Chapter 714

One-Sample Logrank Tests

Introduction

This module computes the sample size and power of the one-sample logrank test which is used to compare the survival curve of a single treatment group to that of a historic control. Such is often the case in clinical phase-II trials with survival endpoints. Accrual time, follow-up time, and hazard rates are parameters that can be set.

Several authors have presented sample size formulas for this situation. We have adopted those of Wu (2015) because his paper included an extensive simulation study that showed that his formulation is the most accurate.

Technical Details

One-Sample Logrank Test Statistic

The following details follow closely the results in Wu (2015).

Suppose N subjects are enrolled in a study during the accrual period of length t_a and then observed during a follow-up period of length t_f. Let t_i and C_i denote the failure time and censoring time of the i^{th} subject. The observed failure time is $X_i = t_i \wedge C_i$ and the observed failure indicator is $\Delta_i = I(t_i \leq C_i)$. The one-sample logrank test L is defined in terms of the number of observed events O and the number of expected events E, as follows.

$$L = \frac{O - E}{\sqrt{E}}$$

where

$$O = \sum_{i=1}^{N} \Delta_i$$

$$E = \sum_{i=1}^{N} \Lambda_0(X_i)$$

Here $\Lambda_0(X_i)$ represents the cumulative hazard function $\Lambda_0(t)$ under the null hypothesis evaluated at X_i. The test statistic L is asymptotically distributed as the standard normal distribution under the null hypothesis.

The cumulative survival function is taken to be the Weibull distribution because of the many different shapes that it can take depending on its shape parameter.

Power Calculation

Wu (2015) gives the following power and sample size formulas for a one-sided hypothesis test based on *L*. Note that we use the subscript 0 to represent the historic control and the subscript 1 to represent the new treatment group.

$$Power \cong \Phi\left(-\frac{\sigma_0}{\sigma}z_{1-\alpha} - \frac{\omega\sqrt{n}}{\sigma}\right)$$

$$n = \frac{(\sigma_0 z_{1-\alpha} + \sigma z_{Power})^2}{\omega^2}$$

where

$$\omega = \sigma_1^2 - \sigma_0^2$$

$$\sigma^2 = p_1 - p_1^2 + 2p_{00} - p_0^2 - 2p_{01} + 2p_0p_1$$

$$\sigma_0^2 = p_0$$

$$\sigma_1^2 = p_1$$

$$p_0 = \int_0^\infty G(t)S_1(t)\lambda_0(t)dt$$

$$p_1 = \int_0^\infty G(t)S_1(t)\lambda_1(t)dt$$

$$p_{00} = \int_0^\infty G(t)S_1(t)\Lambda_0(t)\lambda_0(t)dt$$

$$p_{01} = \int_0^\infty G(t)S_1(t)\Lambda_0(t)\lambda_1(t)dt$$

Note that p_1 gives the probability that a subject experiences a failure during the study.

Assuming a uniform accrual, the censoring distribution function $G(t)$ is given by

$$G(t) = \begin{cases} 1 & \text{if } t \le t_f \\ \dfrac{t_a + t_f - t}{t_a} & \text{if } t_f \le t \le t_a + t_f \\ 0 & \text{otherwise} \end{cases}$$

Note that t_a represents the accrual time and t_f represents the follow-up time.

Assuming that failure times follow a two-parameter Weibull distribution, the cumulative survival function $S(t)$ under null and alternative is given by

$$S_0(t) = exp(-\lambda_0 t^k)$$

$$S_1(t) = exp(-\lambda_1 t^k)$$

The hazard and cumulative hazard functions are given as

$$\lambda_0(t) = k\lambda_0 t^{k-1}$$

$$\lambda_1(t) = k\lambda_1 t^{k-1}$$

$$\Lambda_0(t) = \lambda_0 t^k$$

The values of the p_0, p_1, p_{00}, and p_{01} can be calculated by numeric integration.

The hazard rates λ_0 and λ_1 can be given in terms of the hazard ratio *HR*, the median survival times M_0 and M_1, or the survival proportions S_0 and S_1 at time t_0. These parameters are defined as

$$HR = \lambda_1/\lambda_0$$

$$\lambda_0 = \frac{\log 2}{M_0^k} = \frac{-\log S_0(t_0)}{t_0^k}$$

$$\lambda_1 = \frac{\log 2}{M_1^k} = \frac{-\log S_1(t_0)}{t_0^k}$$

Procedure Options

This section describes the options that are specific to this procedure. These are located on the Design tab. For more information about the options of other tabs, go to the Procedure Window chapter.

Design Tab

The Design tab contains most of the parameters and options that you will be concerned with. This chapter covers four procedures, each of which has different effect size options. However, many of the options are common to all four procedures. These common options will be displayed first, followed by the various effect size options.

Solve For

Solve For

This option specifies the parameter to be solved for from the other parameters. The parameters that may be selected are *Power, Sample Size, and Effect Size*. Note that the *Effect Size* depends on the parameterization that is chosen.

Select *Sample Size* when you want to calculate the sample size needed to achieve a given power and alpha level.

Select *Power* when you want to calculate the power.

Test

Alternative Hypothesis

Specify whether the statistical test is two-sided or one-sided.

- **Two-Sided**

  This option tests whether the two hazards rates, median survival times, or survival proportions are different (Ha: $\lambda_1 \neq \lambda_0$). This option causes α/2 to be substituted for α in the calculations.

- **One-Sided**

  When this option is used and the value of λ_1 is less than λ_0, rejecting the null hypothesis results in the conclusion that the new group's hazard rate (λ_1) is less than the historic control hazard rate (λ_0). Otherwise, the opposite conclusion is reached.

  When you use a one-sided test, you should divide your alpha level by two to keep your significance level comparable to that of a two-sided test.

Power and Alpha

Power

This option specifies one or more values for power. Power is the probability of rejecting a false null hypothesis, and is equal to one minus Beta. Beta is the probability of a type-II error, which occurs when a false null hypothesis is not rejected. In this procedure, a type-II error occurs when you fail to reject the null hypothesis of equal survival curves when in fact the curves are different.

Values must be between zero and one. Historically, the value of 0.80 was used for power. For phase II trials, 0.90 is also commonly used.

A single value may be entered here or a range of values such as *0.8 to 0.90 by 0.05* may be entered.

Alpha

This option specifies one or more values for the probability of a type-I error. A type-I error occurs when you reject the null hypothesis of equal survival curves when in fact the curves are equal.

Values of alpha must be between zero and one. Historically, the value of 0.05 has been used for a two-sided test and 0.025 has been used for a one-sided test. You should pick a value for alpha that represents the risk of a type-I error you are willing to take in your experimental situation.

You may enter a range of values such as *0.01 0.05 0.10* or *0.01 to 0.10 by 0.01*.

Sample Size

N (Sample Size)

Enter a value for the sample size, *N*. This is the number of subjects in the study. You can enter one or more positive integers greater than or equal to 3. You may also enter a range such as “10 to 100 by 10” or a list of values separated by commas or blanks such as “20 40 60 80.”

Ta (Accrual Time)

Enter one or more values for the number of time periods (months, years, etc.) during which subjects are entered into the study. The total duration of the study is equal to the Accrual Time plus the Follow-Up Time.

Accrual times can range from 0 to on up. Enter “0” when all subjects begin the study together.

Tf (Follow-Up Time)

The length of time between the entry of the last individual and the end of the study.

Effect Size

Input Type

Specify which set of parameters you want to use to specify the hazard rates of the historical control (λ0) and the new group from which the sample is drawn (λ1). These parameters are functionally related, so the values of λ0 and λ1 are calculated from the items you enter (if necessary).

The possible choices are

- **λ0, λ1 (Hazard Rates)**
  Enter the values of the two hazards rates (λ0 and λ1) directly.

- **λ0, HR (Hazard Rate, Hazard Ratio)**
  Enter the hazard rate of the historical control (λ0) and the hazard ratio (λ1 / λ0).

- **M0, M1 (Median Survival Times)**
  Enter the median survival times of the historical control (M0) and the new group (M1). The values of λ0 and λ1 are calculated based on the Weibull distribution using

  λ_i = -log(2) / (M_i)^k, where 'x^k' means to raise x to the power k.

- **M0, HR (Median Survival, Hazard Ratio)**
  Enter the median survival times of the historical control (M0) and the hazard ratio (λ1 / λ0).

- **S0, S1 (Proportions Surviving)**
  Enter the proportions surviving for a fixed period of time (T0) of the historical control (S0) and the new group (S1). The values of λ0 and λ1 are calculated based on the Weibull distribution using

  λ_i = -log(S_i(T0)) / (T0)^k.

- **S0, HR (Proportion Surviving, Hazard Ratio)**
  Enter the proportions surviving for a fixed period of time (T0) of the historical control (S0) and the hazard ratio (λ1 / λ0).

λ0 (Hazard Rate – Control)

Enter a value (or range of values) for the hazard rate (event rate or incidence rate) of the distribution of the historical control. This distribution is assumed to be Weibull with a known shape parameter *k*.

This rate is compared to λ_1 by the one-sample logrank test. The ratio of these rates, $HR = \lambda_1 / \lambda_0$, is the amount that this design can detect.

The value must be greater than zero.

Example of Estimating λ0

If 200 control patients were followed for 1 year and 40 experienced the event of interest, the hazard rate would be

λ_0 = 40/(200*1) = 0.2 per patient-year.

Similarly, if 200 patients were followed for 2 years and 40 experienced the event of interest, the hazard rate would be

λ_0 = 40/(200*2) = 0.1 per patient-year.

Note that this estimate does not consider the censoring. For censored survival data, it is often estimated from a survival distribution fitted from historical data. For example,

$$\lambda_0 = -\frac{\ln S(t_0)}{t_0^k}$$

λ1 (Hazard Rate – New)

Enter a value (or range of values) for the hazard rate (event rate or incidence rate) of the distribution of the response values in the new group. This distribution is assumed to be Weibull with a known shape parameter *k*.

This rate is compared to λ_1 by the one-sample logrank test. The ratio of these rates, $HR = \lambda_1 / \lambda_0$, is the amount that this design can detect.

The value must be greater than zero.

Example of Estimating λ_1

Once we have λ_0 and *HR*, λ_1 is obtained as follows

$$\lambda_1 = HR(\lambda_0)$$

HR (Hazard Ratio)

Enter one or more values for HR, the hazard ratio λ_1 / λ_0. This value is used with λ_0 to calculate a value for λ_1. HR can be any number greater than zero and unequal to one. You may enter a single value or a range of values.

M0 (Median Survival - Control)

Specify a single value, or set of values, for the median survival time in the historical control group. Assuming a Weibull distribution with shape parameter *k*, the value of λ_0 is calculated as given in the technical details above.

This value must be a number greater than zero.

M1 (Median Survival - New)

Specify a single value, or set of values, for the median survival time in the new (treatment) group. Assuming a Weibull distribution with shape parameter *k*, the value of λ_1 is calculated as given in the technical details above.

This value must be a number greater than zero.

S0 (Proportion Surviving - Control)

Enter the proportion surviving (S_0) for a fixed period of time (T_0) in the historical control group. The value of λ_0 is calculated as given in the technical details above.

Since this is a proportion, it must be a value between (but not including) zero and one. You may enter a single value or a range of values.

S1 (Median Survival - New)

Specify a single value, or set of values, for the median survival time in the new (treatment) group. Assuming a Weibull distribution with shape parameter *k*, the value of λ_1 is calculated as given in the technical details above.

This value must be a number greater than zero.

T0 (Time of S0 and S1)

When S_0 and S_1 are selected as the *Input Type*, this value is needed to give the amount of time that S_0 and S_1 are related to. Since this value is a time period, it must be a positive value.

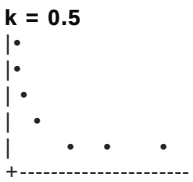
k (Weibull Shape Parameter)

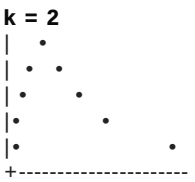
This is the (assumed to be known) value of Weibull shape parameter. Usually, you will need to estimate *k* from the historical controls. If you don't have any information, you can set *k* to one which results in the exponential distribution.

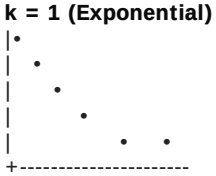
The parameter *k* must be a number greater than zero. Usually it is greater than zero and less than or equal to 5.

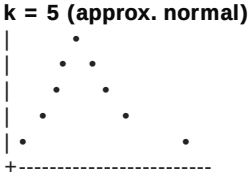
Examples

The shape of the Weibull distribution probability distribution function is quite different depending on the value of *k*. Here are some examples. Note that *elapsed time* is shown on the horizontal axis.









Example 1 – Finding the Sample Size

A researcher is planning a clinical trial to compare the response of a new treatment to that of the current treatment. The median survival time in the current population is 1.54. The current population of responses exhibits a Weibull distribution with a shape parameter of 1.67. The researcher wants a sample size large enough to detect hazard ratios of 0.7 and 0.8 or less at a 5% significance level for a two-sided, one-sample logrank test. The accrual period will be 1 year. The researcher would like to compare the sample requirements if the follow-up period is 1, 2, or 3 years.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the procedure. You may then make the appropriate entries as listed below, or open **Example 1** by going to the **File** menu and choosing **Open Example Template**.

Option	Value
Design Tab	
Solve For	**Sample Size**
Alternative Hypothesis	**Two-Sided**
Power	**0.90**
Alpha	**0.05**
Ta (Accrual Time)	**1**
Tf (Follow-Up Time)	**1 2 3**
Input Type	**M0, HR (Median Survival, Hazard Ratio)**
M0 (Median Survival - Control)	**1.54**
HR (Hazard Ratio - λ1/λ0)	**0.7 0.8**
k (Weibull Shape Parameter)	**1.67**

Annotated Output

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

Numeric Results

Numeric Results for the Two-Sided, One-Sample Logrank Test

Power	N	Events E	Accr Time Ta	FU Time Tf	λ1/λ0 Haz Ratio HR	Cntl Med Surv M0	New Med Surv M1	Wei-bull Shape k	Alpha	Prob Event P1
0.9011	208	77	1.0	1.0	0.700	1.54	1.91	1.67	0.050	0.3706
0.9004	495	203	1.0	1.0	0.800	1.54	1.76	1.67	0.050	0.4098
0.9017	125	82	1.0	2.0	0.700	1.54	1.91	1.67	0.050	0.6591
0.9007	300	212	1.0	2.0	0.800	1.54	1.76	1.67	0.050	0.7066
0.9014	103	87	1.0	3.0	0.700	1.54	1.91	1.67	0.050	0.8481
0.9003	249	220	1.0	3.0	0.800	1.54	1.76	1.67	0.050	0.8833

References

Wu, Jianrong. 2015. 'Sample size calculation for the one-sample log-rank test', Pharmaceutical Statistics, Volume 14, pages 26-33.
Wu, Jianrong. 2014. 'A New One-Sample Log-Rank Test', J Biomet Biostat 5; 210.
Finkelstein D, Muzikansky A, Schoenfeld D. 2003. 'Comparing Survival of a Sample to That of a Standard Population', Journal of the National Cancer Institute, 95, pages 1434-1439.
Sun X, Peng P, Tu D. 2011. 'Phase II cancer clinical trials with a one-sample log-rank test and its corrections based on the Edgeworth expansion', Contemporary Clinical Trials, 32, pages 108-113.
Schmidt R., Kwiecien R, Faldum A, Berthold F, Hero B, Ligges S. 2015. 'Sample size calculation for the one-sample log-rank test', Stat Med, 34(6), pages 1031-40.

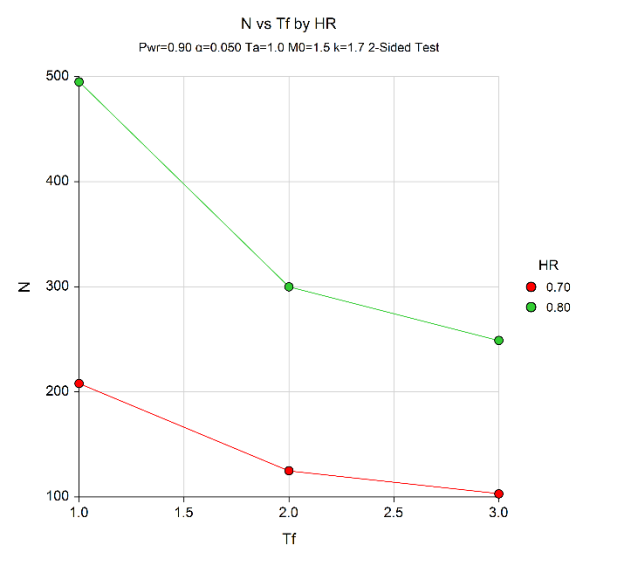
One-Sample Logrank Tests

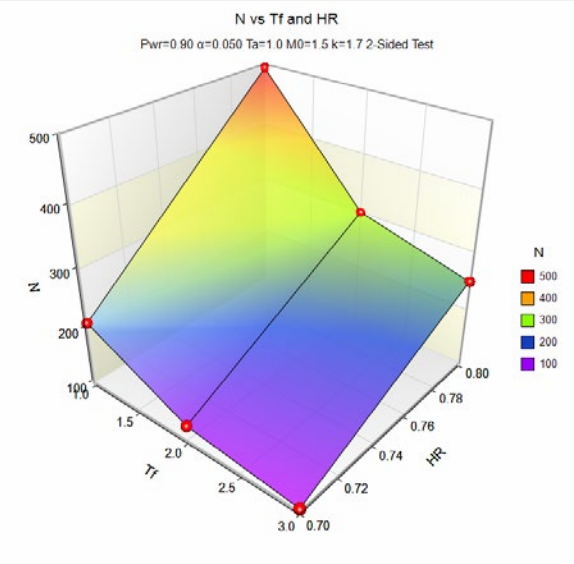
Report Definitions
Power is the probability of rejecting a false null hypothesis.
N is the sample size of the New group, assuming no subject lost to dropout or follow-up during the study.
E is the expected number of events (failures) in the new group during the study.
Ta is the length of the accrual time during which subjects are added to the study. Subjects are added uniformly.
Tf is the length of the follow-up time after the last subject is added to the study.
HR is the hazard ratio (λ1/λ0) is the new group's hazard rate divided by the hazard rate of the historic control.
M0 is the median survival time of the historic control group.
M1 is the median survival time of the new (treatment) group.
k is the shape parameter of the Weibull distribution used for both groups.
Alpha is the probability of rejecting a true null hypothesis.
P1 is the probability that a subject in the new group experiences an event (failure) during the study.

Summary Statements
A two-sided, one-sample logrank test calculated from a sample of 208 subjects achieves 90.1% power at a 0.050 significance level to detect a hazard ratio of 0.700 when the median survival time of the historic control group is 1.54. Subjects are accrued for a period of 1.0. Follow-up continues for a period of 1.0 after the last subject is added. The probability that a subject experiences an event during the study is 0.3706. The expected number of events during the study is 77. It is assumed that the survival time distribution is approximated reasonable well by the Weibull distribution with a shape parameter of 1.67.

This report presents the calculated sample sizes for each scenario as well as the values of the other parameters.

Plots Section





This plot shows the relationship between sample size, follow-up time, and HR.

Example 2 – Validation using Wu (2015)

Wu (2015) gives an example in which the power if 0.80, alpha = 0.05 for a one-sided test, k = 1.22, Ta = 5 and Tf = 3, HR = 0.57143, and M0 = 9. Wu calculates N to be 88.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the procedure. You may then make the appropriate entries as listed below, or open **Example 2** by going to the **File** menu and choosing **Open Example Template**.

Option	Value
Design Tab	
Solve For	**Sample Size**
Alternative Hypothesis	**One-Sided**
Power	**0.80**
Alpha	**0.05**
Ta (Accrual Time)	**5**
Tf (Follow-Up Time)	**3**
Input Type	**M0, HR (Median Survival, Hazard Ratio)**
M0 (Median Survival - Control)	**9**
HR (Hazard Ratio - λ1/λ0)	**0.5714**
k (Weibull Shape Parameter)	**1.22**

Output

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

Numeric Results for the One-Sided, One-Sample Logrank Test

Power	N	Events E	Accr Time Ta	FU Time Tf	λ1/λ0 Haz Ratio HR	Cntl Med Surv M0	New Med Surv M1	Wei-bull Shape k	Alpha	Prob Event P1
0.8032	88	17	5.0	3.0	0.571	9.00	14.24	1.22	0.050	0.1949

PASS has also calculated N as 88.