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 $H_0: \lambda = \lambda_0 \text{ versus } H_a: \lambda < \lambda_0$, 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

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

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

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

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

The hazard and cumulative hazard functions are given as

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

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

$$\Lambda_0(\mathrm{t}) = \lambda_0 t^k$$

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

$$HR = \frac{\lambda_1}{\lambda_0}$$

$$\lambda_0 = \frac{\log 2}{M_0^k} = \frac{-\log S_0(t_0)}{t_0^k} = \theta_0^{-k}$$

$$\lambda_1 = \frac{\log 2}{M_1^k} = \frac{-\log S_1(t_0)}{t_0^k} = \theta_1^{-k}$$

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

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**
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**

Output

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

Numeric Reports

Numeric Results

Solve For: Sample Size
Groups: 0 = Historical Control, 1 = New or Treatment
Hypothesis Type: Two-Sided
Test Statistic: One-sample exponential hazard rate based on the MLE
Data Distribution: Exponential

	New Group					Hazard Rate		Median Survival Time			
Power	Sample Size N	Number of Events E	Accrual Time Ta	Follow-Up Time Tf	Hazard Ratio HR	Control λ0	New λ1	Control M0	New M1	Probability of an Event in the New Group P1	Alpha
0.9002	221	82.6	1	1	0.7	0.45	0.315	1.54	2.20	0.374	0.05
0.9003	510	211.0	1	1	0.8	0.45	0.360	1.54	1.93	0.414	0.05
0.9018	153	82.6	1	2	0.7	0.45	0.315	1.54	2.20	0.543	0.05
0.9001	357	211.0	1	2	0.8	0.45	0.360	1.54	1.93	0.591	0.05
0.9002	124	82.6	1	3	0.7	0.45	0.315	1.54	2.20	0.667	0.05
0.9008	296	211.0	1	3	0.8	0.45	0.360	1.54	1.93	0.715	0.05

Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N The sample size of the New group, assuming no subject lost to dropout or follow-up during the study.
E The expected number of events (failures) in the new group during the study.
Ta The length of the accrual time during which subjects are added to the study.
Tf The length of the follow-up time after the last subject is added to the study.
HR The hazard ratio is the new group's hazard rate divided by the hazard rate of the historical control. HR = λ1/λ0.
λ0 The hazard rate of the historical control (standard).
λ1 The hazard rate of the new group.
M0 The median survival time of the historical control group.
M1 The median survival time of the new (treatment) group.
P1 The probability that a subject in the new group experiences an event (failure) during the study.
Alpha The probability of rejecting a true null hypothesis.

Summary Statements

A single-group design will be used to test whether a new treatment (exponential) hazard rate is different from that of a historical control. The comparison will be made using a two-sided, one-sample Z test based on the maximum likelihood estimate of the hazard rate, with a Type I error rate (α) of 0.05. It is assumed that the survival time distribution is approximated reasonably well by the exponential distribution. The accrual time will be 1 and the follow-up time (time after complete accrual) will be 1. To detect a hazard ratio of 0.7 when the median survival time of the historical control group is 1.54, with 90% power, the number of needed subjects will be 221. The probability that an individual subject experiences an event during the study is 0.374, and the expected number of events during the study is 82.6.

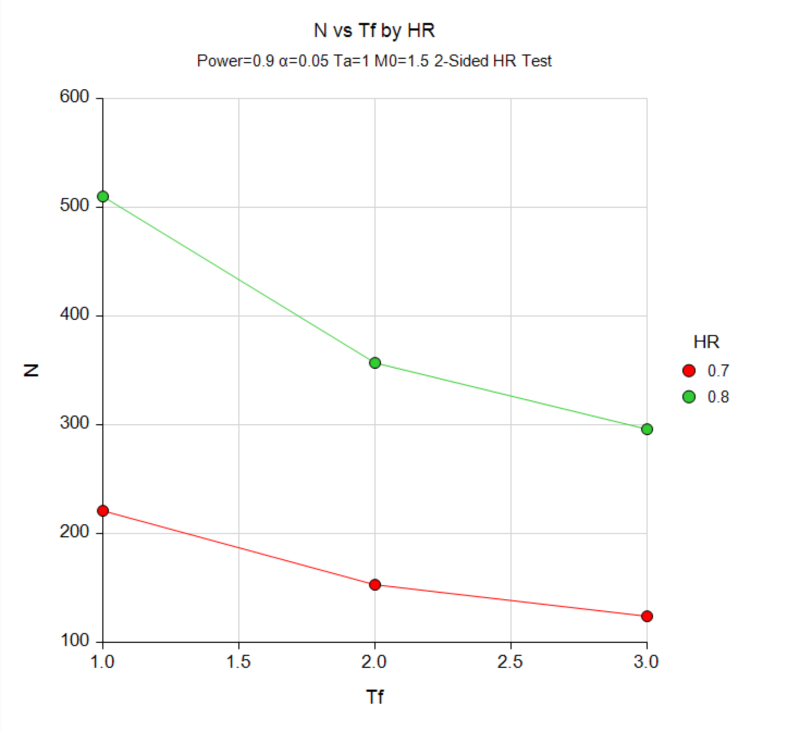
References

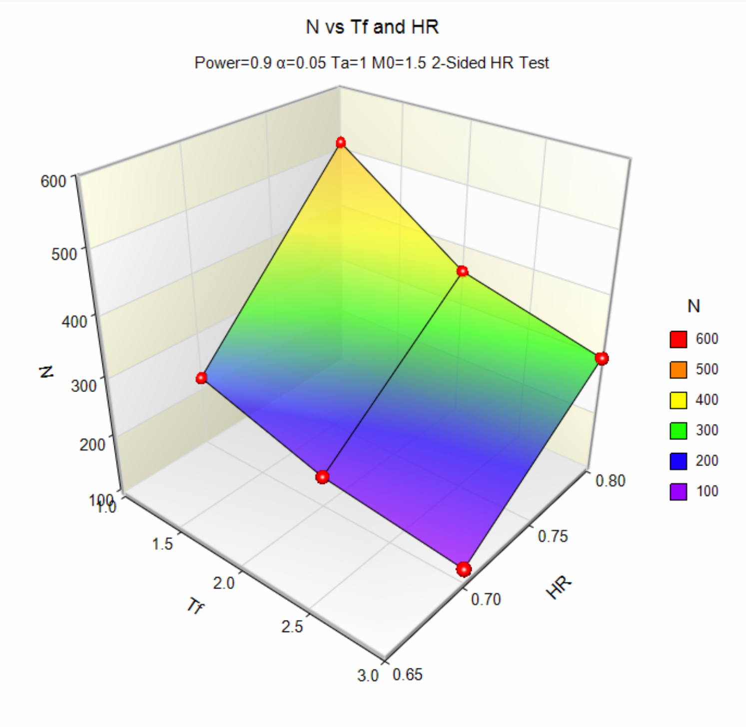
Jung, Sin-Ho. 2013. Randomized Phase II Cancer Clinical Trials. Chapman & Hall / CRC. Boca Raton, Florida.

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

Plots Section

Plots





These plots show 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

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 ....**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

Solve For: Sample Size
Groups: 0 = Historical Control, 1 = New or Treatment
Hypothesis Type: One-Sided
Test Statistic: One-sample exponential hazard rate based on the MLE
Data Distribution: Exponential

	New Group					Hazard Rate			
Power	Sample Size N	Number of Events E	Accrual Rate Ra	Follow-Up Time Tf	Hazard Ratio HR	Control λ0	New λ1	Probability of an Event in the New Group P1	Alpha
0.902	77	40	60	1	0.667	0.693	0.462	0.524	0.1

PASS has also calculated N to be 77.