Chapter 707

Tests for the Difference of Two Hazard Rates Assuming an Exponential Model

Introduction

A clinical trial is often employed to test the equality of survival distributions of two treatment groups. The two-sample t-test is not appropriate for two reasons. First, the data are not normally distributed. Second, some survival times are *censored*. For these reasons, special test statistics such as the logrank test have been developed. This module computes the sample size and power of the logrank test assuming survival times follow exponential distributions. Accrual time and follow-up time are included among the input parameters.

This procedure is based on the *unconditional* method of Chow, Shao, and Wang (2008) which, in turn, is based on the *conditional* methods of Lachin and Foulkes (1986). The conditional procedure does not extend to non-inferiority, non-zero null, or equivalence tests as easily as the unconditional method does (see Chow, Shao, and Wang (2008) page 173).

Technical Details

This section presents the *unconditional* method of Chow, Shao, and Wang (2008).

Basic Model

Suppose a clinical trial consists of two independent groups labeled “1” and “2” (where group 1 is the control group and group 2 is the treatment group). The total sample size is *N* and the sizes of the two groups are N_1 and N_2. Usually, you would plan to have $N_1 = N_2$.

Test Statistic

The power and sample size formulas presented below are for the logrank test statistic. However, they were originally developed for comparing the difference of two exponential hazard rates. Simulation studies then showed that they approximated the power of the logrank test.

Test Comparing Hazard Rate

The original test statistic is the difference of the hazard rates estimated by maximum likelihood divided by their standard error. The maximum likelihood estimate of an exponential hazard rate for a particular group is

$$\hat{h} = \frac{\text{number of events}}{\text{sum of study time of all subjects}}$$

Chow, Shao, and Wang (2008) indicate that the test statistic

$$Z = \frac{\hat{h}_2 - \hat{h}_1}{\sqrt{\frac{\sigma^2\left(\hat{h}_1\right)}{N_1} + \frac{\sigma^2\left(\hat{h}_2\right)}{N_2}}}$$

where

$$\sigma^2(h) = \frac{h^2}{1 + \frac{e^{-hT}\left(1 - e^{hR}\right)}{hR}}$$

follows the standard normal standard normal distribution at least approximately.

Logrank Test

The logrank test statistic is given by

$$L = \frac{\sum_{k=1}^{K}\left(I_k - \frac{Y_{1i}}{Y_{1i} + Y_{2i}}\right)}{\left[\sum_{k=1}^{K}\left(\frac{Y_{1i}Y_{2i}}{\left(Y_{1i} + Y_{2i}\right)^2}\right)\right]^{-1/2}}$$

Where K is the number of deaths, Y_{ij} is the number of subjects at risk just prior to the jth observed event in the ith group, and I_k is is a binary variable indicating whether the kth even is from group 1 or not. L follows the standard normal distribution.

Power Calculations

Assuming an exponential model with hazard rates h_1 and h_2 for the two groups, Chow et al. (2008) give the following equation relating *N* and power of a two-tailed test.

$$\frac{|h_2 - h_1|}{\sqrt{\frac{\sigma^2(h_1, \omega_1, A)}{N_1} + \frac{\sigma^2(h_2, \omega_2, A)}{N_2}}} - z_{1-\alpha/2} = z_{1-\beta}$$

where

$$\sigma^2(h_i, \omega_i, A) = \frac{h_i^2}{E(d_i \mid h_i, \omega_i, A)}$$

$$E(d_i | h_i, \omega_i, A) = \left(\frac{h_i}{h_i + \omega_i}\right)\left(1 + \frac{A\exp\{-(h_i + \omega_i)T\}[1 - \exp\{(h_i + \omega_i - A)R\}]}{(h_i + \omega_i - A)[1 - \exp\{-AR\}]}\right)$$

$$E(d_i | h_i, \omega_i, 0) = \left(\frac{h_i}{h_i + \omega_i}\right)\left(1 + \frac{\exp\{-(h_i + \omega_i)T\}[1 - \exp\{(h_i + \omega_i)R\}]}{(h_i + \omega_i)R}\right)$$

These parameters are interpreted as follows.

Parameter	Interpretation
$\sigma^2(h, \omega, A)$	Variance of $\hat{h}$
$E(d_i \mid h_i, \omega_i, A)$	Expected proportion of events (deaths) in group *i*
d_i	Indicates the a person does $(d_i = 1)$ or does not $(d_i = 0)$ die in group *i*
h_i	Hazard rate of group *i* (see below)
ω_i	Loss to follow-up hazard rate of group *i* (see below)
A	Patient entry parameter (see below)
R	Accrual time
T	Total time
$T - R$	Follow-up time

Exponential Distribution

The hazard rate from the exponential distribution, h, is usually estimated using maximum likelihood techniques. In the planning stages, you have to obtain an estimate of this parameter. To see how to accomplish this, let's briefly review the exponential distribution. The density function of the exponential is defined as

$$f(t) = h \exp\{-ht\}, \quad t \geq 0, h > 0.$$

The cumulative survival distribution function is

$$S(t) = \exp\{-ht\}, \quad t \geq 0.$$

Solving this for h yields

$$h = -\frac{\log\{S(t)\}}{t}$$

Note that $S(t)$ gives the probability of surviving t years. To obtain a planning estimate of h, you need only know the proportion surviving during a particular time period. You can then use the above equation to calculate h.

Patient Entry

Patients are enrolled during the accrual period. ***PASS*** lets you specify the pattern in which subjects are enrolled. Suppose patient entry times are distributed as $g(t)$ where t_i is the entry time of the i^{th} individual and $0 \leq t_i \leq R$. Let $g(t)$ follow the truncated exponential distribution with parameter A, which has the density

$$g(t) = \begin{cases} \dfrac{A\exp\{-At\}}{1 - A\exp\{-AR\}} & \text{if } 0 \leq t \leq R, \quad A \neq 0 \\ 1 & \text{otherwise} \end{cases}$$

where

R is accrual time.

A is interpreted as follows:

$A > 0$ results in a convex (faster than expected) entry distribution.

$A < 0$ results in a concave (slower than expected) entry distribution.

$A = 0$ results in the uniform entry distribution in which $g(t) = 1/R$.

Rather than specify A directly, ***PASS*** has you enter the percentage of the accrual time that will be needed to enroll 50% of the subjects. Using an iterative search, the value of A corresponding to this percentage is calculated and used in the calculations.

Losses to Follow-Up

The staggered patient entry over the accrual period results in censoring times ranging from T - R to T years during the follow-up period. This is often referred to as administrative censoring, since it is caused by the conclusion of the study rather than by some random factor working on an individual. To model the losses to follow-up in each group which come from other causes, we use the exponential distribution again, this time with hazard rates ω_1 and ω_2. You can obtain appropriate loss-to-follow-up hazard rates using the following formula or by using the Survival Parameter Conversion Tool available from the Tools menu or by pressing the small button to the rate of the loss-to-follow-up hazard rate box.

$$\omega = -\frac{\log\{1 - P_{loss}(R)\}}{R}$$

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.

Solve For

Solve For

This option specifies the parameter to be solved for from the other parameters. The parameters that may be selected are *hazard rate, Power*, or *Sample Size*. 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 Direction

Alternative Hypothesis

Specify the direction of the test. The "≠" alternative is leads to a two-sided test. Using the "<" or ">" leads to a one-sided test.

The symbols h1 and h2 stand for the hazard rates of the control and treatment groups, respectively.

The two-sided test (Ha: h2 - h1 ≠ 0) is the standard. Only use the one-sided tests under special circumstances. If you do use a one-sided test, be sure that the alternative hypothesis matches the values of the survival amounts, h1 and h2. That is, if you have set h1 = 0.4 and h2 = 0.5, and you want to analyze a one-sided test, the Alternative Hypothesis should be Ha: h2 - h1 > 0.

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 (Beta = 0.20) was used for power. Now, 0.90 (Beta = 0.10) is also commonly used.

A single value may be entered here or a range of values such as *0.8 to 0.95 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 alpha. This means that about one test in twenty will falsely reject the null hypothesis. 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 (When Solving for Sample Size)

Group Allocation

Select the option that describes the constraints on *N1* or *N2* or both.

The options are

- **Equal (N1 = N2)**

  This selection is used when you wish to have equal sample sizes in each group. Since you are solving for both sample sizes at once, no additional sample size parameters need to be entered.

- **Enter R = N2/N1, solve for N1 and N2**

  For this choice, you set a value for the ratio of *N2* to *N1*, and then PASS determines the needed *N1* and *N2*, with this ratio, to obtain the desired power. An equivalent representation of the ratio, *R*, is

  $$N2 = R * N1.$$

- **Enter percentage in Group 1, solve for N1 and N2**

  For this choice, you set a value for the percentage of the total sample size that is in Group 1, and then PASS determines the needed *N1* and *N2* with this percentage to obtain the desired power.

R (Group Sample Size Ratio)

This option is displayed only if Group Allocation = "Enter R = N2/N1, solve for N1 and N2."

R is the ratio of *N2* to *N1*. That is,

$$R = N2 / N1.$$

Use this value to fix the ratio of *N2* to *N1* while solving for *N1* and *N2*. Only sample size combinations with this ratio are considered.

N2 is related to *N1* by the formula:

$$N2 = [R \times N1],$$

where the value *[Y]* is the next integer $\geq Y$.

For example, setting R = 2.0 results in a Group 2 sample size that is double the sample size in Group 1 (e.g., $N1$ = 10 and $N2$ = 20, or $N1$ = 50 and $N2$ = 100).

R must be greater than 0. If $R < 1$, then $N2$ will be less than $N1$; if $R > 1$, then $N2$ will be greater than $N1$. You can enter a single or a series of values.

Percent in Group 1

This option is displayed only if Group Allocation = "Enter percentage in Group 1, solve for N1 and N2."

Use this value to fix the percentage of the total sample size allocated to Group 1 while solving for $N1$ and $N2$. Only sample size combinations with this Group 1 percentage are considered. Small variations from the specified percentage may occur due to the discrete nature of sample sizes.

The Percent in Group 1 must be greater than 0 and less than 100. You can enter a single or a series of values.

Sample Size (When Not Solving for Sample Size)

Group Allocation

Select the option that describes how individuals in the study will be allocated to Group 1 and to Group 2.

The options are

- **Equal (N1 = N2)**
  This selection is used when you wish to have equal sample sizes in each group. A single per group sample size will be entered.

- **Enter N1 and N2 individually**
  This choice permits you to enter different values for $N1$ and $N2$.

- **Enter N1 and R, where N2 = R * N1**
  Choose this option to specify a value (or values) for $N1$, and obtain $N2$ as a ratio (multiple) of $N1$.

- **Enter total sample size and percentage in Group 1**
  Choose this option to specify a value (or values) for the total sample size (N), obtain $N1$ as a percentage of N, and then $N2$ as $N - N1$.

Sample Size Per Group

This option is displayed only if Group Allocation = "Equal (N1 = N2)."

The Sample Size Per Group is the number of items or individuals sampled from each of the Group 1 and Group 2 populations. Since the sample sizes are the same in each group, this value is the value for $N1$, and also the value for $N2$.

The Sample Size Per Group must be ≥ 2. You can enter a single value or a series of values.

N1 (Sample Size, Group 1)

*This option is displayed if Group Allocation = "Enter N1 and N2 individually" or "Enter N1 and R, where N2 = R * N1."*

$N1$ is the number of items or individuals sampled from the Group 1 population.

$N1$ must be ≥ 2. You can enter a single value or a series of values.

N2 (Sample Size, Group 2)

This option is displayed only if Group Allocation = "Enter N1 and N2 individually."

N2 is the number of items or individuals sampled from the Group 2 population.

N2 must be ≥ 2. You can enter a single value or a series of values.

R (Group Sample Size Ratio)

*This option is displayed only if Group Allocation = "Enter N1 and R, where N2 = R * N1."*

R is the ratio of *N2* to *N1*. That is,

$$R = N2/N1$$

Use this value to obtain *N2* as a multiple (or proportion) of *N1*.

N2 is calculated from *N1* using the formula:

$$N2=[R \times N1],$$

where the value *[Y]* is the next integer ≥ *Y*.

For example, setting *R* = 2.0 results in a Group 2 sample size that is double the sample size in Group 1.

R must be greater than 0. If *R* < 1, then *N2* will be less than N1; if *R* > 1, then *N2* will be greater than *N1*. You can enter a single value or a series of values.

Total Sample Size (N)

This option is displayed only if Group Allocation = "Enter total sample size and percentage in Group 1."

This is the total sample size, or the sum of the two group sample sizes. This value, along with the percentage of the total sample size in Group 1, implicitly defines *N1* and *N2*.

The total sample size must be greater than one, but practically, must be greater than 3, since each group sample size needs to be at least 2.

You can enter a single value or a series of values.

Percent in Group 1

This option is displayed only if Group Allocation = "Enter total sample size and percentage in Group 1."

This value fixes the percentage of the total sample size allocated to Group 1. Small variations from the specified percentage may occur due to the discrete nature of sample sizes.

The Percent in Group 1 must be greater than 0 and less than 100. You can enter a single value or a series of values.

Sample Size – Loss Hazard Rates

ω1 (Loss Hazard Rate of Control Group)

This is the lost to follow-up rates in group 1, the control group. This rate assumes that lost to follow-up follows an exponential distribution. This value is the reciprocal of the average number lost to follow-up per unit of time (months, years, etc.).

If all you have is the proportion lost to follow-up, use the Survival Parameter Conversion Tool to convert this proportion into a hazard rate.

Any non-negative value is valid. Zero is used to indicate no loss to follow-up.

ω2 (Loss Hazard Rate of Treatment Group)

This is the lost to follow-up rates in group 2, the treatment group. This rate assumes that lost to follow-up follows an exponential distribution. This value is the reciprocal of the average number lost to follow-up per unit of time (months, years, etc.).

If all you have is the proportion lost to follow-up, use the *Survival Parameter Conversion Tool* to convert this proportion into a hazard rate.

Any non-negative value is valid. Zero is used to indicate no loss to follow-up.

Equal to ω1

Enter 'ω1' if you want ω2 = ω1.

Sample Size – Duration

R (Accrual, or Recruitment, Time)

The accrual (or recruitment) time is the length of time during which patients enter the study. It is the value of *R*.

Percent of R Until 50% are Accrued

This option controls the pattern of patient entry by specifying the percentage of the accrual time needed to enroll 50% of the patients. PASS assumes that patient entry times follow the truncated exponential distribution. This parameter controls the shape and scale of that distribution. The cumulative truncated exponential distribution is given by the equation:

$$G(T|A)=A \exp(-AT)/[1-\exp(-AR)].$$

When G(T|A) is 50% and R and T are known, this equation may be solved for A.

Range

Values between 1 and 97 may be entered.

Recommended

If you expect uniform patient entry, enter 50. Unless you know that patient enrollment will not be uniform during the accrual period, you should enter 50.

If you expect more patients to enter during the early part of the accrual period, enter an amount less than 50 such as 30. A 30 here means that 50% of the patients will have been enrolled when 30% of the accrual time has elapsed.

If you expect more patients to enter during the latter part of the accrual period, enter an amount greater than 50 such as 70. A 70 here means that 50% of the patients will have been enrolled when 70% of the accrual time has elapsed.

T-R (Follow-Up Time)

The *follow-up time* is the length of time between the entry of the last individual into the study and the end of the study. Since *T* is the total length of the study and *R* is the accrual time, the follow-up time is *T-R*.

Effect Size

Specify Hazard Parameters Using

Specify which of the parameters below will be used to specify the treatment group hazard rate, h2, by checking the appropriate button.

- **Differences**
  Enter the values of D and let the program calculate h2 using h2 = h1 - D.

- **Rates**
  Enter the values of h2 directly.

h1 (Hazard Rate of Control Group)

Specify one or more hazard rates (instantaneous failure rates) for the control group. The exponential survival distribution used in this procedure assumes that the hazard rates are constant throughout the whole experiment and that this hazard rate is equal to one over the mean number of events per unit of time.

An estimate of the hazard rate may be obtained from the median survival time or from the proportion surviving past a certain time point by pressing the *Survival Parameter Conversion Tool* button.

Range

h1 > 0

Examples

The following examples assume an exponential survival distribution.

Median Survival Time	Hazard Rate
0.5	1.386
1.0	0.693
2.0	0.347
3.0	0.231
4.0	0.173
5.0	0.139

h2 (Hazard Rate of Treatment Group)

Specify one or more hazard rates (instantaneous failure rates) for the treatment group under the alternative hypothesis. The exponential survival distribution used in this procedure assumes that the hazard rates are constant throughout the whole experiment and that this hazard rate is equal to one over the mean number of events per unit of time. The difference between these hazard rates, h2 – h1, is used to compute the power.

Note that this is not necessarily the actual value of h2. Instead, this is the value that creates the difference at which the power is calculated.

An estimate of the hazard rate may be obtained from the median survival time or from the proportion surviving past a certain time point by pressing the *Survival Parameter Conversion Tool* button.

Range

h2 > 0

D (Hazard Rate Difference = h2-h1)

Specify one or more values of the difference in hazard rates. This value is used with h1 to calculate a value for h2 using the formula: h2 = h1 + D.

Note that this is not necessarily the value you expect. It is the assumed value under the alternative hypothesis.

An estimate of this value may be obtained by pressing the "Survival Parameter Conversion Tool" button. This tool will let you input the median survival times, hazard rates, or the proportion surviving past a certain time point.

Range

All values must not equal to zero. Enter negative values when you want the treatment hazard rate less than the control hazard rate. Enter positive values for those rare cases when the treatment hazard rate is greater than the control hazard rate.

Null Hypothesis

The null hypothesis is that the hazard rate difference is zero.

Example 1 – Finding the Power

A researcher is planning a clinical trial using a parallel, two-group, equal sample allocation design to compare the survivability of a new treatment with that of the current treatment. The proportion surviving one-year after the current treatment is 0.50 (h1 = 0.693). The power is desired when the proportion surviving in new treatment is 0.75 (h2 = 0.288).

The trial will include a recruitment period of one-year after which participants will be followed for an additional two-years. It is assumed that patients will enter the study uniformly over the accrual period. The researcher estimates a loss-to-follow rate of 15% per year (ω1 = ω2 =0.165) in both the control and the experimental groups.

The researcher decides to investigate various sample sizes between 10 and 250 at the 0.05 significance level.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Tests for the Difference of Two Hazard Rates Assuming an Exponential Model** procedure window by expanding **Survival**, then **Two Survival Curves**, then clicking **Test (Inequality)**, and then clicking on **Tests for the Difference of Two Hazard Rates Assuming an Exponential Model**. 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	**Power**
Alternative Hypothesis	**Ha: h2 - h1 ≠ 0**
Alpha	**0.05**
Group Allocation	**Enter total sample size and percentage in Group 1**
Total Sample Size (N)	**10 25 50 100 150 200 250**
Percent in Group 1	**50**
ω1 (Loss Hazard Rate of Control Group)	**0.165**
ω2 (Loss Hazard Rate of Treatment Group)	**ω1**
R (Accrual, or Recruitment, Time)	**1**
Percent of R Until 50% are Accrued	**50**
T-R (Follow-Up Time)	**2**
Specify Hazard Parameters Using	**Rates**
h1 (Hazard Rate of Control Group)	**0.693**
h2 (Hazard Rate of Treatment Group)	**0.288**

Annotated Output

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

Numeric Results

Numeric Results

Hypotheses: H0: h2 - h1 = 0 vs. Ha: h2 - h1 ≠ 0
Accrual: Uniform

Power	Total Sample Size N	Control Sample Size N1	Trtmnt Sample Size N2	Percent Control %N1	Control Hazard Rate h1	Trtmnt Hazard Rate h2	Hazard Rate Diff h2-h1 D	Hazard Ratio h2/h1 HR	Accr'l Time R	Follow Up Time T-R	Alpha	Rpt Row
0.1614	10	5	5	50.0	0.693	0.288	-0.405	0.416	1.0	2.0	0.050	1
0.3291	25	12	13	50.0	0.693	0.288	-0.405	0.416	1.0	2.0	0.050	2
0.5838	50	25	25	50.0	0.693	0.288	-0.405	0.416	1.0	2.0	0.050	3
0.8668	100	50	50	50.0	0.693	0.288	-0.405	0.416	1.0	2.0	0.050	4
0.9642	150	75	75	50.0	0.693	0.288	-0.405	0.416	1.0	2.0	0.050	5
0.9914	200	100	100	50.0	0.693	0.288	-0.405	0.416	1.0	2.0	0.050	6
0.9981	250	125	125	50.0	0.693	0.288	-0.405	0.416	1.0	2.0	0.050	7

Second Section of Numeric Report

Beta	Total Events E	Control Events E1	Trtmnt Event E2	Control Prob of Event Pr(E1)	Trtmnt Prob of Event Pr(E2)	Control Loss Hazard Rate ω1	Trtmnt Loss Hazard Rate ω2	Var'nce of h1 hat σ²(h1)	Var'nce of h2 hat σ²(h2)	Rpt Row
0.8386	5.7	3.6	2.1	0.710	0.429	0.165	0.165	0.676	0.193	1
0.6709	14.1	8.5	5.6	0.710	0.429	0.165	0.165	0.676	0.193	2
0.4162	28.5	17.8	10.7	0.710	0.429	0.165	0.165	0.676	0.193	3
0.1332	57.0	35.5	21.5	0.710	0.429	0.165	0.165	0.676	0.193	4
0.0358	85.5	53.3	32.2	0.710	0.429	0.165	0.165	0.676	0.193	5
0.0086	113.9	71.0	42.9	0.710	0.429	0.165	0.165	0.676	0.193	6
0.0019	142.4	88.8	53.6	0.710	0.429	0.165	0.165	0.676	0.193	7

References

Chow, S.C., Shao, J., Wang, H. 2008. Sample Size Calculations in Clinical Research, 2nd Edition. Chapman & Hall/CRC.

Lachin, John M. and Foulkes, Mary A. 1986. 'Evaluation of Sample Size and Power for Analyses of Survival with Allowance for Nonuniform Patient Entry, Losses to Follow-up, Noncompliance, and Stratification', Biometrics, Volume 42, September, pages 507-516.

Report Definitions

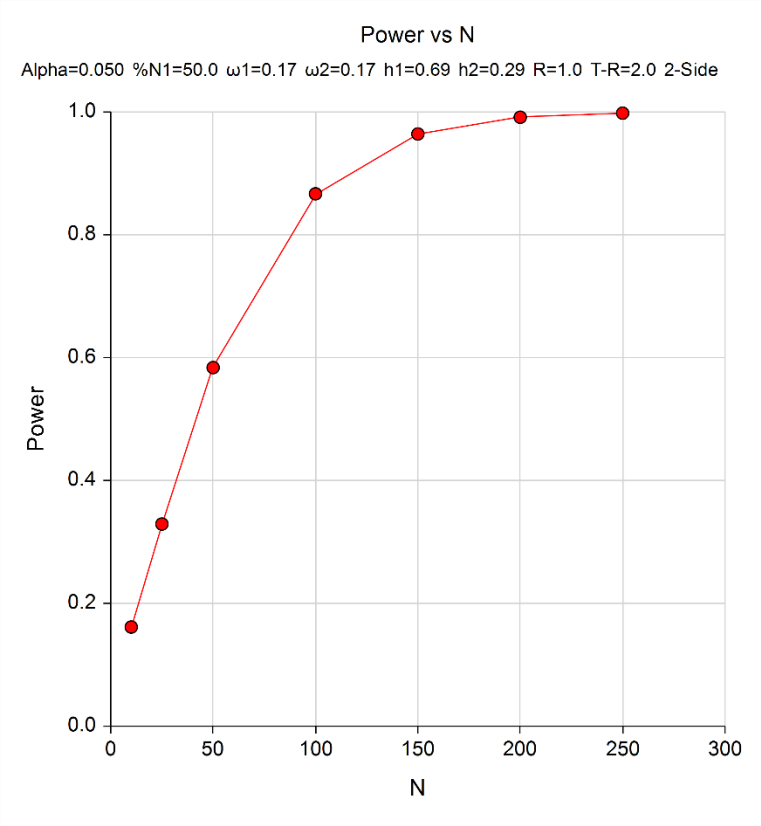
Power is the probability of rejecting a false null hypothesis. Power should be close to one.
N is the total sample size.
N1 and N2 are the sample sizes of the control and treatment groups, respectively.
%N1 is the percent of the total sample that is in group 1, the control group.
h1 and h2 are the hazard rates in the control and treatment groups, respectively.
D is the difference in hazard rates: h2 - h1.
HR is the hazard ratio: h2/h1.
R is the accrual (recruitment) time.
T-R is the follow-up time. Hence, T is the total time of the study.
ω1 and ω2 are the rates at which subjects in groups 1 and 2 are lost to follow up, respectively.
Alpha is the probability of a type one error: rejecting a true null hypothesis.
Beta is the probability of a type two error: failing to reject a false null hypothesis.
Pr(E1) and Pr(E2) are the probabilities of an event in the control and treatment groups, respectively.
E1 and E2 are the number of events required in the control and treatment groups, respectively.
σ²(h1) and σ²(h2) are the variances of the estimates of h1 and h2, respectively.
Rpt Row is a line number assigned to allow corresponding report lines to be identified.

Summary Statements

A two-sided test of the difference between hazard rates with an overall sample size of 10 subjects (of which 5 are in the control group and 5 are in the treatment group) achieves 16% power at a 0.050 significance level when the actual difference is -0.405 between 0.288 and 0.693--the hazard rates in the treatment and control groups, respectively. Patients enter the study during an accrual period of 1.0 time periods. 50% of the enrollment is complete when 50.00% of the accrual time has past. A follow-up period of 2.0 time periods has a 0.165 loss to follow-up rate in the control group and a 0.165 loss to follow-up rate in the treatment group. These results assume that the data are approximately exponentially distributed.

These reports show the values of each of the parameters, one scenario per row. The second report presents information about the number of events that are necessary.

Plots Section



This plot shows the relationship between power and sample size.

Example 2 – Finding the Sample Size

Continuing with the previous example, the researcher wants to investigate the sample size necessary to achieve 90% power for treatment hazard rates of 0.55 to 0.80 at the 0.05 significance level. The follow-up times are 1, 2, and 3 years. All other parameters will remain the same.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Tests for the Difference of Two Hazard Rates Assuming an Exponential Model** procedure window by expanding **Survival**, then **Two Survival Curves**, then clicking **Test (Inequality)**, and then clicking on **Tests for the Difference of Two Hazard Rates Assuming an Exponential Model**. 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	**Ha: h2 - h1 ≠ 0**
Power	**0.90**
Alpha	**0.05**
Group Allocation	**Equal (N1 = N2)**
ω1 (Loss Hazard Rate of Control Group)	**0.165**
ω2 (Loss Hazard Rate of Treatment Group)	**ω1**
R (Accrual, or Recruitment, Time)	**1**
Percent of R Until 50% are Accrued	**50**
T-R (Follow-Up Time)	**1 2 3**
Specify Hazard Parameters Using	**Rates**
h1 (Hazard Rate of Control Group)	**0.693**
h2 (Hazard Rate of Treatment Group)	**0.1 to 0.5 by 0.1**

Output

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

Numeric Results

Numeric Results

Hypotheses: H0: h2 - h1 = 0 vs. Ha: h2 - h1 ≠ 0
Accrual: Uniform

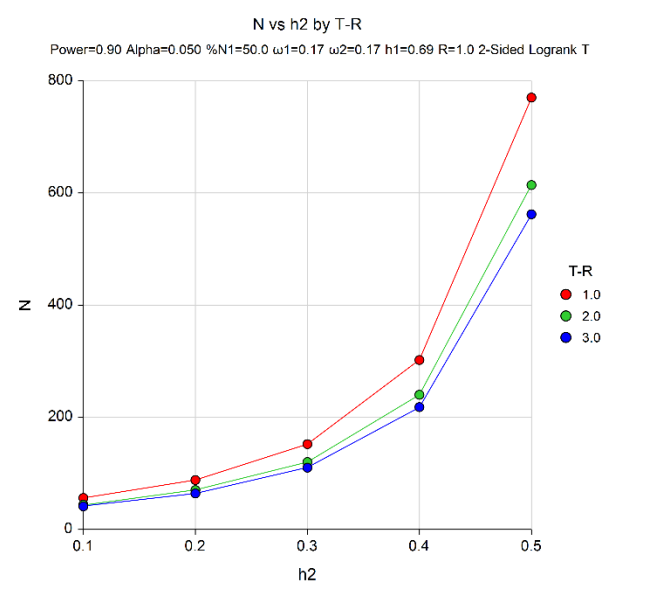
Power	Total Sample Size N	Control Sample Size N1	Trtmnt Sample Size N2	Percent Control %N1	Control Hazard Rate h1	Trtmnt Hazard Rate h2	Hazard Rate Diff h2-h1 D	Hazard Ratio h2/h1 HR	Accr'l Time R	Follow Up Time T-R	Alpha	Rpt Row
0.9074	56	28	28	50.0	0.693	0.100	-0.593	0.144	1.0	1.0	0.050	1
0.9020	44	22	22	50.0	0.693	0.100	-0.593	0.144	1.0	2.0	0.050	2
0.9004	41	20	21	50.0	0.693	0.100	-0.593	0.144	1.0	3.0	0.050	3
0.9034	88	44	44	50.0	0.693	0.200	-0.493	0.289	1.0	1.0	0.050	4
0.9038	70	35	35	50.0	0.693	0.200	-0.493	0.289	1.0	2.0	0.050	5
0.9046	64	32	32	50.0	0.693	0.200	-0.493	0.289	1.0	3.0	0.050	6
0.9014	152	76	76	50.0	0.693	0.300	-0.393	0.433	1.0	1.0	0.050	7
0.9006	120	60	60	50.0	0.693	0.300	-0.393	0.433	1.0	2.0	0.050	8
0.9027	110	55	55	50.0	0.693	0.300	-0.393	0.433	1.0	3.0	0.050	9
0.9007	302	151	151	50.0	0.693	0.400	-0.293	0.577	1.0	1.0	0.050	10
0.9012	240	120	120	50.0	0.693	0.400	-0.293	0.577	1.0	2.0	0.050	11

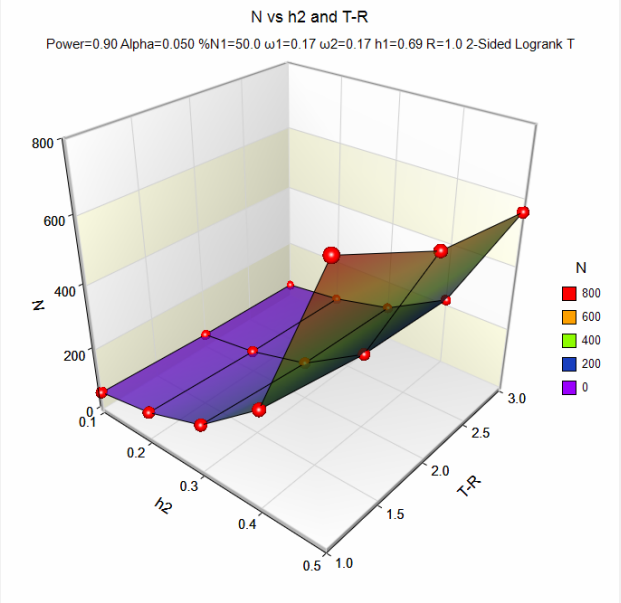
Tests for the Difference of Two Hazard Rates Assuming an Exponential Model

0.9003	218	109	109	50.0	0.693	0.400	-0.293	0.577	1.0	3.0	0.050	12
0.9002	770	385	385	50.0	0.693	0.500	-0.193	0.722	1.0	1.0	0.050	13
0.9000	614	307	307	50.0	0.693	0.500	-0.193	0.722	1.0	2.0	0.050	14
0.9001	562	281	281	50.0	0.693	0.500	-0.193	0.722	1.0	3.0	0.050	15

Second Section of Numeric Report

Beta	Total Events E	Control Events E1	Trtmnt Event E2	Control Prob of Event Pr(E1)	Trtmnt Prob of Event Pr(E2)	Control Loss Hazard Rate ω1	Trtmnt Loss Hazard Rate ω2	Var'nce of h1 hat σ²(h1)	Var'nce of h2 hat σ²(h2)	Rpt Row
0.1000	19.6	16.2	3.4	0.578	0.123	0.165	0.165	0.831	0.081	1
0.1000	19.6	15.6	4.0	0.710	0.182	0.165	0.165	0.676	0.055	2
0.1000	20.1	15.3	4.8	0.766	0.228	0.165	0.165	0.627	0.044	3
0.1000	35.5	25.4	10.1	0.578	0.229	0.165	0.165	0.831	0.174	4
0.1000	36.3	24.9	11.4	0.710	0.327	0.165	0.165	0.676	0.122	5
0.1000	37.1	24.5	12.6	0.766	0.394	0.165	0.165	0.627	0.101	6
0.1000	68.3	43.9	24.4	0.578	0.321	0.165	0.165	0.831	0.280	7
0.1000	69.1	42.6	26.5	0.710	0.442	0.165	0.165	0.676	0.204	8
0.1000	70.6	42.1	28.5	0.766	0.517	0.165	0.165	0.627	0.174	9
0.1000	147.7	87.2	60.5	0.578	0.401	0.165	0.165	0.831	0.399	10
0.1000	149.2	85.2	64.0	0.710	0.533	0.165	0.165	0.676	0.300	11
0.1000	149.9	83.5	66.3	0.766	0.609	0.165	0.165	0.627	0.263	12
0.1000	403.2	222.4	180.7	0.578	0.469	0.165	0.165	0.831	0.533	13
0.1000	404.3	218.0	186.2	0.710	0.607	0.165	0.165	0.676	0.412	14
0.1000	405.6	215.3	190.3	0.766	0.677	0.165	0.165	0.627	0.369	15





This study shows the relative impact of changes in h2 and in T-R.

Example 3 – Validation using Chow et al. (2008)

Chow et al. (2008) page 172 present an example of a parallel, two-group, equal sample allocation design to compare the hazard rates of a new treatment with that of the current treatment using a two-sided, logrank test. They want to compute the required sample size when h1 = 1 and h2 = 2 in a 3-year study with a 1-year, uniform accrual. Their example ignores loss-to-follow up in both groups. Alpha is set to 0.05 and power is 0.80.

They obtain a value of about 39 per group using extensive rounding in their calculations.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Tests for the Difference of Two Hazard Rates Assuming an Exponential Model** procedure window by expanding **Survival**, then **Two Survival Curves**, then clicking **Test (Inequality)**, and then clicking on **Tests for the Difference of Two Hazard Rates Assuming an Exponential Model**. You may then make the appropriate entries as listed below, or open **Example 3** by going to the **File** menu and choosing **Open Example Template**.

Option	Value
Design Tab	
Solve For	**Sample Size**
Alternative Hypothesis	**Ha: h2 - h1 ≠ 0**
Power	**0.80**
Alpha	**0.05**
Group Allocation	**Equal (N1 = N2)**
ω1 (Loss Hazard Rate of Control Group)	**0**
ω2 (Loss Hazard Rate of Treatment Group)	**ω1**
R (Accrual, or Recruitment, Time)	**1**
Percent of R Until 50% are Accrued	**50**
T-R (Follow-Up Time)	**2**
Specify Hazard Parameters Using	**Rates**
h1 (Hazard Rate of Control Group)	**1**
h2 (Hazard Rate of Treatment Group)	**2**

Output

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

Numeric Results

Numeric Results

Hypotheses: H0: h2 - h1 = 0 vs. Ha: h2 - h1 ≠ 0
Accrual: Uniform

Power	Total Sample Size N	Control Sample Size N1	Trtmnt Sample Size N2	Percent Control %N1	Control Hazard Rate h1	Trtmnt Hazard Rate h2	Hazard Rate Diff h2-h1 D	Hazard Ratio h2/h1 HR	Accr'l Time R	Follow Up Time T-R	Alpha
0.8053	81	40	41	50.0	1.000	2.000	1.000	2.000	1.0	2.0	0.050

Second Section of Numeric Report

Beta	Total Events E	Control Events E1	Trtmnt Event E2	Control Prob of Event Pr(E1)	Trtmnt Prob of Event Pr(E2)	Control Loss Hazard Rate ω1	Trtmnt Loss Hazard Rate ω2	Var'nce of h1 hat σ²(h1)	Var'nce of h2 hat σ²(h2)
0.2000	77.3	36.6	40.7	0.914	0.992	0.000	0.000	1.094	4.032

The value of 81 differs from Chow's 78 because of their extensive rounding to just two decimal places throughout their intermediate calculations.