is used in the study.

The "Numbers of Events" table in Output 108.6.5 displays the required number of events for the group sequential clinical trial.

**Output 108.6.5** Required Numbers of Events

| Numbers of Events (D) Two-Sample Log-Rank Test | | |
|---|---|---|
| _Stage_ | D | Information |
| 1 | 16.71 | 4.1766 |
| 2 | 33.41 | 8.3532 |
| 3 | 50.12 | 12.5298 |
| 4 | 66.83 | 16.7064 |

The following statements invoke the SEQDESIGN procedure and provide more detailed sample size information:

```
proc seqdesign boundaryscale=score
               ;
   OneSidedWhitehead: design method=whitehead
                             nstages=4
                             boundarykey=alpha
                             alt=upper
                             stop=both
                             beta=0.20;
   samplesize model=twosamplesurvival
                     ( nullhazard=0.03466
                       hazard=0.01733
                       accrate=10 acctime=20);
   ods output Boundary=Bnd_Surv;
run;
```

The ODS OUTPUT statement with the BOUNDARY=BND_SURV option creates an output data set named BND_SURV which contains the resulting boundary information for the subsequent sequential tests.

With an accrual time of 20 weeks, the "Sample Size Summary" table in Output 108.6.6 displays the follow-up time for the trial.

**Output 108.6.6** Required Sample Size Summary

**The SEQDESIGN Procedure**
**Design: OneSidedWhitehead**

| Sample Size Summary | |
|---|---|
| **Test** | Two-Sample Survival |
| **Null Hazard Rate** | 0.03466 |
| **Hazard Rate (Group A)** | 0.01733 |
| **Hazard Rate (Group B)** | 0.03466 |
| **Hazard Ratio** | 0.5 |
| **log(Hazard Ratio)** | -0.69315 |
| **Reference Hazards** | Alt Ref |
| **Accrual** | Uniform |
| **Accrual Rate** | 10 |
| **Accrual Time** | 20 |
| **Follow-up Time** | 6.474366 |
| **Total Time** | 26.47437 |
| **Max Number of Events** | 66.82552 |
| **Max Sample Size** | 200 |
| **Expected Sample Size (Null Ref)** | 161.5941 |
| **Expected Sample Size (Alt Ref)** | 172.4692 |
| **Follow-up Time (Ceiling Time)** | 7 |
| **Total Time (Ceiling Time)** | 27 |

The "Numbers of Events and Sample Sizes" table in Output 108.6.7 displays the required sample sizes for the group sequential clinical trial.

**Output 108.6.7** Numbers of Events and Sample Sizes

**Numbers of Events (D) and Sample Sizes (N)**
**Two-Sample Log-Rank Test**

| | | | | Fractional Time | | | | |
|---|---|---|---|---|---|---|---|---|
| _Stage_ | D | D(Grp 1) | D(Grp 2) | Time | N | N(Grp 1) | N(Grp 2) | Information |
| 1 | 16.71 | 5.82 | 10.89 | 11.9867 | 119.87 | 59.93 | 59.93 | 4.1766 |
| 2 | 33.41 | 11.84 | 21.57 | 17.3585 | 173.58 | 86.79 | 86.79 | 8.3532 |
| 3 | 50.12 | 18.01 | 32.11 | 21.7480 | 200.00 | 100.00 | 100.00 | 12.5298 |
| 4 | 66.83 | 24.46 | 42.37 | 26.4744 | 200.00 | 100.00 | 100.00 | 16.7064 |

**Numbers of Events (D) and Sample Sizes (N)**
**Two-Sample Log-Rank Test**

| | | | | Ceiling Time | | | | |
|---|---|---|---|---|---|---|---|---|
| _Stage_ | D | D(Grp 1) | D(Grp 2) | Time | N | N(Grp 1) | N(Grp 2) | Information |
| 1 | 16.74 | 5.83 | 10.91 | 12 | 120.00 | 60.00 | 60.00 | 4.1854 |
| 2 | 35.73 | 12.68 | 23.04 | 18 | 180.00 | 90.00 | 90.00 | 8.9322 |
| 3 | 51.07 | 18.37 | 32.70 | 22 | 200.00 | 100.00 | 100.00 | 12.7667 |
| 4 | 68.55 | 25.14 | 43.41 | 27 | 200.00 | 100.00 | 100.00 | 17.1378 |

Thus the study will perform three interim analyses after 12, 18, and 22 weeks and a final analysis after 27 weeks if the study does not stop at any of the interim analyses.

Note that the SEQDESIGN procedure does not compute numbers of events or sample sizes for all statistical models. If the number of events or sample size for a fixed-sample design is available, then the MODEL=INPUTNEVENTS or MODEL=INPUTNOBS option can be used to input fixed-sample information. For example, with a required fixed-sample number of events 51.41, the following SAMPLESIZE statement can be used to produce the same sample size results:

```
samplesize model=inputnevents
                 ( d=51.41 sample=two
                   hazard=0.03466 0.01733
                   accrate=10 acctime=20);
```

Suppose that 120 mice are available after week 12 for the first interim analysis. Output 108.6.8 lists the 10 observations in the data set weeks_1.

**Output 108.6.8** Clinical Trial Data

**First 10 Obs in the Trial Data**

| Obs | TrtGp | Event | Weeks |
|---|---|---|---|
| **1** | 0 | 0 | 11 |
| **2** | 1 | 0 | 11 |
| **3** | 0 | 0 | 11 |
| **4** | 1 | 0 | 11 |
| **5** | 0 | 1 | 6 |
| **6** | 1 | 0 | 11 |
| **7** | 0 | 0 | 11 |
| **8** | 1 | 0 | 11 |
| **9** | 0 | 1 | 9 |
| **10** | 1 | 0 | 11 |

The TrtGp variable is a grouping variable with the value 0 for a mouse in the placebo control group and the value 1 for a mouse in the treatment group. The Weeks variable is the survival time variable measured in weeks and the Event variable is the censoring variable with the value 0 indicating censoring. That is, the values of Weeks are considered censored if the corresponding values of Event are 0; otherwise, they are considered as event times.

The following statements use the LIFETEST procedure to estimate the log-rank statistic at stage 1:

```
proc lifetest data=Surv_1;
   time Weeks*Event(0);
   test TrtGp;
   ods output logunichisq=Parms_Surv1;
run;
```

The following statements create and display (in Output 108.6.9) the data set for the log-rank statistic and its associated standard error:

```
data Parms_Surv1;
   set Parms_Surv1(rename=(Statistic=Estimate));
   if Variable='TrtGp';
   _Scale_='Score';
   _Stage_= 1;
   keep Variable _Scale_ _Stage_ StdErr Estimate;
run;
```

```
proc print data=Parms_Surv1;
   title 'Statistics Computed at Stage 1';
run;
```

**Output 108.6.9** Statistics Computed at Stage 1

**Statistics Computed at Stage 1**

| Obs | Variable | Estimate | StdErr | _Scale_ | _Stage_ |
|---|---|---|---|---|---|
| 1 | TrtGp | 3.2004 | 1.9979 | Score | 1 |

The following statements invoke the SEQTEST procedure to test for early stopping at stage 1:

```
ods graphics on;
proc seqtest Boundary=Bnd_Surv
             Parms(Testvar=TrtGp)=Parms_Surv1
             infoadj=none
             boundaryscale=score
             ;
   ods output Test=Test_Surv1;
run;
```

The BOUNDARY= option specifies the input data set that provides the boundary information for the trial at stage 1, which was generated in the SEQDESIGN procedure. The PARMS=PARMS_SURV1 option specifies the input data set PARMS_SURV1 that contains the test statistic and its associated standard error at stage 1, and the TESTVAR=TRTGP option identifies the test variable TRTGP in the data set. The INFOADJ=NONE option maintains the information levels for future interim stages (2 and 3) at the values provided in the BOUNDARY= data set.

The ODS OUTPUT statement with the TEST=TEST_SURV1 option creates an output data set named TEST_SURV1 which contains the updated boundary information for the test at stage 1. The data set also provides the boundary information that is needed for the group sequential test at the next stage.

The "Design Information" table in Output 108.6.10 displays design specifications. By default (or equivalently if you specify BOUNDARYKEY=ALPHA), the maximum information and the Type I error level $\alpha$ are preserved. Since the computed information level at stage 1 is not the same as the value provided in the BOUNDARY= data set, the power has been modified.

**Output 108.6.10** Design Information

**The SEQTEST Procedure**

| Design Information | |
|---|---|
| **BOUNDARY Data Set** | WORK.BND_SURV |
| **Data Set** | WORK.PARMS_SURV1 |
| **Statistic Distribution** | Normal |
| **Boundary Scale** | Score |
| **Alternative Hypothesis** | Upper |
| **Early Stop** | Accept/Reject Null |
| **Number of Stages** | 4 |
| **Alpha** | 0.05 |
| **Beta** | 0.20055 |
| **Power** | 0.79945 |
| **Max Information (Percent of Fixed Sample)** | 130.0335 |
| **Max Information** | 16.7063807 |
| **Null Ref ASN (Percent of Fixed Sample)** | 62.80859 |
| **Alt Ref ASN (Percent of Fixed Sample)** | 74.19158 |

The "Test Information" table in Output 108.6.11 displays the boundary values for the test statistic with the SCORE statistic scale. Since only the information level at stage 1 is specified in the DATA= data set, the information levels at subsequent stages are derived proportionally from the corresponding information levels provided in the BOUNDARY= data set. At stage 1, the score statistic 3.2004 is between the upper $\beta$ boundary value –1.0386 and the upper $\alpha$ boundary value 4.7142, so the trial continues to the next stage.

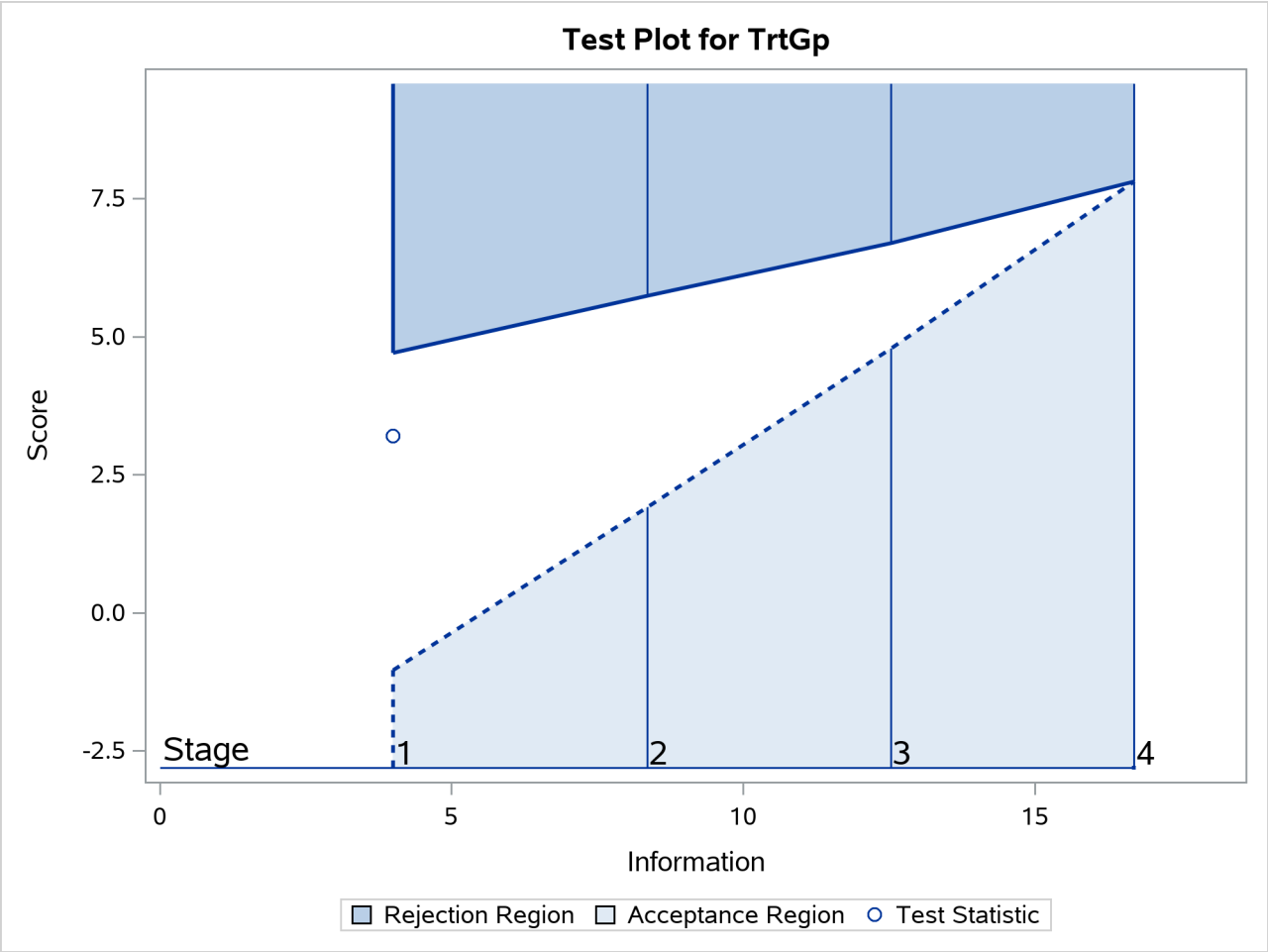
**Output 108.6.11** Sequential Tests

| Test Information (Score Scale) Null Reference = 0 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Information Level | | Alternative Reference | Boundary Values | | Test TrtGp | |
| | | | | Upper | | | |
| _Stage_ | Proportion | Actual | Upper | Beta | Alpha | Estimate | Action |
| 1 | 0.2389 | 3.991698 | 2.76683 | -1.03862 | 4.71423 | 3.20040 | Continue |
| 2 | 0.5000 | 8.35319 | 5.78999 | 1.91799 | 5.73973 | . | |
| 3 | 0.7500 | 12.52979 | 8.68499 | 4.78804 | 6.70287 | . | |
| 4 | 1.0000 | 16.70638 | 11.57998 | 7.81349 | 7.81349 | . | |

Note that the observed information level 3.9917 corresponds to a proportion of 0.2389 in information level. If the observed information level is much smaller than the target proportion of 0.25, then you need to increase the accrual rate, accrual time, or follow-up time to achieve the target maximum information level for the trial. Scharfstein and Tsiatis (1998) use the simulation and bootstrap methods to modify the trial at interim stages to achieve the target maximum information level. These modifications should be specified in the study protocol or study plan before the study starts.

With ODS Graphics enabled, a boundary plot with test statistics is displayed, as shown in Output 108.6.12. As expected, the test statistic is in the continuation region between the upper $\beta$ and $\alpha$ boundary values.

**Output 108.6.12** Sequential Test Plot




Note that the input DATA= option can also be used for the test statistics. For example, the following statements create and display (in Output 108.6.13) the data set for the log-rank statistic and its associated standard error after the LIFETEST procedure. Since the log-rank statistic is a score statistic, the corresponding information level is the variance of the statistic.

```
proc lifetest data=Surv_1;
   time Weeks*Event(0);
   test TrtGp;
   ods output logunichisq=Parms_Surv1a;
run;

data Parms_Surv1a;
   set Parms_Surv1a(rename=(Statistic=TrtGp));
   keep _Scale_ _Stage_ _Info_ TrtGp;
   _Scale_='Score';
   _Stage_= 1;
   _Info_= StdErr * StdErr;
   if Variable='TrtGp';
run;
```

```
proc print data=Parms_Surv1a;
   title 'Statistics Computed at Stage 1';
run;
```

**Output 108.6.13** Statistics Computed at Stage 1

**Statistics Computed at Stage 1**

| Obs | TrtGp | _Scale_ | _Stage_ | _Info_ |
|---|---|---|---|---|
| 1 | 3.2004 | Score | 1 | 3.99170 |

The following statements can be used to invoke the SEQTEST procedure to test for early stopping at stage 1:

```
ods graphics on;
proc seqtest Boundary=Bnd_Surv
             Data(Testvar=TrtGp)=Parms_Surv1a
             infoadj=none
             boundaryscale=score
             ;
   ods output Test=Test_Surv1;
run;
```

The following statements use the LIFETEST procedure to compute the log-rank statistic and its associated standard error at stage 2:

```
proc lifetest data=Surv_2;
   time Weeks*Event(0);
   test TrtGp;
   ods output logunichisq=Parms_Surv2;
run;
```

The following statements create and display (in Output 108.6.14) the data set for the log-rank statistic and its associated standard error for each of the first two stages:

```
data Parms_Surv2;
   set Parms_Surv2 (rename=(Statistic=Estimate));
   if Variable='TrtGp';
   _Scale_='Score';
   _Stage_= 2;
   keep Variable _Scale_ _Stage_ StdErr Estimate;
run;

proc print data=Parms_Surv2;
   title 'Statistics Computed at Stage 2';
run;
```

**Output 108.6.14** Statistics Computed at Stage 2

**Statistics Computed at Stage 2**

| Obs | Variable | Estimate | StdErr | _Scale_ | _Stage_ |
|---|---|---|---|---|---|
| 1 | TrtGp | 7.3136 | 2.9489 | Score | 2 |

The following statements invoke the SEQTEST procedure to test for early stopping at stage 2:

```
ods graphics on;
proc seqtest Boundary=Test_Surv1
             Parms(Testvar=TrtGp)=Parms_Surv2
             infoadj=none
             boundaryscale=score
             citype=lower
             ;
   ods output Test=Test_Surv2;
run;
```

The BOUNDARY= option specifies the input data set that provides the boundary information for the trial at stage 2, which was generated by the SEQTEST procedure at the previous stage. The PARMS= option specifies the input data set that contains the test statistic and its associated standard error at stage 2, and the TESTVAR= option identifies the test variable in the data set. The INFOADJ=NONE option maintains the information level for stage 3 at the value provided in the BOUNDARY= data set.

The ODS OUTPUT statement with the TEST=TEST_SURV2 option creates an output data set named TEST_SURV2 which contains the updated boundary information for the test at stage 2. The data set also provides the boundary information that is needed for the group sequential test at the next stage if the trial does not stop at the current stage.

The "Test Information" table in Output 108.6.15 displays the boundary values for the test statistic. The test statistic 7.31365 is larger than the corresponding upper $\alpha$ boundary 5.79334, so the study stops and rejects the null hypothesis. That is, there is evidence of reduction in hazard rate for the new treatment.

**Output 108.6.15** Sequential Tests

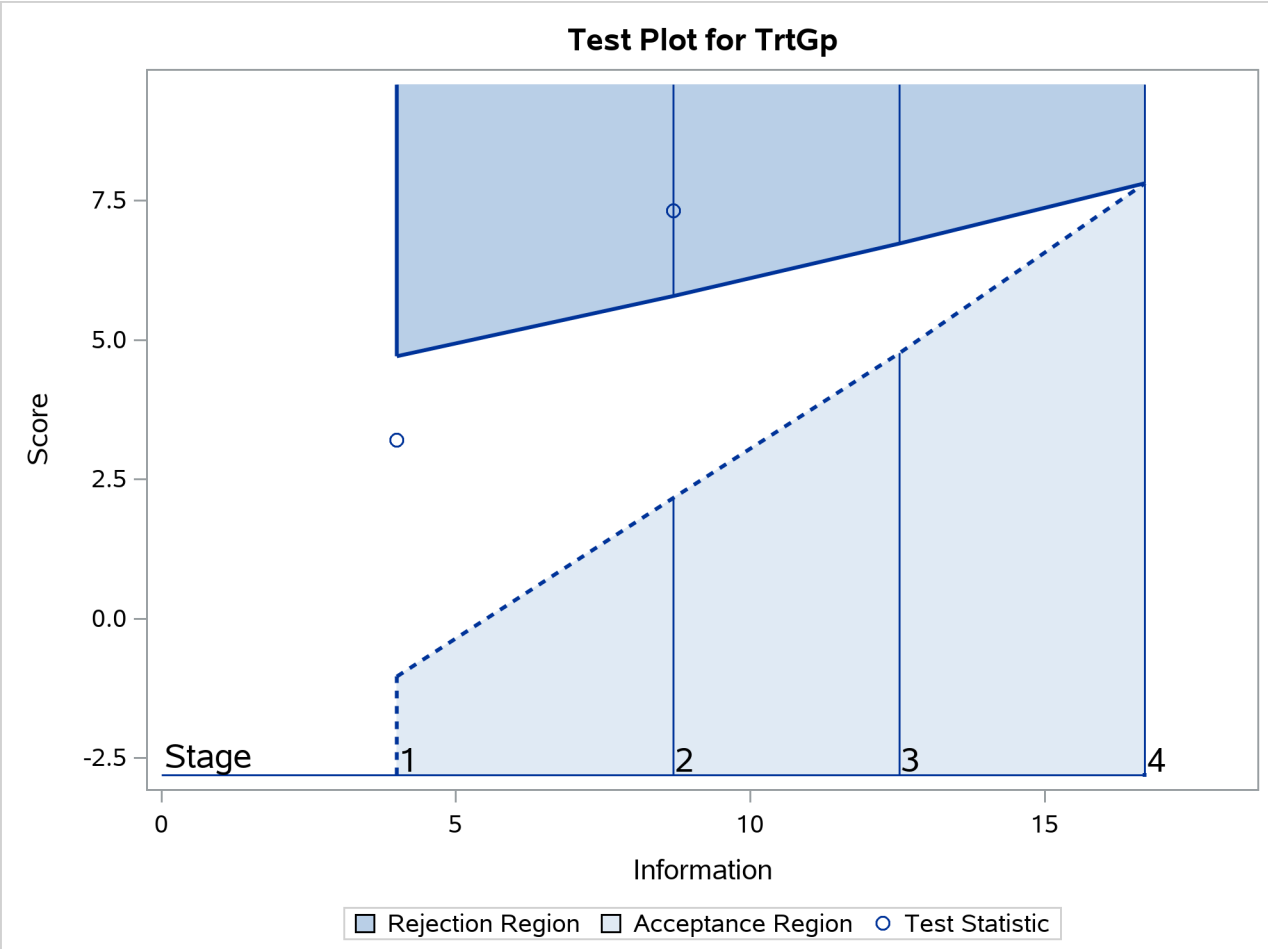
**The SEQTEST Procedure**

**Test Information (Score Scale)**
**Null Reference = 0**

| | Information Level | | Alternative Reference | Boundary Values | | Test TrtGp | |
|---|---|---|---|---|---|---|---|
| _Stage_ | Proportion | Actual | Upper | Upper Beta | Upper Alpha | Estimate | Action |
| 1 | 0.2389 | 3.991698 | 2.76683 | -1.03862 | 4.71423 | 3.20040 | Continue |
| 2 | 0.5205 | 8.696125 | 6.02769 | 2.17041 | 5.79334 | 7.31365 | Reject Null |
| 3 | 0.7500 | 12.52979 | 8.68499 | 4.76308 | 6.72917 | . | |
| 4 | 1.0000 | 16.70638 | 11.57998 | 7.81290 | 7.81290 | . | |

With ODS Graphics enabled, the "Test Plot" displays boundary values of the design and the test statistic at the first two stages, as shown in Output 108.6.16. It also shows that the test statistic is in the "Rejection Region" above the upper $\alpha$ boundary value at stage 2.

**Output 108.6.16** Sequential Test Plot




After the stopping of a trial, the "Parameter Estimates" table in Output 108.6.17 displays the stopping stage, parameter estimate, unbiased median estimate, confidence limits, and $p$-value under the null hypothesis $H_0 : \theta = 0$.

**Output 108.6.17** Parameter Estimates

| Parameter Estimates Stagewise Ordering | | | | | |
|---|---|---|---|---|---|
| Parameter | Stopping Stage | MLE | p-Value for H0:Parm=0 | Median Estimate | Lower 95% CL |
| TrtGp | 2 | 0.841024 | 0.0139 | 0.810329 | 0.21615 |

As expected, the $p$-value 0.0139 is significant at the $\alpha = 0.05$ level and the lower 95% confidence limit is larger than $\theta_0 = 0$. The $p$-value, unbiased median estimate, and lower confidence limit depend on the ordering of the sample space $(k, z)$, where $k$ is the stage number and $z$ is the standardized $Z$ statistic. With the specified stagewise ordering, the $p$-value is $p_1 + p_2$, where $p_1$ is the $\alpha$ spending at stage 1,

$$p_1 = P_{\theta=0}(Z_1\sqrt{I_1} \geq 4.71423) = 0.00915$$

$$p_2 = P_{\theta=0}(Z_2\sqrt{I_2} \geq 7.31365 \ \mid \ -1.03862 < Z_1\sqrt{I_1} < 4.71423)$$

where $Z_k$ is a standardized normal variate and $I_k$ is the information level at stage $k$ for $k = 1, 2$.

## Example 108.7: Testing an Effect in a Proportional Hazards Regression Model

This example compares two survival distributions for the treatment effect. The example uses a power family method to generate two-sided asymmetric boundaries and then uses a proportional hazards regression model to test the hypothesis with a covariate.

A clinic is conducting a clinical study for the effect of a new cancer treatment. The study consists of mice exposed to a carcinogen and randomized to either the control group or the treatment group. The event of interest is the death from cancer induced by the carcinogen, and the response is the time from randomization to death.

Consider the proportional hazards regression model

$$h(t;\ \mathrm{TrtGp},\ \mathrm{Wgt}) = h_0(t)\ \exp(\beta_g\ \mathrm{TrtGp}\ +\ \beta_w \mathrm{Wgt})$$

where $h_0(t)$ is an arbitrary and unspecified baseline hazard function, TrtGp is the grouping variable for the two groups, Wgt is the initial weight of the mice, and $\beta_g$ and $\beta_w$ are the regression parameters associated with the variables TrtGp and Wgt, respectively. The grouping variable has the value 0 for each mouse in the control group and the value 1 for each mouse in the treatment group.

The hypothesis $H_0 : \beta_g = 0$ with an alternative hypothesis $H_1 : \beta_g \neq 0$ is used for the study.

Suppose that from past experience, the median survival time for the control group is $t_0 = 20$ weeks. The study would like to detect a $t_1 = 40$ weeks median survival time with a 80% power in the trial. Assuming exponential survival functions for the two groups, the hazard rates can be computed from

$$S_j(t_j) = e^{-h_j t_j} = \frac{1}{2}$$

where $j = 0, 1$.

Thus, with the hazard rates $h_0 = 0.03466$ and $h_1 = 0.01733$, the hazard ratio $\exp(\beta_g) = h_1/h_0 = 1/2$ and the alternative hypothesis

$$\beta_{g1} = \log(\frac{1}{2}) = -0.69315$$

Following the derivations in the section "Test for a Parameter in the Proportional Hazards Regression Model" on page 8903 in Chapter 107, "The SEQDESIGN Procedure," the required number of events for testing a parameter in $\boldsymbol{\beta}$ is given by

$$D_X = I_X\ \frac{1}{(1 - r_x^2)\ \sigma_x^2}$$

where $\sigma_x^2$ is the variance of TrtGp and $r_x^2$ is the proportion of variance of TrtGp explained by the variable Wgt.

If the two groups have the same number of mice in the study, then the MLE of the variance is $\hat{\sigma}_x^2 = 0.25$. Further, if $r_x^2 = 0.10$, then you can specify the MODEL=PHREG( XVARIANCE=0.25 XRSQUARE=0.10) option in the SAMPLESIZE statement in the SEQDESIGN procedure to compute the required number of events and the individual number of events at each stage.

The following statements invoke the SEQDESIGN procedure and request a four-stage group sequential design for normally distributed data. The design uses a two-sided alternative hypothesis with early stopping to reject the null hypothesis $H_0$. A power family method is used to derive the boundaries.

```
ods graphics on;
proc seqdesign altref=0.69315;
   TwoSidedPowerFamily: design method=pow
                                nstages=4
                                alpha=0.075(lower=0.025)
                                beta=0.20;
   samplesize model=phreg( xvariance=0.25 xrsquare=0.10
                           hazard=0.02451 accrate=10);
run;
```

The ALPHA=0.075(LOWER=0.025) option specifies a lower $\alpha$ level 0.025 for the lower rejection boundary and an upper $\alpha$ level $0.05 = 0.075 - 0.025$ for the upper rejection boundary. The geometric average hazard $\sqrt{h_0 \times h_1} = \sqrt{0.03466 \times 0.01733} = 0.02451$ is used in the HAZARD= option in the SAMPLESIZE statement to compute the required sample size. The specified ACCRATE=10 option indicates that 10 mice will be accrued each week and the resulting minimum and maximum accrual times will be displayed.

The "Design Information" table in Output 108.7.1 displays the design specifications and the derived statistics.

**Output 108.7.1** Design Information

**The SEQDESIGN Procedure**
**Design: TwoSidedPowerFamily**

| Design Information | |
|---|---|
| **Statistic Distribution** | Normal |
| **Boundary Scale** | Standardized Z |
| **Alternative Hypothesis** | Two-Sided |
| **Early Stop** | Reject Null |
| **Method** | Power Family |
| **Boundary Key** | Both |
| **Alternative Reference** | 0.69315 |
| **Number of Stages** | 4 |
| **Alpha** | 0.075 |
| **Alpha (Lower)** | 0.025 |
| **Alpha (Upper)** | 0.05 |
| **Beta (Lower)** | 0.2 |
| **Beta (Upper)** | 0.12764 |
| **Power (Lower)** | 0.8 |
| **Power (Upper)** | 0.87236 |
| **Max Information (Percent of Fixed Sample)** | 106.468 |
| **Max Information** | 17.39288 |
| **Null Ref ASN (Percent of Fixed Sample)** | 104.3691 |
| **Lower Alt Ref ASN (Number of Events)** | 58.04014 |
| **Upper Alt Ref ASN (Number of Events)** | 52.05395 |

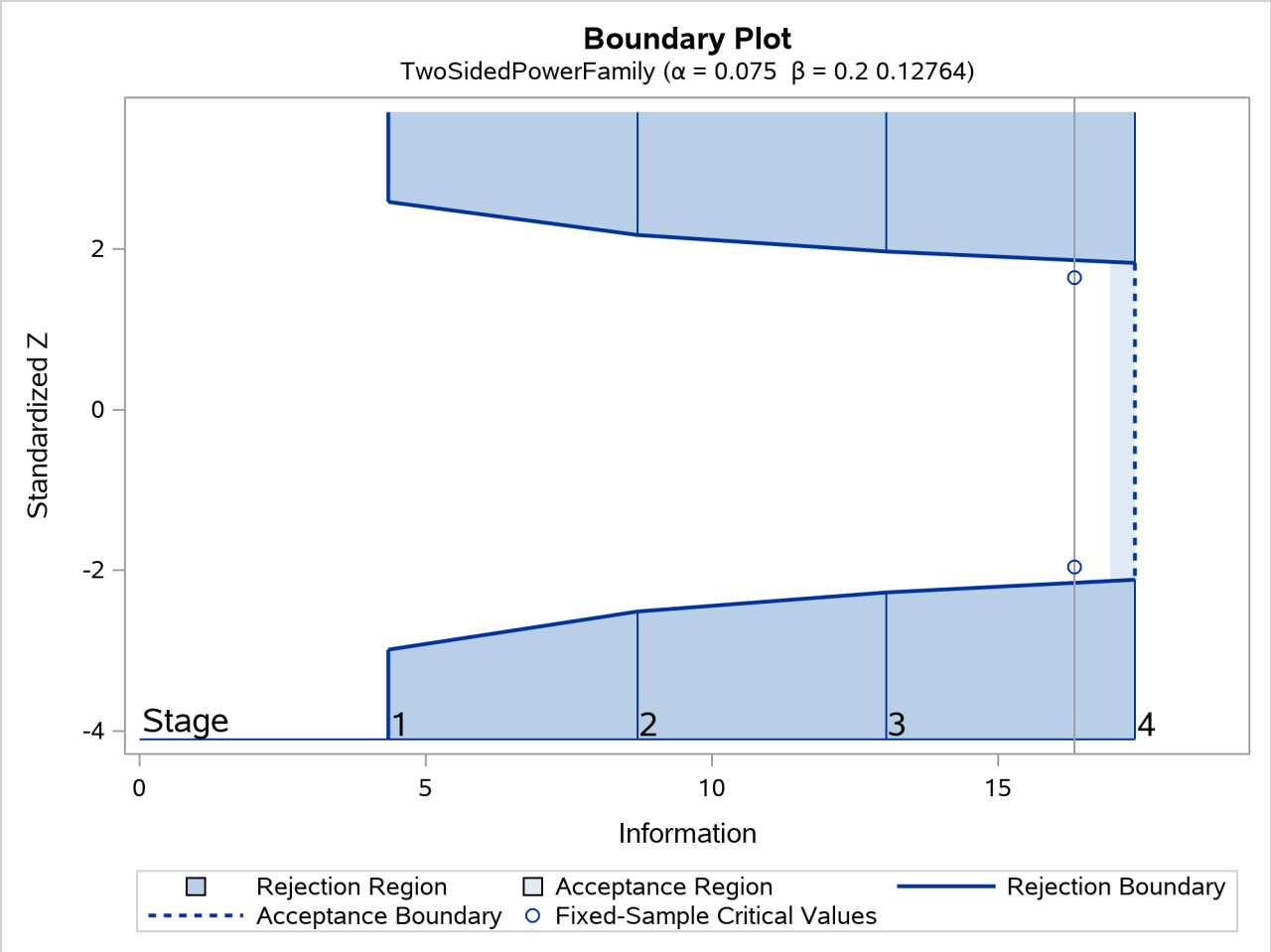
The "Boundary Information" table in Output 108.7.2 displays the information level, alternative reference, and boundary values at each stage. By default (or equivalently if you specify BOUNDARYSCALE=STDZ), the procedure displays the output boundaries with the standardized $Z$ statistic.

**Output 108.7.2** Boundary Information

| Boundary Information (Standardized Z Scale) Null Reference = 0 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Information Level | | | Alternative Reference | | Boundary Values | |
| _Stage_ | Proportion | Actual | Events | Lower | Upper | Lower Alpha | Upper Alpha |
| 1 | 0.2500 | 4.348221 | 19.32543 | -1.44538 | 1.44538 | -2.98871 | 2.59149 |
| 2 | 0.5000 | 8.696441 | 38.65085 | -2.04408 | 2.04408 | -2.51320 | 2.17917 |
| 3 | 0.7500 | 13.04466 | 57.97628 | -2.50348 | 2.50348 | -2.27093 | 1.96910 |
| 4 | 1.0000 | 17.39288 | 77.3017 | -2.89077 | 2.89077 | -2.11334 | 1.83246 |

With ODS Graphics enabled, a detailed boundary plot with the rejection and acceptance regions is displayed, as shown in Output 108.7.3.

**Output 108.7.3** Boundary Plot




With the MODEL=PHREG option in the SAMPLESIZE statement, the "Sample Size Summary" table in Output 108.7.4 displays the parameters used in the sample size computation for the proportional hazards regression model.

**Output 108.7.4** Required Sample Size Summary

| Sample Size Summary | |
|---|---|
| **Test** | PH Reg Parameter |
| **Parameter** | 0.69315 |
| **X Variance** | 0.25 |
| **R Square (X)** | 0.1 |
| **Hazard Rate** | 0.02451 |
| **Accrual** | Uniform |
| **Accrual Rate** | 10 |
| **Min Accrual Time** | 7.73017 |
| **Min Sample Size** | 77.3017 |
| **Max Accrual Time** | 27.97872 |
| **Max Sample Size** | 279.7872 |
| **Max Number of Events** | 77.3017 |

With a minimum accrual time of 7.73 weeks and maximum accrual time of 27.98 weeks, an accrual time of 20 weeks is used in the study. The "Numbers of Events" table in Output 108.7.5 displays the required numbers of events for the group sequential clinical trial.

**Output 108.7.5** Required Sample Sizes

| Numbers of Events (D)<br>Z Test for PH Regression Parameter | | |
|---|---|---|
| _Stage_ | D | Information |
| 1 | 19.33 | 4.3482 |
| 2 | 38.65 | 8.6964 |
| 3 | 57.98 | 13.0447 |
| 4 | 77.30 | 17.3929 |

The following statements invoke the SEQDESIGN procedure and provide more detailed sample size information with a 20-week accrual time:

```
proc seqdesign altref=0.69315;
   TwoSidedPowerFamily: design method=pow
                               nstages=4
                               alpha=0.075(lower=0.025)
                               beta=0.20;
   samplesize model=phreg( xvariance=0.25 xrsquare=0.10
                           hazard=0.02451
                           accrate=10 acctime=20);
   ods output Boundary=Bnd_Time;
run;
```

The ODS OUTPUT statement with the BOUNDARY=BND_TIME option creates an output data set named BND_TIME which contains the resulting boundary information for the subsequent sequential tests.

With an accrual time of 20 weeks, the "Sample Size Summary" table in Output 108.7.6 displays the follow-up time for the trial.

**Output 108.7.6** Sample Size Summary

**The SEQDESIGN Procedure**
**Design: TwoSidedPowerFamily**

| Sample Size Summary | |
|---|---|
| **Test** | PH Reg Parameter |
| **Parameter** | 0.69315 |
| **X Variance** | 0.25 |
| **R Square (X)** | 0.1 |
| **Hazard Rate** | 0.02451 |
| **Accrual** | Uniform |
| **Accrual Rate** | 10 |
| **Accrual Time** | 20 |
| **Follow-up Time** | 10.34195 |
| **Total Time** | 30.34195 |
| **Max Number of Events** | 77.3017 |
| **Max Sample Size** | 200 |
| **Expected Sample Size (Null Ref)** | 199.4282 |
| **Expected Sample Size (Alt Ref)** | 188.6561 |
| **Follow-up Time (Ceiling Time)** | 11 |
| **Total Time (Ceiling Time)** | 31 |

The "Numbers of Events and Sample Sizes" table in Output 108.7.7 displays the required sample sizes for the group sequential clinical trial.

**Output 108.7.7** Numbers of Events and Sample Sizes

**Numbers of Events (D) and Sample Sizes (N)**
**Z Test for PH Regression Parameter**

| | Fractional Time | | | | Ceiling Time | | | |
|---|---|---|---|---|---|---|---|---|
| _Stage_ | D | Time | N | Information | D | Time | N | Information |
| 1 | 19.33 | 13.2362 | 132.36 | 4.3482 | 21.49 | 14 | 140.00 | 4.8359 |
| 2 | 38.65 | 19.1466 | 191.47 | 8.6964 | 41.90 | 20 | 200.00 | 9.4281 |
| 3 | 57.98 | 24.3744 | 200.00 | 13.0447 | 60.14 | 25 | 200.00 | 13.5309 |
| 4 | 77.30 | 30.3420 | 200.00 | 17.3929 | 79.26 | 31 | 200.00 | 17.8346 |

Thus, the study will perform three interim analyses after 14, 20, and 25 weeks and a final analysis after 31 weeks if the study does not stop at any of the interim analyses.

Suppose 140 mice are available for the first interim analysis after week 14. Output 108.7.8 lists the first 10 observations in the data set weeks_1.

**Output 108.7.8** Clinical Trial Data

**First 10 Obs in the Trial Data**

| Obs | TrtGp | Event | Wgt | Weeks |
|---|---|---|---|---|
| 1 | 0 | 0 | 22.1659 | 12 |
| 2 | 1 | 0 | 28.4458 | 12 |
| 3 | 0 | 0 | 26.2857 | 12 |
| 4 | 1 | 0 | 25.0283 | 12 |
| 5 | 0 | 0 | 21.5114 | 12 |
| 6 | 1 | 0 | 23.2240 | 12 |
| 7 | 0 | 1 | 22.6845 | 6 |
| 8 | 1 | 0 | 27.9292 | 12 |
| 9 | 0 | 0 | 22.5514 | 12 |
| 10 | 1 | 1 | 27.3793 | 11 |

The TrtGp variable is a grouping variable with the value 0 for a mouse in the placebo control group and the value 1 for a mouse in the treatment group.

The Weeks variable is the survival time variable measured in weeks and the Event variable is the censoring variable with the value 0 indicating censoring. That is, the values of Weeks are considered censored if the corresponding values of Event are 0; otherwise, they are considered as event times.

The following statements use the PHREG procedure to estimate the treatment effect after adjusting for the Wgt variable at stage 1:

```
proc phreg data=Time_1;
   model Weeks*Event(0)= TrtGp Wgt;
   ods output parameterestimates=Parms_Time1;
run;
```

The following statements create and display (in Output 108.7.9) the data set for the treatment effect MLE statistic and its associated standard error. Note that for a MLE statistic, the inverse of the variance of the statistic is the information.

```
data Parms_Time1;
   set Parms_Time1;
   if Parameter='TrtGp';
   _Scale_='MLE';
   _Stage_= 1;
   keep _Scale_ _Stage_ Parameter Estimate StdErr;
run;

proc print data=Parms_Time1;
   title 'Statistics Computed at Stage 1';
run;
```

**Output 108.7.9** Statistics Computed at Stage 1

**Statistics Computed at Stage 1**

| Obs | Parameter | Estimate | StdErr | _Scale_ | _Stage_ |
|---|---|---|---|---|---|
| 1 | TrtGp | 0.00836 | 0.46588 | MLE | 1 |

The following statements invoke the SEQTEST procedure to test for early stopping at stage 1:

```
ods graphics on;
proc seqtest Boundary=Bnd_Time
             Parms(Testvar=TrtGp)=Parms_Time1
             infoadj=prop
             order=lr
             ;
   ods output Test=Test_Time1;
run;
```

The BOUNDARY= option specifies the input data set that provides the boundary information for the trial at stage 1, which was generated in the SEQDESIGN procedure. The PARMS=PARMS_TIME1 option specifies the input data set PARMS_TIME1 that contains the test statistic and its associated standard error at stage 1, and the TESTVAR=TRTGP option identifies the test variable TRTGP in the data set.

If the computed information level for stage 1 is not the same as the value provided in the BOUNDARY= data set, the INFOADJ=PROP option (which is the default) proportionally adjusts the information levels at future interim stages from the levels provided in the BOUNDARY= data set. The ORDER=LR option uses the LR ordering to derive the $p$-value, the unbiased median estimate, and the confidence limits for the regression slope estimate.

The ODS OUTPUT statement with the TEST=TEST_TIME1 option creates an output data set named TEST_TIME1 which contains the updated boundary information for the test at stage 1. The data set also provides the boundary information that is needed for the group sequential test at the next stage.

The "Design Information" table in Output 108.7.10 displays design specifications. By default (or equivalently if you specify BOUNDARYKEY=ALPHA), the boundary values are modified for the new information levels to maintain the Type I $\alpha$ level. Since the computed information level at stage 1 is not the same as the value provided in the BOUNDARY= data set, the power has been modified.

**Output 108.7.10** Design Information

**The SEQTEST Procedure**

| Design Information | |
|---|---|
| **BOUNDARY Data Set** | WORK.BND_TIME |
| **Data Set** | WORK.PARMS_TIME1 |
| **Statistic Distribution** | Normal |
| **Boundary Scale** | Standardized Z |
| **Alternative Hypothesis** | Two-Sided |
| **Early Stop** | Reject Null |
| **Number of Stages** | 4 |
| **Alpha** | 0.075 |
| **Alpha (Lower)** | 0.025 |
| **Alpha (Upper)** | 0.05 |
| **Beta (Lower)** | 0.20048 |
| **Beta (Upper)** | 0.12795 |
| **Power (Lower)** | 0.79952 |
| **Power (Upper)** | 0.87205 |
| **Max Information (Percent of Fixed Sample)** | 106.5982 |
| **Max Information** | 17.3928828 |
| **Null Ref ASN (Percent of Fixed Sample)** | 104.4715 |
| **Lower Alt Ref ASN (Percent of Fixed Sample)** | 79.7886 |
| **Upper Alt Ref ASN (Percent of Fixed Sample)** | 71.53877 |

The "Test Information" table in Output 108.7.11 displays the boundary values for the test statistic with the MLE statistic scale.

**Output 108.7.11** Sequential Tests

**Test Information (Standardized Z Scale)**
**Null Reference = 0**

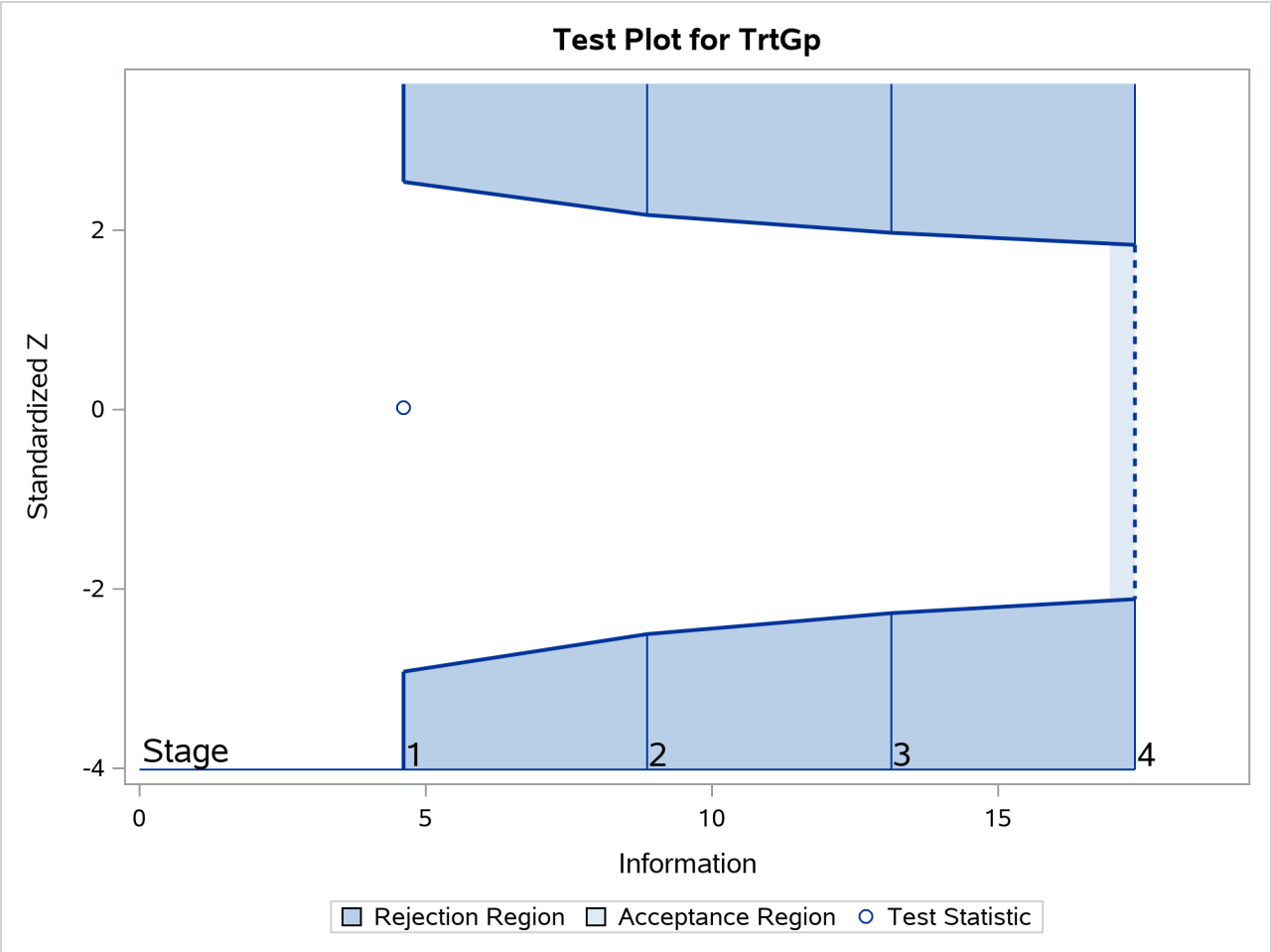
| | Information Level | | Alternative Reference | | Boundary Values | | Test TrtGp | |
|---|---|---|---|---|---|---|---|---|
| _Stage_ | Proportion | Actual | Lower | Upper | Lower Alpha | Upper Alpha | Estimate | Action |
| 1 | 0.2649 | 4.607347 | -1.48783 | 1.48783 | -2.92457 | 2.54086 | 0.01795 | Continue |
| 2 | 0.5099 | 8.869192 | -2.06428 | 2.06428 | -2.50505 | 2.17290 | . | |
| 3 | 0.7550 | 13.13104 | -2.51175 | 2.51175 | -2.27093 | 1.96941 | . | |
| 4 | 1.0000 | 17.39288 | -2.89077 | 2.89077 | -2.11635 | 1.83531 | . | |

With the INFOADJ=PROP option (which is the default), the information levels at interim stages 2 and 3 are derived proportionally from the information levels in the BOUNDARY= data set. At stage 1, the standardized $Z$ statistic 0.01795 is between the lower and upper $\alpha$ boundary values of –2.92457 and 2.54086, so the trial continues to the next stage.

Note that the observed information level 4.6073 corresponds to a proportion of 0.2649 in the information level. If the observed information level is much larger than the target proportion of 0.25, then you can decrease the accrual rate, accrual time, or follow-up time to achieve target information levels for subsequent stages. These modifications should be specified in the study plan before the study begins.

With ODS Graphics enabled, a boundary plot with test statistics is displayed, as shown in Output 108.7.12. As expected, the test statistic is in the continuation region between the lower and upper $\alpha$ boundary values.

**Output 108.7.12** Sequential Test Plot




The following statements use the PHREG procedure to compute the MLE statistic and its associated standard error at stage 2:

```
proc phreg data=Time_2;
   model Weeks*Event(0)= TrtGp Wgt;
   ods output parameterestimates= Parms_Time2;
run;
```

The following statements create the data set for the MLE statistic and its associated standard error at stage 2:

```
data Parms_Time2;
   set Parms_Time2;
   if Parameter='TrtGp';
   _Scale_='MLE';
   _Stage_= 2;
   keep _Scale_ _Stage_ Parameter Estimate StdErr;
run;
```

The following statements invoke the SEQTEST procedure to test for early stopping at stage 2:

```
proc seqtest Boundary=Test_Time1
             Parms(Testvar=TrtGp)=Parms_Time2
             infoadj=prop
             order=lr
             ;
   ods output Test=Test_Time2;
run;
```

The BOUNDARY= option specifies the input data set that provides the boundary information for the trial at stage 2, which was generated by the SEQTEST procedure at the previous stage. The PARMS= option specifies the input data set that contains the test statistic and its associated standard error at stage 2, and the TESTVAR= option identifies the test variable in the data set.

The ODS OUTPUT statement with the TEST=TEST_TIME2 option creates an output data set named TEST_TIME2 which contains the updated boundary information for the test at stage 2. The data set also provides the boundary information that is needed for the group sequential test at the next stage.

The "Test Information" table in Output 108.7.13 displays the boundary values for the test statistic with the MLE statistic scale. At stage 2, the standardized $Z$ statistic –0.43552 is between the lower $\alpha$ and upper boundary values, –2.47689 and 2.14819, respectively, so the trial continues to the next stage.

**Output 108.7.13** Sequential Tests

**The SEQTEST Procedure**

**Test Information (Standardized Z Scale)**
**Null Reference = 0**

| | Information Level | | Alternative Reference | | Boundary Values | | Test TrtGp | |
|---|---|---|---|---|---|---|---|---|
| _Stage_ | Proportion | Actual | Lower | Upper | Lower Alpha | Upper Alpha | Estimate | Action |
| 1 | 0.2649 | 4.607347 | -1.48783 | 1.48783 | -2.92457 | 2.54086 | 0.01795 | Continue |
| 2 | 0.5251 | 9.132918 | -2.09475 | 2.09475 | -2.47689 | 2.14819 | -0.43552 | Continue |
| 3 | 0.7625 | 13.2629 | -2.52433 | 2.52433 | -2.26878 | 1.96770 | . | |
| 4 | 1.0000 | 17.39288 | -2.89077 | 2.89077 | -2.12017 | 1.83880 | . | |

Since the data set PARMS_Time2 contains the test information only at stage 2, the information level at stage 1 in the TEST_Time1 data set is used to generate boundary values for the test.

Similarly, the test statistic at stage 3 is also between its corresponding lower and upper $\alpha$ boundary values. The trial continues to the next stage.

The following statements use the PHREG procedure to compute the MLE statistic and its associated standard error at the final stage:

```
proc phreg data=Time_4;
   model Weeks*Event(0)= TrtGp Wgt;
   ods output parameterestimates= Parms_Time4;
run;
```

The following statements create and display (in Output 108.7.14) the data set for the MLE statistic and its associated standard error at each stage of the study:

```
data Parms_Time4;
   set Parms_Time4;
   if Parameter='TrtGp';
   _Scale_='MLE';
   _Stage_= 4;
   keep _Scale_ _Stage_ Parameter Estimate StdErr;
run;

proc print data=Parms_Time4;
   title 'Statistics Computed at Stage 4';
run;
```

**Output 108.7.14** Statistics Computed at Stage 4

**Statistics Computed at Stage 4**

| Obs | Parameter | Estimate | StdErr | _Scale_ | _Stage_ |
|---|---|---|---|---|---|
| 1 | TrtGp | -0.04451 | 0.23971 | MLE | 4 |

The following statements invoke the SEQTEST procedure to test the hypothesis at stage 4:

```
ods graphics on;
proc seqtest Boundary=Test_Time3
             Parms(Testvar=TrtGp)=Parms_Time4
             order=lr
             ;
run;
```

The BOUNDARY= option specifies the input data set that provides the boundary information for the trial at stage 4, which was generated by the SEQTEST procedure at the previous stage. The PARMS= option specifies the input data set that contains the test statistic and its associated standard error at stage 4, and the TESTVAR= option identifies the test variable in the data set.

The "Test Information" table in Output 108.7.15 displays the boundary values for the test statistic. The standardized test statistic –0.1857 is between the lower and upper $\alpha$ boundary values of –2.10447 and 1.82112, respectively, so the study stops and accepts the null hypothesis. That is, there is no evidence of reduction in hazard rate for the new treatment.

**Output 108.7.15** Sequential Tests

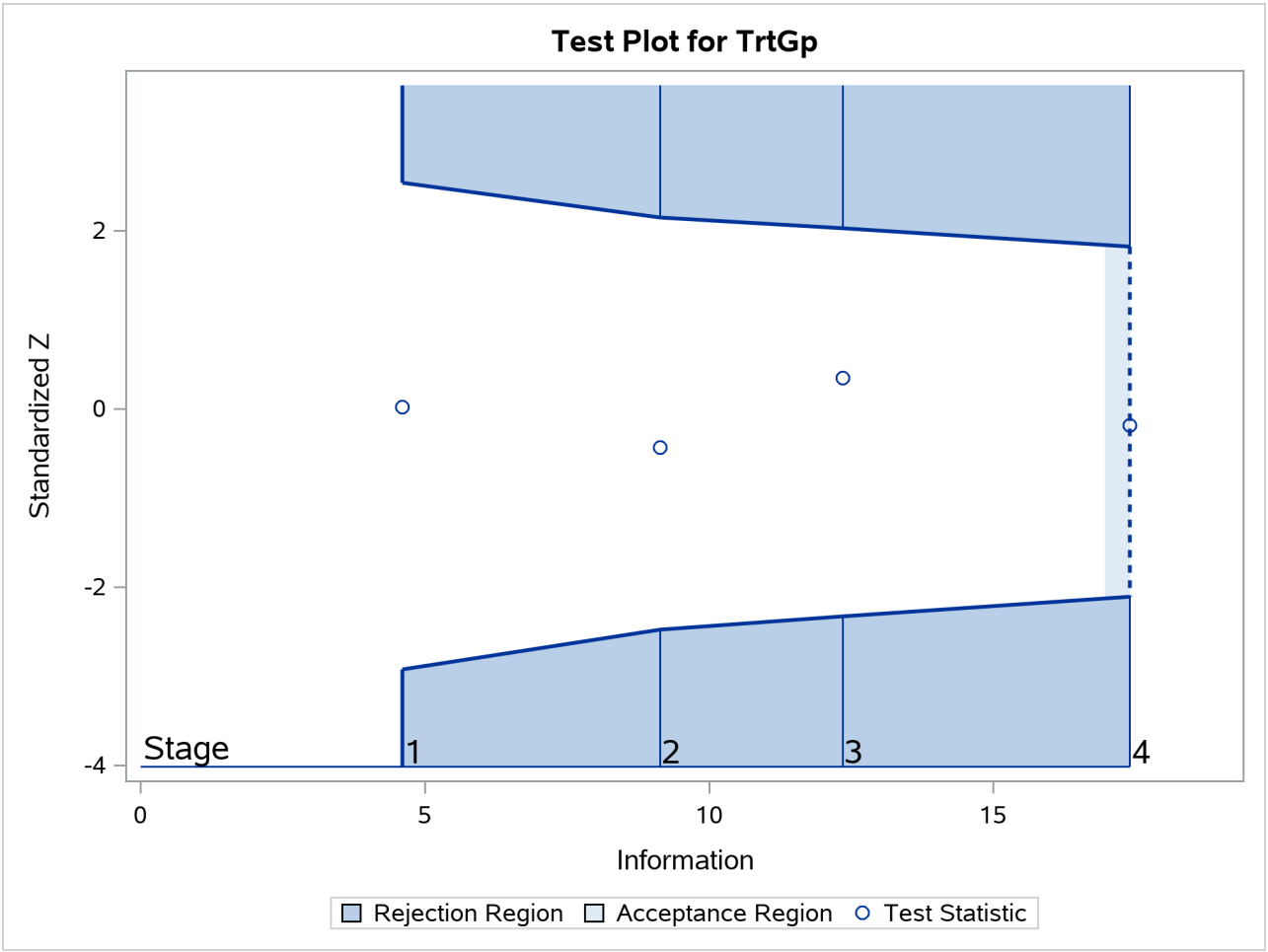
**The SEQTEST Procedure**

**Test Information (Standardized Z Scale)**
**Null Reference = 0**

| | Information Level | | Alternative Reference | | Boundary Values | | Test TrtGp | |
|---|---|---|---|---|---|---|---|---|
| _Stage_ | Proportion | Actual | Lower | Upper | Lower Alpha | Upper Alpha | Estimate | Action |
| 1 | 0.2647 | 4.607347 | -1.48783 | 1.48783 | -2.92457 | 2.54086 | 0.01795 | Continue |
| 2 | 0.5248 | 9.132918 | -2.09475 | 2.09475 | -2.47689 | 2.14819 | -0.43552 | Continue |
| 3 | 0.7095 | 12.34753 | -2.43566 | 2.43566 | -2.32705 | 2.02634 | 0.34864 | Continue |
| 4 | 1.0000 | 17.40274 | -2.89159 | 2.89159 | -2.10447 | 1.82112 | -0.18570 | Accept Null |

The "Test Plot" displays boundary values of the design and the test statistic at the first two stages, as shown in Output 108.7.16. It also shows that the test statistic is in the "Acceptance Region" between the lower and upper $\alpha$ boundary values at stage 4.

**Output 108.7.16** Sequential Test Plot




After the stopping of a trial, the "Parameter Estimates" table in Output 108.7.17 displays the stopping stage, parameter estimate, unbiased median estimate, confidence limits, and $p$-value under the null hypothesis $H_0 : \theta = 0$.

**Output 108.7.17** Parameter Estimates

| Parameter Estimates LR Ordering | | | | | | |
|---|---|---|---|---|---|---|
| Parameter | Stopping Stage | MLE | p-Value for H0:Parm=0 | Median Estimate | 95% Confidence Limits | |
| TrtGp | 4 | -0.044514 | 0.8525 | -0.044577 | -0.51461 | 0.42538 |

As expected, the two-sided $p$-value 0.8525 is not significant at the lower $\alpha = 0.025$ level and the upper $\alpha = 0.05$ level, and the two-sided 95% confidence interval contains the null value zero. The $p$-value, unbiased median estimate, and lower confidence limit depend on the ordering of the sample space $(k, z)$, where $k$ is

the stage number and $z$ is the standardized $Z$ statistic. With the specified LR ordering, the two-sided $p$-value is derived from the one-sided $p$-value

$$p_u = \sum_{k=1}^{4} P_{\theta=0}\left(Z_k \geq z_4 \mid _a_{k'} < Z_{k'} < a_{k'}, k' < k\right)$$

where $z_4 = -0.1857$ is the observed test statistic at stage 4, $Z_k$ is a standardized normal variate at stage $k$, and $_a_{k'}$ and $a_{k'}$ are the stage $k$ lower and upper rejection boundary values, respectively.

Thus,

$$p_u = \alpha_u + P_{\theta=0}\left(z_4 \leq Z_4 < a_4 \mid _a_{k'} < Z_{k'} < a_{k'}, k' < 4\right)$$

where $\alpha_u = 0.05$ is the upper $\alpha$ level and $a_4 = 1.82112$.

Since $P_{\theta=0}\left(z_4 \leq Z_4 \leq a_4 \mid _a_{k'} < Z_{k'} < a_{k'}, k' < 4\right) = 0.52374$, $p_u = 0.05 + 0.52374 = 0.57374$, which is greater than 0.50. Thus, the two-sided $p$-value is given by $2 \times (1.0 - p_u) = 0.8525$.

## Example 108.8: Testing an Effect in a Logistic Regression Model

This example requests a two-sided test for the dose effect in a dose-response model (Whitehead 1997, pp. 262–263). Consider the logistic regression model

$$\text{logit}(p) = \log(\frac{p}{1-p}) = \beta_0 + \beta_1 \text{ LDose}$$

where $p = \text{Prob}(\text{Resp} = 1 \mid \text{LDose})$ is the response probability to be modeled for the binary response Resp and LDose = log( Dose +1) is the covariate. The dose levels are 0 for the control group, and they are 1, 3, and 6 for the three treatment groups.

Following the derivations in the section "Test for a Parameter in the Logistic Regression Model" on page 8902 in Chapter 107, "The SEQDESIGN Procedure," the required sample size can be derived from

$$N = I_X \frac{\sigma_y^2}{(1 - r_x^2)\,\sigma_x^2}$$

where $\sigma_y^2$ is the variance of the response variable in the logistic regression model, $r_x^2$ is the proportion of variance of LDose explained by other covariates, and $\sigma_x^2$ is the variance of LDose.

Since LDose is the only covariate in the model, $r_x^2 = 0$. For a logistic model, the variance $\sigma^2$ can be estimated by

$$\sigma_y^2 = \frac{1}{\hat{p}(1-\hat{p})}$$

where $\hat{p}$ is the estimated probability of the response variable Resp. Thus, the sample size can be computed as

$$N = I_X \frac{1}{p(1-p)} \frac{1}{\sigma_x^2}$$

The null hypothesis $H_0 : \beta_1 = 0$ corresponds to no treatment effect. Suppose that the alternative hypothesis $H_1 : \beta_1 = 0.5$ is the reference improvement that should be detected at a 0.90 level.

Note that $\beta_1 = 0.5$ corresponds to an odds ratio of 2 between the treatment group with dose level 3 and the control group. The log odds ratio between the two groups is

$$\log\left(\frac{p_t(1-p_c)}{(1-p_t)p_0}\right) = \log\left(\frac{p_t}{1-p_t}\right) - \log\left(\frac{p_c}{1-p_c}\right)$$

which corresponds to

$$(\beta_0 + \beta_1 \log(3+1)) - (\beta_0 + \beta_1 \log(1)) = \beta_1 \log(4) = \log(2)$$

If the same number of patients are assigned in each of the four groups, then the MLE of the variance of LDose is $\hat{\sigma}_x^2 = 0.5345$. Further, if the response rate is 0.40, then the required sample size can be derived using the SAMPLESIZE statement in the SEQDESIGN procedure.

The following statements invoke the SEQDESIGN procedure and request a three-stage group sequential design for normally distributed data. The design has a null hypothesis of no treatment effect $H_0 : \beta_1 = 0$ with early stopping to reject the null hypothesis with a two-sided alternative hypothesis $H_1 : \beta_1 = \pm 0.5$.

```
ods graphics on;
proc seqdesign altref=0.5;
   TwoSidedErrorSpending: design method=errfuncpow
                                 method(loweralpha)=errfuncpow(rho=1)
                                 method(upperalpha)=errfuncpow(rho=3)
                                 nstages=3
                                 stop=both;
   samplesize model=logistic( prop=0.4 xvariance=0.5345);
   ods output Boundary=Bnd_Dose;
run;
```

The ODS OUTPUT statement with the BOUNDARY=BND_DOSE option creates an output data set named BND_DOSE which contains the resulting boundary information for the subsequent sequential tests.

The “Design Information” table in Output 108.8.1 displays design specifications and derived statistics. Since the alternative reference is specified, the maximum information 47.22445 is derived.

**Output 108.8.1** Error Spending Design Information

**The SEQDESIGN Procedure**
**Design: TwoSidedErrorSpending**

| Design Information | |
|---|---|
| **Statistic Distribution** | Normal |
| **Boundary Scale** | Standardized Z |
| **Alternative Hypothesis** | Two-Sided |
| **Early Stop** | Accept/Reject Null |
| **Method** | Error Spending |
| **Boundary Key** | Both |
| **Alternative Reference** | 0.5 |
| **Number of Stages** | 3 |
| **Alpha** | 0.05 |
| **Beta (Lower)** | 0.1 |
| **Beta (Upper)** | 0.07871 |
| **Power (Lower)** | 0.9 |
| **Power (Upper)** | 0.92129 |
| **Max Information (Percent of Fixed Sample)** | 103.7223 |
| **Max Information** | 47.22445 |
| **Null Ref ASN (Percent of Fixed Sample)** | 79.47628 |
| **Lower Alt Ref ASN (Sample Size)** | 234.1646 |
| **Upper Alt Ref ASN (Sample Size)** | 270.4058 |

The "Boundary Information" table in Output 108.8.2 displays the information level, alternative reference, and boundary values at each stage. By default (or equivalently if you specify BOUNDARYSCALE=STDZ), the boundary values are displayed with the standardized $Z$ statistic scale.

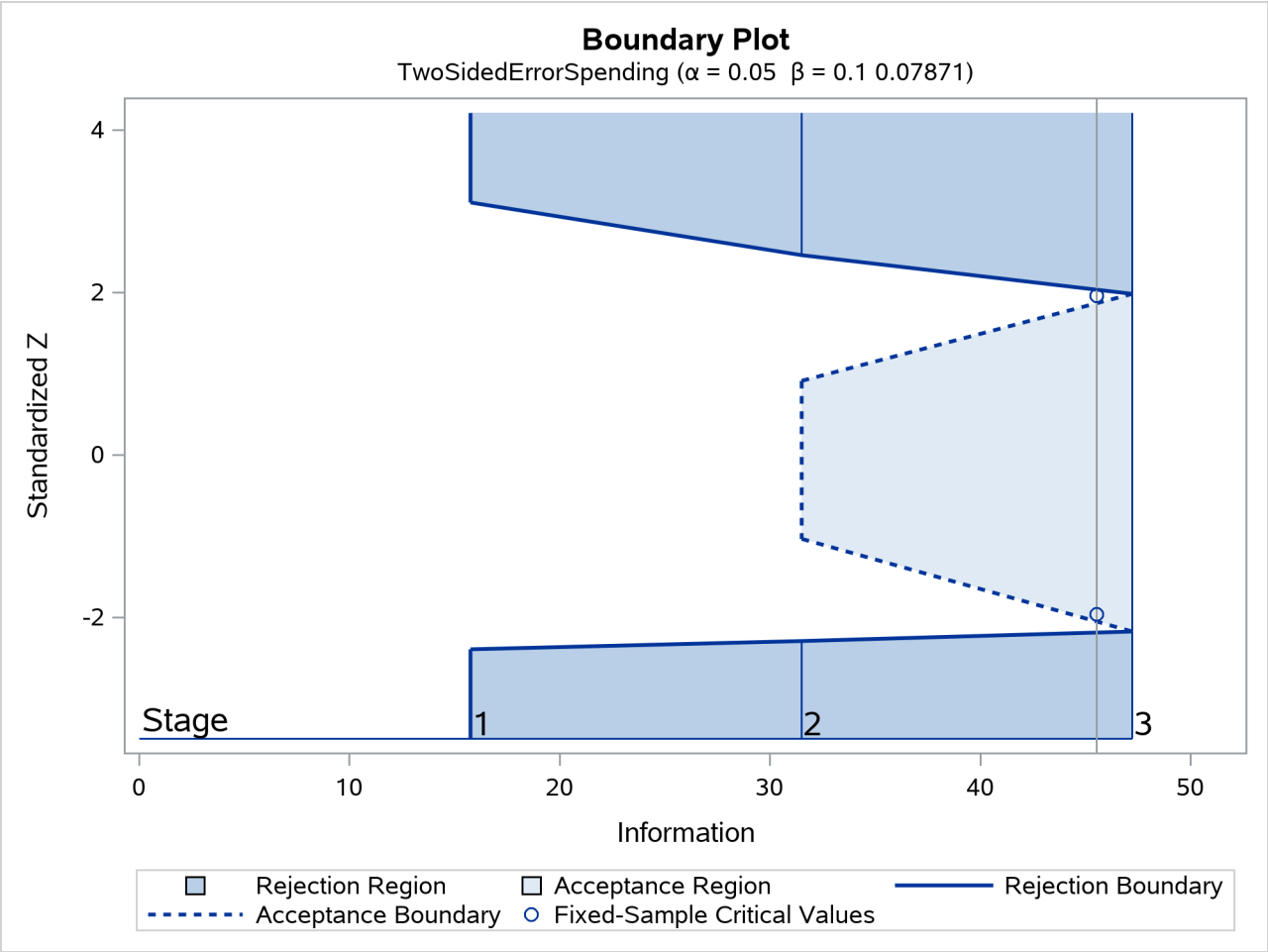
**Output 108.8.2** Boundary Information

**Boundary Information (Standardized Z Scale)**
**Null Reference = 0**

| | Information Level | | | Alternative Reference | | Boundary Values | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Lower | | Upper | |
| _Stage_ | Proportion | Actual | N | Lower | Upper | Alpha | Beta | Beta | Alpha |
| 1 | 0.3333 | 15.74148 | 122.7119 | -1.98378 | 1.98378 | -2.39398 | . | . | 3.11302 |
| 2 | 0.6667 | 31.48297 | 245.4238 | -2.80548 | 2.80548 | -2.29380 | -1.02812 | 0.91855 | 2.46193 |
| 3 | 1.0000 | 47.22445 | 368.1357 | -3.43600 | 3.43600 | -2.17479 | -2.17479 | 1.98311 | 1.98311 |

With ODS Graphics enabled, a detailed boundary plot with the rejection and acceptance regions is displayed, as shown in Output 108.8.3.

**Output 108.8.3** Boundary Plot




With the SAMPLESIZE statement, the "Sample Size Summary" table in Output 108.8.4 displays the parameters for the sample size computation.

**Output 108.8.4** Required Sample Size Summary

| Sample Size Summary | |
|---|---|
| **Test** | Logistic Reg Parameter |
| **Parameter** | 0.5 |
| **Proportion** | 0.4 |
| **X Variance** | 0.5345 |
| **R Square (X)** | 0 |
| **Max Sample Size** | 368.1357 |
| **Expected Sample Size (Null Ref)** | 282.0807 |
| **Expected Sample Size (Alt Ref)** | 270.4058 |

The "Sample Sizes" table in Output 108.8.5 displays the required sample sizes for the group sequential clinical trial.

**Output 108.8.5** Required Sample Sizes

| Sample Sizes (N) Z Test for Logistic Regression Parameter | | | | |
|---|---|---|---|---|
| | Fractional N | | Ceiling N | |
| _Stage_ | N | Information | N | Information |
| 1 | 122.71 | 15.7415 | 123 | 15.7784 |
| 2 | 245.42 | 31.4830 | 246 | 31.5569 |
| 3 | 368.14 | 47.2245 | 369 | 47.3353 |

That is, 123 new patients are needed in each stage and the number is rounded up to 124 for each stage to have a multiple of four for the four dose levels in the trial. Note that since the sample sizes are derived from an estimated response probability and are rounded up, the actual information levels might not match the corresponding target information levels.

Output 108.8.6 lists the first 10 observations of the trial data.

**Output 108.8.6** Clinical Trial Data

**First 10 Obs in the Trial Data**

| Obs | Resp | Dose | LDose |
|---|---|---|---|
| **1** | 0 | 0 | 0.00000 |
| **2** | 0 | 1 | 0.69315 |
| **3** | 1 | 3 | 1.38629 |
| **4** | 1 | 6 | 1.94591 |
| **5** | 1 | 0 | 0.00000 |
| **6** | 1 | 1 | 0.69315 |
| **7** | 1 | 3 | 1.38629 |
| **8** | 1 | 6 | 1.94591 |
| **9** | 0 | 0 | 0.00000 |
| **10** | 0 | 1 | 0.69315 |

The following statements use the LOGISTIC procedure to estimate the slope $\beta_1$ and its associated standard error at stage 1:

```
proc logistic data=Dose_1;
   model Resp(event='1')= LDose;
   ods output ParameterEstimates=Parms_Dose1;
run;
```

The following statements create and display (in Output 108.8.7) the input data set that contains slope $\beta_1$ and its associated standard error for the SEQTEST procedure:

```
data Parms_Dose1;
   set Parms_Dose1;
   if Variable='LDose';
   _Scale_='MLE';
   _Stage_= 1;
```

```
   keep _Scale_ _Stage_ Variable Estimate StdErr;
run;

proc print data=Parms_Dose1;
   title 'Statistics Computed at Stage 1';
run;
```

**Output 108.8.7** Statistics Computed at Stage 1

**Statistics Computed at Stage 1**

| Obs | Variable | Estimate | StdErr | _Scale_ | _Stage_ |
|---|---|---|---|---|---|
| 1 | LDose | 0.5741 | 0.2544 | MLE | 1 |

The following statements invoke the SEQTEST procedure to test for early stopping at stage 1:

```
ods graphics on;
proc seqtest Boundary=Bnd_Dose
             Parms(testvar=LDose)=Parms_Dose1
             infoadj=prop
             order=mle
             boundaryscale=mle
             ;
   ods output Test=Test_Dose1;
run;
```

The BOUNDARY= option specifies the input data set that provides the boundary information for the trial at stage 1, which was generated in the SEQDESIGN procedure. The PARMS=PARMS_DOSE1 option specifies the input data set PARMS_DOSE1 that contains the test statistic and its associated standard error at stage 1, and the TESTVAR=LDOSE option identifies the test variable LDOSE in the data set.

If the computed information level for stage 1 is not the same as the value provided in the BOUNDARY= data set, the INFOADJ=PROP option (which is the default) proportionally adjusts the information levels at future interim stages from the levels provided in the BOUNDARY= data set. The ORDER=MLE option uses the MLE ordering to derive the $p$-value, the unbiased median estimate, and the confidence limits for the regression slope estimate.

The ODS OUTPUT statement with the TEST=TEST_DOSE1 option creates an output data set named TEST_DOSE1 which contains the updated boundary information for the test at stage 1. The data set also provides the boundary information that is needed for the group sequential test at the next stage.

The "Design Information" table in Output 108.8.8 displays design specifications. By default (or equivalently if you specify BOUNDARYKEY=ALPHA), the boundary values are modified for the new information levels to maintain the Type I $\alpha$ level. The maximum information remains the same as the design stored in the BOUNDARY= data set, but the derived Type II error probability $\beta$ and power $1 - \beta$ are different because of the new information levels.

**Output 108.8.8** Design Information

**The SEQTEST Procedure**

| Design Information | |
|---|---|
| **BOUNDARY Data Set** | WORK.BND_DOSE |
| **Data Set** | WORK.PARMS_DOSE1 |
| **Statistic Distribution** | Normal |
| **Boundary Scale** | MLE |
| **Alternative Hypothesis** | Two-Sided |
| **Early Stop** | Accept/Reject Null |
| **Number of Stages** | 3 |
| **Alpha** | 0.05 |
| **Beta (Lower)** | 0.09992 |
| **Beta (Upper)** | 0.07871 |
| **Power (Lower)** | 0.90008 |
| **Power (Upper)** | 0.92129 |
| **Max Information (Percent of Fixed Sample)** | 103.7231 |
| **Max Information** | 47.2244524 |
| **Null Ref ASN (Percent of Fixed Sample)** | 79.45049 |
| **Lower Alt Ref ASN (Percent of Fixed Sample)** | 66.05269 |
| **Upper Alt Ref ASN (Percent of Fixed Sample)** | 76.24189 |

The "Test Information" table in Output 108.8.9 displays the boundary values for the test statistic with the specified MLE scale.

**Output 108.8.9** Sequential Tests

**Test Information (MLE Scale)**
**Null Reference = 0**

| | Information Level | | Alternative Reference | | Boundary Values Lower | | Upper | | Test LDose | |
|---|---|---|---|---|---|---|---|---|---|---|
| _Stage_ | Proportion | Actual | Lower | Upper | Alpha | Beta | Beta | Alpha | Estimate | Action |
| 1 | 0.3272 | 15.45062 | -0.50000 | 0.50000 | -0.61078 | . | . | 0.79337 | 0.57409 | Continue |
| 2 | 0.6636 | 31.33753 | -0.50000 | 0.50000 | -0.40974 | -0.18169 | 0.16222 | 0.44033 | . | |
| 3 | 1.0000 | 47.22445 | -0.50000 | 0.50000 | -0.31633 | -0.31633 | 0.28860 | 0.28860 | . | |

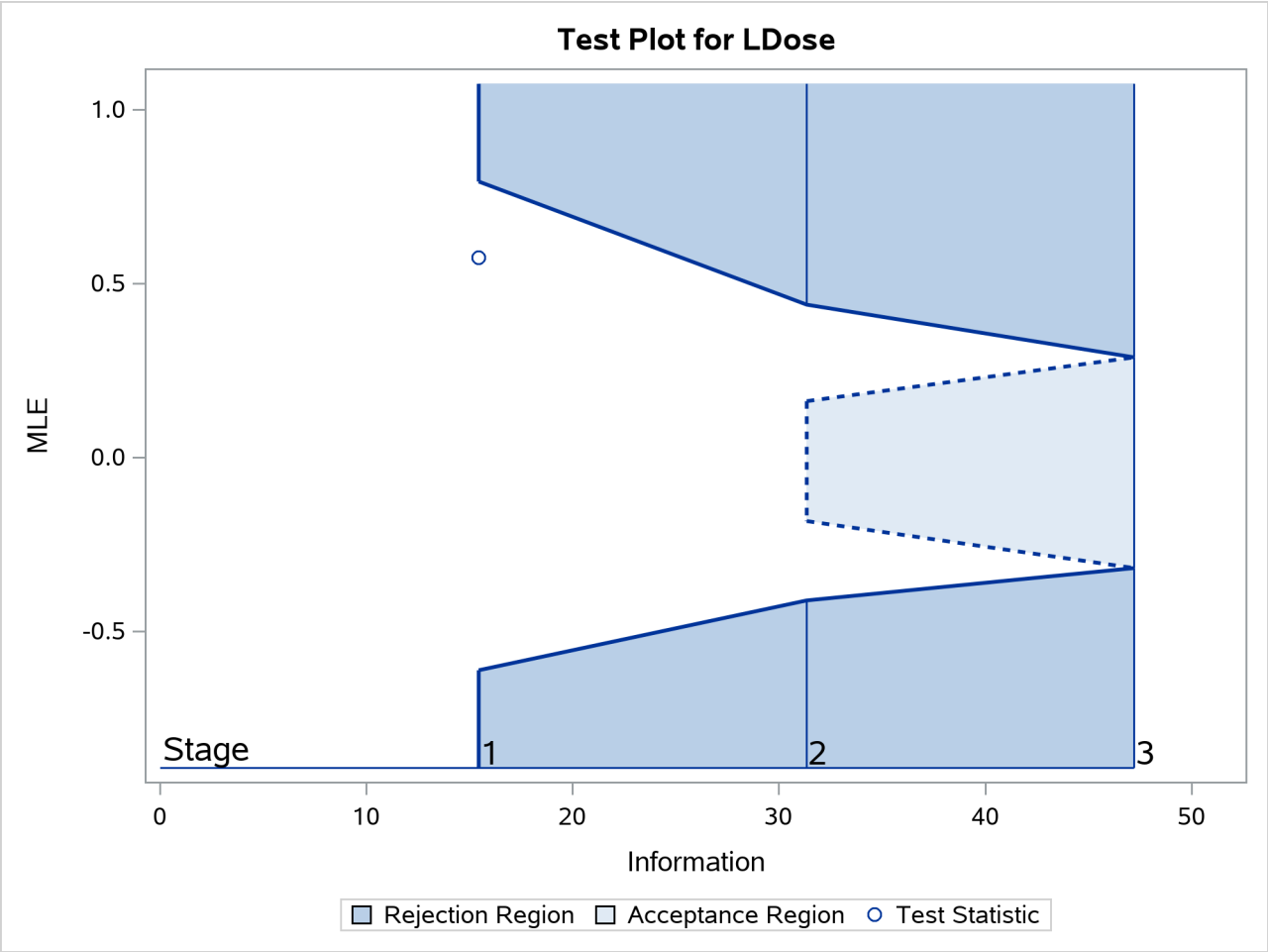
The information level at stage 1 is derived from the standard error $s_1$ in the PARMS= data set,

$$I_1 = \frac{1}{s_1^2} = \frac{1}{0.2544^2} = 15.45$$

With the INFOADJ=PROP option (which is the default), the information level at stage 2 is derived proportionally from the observed information at stage 1 and the information levels in the BOUNDARY= data set. At stage 1, the $\beta$ boundary values are missing and there is no early stopping to accept $H_0$. The MLE statistic 0.57409 is between the lower and upper $\alpha$ boundaries, so the trial continues to the next stage.

With ODS Graphics enabled, a boundary plot with the boundary values and test statistics is displayed, as shown in Output 108.8.10. As expected, the test statistic is in the continuation region below the upper alpha boundary.

**Output 108.8.10** Sequential Test Plot




The following statements use the LOGISTIC procedure to estimate the slope $\beta_1$ and its associated standard error at stage 2:

```
proc logistic data=dose_2;
   model Resp(event='1')=LDose;
   ods output ParameterEstimates=Parms_Dose2;
run;
```

The following statements create and display (in Output 108.8.11) the input data set that contains slope $\beta_1$ and its associated standard error at stage 2 for the SEQTEST procedure:

```
data Parms_Dose2;
   set Parms_Dose2;
   if Variable='LDose';
   _Scale_='MLE';
   _Stage_= 2;
   keep _Scale_ _Stage_ Variable Estimate StdErr;
run;

proc print data=Parms_Dose2;
   title 'Statistics Computed at Stage 2';
run;
```

**Output 108.8.11** Statistics Computed at Stage 2

**Statistics Computed at Stage 2**

| Obs | Variable | Estimate | StdErr | _Scale_ | _Stage_ |
|---|---|---|---|---|---|
| 1 | LDose | 0.5213 | 0.1788 | MLE | 2 |

The following statements invoke the SEQTEST procedure to test for early stopping at stage 2:

```
ods graphics on;
proc seqtest Boundary=Test_Dose1
             Parms(Testvar=LDose)=Parms_Dose2
             infoadj=prop
             order=mle
             boundaryscale=mle
             rci
             plots=rci
             ;
   ods output Test=Test_Dose2;
run;
```

The BOUNDARY= option specifies the input data set that provides the boundary information for the trial at stage 2, which was generated by the SEQTEST procedure at the previous stage. The PARMS= option specifies the input data set that contains the test statistic and its associated standard error at stage 2, and the TESTVAR= option identifies the test variable in the data set.

The ORDER=MLE option uses the MLE ordering to derive the $p$-value, unbiased median estimate, and confidence limits for the regression slope estimate.

The ODS OUTPUT statement with the TEST=TEST_DOSE2 option creates an output data set named TEST_DOSE2 which contains the updated boundary information for the test at stage 2. The data set also provides the boundary information that is needed for the group sequential test at the next stage.

The "Design Information" table in Output 108.8.12 displays design specifications. By default (or equivalently if you specify BOUNDARYKEY=ALPHA), the boundary values are modified for the new information levels to maintain the Type I $\alpha$ level.

**Output 108.8.12** Design Information

**The SEQTEST Procedure**

| Design Information | |
|---|---|
| **BOUNDARY Data Set** | WORK.TEST_DOSE1 |
| **Data Set** | WORK.PARMS_DOSE2 |
| **Statistic Distribution** | Normal |
| **Boundary Scale** | MLE |
| **Alternative Hypothesis** | Two-Sided |
| **Early Stop** | Accept/Reject Null |
| **Number of Stages** | 3 |
| **Alpha** | 0.05 |
| **Beta (Lower)** | 0.0999 |
| **Beta (Upper)** | 0.07871 |
| **Power (Lower)** | 0.9001 |
| **Power (Upper)** | 0.92129 |
| **Max Information (Percent of Fixed Sample)** | 103.7227 |
| **Max Information** | 47.2244524 |
| **Null Ref ASN (Percent of Fixed Sample)** | 79.44086 |
| **Lower Alt Ref ASN (Percent of Fixed Sample)** | 66.04641 |
| **Upper Alt Ref ASN (Percent of Fixed Sample)** | 76.22739 |

The information is derived from the standard error associated with the slope estimate at the final stage and is larger than the target level. The derived Type II error probability $\beta$ and power $1 - \beta$ are different because of the new information levels.

The "Test Information" table in Output 108.8.13 displays the boundary values for the test statistic with the specified MLE scale. The information levels are derived from the standard errors in the PARMS= data set. At stage 2, the slope estimate 0.52128 is larger than 0.44091, the upper $\alpha$ boundary value, the trial stops to reject the null hypothesis of no treatment effect.

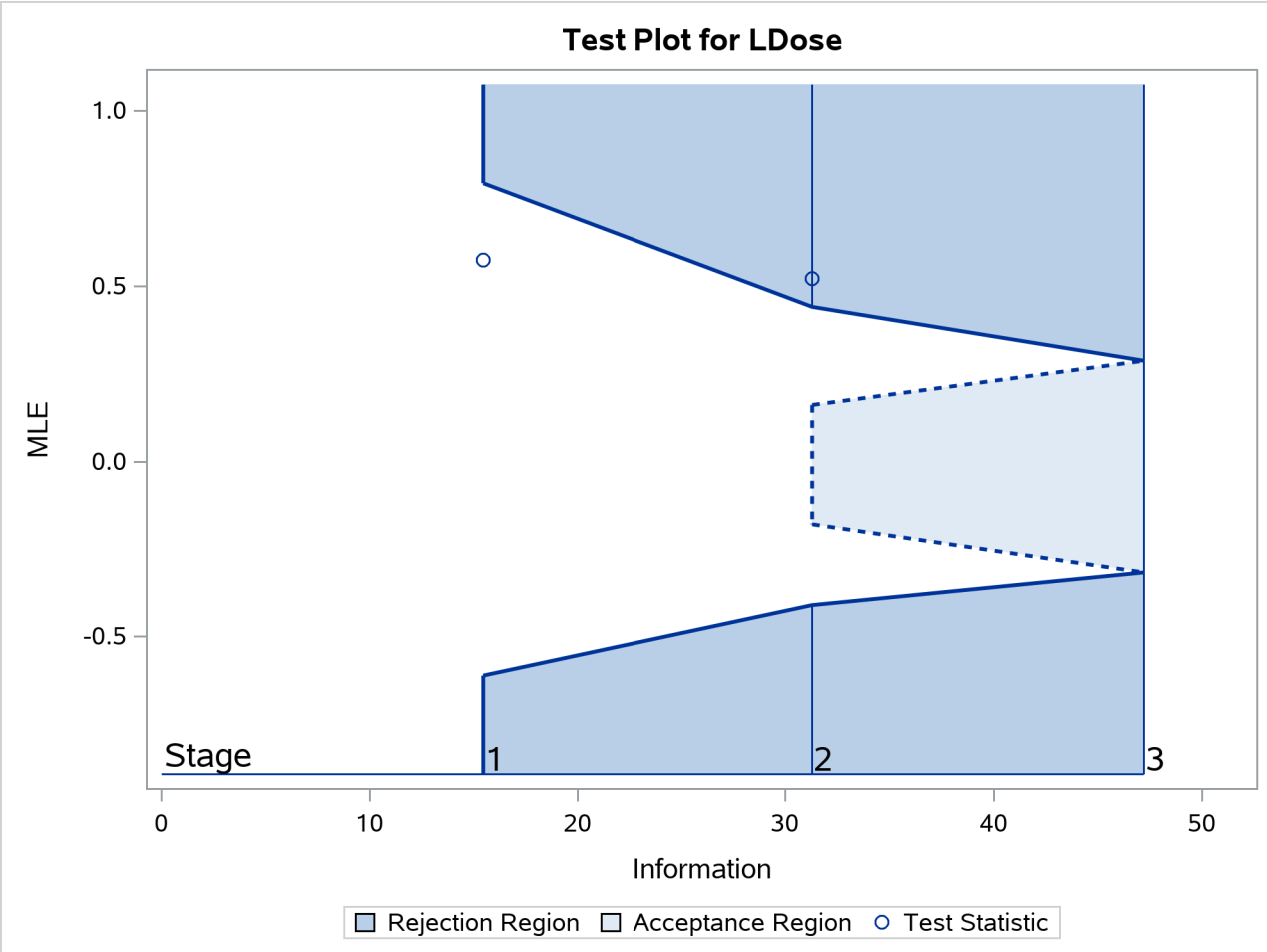
**Output 108.8.13** Sequential Tests

**Test Information (MLE Scale)**
**Null Reference = 0**

| | Information Level | | Alternative Reference | | Boundary Values | | | | Test LDose | |
|---|---|---|---|---|---|---|---|---|---|---|
| _Stage_ | Proportion | Actual | Lower | Upper | Lower Alpha | Lower Beta | Upper Beta | Upper Alpha | Estimate | Action |
| 1 | 0.3272 | 15.45062 | -0.50000 | 0.50000 | -0.61078 | . | . | 0.79337 | 0.57409 | Continue |
| 2 | 0.6624 | 31.28346 | -0.50000 | 0.50000 | -0.41028 | -0.18112 | 0.16166 | 0.44091 | 0.52128 | Reject Null |
| 3 | 1.0000 | 47.22445 | -0.50000 | 0.50000 | -0.31628 | -0.31628 | 0.28861 | 0.28861 | . | |

With ODS Graphics enabled, a boundary plot with the boundary values and test statistics is displayed, as shown in Output 108.8.14. As expected, the test statistic is above the upper $\alpha$ boundary in the upper rejection region at stage 2.

**Output 108.8.14** Sequential Test Plot




After a trial is stopped, the "Parameter Estimates" table in Output 108.8.15 displays the stopping stage, parameter estimate, unbiased median estimate, confidence limits, and the $p$-value under the null hypothesis $H_0 : \beta_1 = 0$.

**Output 108.8.15** Parameter Estimates

| Parameter Estimates MLE Ordering | | | | | | |
|---|---|---|---|---|---|---|
| Parameter | Stopping Stage | MLE | p-Value for H0:Parm=0 | Median Estimate | 95% Confidence Limits | |
| LDose | 2 | 0.521275 | 0.0050 | 0.502647 | 0.15745 | 0.85154 |

With the ORDER=MLE option, the MLE ordering is used to compute the $p$-value, unbiased median estimate, and confidence limits. As expected, the $p$-value 0.005 is significant at the $\alpha = 0.05$ level and the confidence interval does not contain the null reference zero.

With the RCI option, the "Repeated Confidence Intervals" table in Output 108.8.16 displays repeated confidence intervals for the parameter. For a two-sided test, since the rejection lower repeated confidence limit 0.0804 is greater than the null reference zero, the trial is stopped to reject the hypothesis.

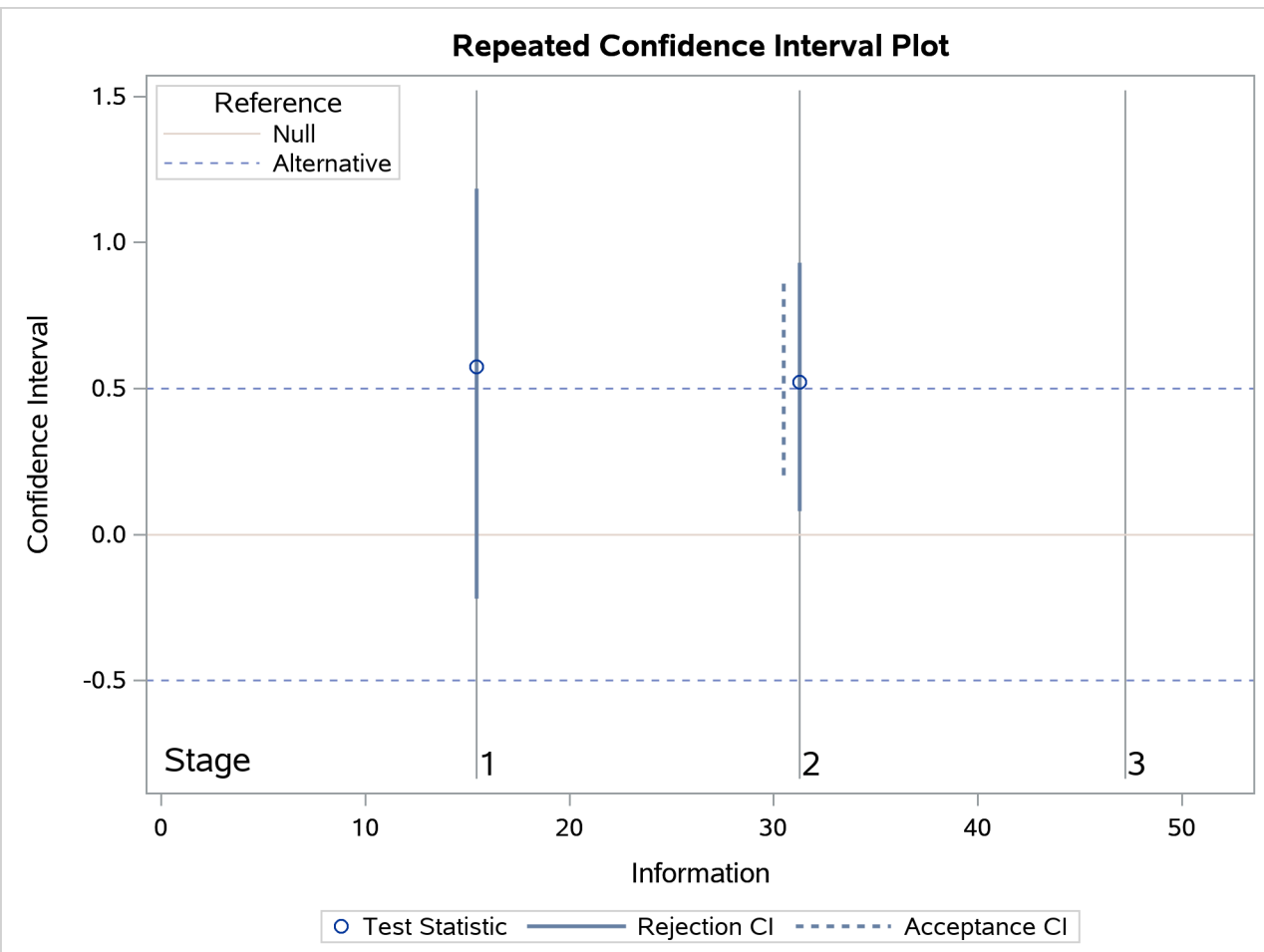
**Output 108.8.16** Repeated Confidence Intervals

| Repeated Confidence Intervals | | | | |
|---|---|---|---|---|
| | | | Rejection Boundary | |
| _Stage_ | Information Level | Parameter Estimate | Lower 97.5% Repeated CL | Upper 97.5% Repeated CL |
| 1 | 15.4506 | 0.57409 | -0.2193 | 1.1849 |
| 2 | 31.2835 | 0.52128 | 0.0804 | 0.9316 |

| Repeated Confidence Intervals | | |
|---|---|---|
| | Acceptance Boundary | |
| _Stage_ | Lower 90.01% Repeated CL | Upper 92.13% Repeated CL |
| 1 | . | . |
| 2 | 0.2024 | 0.8596 |

With the PLOTS=RCI option, the "Repeated Confidence Intervals Plot" displays repeated confidence intervals for the parameter, as shown in Output 108.8.17. It shows that the null reference zero is inside the rejection repeated confidence interval at stage 1 but outside the rejection repeated confidence interval at stage 2. This implies that the study stops at stage 2 to reject the hypothesis.

**Output 108.8.17** Repeated Confidence Intervals Plot



Note that the hypothesis is accepted if at any stage, the acceptance repeated confidence interval falls within the interval $(-0.5, 0.5)$ of the alternative references.

## Example 108.9: Conducting a Trial with a Nonbinding Acceptance Boundary

This example demonstrates a trail with a nonbinding acceptance boundary. The design is similar to the design in Example 108.1, but has a nonbinding beta boundary.

A clinic is studying the effect of vitamin C supplements in treating flu symptoms. The study consists of patients in the clinic who have exhibited the first sign of flu symptoms within the last 24 hours. These patients are randomly assigned to either the control group (which receives placebo pills) or the treatment group (which receives large doses of vitamin C supplements). At the end of a five-day period, the flu symptoms of each patient are recorded.

Suppose that you know from past experience that flu symptoms disappear in five days for 60% of patients who experience flu symptoms. The clinic would like to detect a 75% symptom disappearance with a high probability. A test that compares the proportions directly specifies the null hypothesis $H_0 : \theta = p_t - p_c = 0$ with a one-sided alternative $H_1 : \theta > 0$ and a power of 0.90 at $H_1 : \theta = 0.15$, where $p_t$ and $p_c$ are the proportions of symptom disappearance in the treatment group and control group, respectively.

The following statements invoke the SEQDESIGN procedure and request a four-stage group sequential design by using an O'Brien-Fleming method for normally distributed data.

```
ods graphics on;
proc seqdesign altref=0.15 errspend
               ;
   NonbindingDesign: design nstages=4
                     method=obf
                     alt=upper
                     stop=both(betaboundary=nonbinding)
                     alpha=0.025
                     ;
   samplesize model=twosamplefreq(nullprop=0.6 test=prop);
ods output Boundary=Bnd_Count;
run;
```

The ALT=UPPER option specifies a one-sided alternative hypothesis, and the STOP=BOTH option specifies early stopping to reject or accept the null hypothesis $H_0$, The BETABOUNDARY=NONBINDING suboption requests nonbinding beta boundary to have the flexibility to continue the trial when a test statistic falls in the acceptance region at interim stages (Zhu, Ni, and Yao 2011, pp. 132–133). The ODS OUTPUT statement with the BOUNDARY=BND_COUNT option creates an output data set named BND_COUNT which contains the resulting boundary information for the subsequent sequential tests.

The "Design Information" table in Output 108.9.1 displays design specifications. With the specified alternative hypothesis $H_1 : \theta = 0.15$, the maximum information is derived to achieve a power of 0.90 at $H_1$. The derived fixed-sample information ratio 1.107 is the maximum information needed for a group sequential design relative to its corresponding fixed-sample design. Compare to the default BETABOUNDARY=BINDING option, the BETABOUNDARY=NONBINDING option requires a larger sample size for the design.

**Output 108.9.1** O'Brien-Fleming Design Information

**The SEQDESIGN Procedure**
**Design: NonbindingDesign**

| Design Information | |
|---|---|
| **Statistic Distribution** | Normal |
| **Boundary Scale** | Standardized Z |
| **Alternative Hypothesis** | Upper |
| **Early Stop** | Accept(Nonbinding)/Reject Null |
| **Method** | O'Brien-Fleming |
| **Boundary Key** | Both |
| **Alternative Reference** | 0.15 |
| **Number of Stages** | 4 |
| **Alpha (Binding Beta Boundary)** | 0.02228 |
| **Alpha (Nonbinding Beta Boundary)** | 0.025 |
| **Beta** | 0.1 |
| **Power** | 0.9 |
| **Max Information (Percent of Fixed Sample)** | 110.7138 |
| **Max Information** | 517.0296 |
| **Null Ref ASN (Percent of Fixed Sample)** | 62.29796 |
| **Alt Ref ASN (Percent of Fixed Sample)** | 78.5392 |

The "Boundary Information" table in Output 108.9.2 displays the information level, alternative reference, and boundary values at each stage. With the default BOUNDARYSCALE=STDZ option, the SEQDESIGN procedure displays the output boundaries with the standardized normal $Z$ scale.

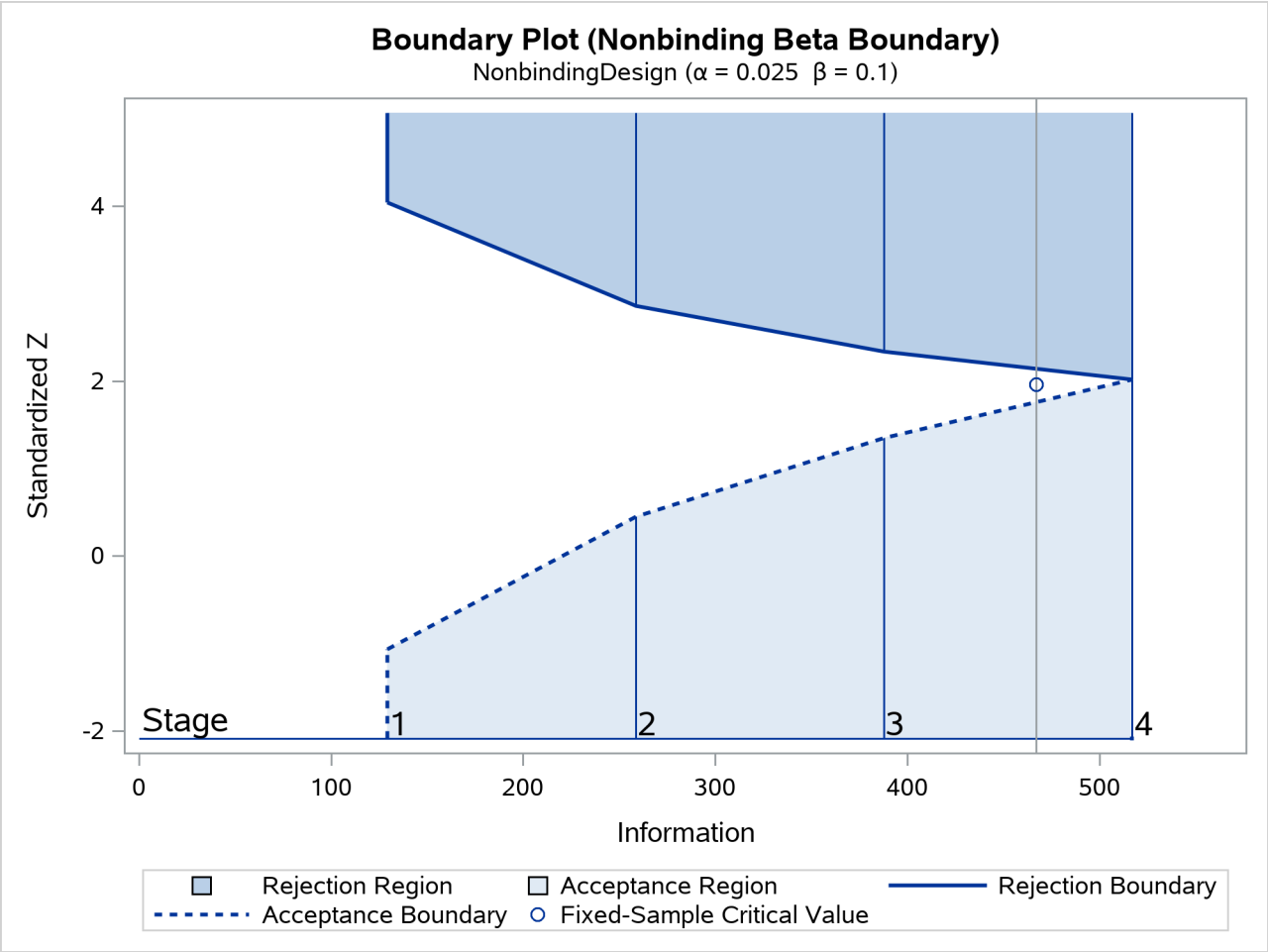
**Output 108.9.2** O'Brien-Fleming Boundary Information

**Boundary Information (Standardized Z Scale)**
**Nonbinding Beta Boundary, Null Reference = 0**

| | Information Level | | | Alternative Reference | Boundary Values | |
|---|---|---|---|---|---|---|
| | | | | | Upper | |
| _Stage_ | Proportion | Actual | N | Upper | Beta | Alpha |
| 1 | 0.2500 | 129.2574 | 110.5151 | 1.70537 | -1.06752 | 4.04859 |
| 2 | 0.5000 | 258.5148 | 221.0302 | 2.41176 | 0.45103 | 2.86279 |
| 3 | 0.7500 | 387.7722 | 331.5452 | 2.95379 | 1.35286 | 2.33746 |
| 4 | 1.0000 | 517.0296 | 442.0603 | 3.41074 | 2.02430 | 2.02430 |

With ODS Graphics enabled, a detailed boundary plot with the rejection and acceptance regions is displayed, as shown in Output 108.9.3. The horizontal axis indicates the information levels for the design. The stages are indicated by vertical lines with accompanying stage numbers. If the test statistic at a stage is in a rejection region, the trial stops and the hypothesis is rejected. If the test statistic is in an acceptance region, then the trial either stops to accept the hypothesis or continues to the next stage. If the statistic is not in a rejection or an acceptance region, the trial continues to the next stage.

**Output 108.9.3** O'Brien-Fleming Boundary Plot




The boundary plot also displays the information level and critical value for the corresponding fixed-sample design. The solid and dashed lines at the fixed-sample information level correspond to the rejection and acceptance lines, respectively.

The "Error Spending Information (Nonbinding Beta Boundary)" in Output 108.9.4 displays cumulative error spending at each stage for each boundary. With a nonbinding beta boundary, the $\alpha$ spending at each stage is computed by using the $\alpha$ boundary only.

**Output 108.9.4** Error Spending Information

**Error Spending Information (Nonbinding Beta Boundary)**

| | Information Level | Cumulative Error Spending | |
|---|---|---|---|
| | | Upper | |
| _Stage_ | Proportion | Beta | Alpha |
| 1 | 0.2500 | 0.00278 | 0.00003 |
| 2 | 0.5000 | 0.02603 | 0.00211 |
| 3 | 0.7500 | 0.06343 | 0.01046 |
| 4 | 1.0000 | 0.10000 | 0.02500 |

With the SAMPLESIZE statement, the maximum information is used to derive the required sample size for the study. The "Sample Size Summary" table in Output 108.9.5 displays parameters for the sample size computation.

**Output 108.9.5** Required Sample Size Summary

| Sample Size Summary | |
|---|---|
| **Test** | Two-Sample Proportions |
| **Null Proportion** | 0.6 |
| **Proportion (Group A)** | 0.75 |
| **Test Statistic** | Z for Proportion |
| **Reference Proportions** | Alt Ref |
| **Max Sample Size** | 442.0603 |
| **Expected Sample Size (Null Ref)** | 248.7446 |
| **Expected Sample Size (Alt Ref)** | 313.5929 |

With the derived maximum information and the specified MODEL= option in the SAMPLESIZE statement, the total sample size in each group for testing the difference between two proportions under the alternative hypothesis is

$$N_1 = N_2 = (p_{1c}\,(1 - p_{1c}) + p_{1t}\,(1 - p_{1t}))\ I_X$$

where $p_{1c} = 0.6$ and $p_{1t} = p_{1c} + \theta_1 = 0.75$. By default (or equivalently if you specify REF=PROP in the MODEL=TWOSAMPLEFREQ option), the required sample sizes are computed under the alternative hypothesis. See the section "Test for the Difference between Two Binomial Proportions" on page 8895 in Chapter 107, "The SEQDESIGN Procedure," for more information about these parameters.

The "Sample Sizes (N)" table in Output 108.9.6 displays the required sample sizes at each stage, in both fractional and integer numbers. The derived sample sizes under the heading Fractional N which correspond to the design are not integers. These sample sizes are rounded up to integers under the heading Ceiling N. In practice, integer sample sizes are used, and the information levels increase slightly. Thus, 56, 111, 166, and 222 patients are needed in each group for the four stages, respectively.

**Output 108.9.6** Required Sample Sizes

| Sample Sizes (N) Two-Sample Z Test for Proportion Difference | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Fractional N | | | | Ceiling N | | | |
| _Stage_ | N | N(Grp 1) | N(Grp 2) | Information | N | N(Grp 1) | N(Grp 2) | Information |
| 1 | 110.52 | 55.26 | 55.26 | 129.3 | 112 | 56 | 56 | 131.0 |
| 2 | 221.03 | 110.52 | 110.52 | 258.5 | 222 | 111 | 111 | 259.6 |
| 3 | 331.55 | 165.77 | 165.77 | 387.8 | 332 | 166 | 166 | 388.3 |
| 4 | 442.06 | 221.03 | 221.03 | 517.0 | 444 | 222 | 222 | 519.3 |

Suppose the trial follows the study plan, and 56 patients are available in each group at stage 1. The data set count_1 contains these 108 patients. Output 108.9.7 lists the first 10 observations of the data set.

**Output 108.9.7** Clinical Trial Data

**First 10 Obs in the Trial Data**

| Obs | Trt | Resp |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 1 | 1 |
| 3 | 0 | 1 |
| 4 | 1 | 1 |
| 5 | 0 | 1 |
| 6 | 1 | 0 |
| 7 | 0 | 0 |
| 8 | 1 | 1 |
| 9 | 0 | 1 |
| 10 | 1 | 0 |

The Trt variable is a grouping variable with value 0 for a patient in the placebo control group and value 1 for a patient in the treatment group who is given vitamin C supplements. The Resp variable is an indicator variable with value 1 for a patient without flu symptoms after five days and value 0 for a patient with flu symptoms after five days.

The following statements use the GENMOD procedure to estimate the treatment effect at stage 1:

```
proc genmod data=count_1;
   model Resp= Trt;
ods output ParameterEstimates=Parms_Count1;
run;
```

Output 108.9.8 displays the treatment effect at stage 1.

**Output 108.9.8** Stage 1 Treatment Difference

**The GENMOD Procedure**

**Analysis Of Maximum Likelihood Parameter Estimates**

| Parameter | DF | Estimate | Standard Error | Wald 95% Confidence Limits | | Wald Chi-Square | Pr > ChiSq |
|---|---|---|---|---|---|---|---|
| Intercept | 1 | 0.6786 | 0.0619 | 0.5572 | 0.7999 | 120.07 | <.0001 |
| Trt | 1 | 0.0179 | 0.0876 | -0.1538 | 0.1895 | 0.04 | 0.8384 |
| Scale | 1 | 0.4634 | 0.0310 | 0.4065 | 0.5283 | | |

**Note:** The scale parameter was estimated by maximum likelihood.

The test statistic is $\hat{\theta}_1 = \hat{p}_t - \hat{p}_c = 0.0179$, and its associated standard error is

$$\sqrt{\mathrm{Var}(\hat{\theta}_1)} = \sqrt{\frac{\hat{p}_c(1-\hat{p}_c)}{56} + \frac{\hat{p}_t(1-\hat{p}_t)}{56}} = 0.0876$$

The following statements create and display (in Output 108.9.9) the data set that contains the parameter estimate at stage 1, $\hat{\theta}_1 = 0.0179$, and its associated standard error $\sqrt{\mathrm{Var}(\hat{\theta}_1)} = 0.0876$ which are used in the SEQTEST procedure:

```
data Parms_Count1;
   set Parms_Count1;
   if Parameter='Trt';
   _Scale_='MLE';
   _Stage_= 1;
   keep _Scale_ _Stage_ Parameter Estimate StdErr;
run;

proc print data=Parms_Count1;
   title 'Statistics Computed at Stage 1';
run;
```

**Output 108.9.9** Statistics Computed at Stage 1

**Statistics Computed at Stage 1**

| Obs | Parameter | Estimate | StdErr | _Scale_ | _Stage_ |
|---|---|---|---|---|---|
| 1 | Trt | 0.0179 | 0.0876 | MLE | 1 |

The initial required sample sizes are derived with the proportions $p_c = 0.6$ and $p_t = 0.75$. If the observed proportions are different from these assumed values, or if the number of available patients is different from the study plan in one of the stages, then the information level that corresponds to the test statistic is estimated from

$$I_k = \frac{1}{\mathrm{Var}(\hat{\theta}_k)}$$

The following statements invoke the SEQTEST procedure and test for early stopping at stage 1:

```
ods graphics on;
proc seqtest Boundary=Bnd_Count
             Parms(Testvar=Trt)=Parms_Count1
             betaboundary=nonbinding
             infoadj=none
             errspendmin=0.001
             errspend
             ;
ods output Test=Test_Count1;
run;
```

The BOUNDARY= option specifies the input data set that provides the boundary information for the trial at stage 1, which was generated in the SEQDESIGN procedure. The PARMS=PARMS_COUNT1 option specifies the input data set PARMS_COUNT1 that contains the test statistic and its associated standard error at stage 1, and the TESTVAR=TRT option identifies the test variable TRT in the data set.

The BETABOUNDARY=NONBINDING option requests nonbinding beta boundary to have the flexibility to continue the trial when the test statistic falls in the acceptance region at stage 1. The INFOADJ=NONE option maintains the information levels at future interim stages (2 and 3) as provided in the BOUNDARY= data set. The default BOUNDARYSCALE=STDZ option displays the output boundaries in terms of the standardized normal $Z$ scale.

The O'Brien-Fleming design is conservative in early stages and might not be desirable in a clinical trial. The ERRSPENDMIN=0.001 option specifies the minimum error spending at each stage to be 0.001, and

it might increase the corresponding nominal $p$-value in early stages for the trial. The default BOUNDARYSCALE=STDZ option uses the standardized normal $Z$ scale to display test statistics in the boundary table and boundary plots.

The ODS OUTPUT statement with the TEST=TEST_COUNT1 option creates an output data set named TEST_COUNT1 which contains the updated boundary information for the test at stage 1. The data set also provides the boundary information that is needed for the group sequential test at the next stage.

The "Design Information" table in Output 108.9.10 displays design specifications. The derived statistics, such as the overall $\alpha$ and $\beta$ levels, are derived from the specified maximum information and boundary values in the BOUNDARY= data set. Note that with a minor change in the information level at stage 1, the power also changes slightly from the design provided in the BOUNDARY= data set.

**Output 108.9.10** Design Information

**The SEQTEST Procedure**

| Design Information | |
|---|---|
| **BOUNDARY Data Set** | WORK.BND_COUNT |
| **Data Set** | WORK.PARMS_COUNT1 |
| **Statistic Distribution** | Normal |
| **Boundary Scale** | Standardized Z |
| **Alternative Hypothesis** | Upper |
| **Early Stop** | Accept(Nonbinding)/Reject Null |
| **Number of Stages** | 4 |
| **Alpha (Binding Beta Boundary)** | 0.02237 |
| **Alpha (Nonbinding Beta Boundary)** | 0.025 |
| **Beta** | 0.10142 |
| **Power** | 0.89858 |
| **Max Information (Percent of Fixed Sample)** | 111.2654 |
| **Max Information** | 517.029617 |
| **Null Ref ASN (Percent of Fixed Sample)** | 62.27694 |
| **Alt Ref ASN (Percent of Fixed Sample)** | 76.31328 |

With the ERRSPEND option, the "Error Spending Information" table in Output 108.9.11 displays cumulative error spending at each stage for each boundary. By default (or equivalently if you specify BOUNDARYKEY=ALPHA), the Type I error level with nonbinding beta boundary $\alpha = 0.025$ is maintained. Furthermore, with the ERRSPENDMIN=0.001 option, the $\alpha$ spending at each stage is greater than or equal to 0.001.

**Output 108.9.11** Error Spending Information

| Error Spending Information (Nonbinding Beta Boundary) | | | | |
|---|---|---|---|---|
| | | | Cumulative Error Spending | |
| | Information Level | | Upper | |
| _Stage_ | Proportion | Actual | Beta | Alpha |
| 1 | 0.2522 | 130.3756 | 0.00302 | 0.00100 |
| 2 | 0.5000 | 258.5148 | 0.02640 | 0.00299 |
| 3 | 0.7500 | 387.7722 | 0.06433 | 0.01101 |
| 4 | 1.0000 | 517.0296 | 0.10142 | 0.02500 |

The "Test Information" table in Output 108.9.12 displays the boundary values for the design, test statistic, and resulting action at each stage. With the default BOUNDARYSCALE=STDZ option, the standardized normal $Z$ scale is used for the test statistic and boundary values. The table shows that the test statistic 0.2039 is between the upper $\alpha$ and $\beta$ boundaries, so the trial continues to the next stage.

**Output 108.9.12** Sequential Test

**Test Information (Standardized Z Scale)**
**Nonbinding Beta Boundary, Null Reference = 0**

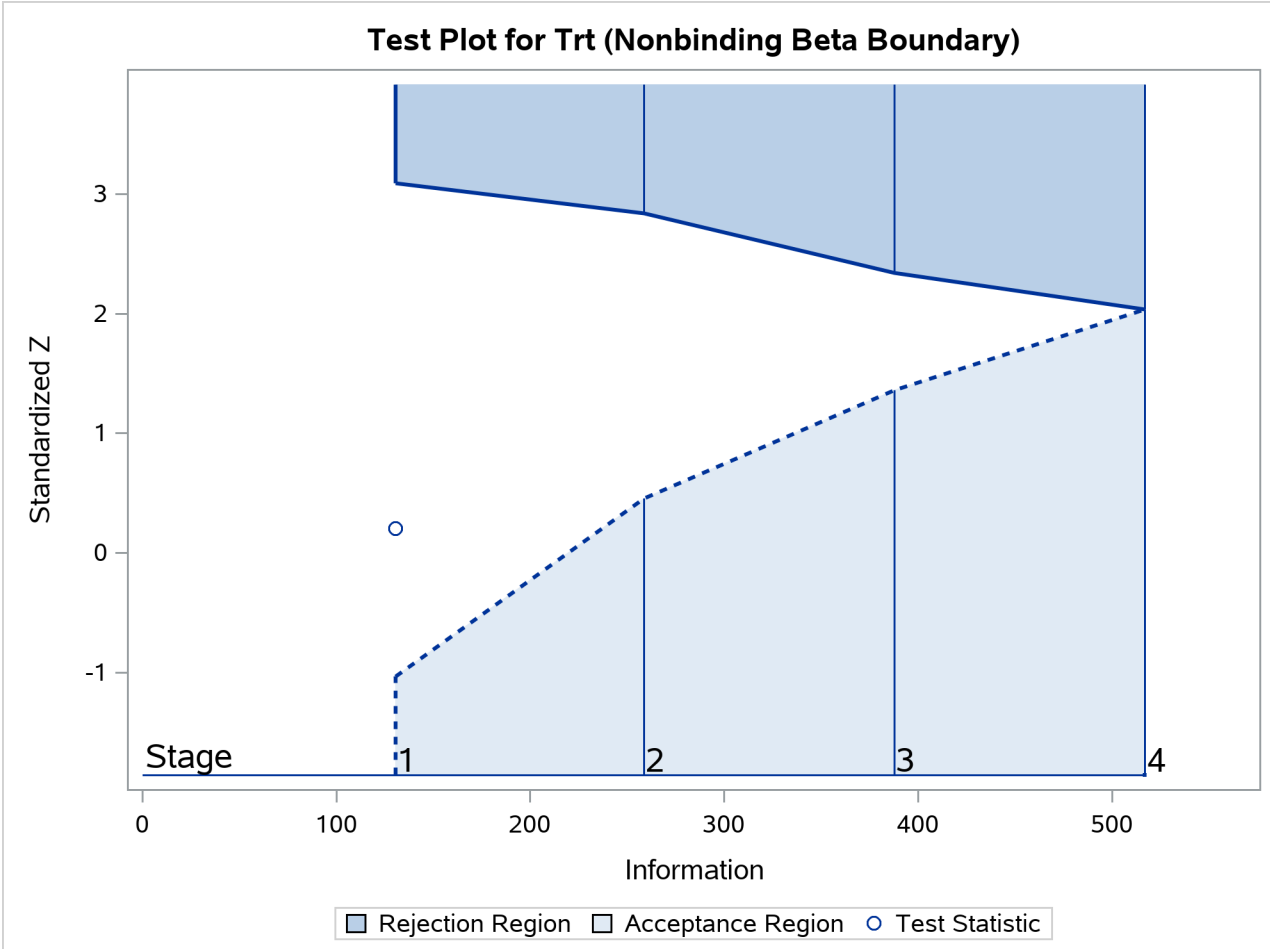
| | Information Level | | Alternative Reference | Boundary Values | | Test | |
|---|---|---|---|---|---|---|---|
| | | | | Upper | | Trt | |
| _Stage_ | Proportion | Actual | Upper | Beta | Alpha | Estimate | Action |
| 1 | 0.2522 | 130.3756 | 1.71273 | -1.03271 | 3.09023 | 0.20390 | Continue |
| 2 | 0.5000 | 258.5148 | 2.41176 | 0.45564 | 2.84016 | . | |
| 3 | 0.7500 | 387.7722 | 2.95379 | 1.36069 | 2.34211 | . | |
| 4 | 1.0000 | 517.0296 | 3.41074 | 2.03599 | 2.03599 | . | |

The information level at stage 1 is derived from the standard error,

$$I_1 = \frac{1}{\mathrm{Var}(\hat{\theta}_1)} = \frac{1}{(\mathrm{s.e.}(\hat{\theta}_1))^2} = 130.376$$

By default (or equivalently if you specify PLOTS=TEST), the "Test Plot" graph displays boundary values of the design and the test statistic at stage 1, as shown in Output 108.9.13. It also shows that the observed statistic is in the continuation region.

**Output 108.9.13** Sequential Test Plot




The observed information level at stage 1, $I_1 = 130.376$, is slightly larger than the target information level at the design. If an observed information level in the study is substantially different from its target level in the design, then the sample sizes should be adjusted in the subsequent stages to achieve the target information levels.

Suppose the trial continues to the next stage, and 111 patients are available in each group at stage 2. The data set COUNT_2 contains these 222 patients.

The following statements use the GENMOD procedure to estimate the treatment effect at stage 2:

```
proc genmod data=Count_2;
   model Resp= Trt;
ods output ParameterEstimates=Parms_Count2;
run;
```

The following statements create the parameter estimate at stage 2, $\hat{\theta}_2 = \hat{p}_2 - \hat{p}_1 = 0.027$, and its associated standard error $\sqrt{\mathrm{Var}(\hat{\theta}_2)} = 0.0621$ into a test data set:

```
data Parms_Count2;
   set Parms_Count2;
   if Parameter='Trt';
   _Scale_='MLE';
   _Stage_= 2;
   keep _Scale_ _Stage_ Parameter Estimate StdErr;
run;

proc print data=Parms_Count2;
   title 'Statistics Computed at Stage 2';
run;
```

Output 108.9.14 displays the test statistics at stage 2.

**Output 108.9.14** Statistics Computed at Stage 2

**Statistics Computed at Stage 2**

| Obs | Parameter | Estimate | StdErr | _Scale_ | _Stage_ |
|---|---|---|---|---|---|
| 1 | Trt | 0.0270 | 0.0621 | MLE | 2 |

The following statements invoke the SEQTEST procedure and test for early stopping at stage 2:

```
ods graphics on;
proc seqtest Boundary=Test_Count1
             Parms(Testvar=Trt)=Parms_Count2
             betaboundary=nonbinding
             infoadj=none
             ;
ods output Test=Test_Count2;
run;
```

The BOUNDARY= option specifies the input data set that provides the boundary information for the trial at stage 2, which was generated by the SEQTEST procedure at the previous stage. The PARMS= option specifies the input data set that contains the test statistic and its associated standard error at stage 2, and the TESTVAR= option identifies the test variable in the data set.

The ODS OUTPUT statement with the TEST=TEST_COUNT2 option creates an output data set named TEST_COUNT2 which contains the updated boundary information for the test at stage 2. The data set also provides the boundary information that is needed for the group sequential test at the next stage.

The "Test Information" table in Output 108.9.15 displays the boundary values, test statistic, and resulting action at each stage. The table shows that the test statistic 0.43522 is less than the corresponding upper beta boundary value, so the trial can be stopped to accept the hypothesis. With the BETABOUNDARY=NONBINDING option, The clinic has the option to continue the trial while still maintaining the Type I error level.

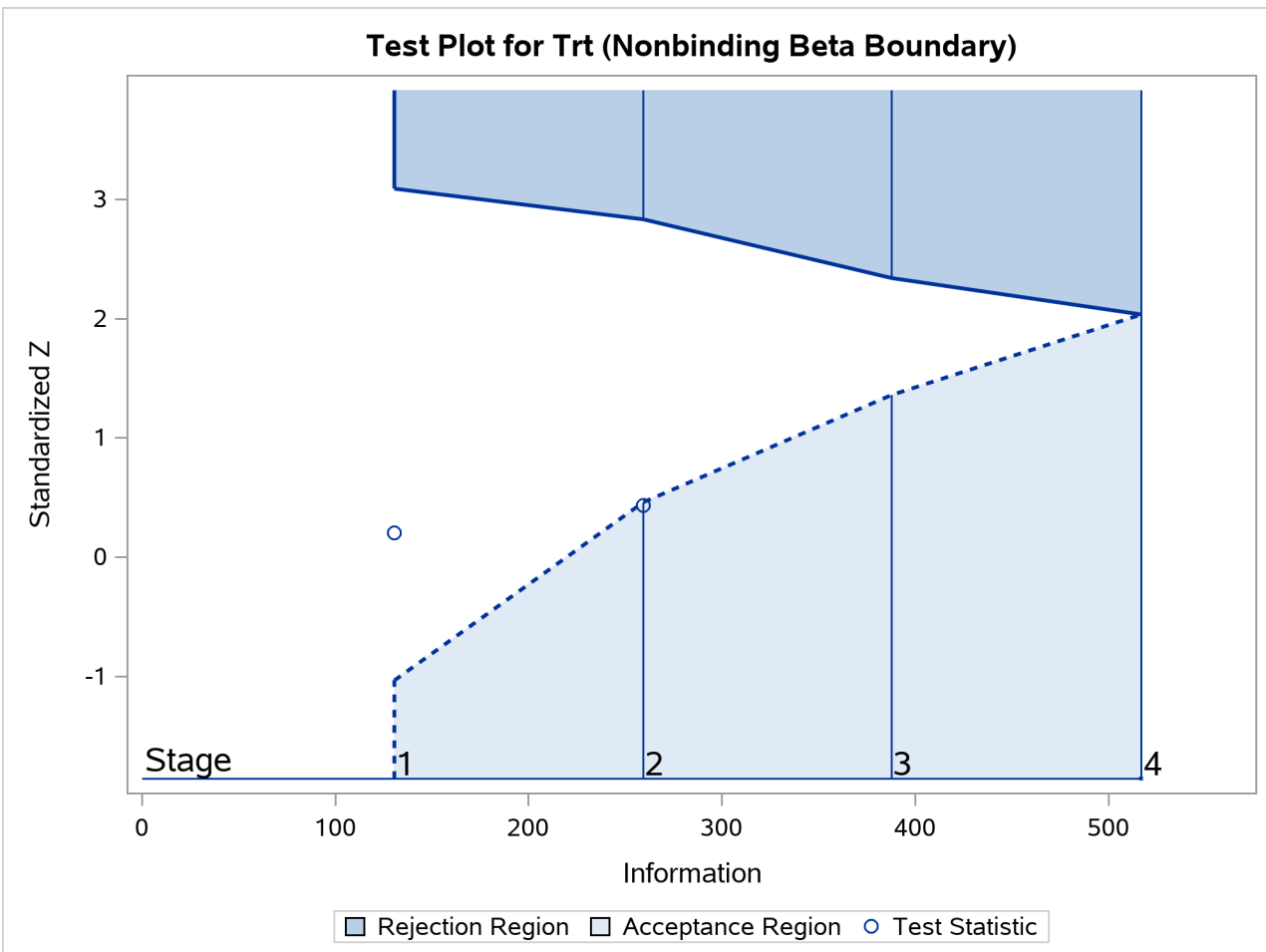
**Output 108.9.15** Sequential Test

**The SEQTEST Procedure**

| Test Information (Standardized Z Scale) Nonbinding Beta Boundary, Null Reference = 0 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Information Level | | Alternative Reference | Boundary Values Upper | | | Test Trt |
| _Stage_ | Proportion | Actual | Upper | Beta | Alpha | Estimate | Action |
| 1 | 0.2522 | 130.3756 | 1.71273 | -1.03271 | 3.09023 | 0.20390 | Continue |
| 2 | 0.5015 | 259.3157 | 2.41549 | 0.46349 | 2.83297 | 0.43522 | Accept Null (Nonbinding) |
| 3 | 0.7500 | 387.7722 | 2.95379 | 1.36018 | 2.34294 | . | |
| 4 | 1.0000 | 517.0296 | 3.41074 | 2.03610 | 2.03610 | . | |

With ODS Graphics enabled, the "Test Plot" is displayed, as shown in Output 108.9.16. The plot displays boundary values of the design and the test statistics at the first two stages. As expected, the test statistic at stage 2 is in the "Upper Acceptance Region" below the upper beta boundary.

**Output 108.9.16** Sequential Test Plot



Suppose the clinic decides to continue the trial, and at the next stage, 108 patients are available in each group at stage 3. The data set COUNT_3 contains these 332 patients.

The following statements use the GENMOD procedure to estimate the treatment effect at stage 3:

```
proc genmod data=Count_3;
   model Resp= Trt;
ods output ParameterEstimates=Parms_Count3;
run;
```

The following statements create the parameter estimate at stage 2, $\hat{\theta}_2 = \hat{p}_2 - \hat{p}_1 = 0.1205$, and its associated standard error $\sqrt{\mathrm{Var}(\hat{\theta}_2)} = 0.0507$ into a test data set:

```
data Parms_Count3;
   set Parms_Count3;
   if Parameter='Trt';
   _Scale_='MLE';
   _Stage_= 3;
   keep _Scale_ _Stage_ Parameter Estimate StdErr;
run;

proc print data=Parms_Count3;
   title 'Statistics Computed at Stage 3';
run;
```

Output 108.9.17 displays the test statistics at stage 3.

**Output 108.9.17** Statistics Computed at Stage 3

**Statistics Computed at Stage 3**

| Obs | Parameter | Estimate | StdErr | _Scale_ | _Stage_ |
|---|---|---|---|---|---|
| 1 | Trt | 0.1205 | 0.0507 | MLE | 3 |

The following statements invoke the SEQTEST procedure and test for early stopping at stage 3:

```
ods graphics on;
proc seqtest Boundary=Test_Count2
             Parms(Testvar=Trt)=Parms_Count3
             betaboundary=nonbinding
             ;
ods output Test=Test_Count3;
run;
```

The “Test Information” table in Output 108.9.18 displays the boundary values, test statistic, and resulting action at each stage. The table shows that the test statistic 2.37437 is greater than the corresponding upper alpha boundary value, so the trial stops to reject the hypothesis.

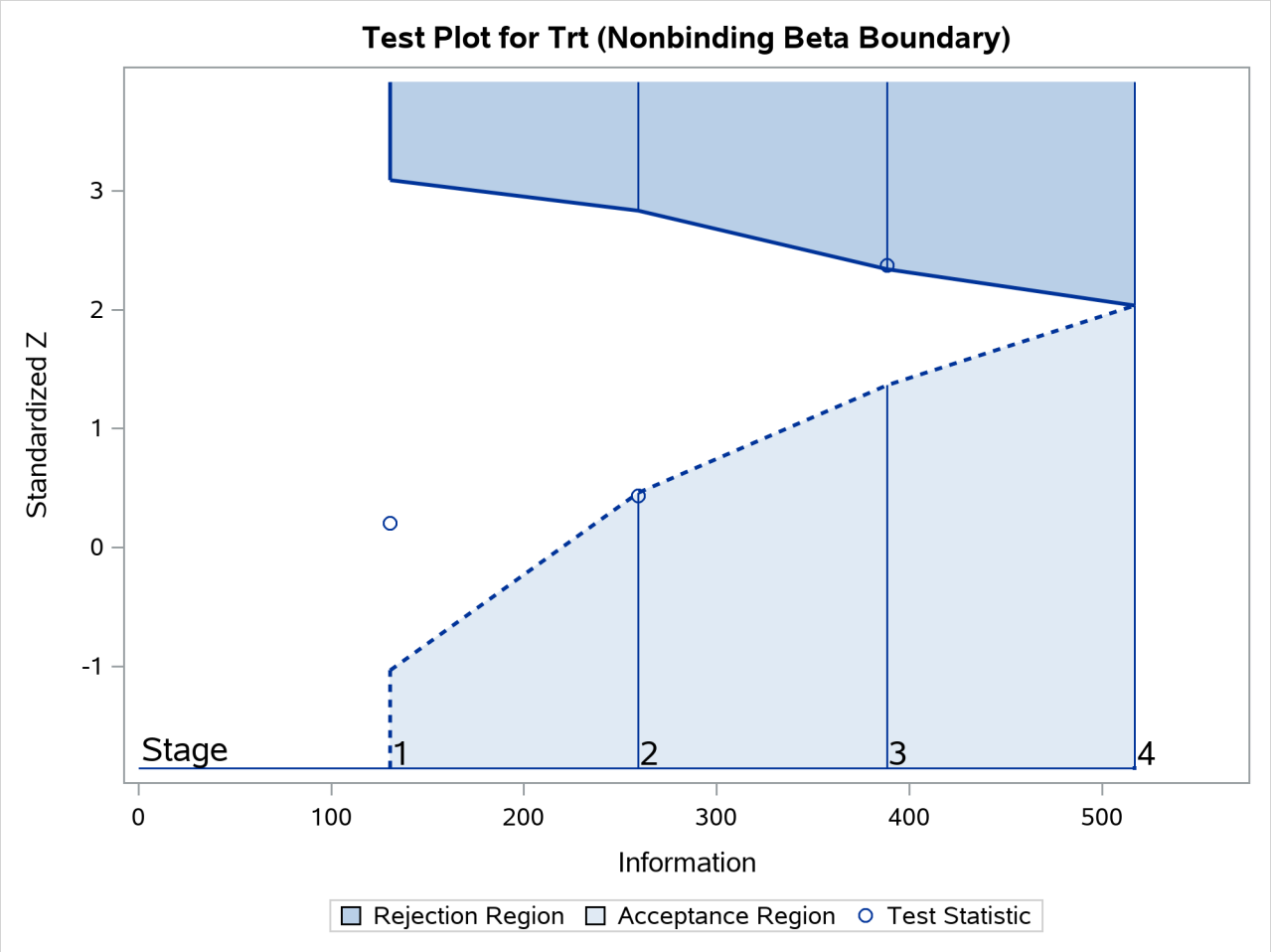
**Output 108.9.18** Sequential Test

**The SEQTEST Procedure**

| Test Information (Standardized Z Scale) Nonbinding Beta Boundary, Null Reference = 0 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Information Level | | Alternative Reference | Boundary Values Upper | | | Test Trt |
| _Stage_ | Proportion | Actual | Upper | Beta | Alpha | Estimate | Action |
| 1 | 0.2522 | 130.3756 | 1.71273 | -1.03271 | 3.09023 | 0.20390 | Continue |
| 2 | 0.5015 | 259.3157 | 2.41549 | 0.46349 | 2.83297 | 0.43522 | Accept Null (Nonbinding) |
| 3 | 0.7512 | 388.3763 | 2.95609 | 1.36434 | 2.34036 | 2.37437 | Reject Null |
| 4 | 1.0000 | 517.0296 | 3.41074 | 2.03658 | 2.03658 | . | |

With ODS Graphics enabled, the "Test Plot" is displayed, as shown in Output 108.9.19. The plot displays boundary values of the design and the test statistics at the first two stages. As expected, the test statistic at stage 3 is in the "Upper Rejection Region" above the upper alpha boundary.

**Output 108.9.19** Sequential Test Plot



After a trial is stopped, the "Parameter Estimates" table in Output 108.9.20 displays the stopping stage and the maximum likelihood estimate of the parameter. It also displays the $p$-value, median estimate, and confidence limits for the parameter that correspond to the observed statistic by using the specified sample space ordering.

**Output 108.9.20** Parameter Estimates

| Parameter Estimates Stagewise Ordering | | | | | |
|---|---|---|---|---|---|
| Parameter | Stopping Stage | MLE | p-Value for H0:Parm=0 | Median Estimate | Lower 95% CL |
| Trt | 3 | 0.120482 | 0.0103 | 0.119371 | 0.03494 |

The MLE statistic at the stopping stage is the maximum likelihood estimate of the parameter and is biased. The computation of $p$-value, unbiased median estimate, and confidence limits depends on the ordering of the sample space $(k, z)$, where $k$ is the stage number and $z$ is the observed standardized $Z$ statistic. By default (or equivalently if you specify ORDER=STAGEWISE), the stagewise ordering that uses counterclockwise ordering around the continuation region is used to compute the $p$-value, unbiased median estimate, and confidence limits. As expected, the $p$-value is less than 0.025, and the confidence interval does not contain the null reference zero.

See the section "Available Sample Space Orderings in a Sequential Test" on page 9065 for a detailed description of the stagewise ordering.

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