Chapter 710

Group-Sequential Logrank Tests (Legacy)

This procedure is the original two-sample Logrank (survival) group-sequential procedure in PASS. Power calculations and boundaries are generated from analytic calculations (simulation is not used). This procedure does not give any options for futility boundaries.

Introduction

This procedure uses analytic methods for sample size and power calculations for group-sequential Logrank tests. **PASS** also has procedures for group-sequential Logrank tests based on simulations. The simulation procedures are more flexible in terms of input parameters, and also allow for both significance and futility boundaries.

Clinical trials are longitudinal. They accumulate data sequentially through time. The participants cannot be enrolled and randomized on the same day. Instead, they are enrolled as they enter the study. It may take several years to enroll enough patients to meet sample size requirements. Because clinical trials are long term studies, it is in the interest of both the participants and the researchers to monitor the accumulating information for early convincing evidence of either harm or benefit. This permits early termination of the trial.

Group sequential methods allow statistical tests to be performed on accumulating data while a phase III clinical trial is ongoing. Statistical theory and practical experience with these designs have shown that making four or five *interim analyses* is almost as effective in detecting large differences between treatment groups as performing a new analysis after each new data value. Besides saving time and resources, such a strategy can reduce the experimental subject's exposure to an inferior treatment and make superior treatments available sooner.

When repeated significance testing occurs on the same data, adjustments have to be made to the hypothesis testing procedure to maintain overall significance and power levels. The landmark paper of Lan & DeMets (1983) provided the theory behind the *alpha spending function* approach to group sequential testing. This paper built upon the earlier work of Armitage, McPherson, & Rowe (1969), Pocock (1977), and O'Brien & Fleming (1979). **PASS** implements the methods given in Reboussin, DeMets, Kim, & Lan (1992) to calculate the power and sample sizes of various group sequential designs.

This module calculates sample size and power for group sequential designs used to compare two survival curves. Other modules perform similar analyses for the comparison of means and proportions. The program allows you to vary the number and times of interim tests, type of alpha spending function, and test boundaries. It also gives you complete flexibility in solving for power, significance level, sample size, or effect size. The results are displayed in both numeric reports and informative graphics.

Technical Details

In many clinical trials, patients are recruited and randomized to receive a particular treatment, either experimental or control, and then monitored until either a critical event occurs, or the study is ended. The length of time the patient is monitored until the critical event occurs is called the *follow-up time*. After the study is ended, the follow-up times of the patients in the two groups are compared using the *logrank test* in what is often called a *survival analysis*.

When the critical event does not occur for a patient by the time the study is ended, the follow-up time is said to have been *censored*. Although the actual event time is not known for this patient, it is known that the event time will be greater than the follow-up time. Hence, some information is gleaned from these participants. Because of this censoring, the usual tests of means or proportions cannot be used. The logrank test was developed to provide a statistical test comparing the efficacy of the two treatments.

The Hazard Ratio (HR)

Suppose the critical event is death. The survival distribution of each treatment can be characterized by the *instantaneous death rates*, λ_1 and λ_2. An instantaneous death rate, often called the *hazard*, is the probability of death in a short interval of time. The comparison of the efficacies of the two treatments is often formalized by considering the ratio of the hazard, or *hazard ratio* (HR).

$$HR = \frac{\lambda_2}{\lambda_1}$$

Although the logrank test concerns the ratio of the hazard rates of the two groups, when planning a study, it may be easier to obtain information about the expected proportion surviving during the trial. It turns out that the hazard ratio can be computed from the survival proportions, *S1* and *S2*, using the equation

$$HR = \frac{\log(S2)}{\log(S1)}$$

when the hazard ratio is constant through time.

Assuming that group one is the control group, it may be easiest during the planning stages of a study to find *S1* and state the minimum value of *HR* that would make the experimental treatment useful. The last equation can then be manipulated to calculate a value for *S2* as follows

$$S2 = \exp\{HR(\log(S1))\}.$$

Sometimes it is more convenient to state hazard ratio in terms of the median survival times. In this case, the hazard ratio is estimated using

$$HR = \frac{M_1}{M_2}$$

when the hazard ratio is constant for different times.

The Logrank Statistic

The following results are excerpted from Reboussin (1992). The logrank statistic is given by the equation

$$L(d) = \sum_{i=1}^{d} \left(\frac{x_i r_{ic}}{r_{ic} + r_{it}} \right)$$

where *d* is the number of events, x_i is 1 if the event at time t_i is in the control group and 0 if it is in the treatment group, r_{ic} is the number of patients in the control group at risk just be before t_i, and r_{it} is the corresponding number of patients at risk in the treatment group.

If $r_{ic} \approx r_{it}$ and *HR* is close to 1, then the sequential logrank statistic is (approximately)

$$z_k = 2 \frac{L(d_k)}{\sqrt{d_k}}$$

The subscript *k* indicates that the computations use all data that are available at the time of the k^{th} interim analysis or k^{th} *look* (*k* goes from 1 to K).

Spending Functions

Lan and DeMets (1983) introduced alpha spending functions, $\alpha(\tau)$, that determine a set of boundaries $b_1, b_2, \ldots, b_K$ for the sequence of test statistics $z_1, z_2, \ldots, z_K$. These boundaries are the critical values of the sequential hypothesis tests. That is, after each interim test, the trial is continued as long as $|z_k| < b_k$. When $|z_k| \geq b_k$, the hypothesis of equal means is rejected, and the trial is stopped early.

The time argument τ either represents the proportion of elapsed time to the maximum duration of the trial or the proportion of the sample that has been collected. When elapsed time is used, it is referred to as *calendar time*. When time is measured in terms of the sample, it is referred to as *information time*. Since it is a proportion, τ can only vary between zero and one.

Alpha spending functions have the characteristics:

$$\alpha(0) = 0$$

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

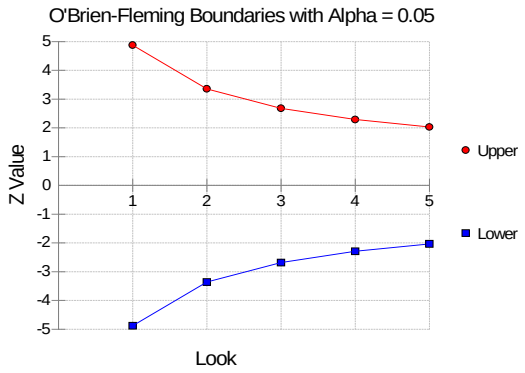
The last characteristic guarantees a fixed α level when the trial is complete. That is,

$$\Pr(|z_1| \geq b_1 \text{ or } |z_2| \geq b_2 \text{ or } \ldots \text{ or } |z_k| \geq b_k) = \alpha(\tau)$$

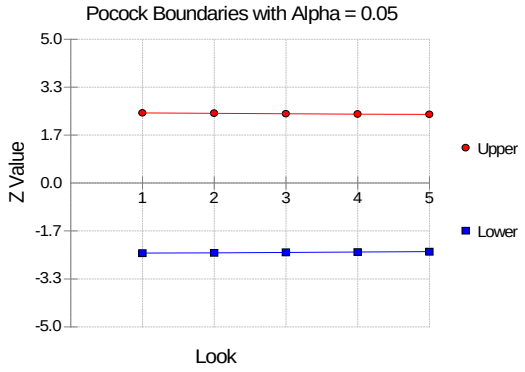
This methodology is very flexible since neither the times nor the number of analyses must be specified in advance. Only the functional form of $\alpha(\tau)$ must be specified.

PASS provides five popular spending functions plus the ability to enter and analyze your own boundaries. These are calculated as follows:

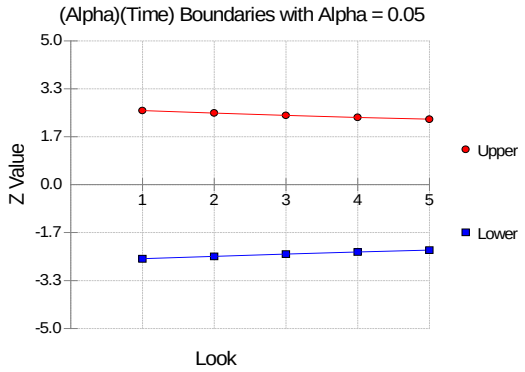
1. O'Brien-Fleming $2 - 2\Phi\left(\frac{Z_{\alpha/2}}{\sqrt{t}}\right)$



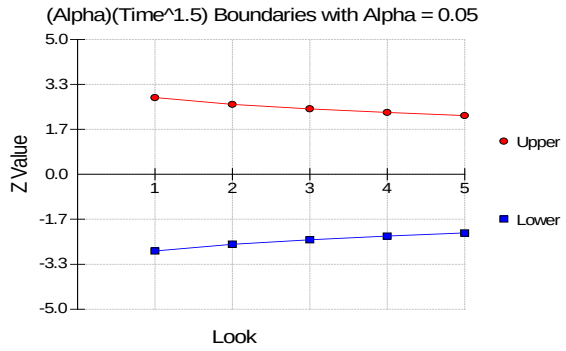
2. Pocock $\alpha \cdot \ln(1 + (e - 1)t)$



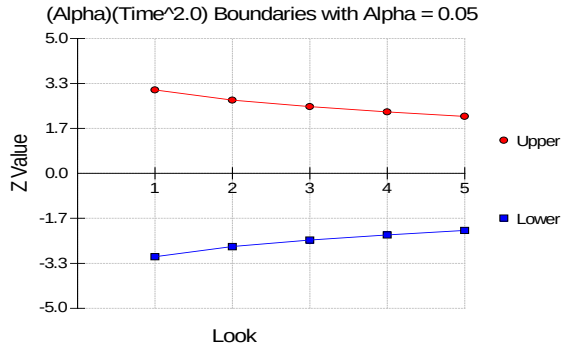
3. Alpha * time $\alpha \cdot t$



4. Alpha * time^1.5 $\alpha \cdot t^{3/2}$



5. Alpha * time^2 $\alpha \cdot t^2$



6. User Supplied

A custom set of boundaries may be entered.

The O'Brien-Fleming boundaries are commonly used because they do not significantly increase the overall sample size and because they are conservative early in the trial. Conservative in the sense that the means must be extremely different before statistical significance is indicated. The Pocock boundaries are nearly equal for all times. The Alpha*t boundaries use equal amounts of alpha when the looks are equally spaced. You can enter your own set of boundaries using the User Supplied option.

Sequential Theory

A detailed account of the methodology is contained in Lan & DeMets (1983), DeMets & Lan (1984), Lan & Zucker (1993), and DeMets & Lan (1994). A brief summary of the theoretical basis of the method will be presented here.

Group sequential procedures for interim analysis are based on their equivalence to discrete boundary crossing of a Brownian motion process with drift parameter θ. The test statistics z_k follow the multivariate normal distribution with means $\theta\sqrt{\tau_k}$ and, for $j \leq k$, covariances $\sqrt{\tau_k/\tau_j}$. The drift parameter is related to the parameters of the z-test through the equations

$$\theta = \frac{\log(HR)\sqrt{d_k}}{2} \text{ (exponential survival)} \quad \text{or} \quad \theta = \frac{|1-HR|\sqrt{d_k}}{1+HR} \text{ (proportional hazards).}$$

These equations may be solved for d_k, the required number of events, giving

$$d_k = \frac{4\theta^2}{[\log(HR)]^2} \text{ (exponential survival)} \quad \text{or} \quad d_k = \left(\frac{(1+HR)\theta}{1-HR}\right)^2 \text{ (proportional hazards).}$$

In survival analysis, the size of a sample is measured in terms of number of events rather than number of patients because it is probable that many of the patients will be censored—their event times are not known. In order to ensure that the sample size produces the required number of events, it must be inflated by the event rates.

The expected number of events can be computed from the proportion surviving using the equation

$$d_k = \frac{N(1-S_1) + N(1-S_2)}{2}$$

where *N* is the total sample size (assumed to be split evenly between groups). This can be solved for *N* to give the sample size as

$$N = \frac{2d_k}{2 - S_1 - S_2}$$

Hence, the algorithm is as follows:

1. Compute boundary values based on a specified spending function and alpha value.
2. Calculate the drift parameter based on those boundary values and a specified power value.
3. Use the drift parameter and the above equation to calculate the appropriate event size per group d_k.
4. Use the event size to compute the appropriate sample size, *N*.

Example 1 – Finding the Sample Size

A clinical trial is to be conducted over a two-year period to compare the hazard rate of a new treatment to that of the current treatment. The proportion surviving for two years using the current treatment is 0.3. The health community will be interested in the new treatment if the proportion surviving is increased to 0.45, a 50% increase. So that the sample size requirements for several survival proportions can be compared, it is also of interest to compute the sample size at response rates of 0.30, 0.35, 0.40, and 0.50. Assume the survival times are exponential.

Testing will be done at the 0.05 significance level and the power should be set to 0.10. A total of four tests are going to be performed on the data as they are obtained. The O'Brien-Fleming boundaries will be used.

Find the necessary sample sizes and test boundaries assuming equal sample sizes for each arm and two-sided hypothesis tests.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 1** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab	
Solve For	**Sample Size**
Alternative Hypothesis	**Two-Sided**
Survival Time Assumption	**Exponential Survival**
Power	**0.90**
Alpha	**0.05**
S1 (Proportion Surviving 1)	**0.3**
S2 (Proportion Surviving 2)	**0.35 0.40 0.45 0.50**
Number of Looks	**4**
Spending Function	**O'Brien-Fleming**
Boundary Truncation	**None**
Max Time	**2**
Times	**Equally Spaced**
Informations	**Blank**

Output

Click the Calculate button to perform the calculations and generate the following output.

Numeric Reports

Numeric Results for Two-Sided Logrank Test (Assuming Exponential Survival)

Solve For: Sample Size

Power	Total Sample Size N	Total Required Events E	Alpha	Beta	Proportion Surviving S1	Proportion Surviving S2	Hazard Ratio HR
0.900003	3378	2280	0.05	0.099997	0.3	0.35	0.8720
0.900267	884	575	0.05	0.099733	0.3	0.40	0.7611
0.900626	407	254	0.05	0.099374	0.3	0.45	0.6632
0.900018	234	140	0.05	0.099982	0.3	0.50	0.5757

Power	The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N	The total number of items sampled. There are N/2 in each group.
E	The total number of events that must occur in each group.
Alpha	The probability of rejecting a true null hypothesis in at least one of the sequential tests.
Beta	The probability of accepting a false null hypothesis at the conclusion of all tests.
S1	The proportion surviving in group 1.
S2	The proportion surviving in group 2.
HR	The hazard ratio. HR = Log(S2)/Log(S1).

Summary Statements

A total sample size of 3378 (split equally between the two groups), or 2280 events, achieves 90% power to detect a hazard ratio of 0.872 when the proportions surviving in each group are 0.3 and 0.35 at a significance level (alpha) of 0.05 using a two-sided log rank test. These results assume that 4 sequential tests are made using the O'Brien-Fleming spending function to determine the test boundaries and that the survival times are exponential.

Details when Spending = O'Brien-Fleming, N = 3378, E = 2280, S1 = 0.3, S2 = 0.35

Look	Time	Lower Bndry	Upper Bndry	Nominal Alpha	Inc Alpha	Total Alpha	Inc Power	Total Power
1	0.5	-4.33263	4.33263	0.000015	0.000015	0.000015	0.003497	0.003497
2	1.0	-2.96311	2.96311	0.003045	0.003036	0.003051	0.254384	0.257882
3	1.5	-2.35902	2.35902	0.018323	0.016248	0.019299	0.427386	0.685268
4	2.0	-2.01406	2.01406	0.044003	0.030701	0.050000	0.214736	0.900003

Drift = 3.27108

Details when Spending = O'Brien-Fleming, N = 884, E = 575, S1 = 0.3, S2 = 0.4

Look	Time	Lower Bndry	Upper Bndry	Nominal Alpha	Inc Alpha	Total Alpha	Inc Power	Total Power
1	0.5	-4.33263	4.33263	0.000015	0.000015	0.000015	0.003505	0.003505
2	1.0	-2.96311	2.96311	0.003045	0.003036	0.003051	0.254722	0.258228
3	1.5	-2.35902	2.35902	0.018323	0.016248	0.019299	0.427505	0.685732
4	2.0	-2.01406	2.01406	0.044003	0.030701	0.050000	0.214535	0.900267

Drift = 3.2726

Details when Spending = O'Brien-Fleming, N = 407, E = 254, S1 = 0.3, S2 = 0.45

Look	Time	Lower Bndry	Upper Bndry	Nominal Alpha	Inc Alpha	Total Alpha	Inc Power	Total Power
1	0.5	-4.33263	4.33263	0.000015	0.000015	0.000015	0.003516	0.003516
2	1.0	-2.96311	2.96311	0.003045	0.003036	0.003051	0.255183	0.258699
3	1.5	-2.35902	2.35902	0.018323	0.016248	0.019299	0.427665	0.686364
4	2.0	-2.01406	2.01406	0.044003	0.030701	0.050000	0.214262	0.900626

Drift = 3.27466

Details when Spending = O'Brien-Fleming, N = 234, E = 140, S1 = 0.3, S2 = 0.5

Look	Time	Lower Bndry	Upper Bndry	Nominal Alpha	Inc Alpha	Total Alpha	Inc Power	Total Power
1	0.5	-4.33263	4.33263	0.000015	0.000015	0.000015	0.003498	0.003498
2	1.0	-2.96311	2.96311	0.003045	0.003036	0.003051	0.254403	0.257901
3	1.5	-2.35902	2.35902	0.018323	0.016248	0.019299	0.427393	0.685293
4	2.0	-2.01406	2.01406	0.044003	0.030701	0.050000	0.214724	0.900018

Drift = 3.27117

References

Chow, S.C., Shao, J., and Wang, H. 2003. Sample Size Calculations in Clinical Research. Marcel Dekker. New York.

Lan, K.K.G. and DeMets, D.L. 1983. 'Discrete sequential boundaries for clinical trials.' Biometrika, 70, pages 659-663.

O'Brien, P.C. and Fleming, T.R. 1979. 'A multiple testing procedure for clinical trials.' Biometrics, 35, pages 549-556.

Pocock, S.J. 1977. 'Group sequential methods in the design and analysis of clinical trials.' Biometrika, 64, pages 191-199.

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

This Numeric Results report shows the values of each of the parameters, one scenario per row. Note that 254 events are required when *S2* = 0.45. Based on the expected survival proportions, this many events will occur if the overall sample size is 407.

The Details Reports show information about the individual interim tests. One detail report is generated for each scenario (row).

Look

These are the sequence numbers of the interim tests.

Time

These are the time points at which the interim tests are conducted. Since the Max Time was set to 2 (for two years), these time values are in years. Hence, the first interim test is at half a year, the second at one year, and so on.

We could have set Max Time to 24 so that the time scale was in months.

Lower and Upper Boundary

These are the test boundaries. If the computed value of the test statistic *z* is between these values, the trial should continue. Otherwise, the trial can be stopped.

Nominal Alpha

This is the value of alpha for these boundaries if they were used for a single, standalone, test. Hence, this is the significance level that must be found for this look in a standard statistical package that does not adjust for multiple looks.

Inc Alpha

This is the amount of alpha that is *spent* by this interim test. It is close to, but not equal to, the value of alpha that would be achieved if only a single test was conducted. For example, if we lookup the third value, 2.35902, in normal probability tables, we find that this corresponds to a (two-sided) alpha of 0.018323. However, the entry is 0.016248. The difference is due to the correction that must be made for multiple tests.

Total Alpha

This is the total amount of alpha that is used up to and including the current test.

Inc Power

These are the amounts that are added to the total power at each interim test. They are often called the exit probabilities because they give the probability that significance is found and the trial is stopped, given the alternative hypothesis.

Total Power

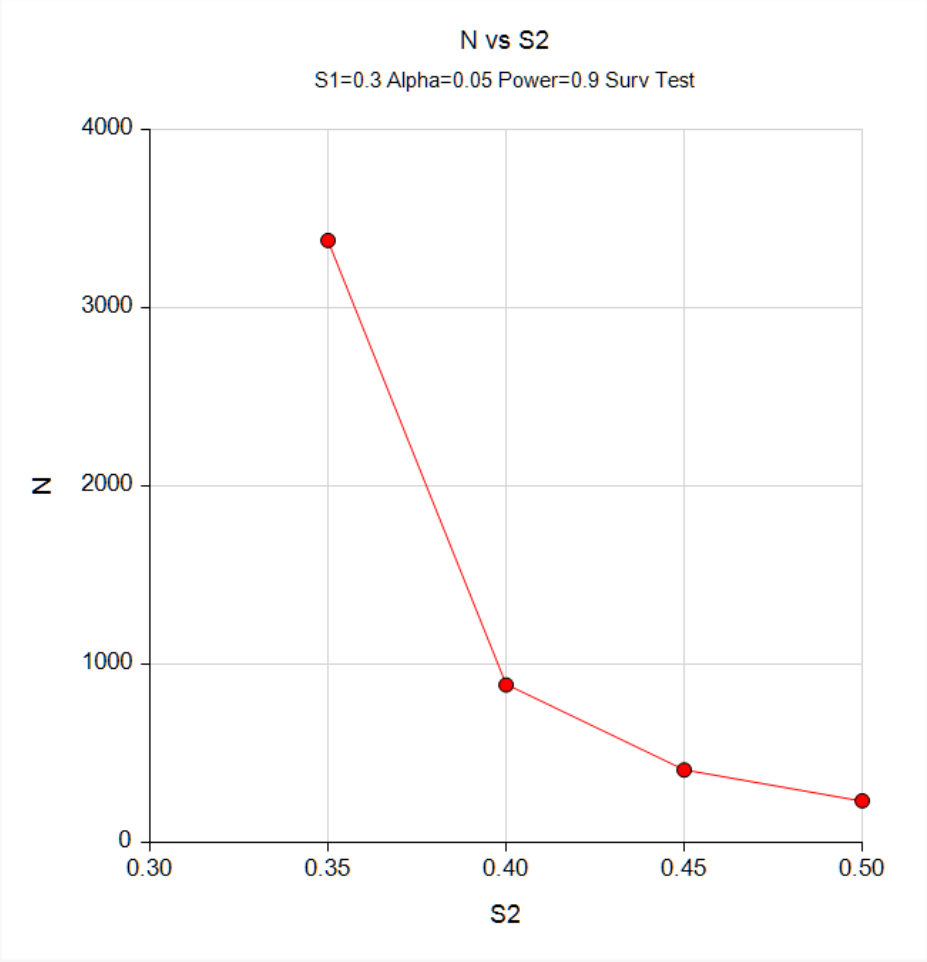
These are the cumulative power values. They are also the cumulative exit probabilities. That is, they are the probability that the trial is stopped at or before the corresponding time.

Drift

This is the value of the Brownian motion drift parameter.

Plots Section

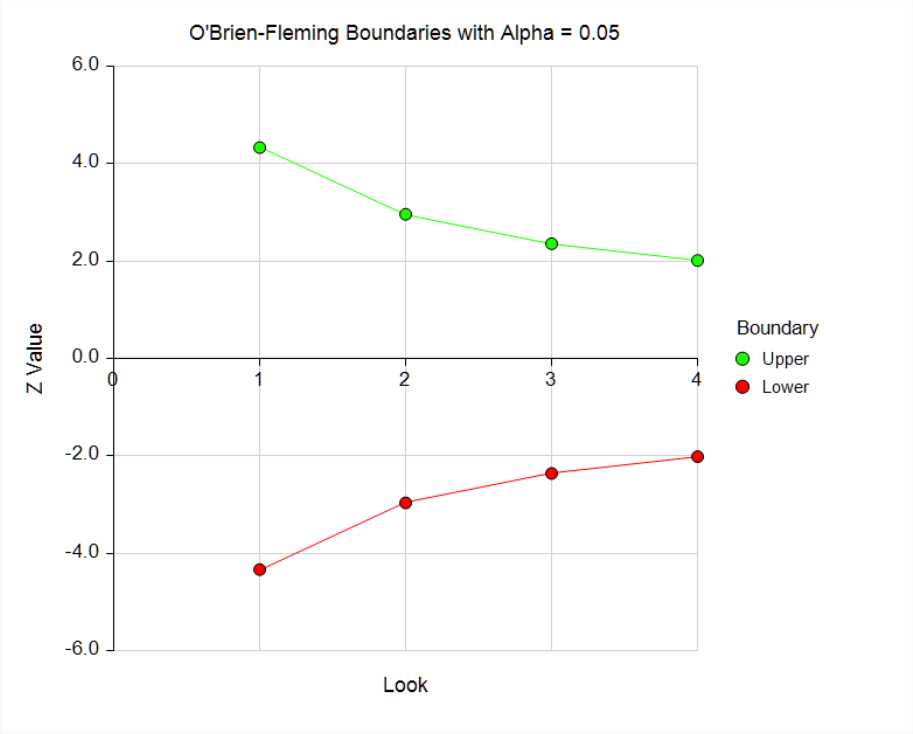
Plots

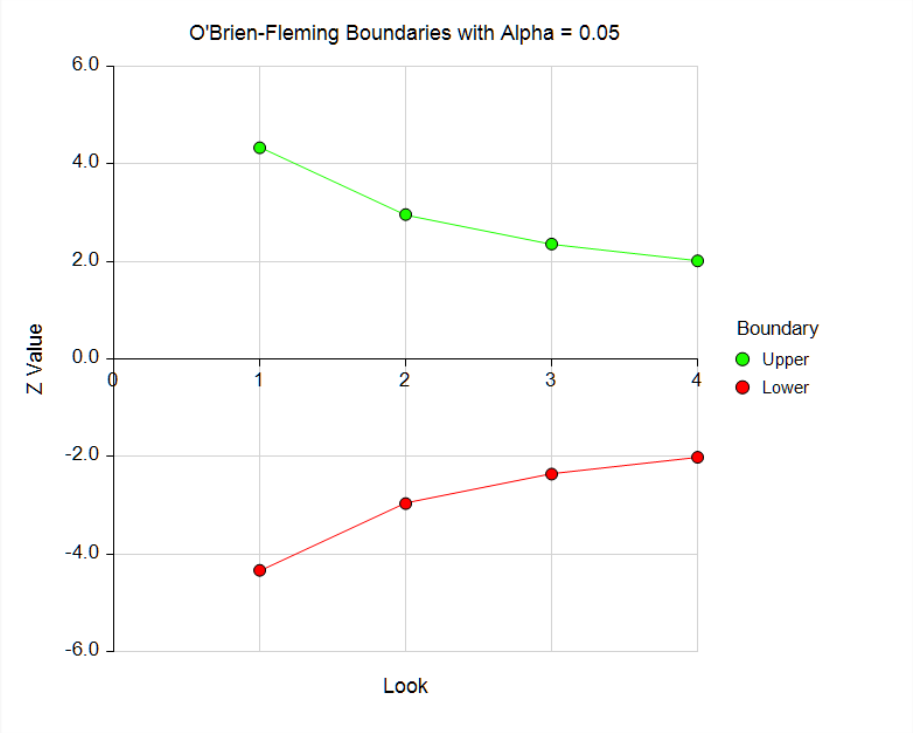


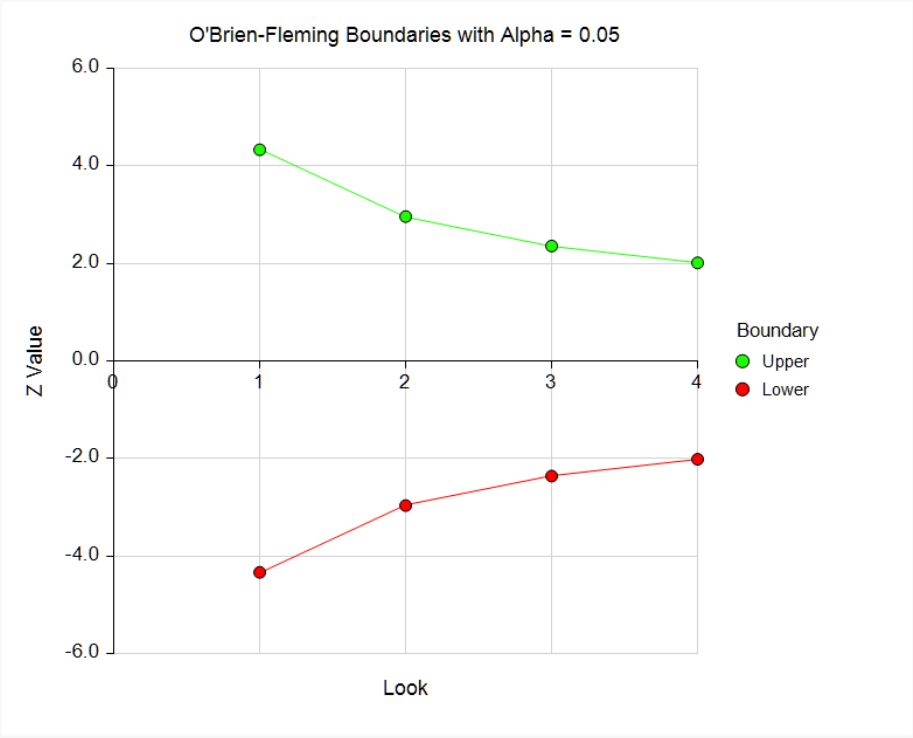
This plot shows that an increase in sample size from under 1000 to well over 3000 is necessary when the detectable proportion surviving is reduced from 0.4 to 0.35.

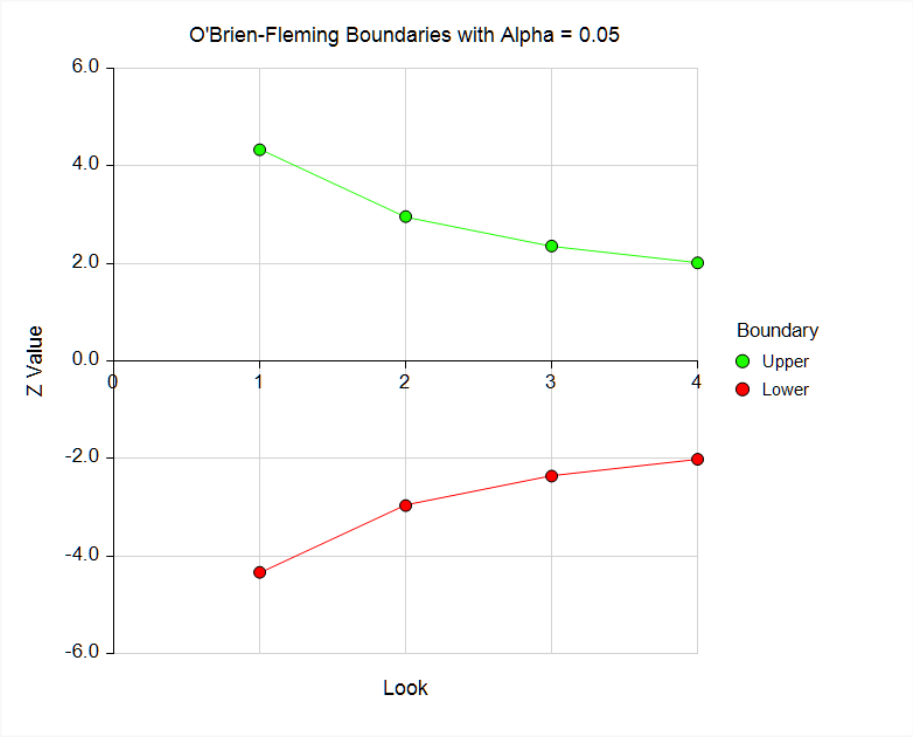
Boundary Plots

Plots









This plot shows the interim boundaries for each look. This plot shows very dramatically that the results must be extremely significant at early looks, but that they are near the single test boundary (1.96 and -1.96) at the last look.

Example 2 – Finding the Power

Continuing the scenario began in Example1, the researcher wishes to calculate the power of the design at sample sizes 50, 250, 450, 650, and 850. Testing will be done at the 0.01, 0.05, 0.10 significance levels and the overall power will be set to 0.10. Find the power of these sample sizes and test boundaries assuming equal sample sizes per arm and two-sided hypothesis tests.

Proceeding as in Example1, we decide to translate the mean and standard deviation into a percent of mean scale.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 2** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab	
Solve For	**Power**
Alternative Hypothesis	**Two-Sided**
Survival Time Assumption	**Exponential Survival**
Alpha	**0.01 0.05 0.10**
N (Total Sample Size)	**50 to 850 by 200**
S1 (Proportion Surviving 1)	**0.3**
S2 (Proportion Surviving 2)	**0.45**
Number of Looks	**4**
Spending Function	**O'Brien-Fleming**
Boundary Truncation	**None**
Max Time	**2**
Times	**Equally Spaced**
Informations	**Blank**

Output

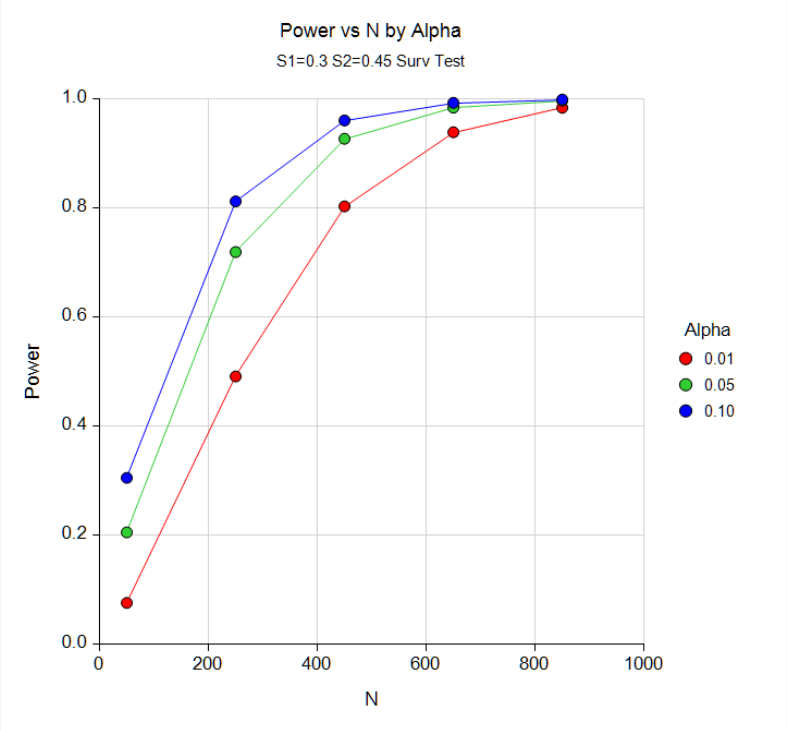
Click the Calculate button to perform the calculations and generate the following output.

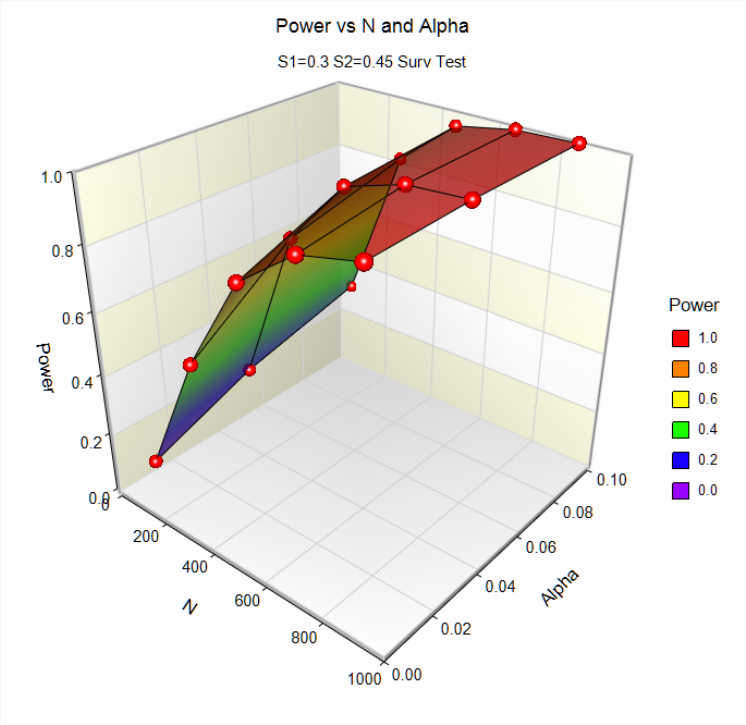
Numeric Results for Two-Sided Logrank Test (Assuming Exponential Survival)

Solve For: Power

Power	Total Sample Size N	Total Required Events E	Alpha	Beta	Proportion Surviving S1	Proportion Surviving S2	Hazard Ratio HR
0.075632	50	31	0.01	0.924368	0.3	0.45	0.6632
0.491011	250	156	0.01	0.508989	0.3	0.45	0.6632
0.802921	450	281	0.01	0.197079	0.3	0.45	0.6632
0.938923	650	406	0.01	0.061077	0.3	0.45	0.6632
0.983780	850	531	0.01	0.016220	0.3	0.45	0.6632
0.205032	50	31	0.05	0.794968	0.3	0.45	0.6632
0.719225	250	156	0.05	0.280775	0.3	0.45	0.6632
0.926894	450	281	0.05	0.073106	0.3	0.45	0.6632
0.984044	650	406	0.05	0.015956	0.3	0.45	0.6632
0.996907	850	531	0.05	0.003093	0.3	0.45	0.6632
0.305105	50	31	0.10	0.694895	0.3	0.45	0.6632
0.812103	250	156	0.10	0.187897	0.3	0.45	0.6632
0.960490	450	281	0.10	0.039510	0.3	0.45	0.6632
0.992807	650	406	0.10	0.007193	0.3	0.45	0.6632
0.998800	850	531	0.10	0.001200	0.3	0.45	0.6632

Plots





These data show the power for various sample sizes and alphas. It is interesting to note that once the sample size is greater than about 450, the value of alpha has comparatively little difference on the value of power.

Example 3 – Effect of Number of Looks

Continuing with examples one and two, it is interesting to determine the impact of the number of looks on power. **PASS** allows only one value for the Number of Looks parameter per run, so it will be necessary to run several analyses. To conduct this study, set alpha to 0.05, *N* to 407, and leave the other parameters as before. Run the analysis with Number of Looks equal to 1, 2, 5, and 10. Record the power for each run.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 3** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab

Solve For	**Power**
Alternative Hypothesis	**Two-Sided**
Survival Time Assumption	**Exponential Survival**
Alpha	**0.05**
N (Total Sample Size)	**407**
S1 (Proportion Surviving 1)	**0.3**
S2 (Proportion Surviving 2)	**0.45**
Number of Looks	**1 (Also run with 2, 5, and 10)**
Spending Function	**O'Brien-Fleming**
Boundary Truncation	**None**
Max Time	**2**
Times	**Equally Spaced**
Informations	**Blank**

Output

Click the Calculate button to perform the calculations and generate the following output.

Numeric Results for Two-Sided Logrank Test (Assuming Exponential Survival)

Solve For: Power

Power	Total Sample Size N	Total Required Events E	Alpha	Beta	Proportion Surviving S1	Proportion Surviving S2	Hazard Ratio HR	Looks
0.905693	407	254	0.05	0.094307	0.3	0.45	0.6632	1
0.904719	407	254	0.05	0.095281	0.3	0.45	0.6632	2
0.899278	407	254	0.05	0.100722	0.3	0.45	0.6632	5
0.895758	**407**	**254**	**0.05**	**0.104242**	**0.3**	**0.45**	**0.6632**	**10**

This analysis shows how little the number of looks impacts the power of the design. The power of a study with no interim looks is 0.905693. When ten interim looks are made, the power falls to 0.895758—a very small change.

Example 4 – Studying a Boundary Set

Continuing with the previous examples, suppose that you are presented with a set of boundaries and want to find the quality of the design (as measured by alpha and power). This is easy to do with ***PASS***. Suppose that the analysis is to be run with five interim looks at equally spaced time points. The upper boundaries to be studied are 3.5, 3.5, 3.0, 2.5, 2.0. The lower boundaries are symmetric. The analysis would be run as follows.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 4** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab	
Solve For	**Power**
Alternative Hypothesis	**Two-Sided**
Survival Time Assumption	**Exponential Survival**
Alpha	**0.05 (will be calculated from boundaries)**
N (Total Sample Size)	**407**
S1 (Proportion Surviving 1)	**0.30**
S2 (Proportion Surviving 2)	**0.45**
Number of Looks	**5**
Spending Function	**User Supplied**
Boundary Truncation	**None**
Max Time	**2**
Times	**Equally Spaced**
Informations	**Blank**
Upper Boundaries	**3.5 3.5 3.0 2.5 2.0**
Lower Boundaries	**Symmetric**

Output

Click the Calculate button to perform the calculations and generate the following output.

Numeric Results for Two-Sided Logrank Test (Assuming Exponential Survival)

Solve For: Power

Power	Total Sample Size N	Total Required Events E	Alpha	Beta	Proportion Surviving S1	Proportion Surviving S2	Hazard Ratio HR
0.900747	407	254	0.048157	0.099253	0.3	0.45	0.6632

Details when Spending = User Supplied, N = 407, E = 254, S1 = 0.3, S2 = 0.45

Look	Time	Lower Bndry	Upper Bndry	Nominal Alpha	Inc Alpha	Total Alpha	Inc Power	Total Power
1	0.4	-3.5	3.5	0.000465	0.000465	0.000465	0.020899	0.020899
2	0.8	-3.5	3.5	0.000465	0.000408	0.000874	0.063132	0.084031
3	1.2	-3.0	3.0	0.002700	0.002410	0.003284	0.243522	0.327553
4	1.6	-2.5	2.5	0.012419	0.010331	0.013615	0.343072	0.670625
5	2.0	-2.0	2.0	0.045500	0.034542	0.048157	0.230122	0.900747

Drift = 3.27466

The power for this design is about 0.90. This value depends on both the boundaries and the sample size. The alpha level is about 0.048. This value only depends on the boundaries.

Example 5 – Validation using O'Brien-Fleming Boundaries

Reboussin (1992) presents an example for binomial distributed data for a design with two-sided O'Brien-Fleming boundaries, looks = 3, alpha = 0.05, beta = 0.10, *S1* = 0.30, *S2* = 0.786 (which gives a hazard ratio of 0.20). They compute a drift of 3.261 and the number of events at 16.42. The upper boundaries are: 4.8769, 3.3569, 2.6803, 2.2898, 2.0310.

To test that **PASS** provides the same result, enter the following.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 5** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab	
Solve For	**Sample Size**
Alternative Hypothesis	**Two-Sided**
Survival Time Assumption	**Exponential Survival**
Power	**0.90**
Alpha	**0.05**
S1 (Proportion Surviving 1)	**0.30**
S2 (Proportion Surviving 2)	**0.786**
Number of Looks	**5**
Spending Function	**O'Brien-Fleming**
Boundary Truncation	**None**
Max Time	**1**
Times	**Equally Spaced**
Informations	**Blank**

Output

Click the Calculate button to perform the calculations and generate the following output.

Numeric Results for Two-Sided Logrank Test (Assuming Exponential Survival)

Solve For: Sample Size

Power	Total Sample Size N	Total Required Events E	Alpha	Beta	Proportion Surviving S1	Proportion Surviving S2	Hazard Ratio HR
0.905173	37	17	0.05	0.094827	0.3	0.786	0.2

Details when Spending = O'Brien-Fleming, N = 37, E = 17, S1 = 0.3, S2 = 0.786

Look	Time	Lower Bndry	Upper Bndry	Nominal Alpha	Inc Alpha	Total Alpha	Inc Power	Total Power
1	0.2	-4.87688	4.87688	0.000001	0.000001	0.000001	0.000341	0.000341
2	0.4	-3.35695	3.35695	0.000788	0.000787	0.000788	0.102760	0.103101
3	0.6	-2.68026	2.68026	0.007357	0.006828	0.007616	0.352450	0.455551
4	0.8	-2.28979	2.28979	0.022034	0.016807	0.024424	0.298953	0.754504
5	1.0	-2.03100	2.03100	0.042255	0.025576	0.050000	0.150669	0.905173

Drift = 3.30902

The number of events, rounded to 17, matches the 16.42 reported in Reboussin (1992).