Chapter 712

One-Sample Tests for Exponential Hazard Rate

Introduction

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

The procedure is documented in Jung (2013).

Technical Details

One-Sample Exponential Hazard Rate Test Statistic

The following details follow closely the results in Jung (2013).

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. Let X_i be the minimum of t_i and C_i. The observed failure indicator is $\delta_i = I(t_i \leq C_i)$. The MLE of hazard rate is defined as the ratio of the number of observed events E and the total observed survival time X, as follows.

$$\hat{\lambda} = \frac{E}{X}$$

where

$$E = \sum_{i=1}^{N} \delta_i$$

$$X = \sum_{i=1}^{N} X_i$$

To test the statistical hypothesis $H_0: \lambda = \lambda_0$ versus $H_a: \lambda < \lambda_0$, we use fact that $\sqrt{E}\left(\ln\left(\hat{\lambda}\right) - \ln(\lambda)\right)$ is approximately distributed as a unit normal under H_0. So, we can reject H_0 in favor of H_a if $\sqrt{E}\left(\ln\left(\hat{\lambda}\right) - \ln(\lambda)\right) < -z_{1-\alpha}$.

Power Calculation

Jung (2013) gives the following power and sample size formulas for a one-sided hypothesis test based on $\hat{\lambda}$. Note that we use the subscript 0 to represent the historic control and the subscript 1 to represent the new treatment group.

$$Power = \Phi\left(\sqrt{E}\left(\ln\left(\hat{\lambda}\right) - \ln(\lambda)\right) < -z_{1-\alpha} | H_a\right)$$

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

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

where t_a represents the accrual time and t_f represents the follow-up time.

The required number of events is

$$E = \frac{\left(z_{1-\alpha} + z_{1-\beta}\right)^2}{\left[\ln\left(\frac{\lambda_0}{\lambda_1}\right)\right]^2}$$

Under the uniform accrual assumption, the sample size is

$$N = \frac{\left(z_{1-\alpha} + z_{1-\beta}\right)^2}{P_1\left[\ln\left(\frac{\lambda_0}{\lambda_1}\right)\right]^2}$$

where

$$P_1 = 1 - (1 - \exp(-\lambda_1 t_a)\left(\frac{\exp(-\lambda_1 t_f)}{\lambda_1 t_a}\right)$$

P_1 is the probability that a subject experiences an event during the study.

This sample size formula can be rearranged to give an expression for power.

Accrual Rate Known

If only the accrual rate R_a is known instead of the accrual time t_a, the accrual time is unknown at the time of sample size calculation. The required value of R_a is found by solving

$$t_a R_a P_1 = \frac{\left(z_{1-\alpha} + z_{1-\beta}\right)^2}{\left[\ln\left(\frac{\lambda_0}{\lambda_1}\right)\right]^2}$$

for t_a. Note that P_1 is also a function of t_a.

Alternative Hazard Rate Input Types

There are multiple quantities that can be used. 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 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 cumulative survival proportions S_0 and S_1 at time t_0. These various parameters are defined as

$$HR = \lambda_1/\lambda_0$$

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

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

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

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

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 $\alpha/2$ 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 hazard rates when in fact the hazard rates 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 hazard rates when in fact the hazard rates 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."

Accrual Input Type

Specify what you will enter to indicate how subjects will be added to the study.

Your choices are

- **Ta (Accrual Time)**
  Specify Ta, the accrual time. Assume that subjects will be added to the study at a constant rate during this period.

- **Ra (Accrual Rate)**
  Specify Ra, the accrual rate. Assume that subjects will be added to the study at this rate during the yet to be determined accrual period.

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.

Ra (Accrual Rate)

Enter one or more values for the rate at which subjects are added to the study group. Specify this rate using the same time units as the follow-up time and the hazard rates. Common choices are years, months, or days.

Note that using months as the time period may cause confusion because of the variable number of days per month.

The range is Ra > 0.

Tf (Follow-Up Time)

The length of time between the entry of the last individual and the end of the study. Tf > 0.

Effect Size

Hazard Rates 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 exponential distribution using

  $\lambda_i = -\log(2) / M_i$.

- **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 exponential distribution using
  $\lambda_i = -\log(S_i(T0)) / (T0)$.

- **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 exponential hazard rate (event rate or incidence rate) of the historical control.

This rate is compared to λ_1 by the test based on the average hazard rate described above. 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

$\lambda_0 = 40/(200*1) = 0.2$ per patient-year.

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

$\lambda_0 = 40/(200*2) = 0.1$ 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,

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

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 exponential.

This rate is compared to λ_1 by the test based on the average hazard rate described above. 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 an exponential distribution, 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 an exponential distribution, 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.

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 an exponential distribution. The researcher wants to know the sample sizes needed to detect hazard ratios of 0.7 and 0.8 at 90% power and a 5% significance level for a two-sided, test of the estimated hazard rate. 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**
Accrual Input Type	**Ta (Accrual Time)**
Ta (Accrual Time)	**1**
Tf (Follow-Up Time)	**1 2 3**
Hazard Rates Input Type	**M0, HR (Median Survival, Hazard Ratio)**
M0 (Median Survival - Control)	**1.54**
HR (Hazard Ratio - λ1/λ0)	**0.7 0.8**

Annotated Output

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

Numeric Results

Numeric Results
Hypothesis Type: Two-Sided
Test Statistic: One-sample exponetial hazard rate based on the MLE
Data Distribution: Exponential

Power	N	Events E	Accr Time Ta	Accr Rate Ra	Follow Up Time Tf	λ1/λ0 Haz Ratio HR	Cntl Haz Rate λ0	New Haz Rate λ1	Cntl Med Surv M0	New Med Surv M1	Alpha	Prob Event P1
0.9002	221	82.6	1.0	221.0	1.0	0.700	0.450	0.315	1.54	2.20	0.050	0.374
0.9003	510	211.0	1.0	510.0	1.0	0.800	0.450	0.360	1.54	1.93	0.050	0.414
0.9018	153	82.6	1.0	153.0	2.0	0.700	0.450	0.315	1.54	2.20	0.050	0.543
0.9001	357	211.0	1.0	357.0	2.0	0.800	0.450	0.360	1.54	1.93	0.050	0.591
0.9002	124	82.6	1.0	124.0	3.0	0.700	0.450	0.315	1.54	2.20	0.050	0.667
0.9008	296	211.0	1.0	296.0	3.0	0.800	0.450	0.360	1.54	1.93	0.050	0.715

References
Jung, Sin-Ho. 2013. Randomized Phase II Cancer Clinical Trials. Chapman & Hall / CRC. Boca Raton, Florida.

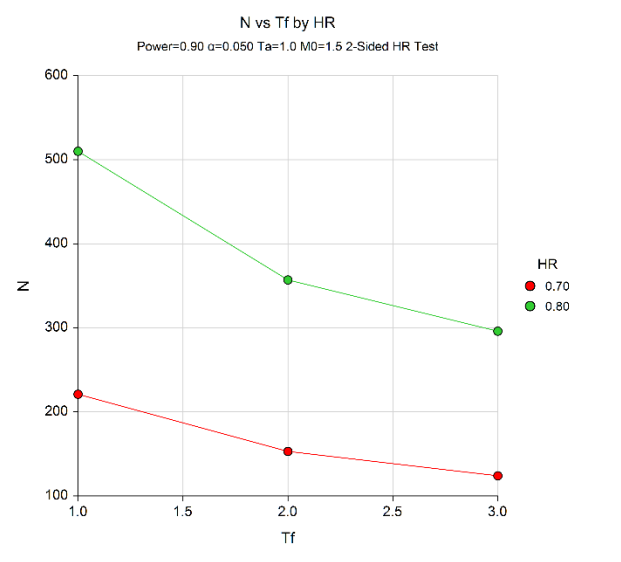
One-Sample Tests for Exponential Hazard Rate

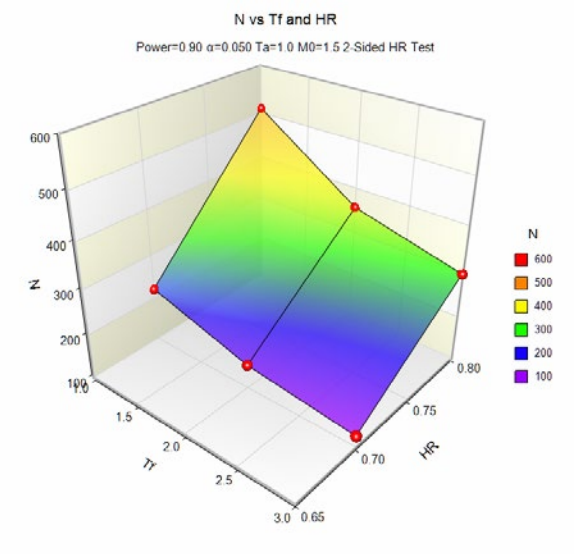
Report Definitions
Power is the probability of rejecting a false null hypothesis.
N is the sample size of the New group, assuming no subject lost to dropout or follow-up during the study.
E is the expected number of events (failures) in the new group during the study.
Ta is the length of the accrual time during which subjects are added to the study.
Ra is accrual rate at which subjects are added to the study. Subjects are added uniformly during the accrual period.
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.
λ0 is the hazard rate of the historic control (standard).
λ1 is the hazard rate of the new group.
M0 is the median survival time of the historic control group.
M1 is the median survival time of the new (treatment) group.
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 test using the MLE of exponential data calculated from a sample of 221 subjects achieves 90.0% 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 time 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 0.374. The expected number of events during the study is 82.6. It is assumed that the survival time distribution is approximated reasonable well by the exponential distribution.

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 Jung (2013)

Jung (2013) page 59 gives an example in which the power = 0.80, alpha = 0.1 for a one-sided test, Ra = 60 and Tf = 1, $\lambda_0 = 0.693,$ and $\lambda_1 = 0.462$. Jung calculates N to be 77.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the. 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	**0.90**
Alpha	**0.1**
Accrual Input Type	**Ra (Accrual Rate)**
Ra (Accrual Rate)	**60**
Tf (Follow-Up Time)	**1**
Hazard Rates Input Type	**λ0, λ1 (Hazard Rates)**
λ0 (Hazard Rate - Control)	**0.693**
λ1 (Hazard Rate - New)	**0.462**

Output

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

Numeric Results

Hypothesis Type: One-Sided
Test Statistic: One-sample exponetial hazard rate based on the MLE
Data Distribution: Exponential

Power	N	Events E	Accr Time Ta	Accr Rate Ra	Follow Up Time Tf	λ1/λ0 Haz Ratio HR	Cntl Haz Rate λ0	New Haz Rate λ1	Alpha	Prob Event P1
0.9020	77	40.0	1.3	60.0	1.0	0.667	0.693	0.462	0.100	0.524

PASS has also calculated N as 77. Thus, the procedure is validated.