Chapter 704

Superiority by a Margin Tests for the Difference of Two Hazard Rates Assuming an Exponential Model

Introduction

A clinical trial is often employed to test the clinical superiority of a treatment over a control in regard to the survival distributions. 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 for a clinical superiority test similar to 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 this case (see Chow, Shao, and Wang (2008) page 173).

Technical Details

This section presents the *unconditional* clinical superiority 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 $N_1 = N_2$.

Clinical Superiority Hypothesis

Assuming that lower hazard rates are better, clinical superiority is established by concluding that the treatment hazard rate is lower than the control hazard rate by at least a small margin Δ. The statistical hypotheses that yields this conclusion when the null hypothesis is rejected is

$$H_0\colon\ (h_2 - h_1) \geq -\Delta \quad \text{versus} \quad H_a\colon (h_2 - h_1) < -\Delta$$

or

$$H_0\colon\ h_2 \geq h_1 - \Delta \quad \text{versus} \quad H_a\colon h_2 < h_1 - \Delta$$

If, however, higher hazard rates are better, non-inferiority is established by concluding that the treatment hazard rate is at most, only slightly lower than the control hazard rate. The statistical hypotheses that yields this conclusion when the null hypothesis is rejected is

$$H_0\colon\ (h_2 - h_1) \le \Delta \quad \text{versus} \quad H_a\colon (h_2 - h_1) > \Delta$$

or

$$H_0\colon\ h_2 \le h_1 + \Delta \quad \text{versus} \quad H_a\colon h_2 > h_1 + \Delta.$$

Test Statistic

The power and sample size formulas presented below are for the difference of two exponential hazard rates. Simulation studies have shown that they also approximate the power of the logrank test. It is anticipated that the actual test statistic is the regression coefficient from a Cox regression.

Test Comparing Hazard Rates

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

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

where

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

This Z statistic is approximately normally distributed.

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 superiority test, assuming that lower hazards are better.

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

where

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

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

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

These parameters are interpreted as follows.

Parameter	Interpretation
$\sigma^2(h, \omega, A)$	Variance of $\hat{h}$
$E(d_i\|h_i, \omega_i, A)$	Expected proportion of events (deaths) in group *i*
d_i	Indicates 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

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

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.

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

Example 1 – Finding the Sample Size

Suppose the hazard rate when using the current treatment of a disease is 2. A company wants to show that their new treatment for the disease is clinically better. In fact, they want to show that the hazard rate decreases by at least 25%. How large of a sample is needed if the recruitment period is one-year after which the study continues for an additional two-years? It is assumed that patients will enter the study uniformly over the recruitment period. The researcher estimates the loss-to-follow rate to be 0.165 in both the current and the groups. The company would like to compare sample sizes when the power is 0.80 and 0.90 and when D is between -1.6 and -0.80. The researcher will test at the 0.05 significance level.

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**
Higher Hazards Are	**Worse (Ha: h2 < h1 - Δ)**
Power	**0.8 0.9**
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)	**2**
Specify Hazard Parameters Using	**Differences**
h1 (Hazard Rate of Control Group)	**2**
D (Hazard Rate Difference = h2-h1)	**-1.6 to -0.8 by 0.2**
Δ (Clinical Superiority Margin)	**0.5**

Output

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

Numeric Reports

Numeric Results

Solve For: Sample Size
Groups: 1 = Control, 2 = Treatment
Hypotheses: H0: h2 ≥ h1 - Δ vs. Ha: h2 < h1 - Δ
Accrual: Uniform

	Sample Size			Hazard Rate		Hazard Rate Difference	Superiority		Loss Hazard Rate		Time			
Power	N	N1	N2	h1	h2	D	Margin Δ	Boundary B	ω1	ω2	Accrual R	Follow-Up T - R	Alpha	Report Row
0.8032	48	24	24	2	0.4	-1.6	0.5	1.5	0.165	0.165	1	2	0.05	1
0.8059	76	38	38	2	0.6	-1.4	0.5	1.5	0.165	0.165	1	2	0.05	2
0.8017	132	66	66	2	0.8	-1.2	0.5	1.5	0.165	0.165	1	2	0.05	3
0.8019	278	139	139	2	1.0	-1.0	0.5	1.5	0.165	0.165	1	2	0.05	4
0.8002	832	416	416	2	1.2	-0.8	0.5	1.5	0.165	0.165	1	2	0.05	5
0.9005	66	33	33	2	0.4	-1.6	0.5	1.5	0.165	0.165	1	2	0.05	6
0.9013	104	52	52	2	0.6	-1.4	0.5	1.5	0.165	0.165	1	2	0.05	7
0.9001	182	91	91	2	0.8	-1.2	0.5	1.5	0.165	0.165	1	2	0.05	8
0.9007	384	192	192	2	1.0	-1.0	0.5	1.5	0.165	0.165	1	2	0.05	9
0.9001	1152	576	576	2	1.2	-0.8	0.5	1.5	0.165	0.165	1	2	0.05	10

	Number of Events			Percent Group 1	Hazard Ratio	Variance		
Power	E	E1	E2	%N1	HR	σ²(h1)	σ²(h2)	Report Row
0.8032	34.8	22.1	12.8	50	0.2	4.353	0.300	1
0.8059	60.2	34.9	25.3	50	0.3	4.353	0.541	2
0.8017	110.3	60.6	49.6	50	0.4	4.353	0.851	3
0.8019	240.2	127.7	112.5	50	0.5	4.353	1.236	4
0.8002	734.9	382.2	352.7	50	0.6	4.353	1.698	5
0.9005	47.9	30.3	17.6	50	0.2	4.353	0.300	6
0.9013	82.4	47.8	34.6	50	0.3	4.353	0.541	7
0.9001	152.0	83.6	68.4	50	0.4	4.353	0.851	8
0.9007	331.7	176.4	155.3	50	0.5	4.353	1.236	9
0.9001	1017.6	529.2	488.4	50	0.6	4.353	1.698	10

Power	The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N	The total sample size.
N1 and N2	The sample sizes of the control and treatment groups.
h1 and h2	The hazard rates in the control and treatment groups.
D	The difference in hazard rates. D = h2 - h1.
Δ	The clinical superiority margin.
B	The superiority boundary. B = h1 - Δ.
ω1 and ω2	The rates at which subjects in groups 1 and 2 are lost to follow up.
R	The accrual (recruitment) time.
T - R	The follow-up time. Hence, T is the total time of the study.
Alpha	The probability of rejecting a true null hypothesis.
E	The total number of events required.
E1 and E2	The number of events required in the control and treatment groups.
%N1	The percent of the total sample that is in group 1, the control group.
HR	The hazard ratio. HR = h2 / h1.
σ²(h1) and σ²(h2)	The variances of the estimates of h1 and h2.

Summary Statements

A parallel, two-group design (where higher hazard rates are considered worse) will be used to test whether the Group 2 (treatment) hazard rate is superior to the Group 1 (control) hazard rate by a margin, with a superiority margin of 0.5 (H0: h2 - h1 ≥ -0.5 versus Ha: h2 - h1 < -0.5).The comparison will be made using a one-sided, two-sample maximum likelihood estimation Z test with a Type I error rate (α) of 0.05. Patients will enter the study during an accrual period of 1 time period. 50% of the enrollment will be complete when 50% of the accrual time has passed (uniform accrual). A follow-up period of 2 time periods will have a 0.165 loss to follow-up hazard rate in the control group and a 0.165 loss to follow-up hazard rate in the treatment group. The calculations are based on the assumption that the survival times are exponentially distributed. To detect a hazard rate difference of -1.6 (h1 = 2, h2 = 0.4) with 80% power, the number of needed subjects will be 24 in Group 1 and 24 in Group 2 (totaling 48 subjects). The corresponding required number of events is 22.1 in Group 1 and 12.8 in Group 2 (totaling 34.8 events).

References

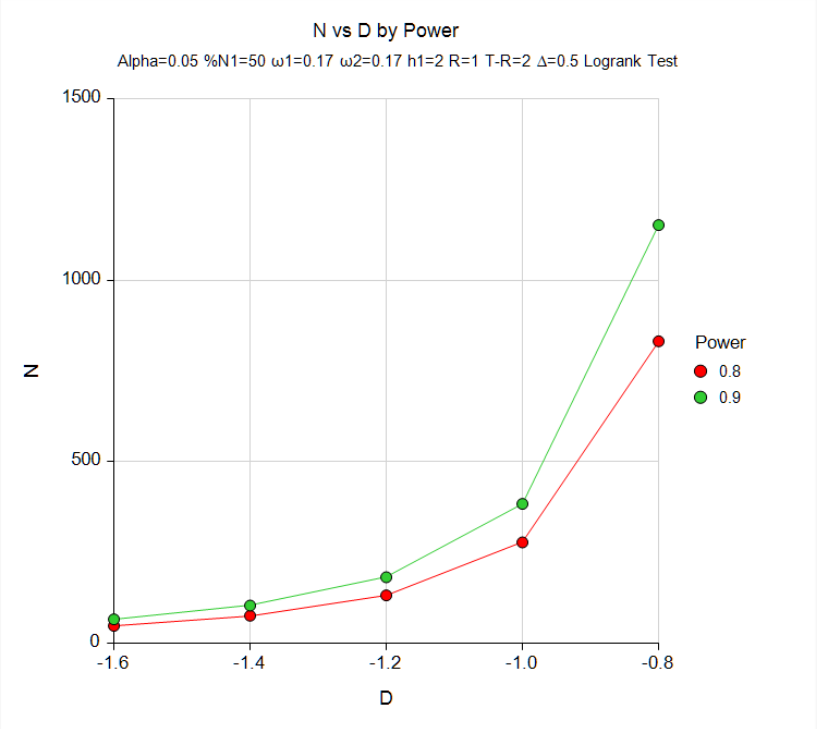
Chow, S.C., Shao, J., Wang, H. 2008. Sample Size Calculations in Clinical Research, 2nd Edition. Chapman & Hall/CRC.

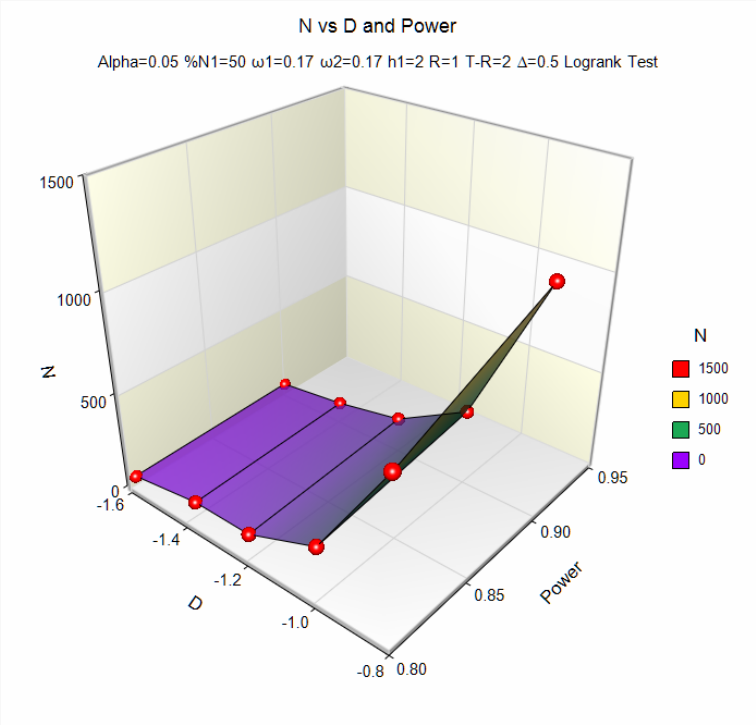
Lachin, John M. and Foulkes, Mary A. 1986. 'Evaluation of Sample Size and L.Power for Analyses of Survival with Allowance for Nonuniform Patient Entry, Losses to Follow-up, Noncompliance, and Stratification', Biometrics, Volume 42, September, pages 507-516.

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

Plots





These plots show the relationship between power and sample size.

Example 2 – Validation using Chow et al. (2008)

Chow et al. (2008) page 172 presents an example of a two-group, equal sample allocation superiority design to compare the hazard rates of a new treatment with that of the current treatment using a logrank test. The sample size is to be large enough to detect non-inferiority when h1 = 2, h2 = 1, and Δ = 0.2. A 3-year study is contemplated with a 1-year, uniform accrual. There is no loss-to-follow up. Alpha is set to 0.05 and power is 0.80. Chow et al. (2008) carried out their calculations to only two decimal places. Their results were

$$N1 = \left(\frac{1.64 + 0.84}{2 - 1 - 0.2}\right)^2 (.97 + 3.94)$$

$$= 47.185$$

$$\approx 48$$

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	**Ha: h2 < h1 - Δ [Lower Hazard Better]**
Power	**0.8**
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**
h1 (Hazard Rate of Control Group)	**2**
Specify Hazard Parameters Using	**Differences**
D (Difference, h2-h1)	**-1**
Δ (Clinical Superiority Margin)	**0.2**

Output

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

Numeric Results

Solve For: Sample Size
Groups: 1 = Control, 2 = Treatment
Hypotheses: H0: h2 ≥ h1 - Δ vs. Ha: h2 < h1 - Δ
Accrual: Uniform

	Sample Size			Hazard Rate		Hazard Rate Difference	Superiority		Loss Hazard Rate		Time		
Power	N	N1	N2	h1	h2	D	Margin Δ	Boundary B	ω1	ω2	Accrual R	Follow-Up T - R	Alpha
0.8034	100	50	50	2	1	-1	0.2	1.8	0	0	1	2	0.05

	Number of Events			Percent Group 1	Hazard Ratio	Variance	
Power	E	E1	E2	%N1	HR	$\sigma^2(h1)$	$\sigma^2(h2)$
0.8034	95.3	49.6	45.7	50	0.5	4.032	1.094

The value of N1 = 50 is close to Chow's hand calculated 48, with difference due to rounding.