Chapter 703

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

Introduction

A clinical trial can be employed to test the clinical equivalence of a treatment and 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 an equivalence 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 $N_1 = N_2$.

Equivalence Hypothesis

The equivalence of two hazard rates is established by concluding the difference between the hazard rates is less than a small margin Δ. The statistical hypotheses that yields this conclusion when the null hypothesis is rejected is

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

Test Statistic

The power and sample size formulas presented below are for the difference of two exponential hazard rates. 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 statistics

$$Z_1 = \frac{(\hat{h}_2 - \hat{h}_1) - \Delta}{\sqrt{\frac{\sigma^2(\hat{h}_1)}{N_1} + \frac{\sigma^2(\hat{h}_2)}{N_2}}} \quad \text{and} \quad Z_2 = \frac{(\hat{h}_2 - \hat{h}_1) + \Delta}{\sqrt{\frac{\sigma^2(\hat{h}_1)}{N_1} + \frac{\sigma^2(\hat{h}_2)}{N_2}}}$$

where

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

can be used to test the hypothesis of equivalence.

Specifically, the null hypothesis of non-equivalence is rejected if

$$Z_1 < -z_{1-\alpha} \quad \text{and} \quad Z_2 > z_{1-\alpha}$$

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 for the power of the above equivalence test.

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

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 the hazard rate of their new treatment is equivalent to the current treatment in that the hazard rate is within a small margin of that of the current treatment. They want to look at value of δ between 0.2 and 0.6.

How large of a sample is needed if the recruitment period is two-years 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 treatment groups. The company would like to compare sample sizes when the power is 0.90, D is 0, and the significance level is 0.05.

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**
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)	**2**
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)	**0**
Δ (Equivalence Margin)	**0.2 to 0.6 by 0.1**

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	Equivalence		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
0.9001	4701	2350	2351	2	2	0	0.2	2.2	0.165	0.165	2	2	0.05	1
0.9000	2089	1044	1045	2	2	0	0.3	2.3	0.165	0.165	2	2	0.05	2
0.9003	1176	588	588	2	2	0	0.4	2.4	0.165	0.165	2	2	0.05	3
0.9004	753	376	377	2	2	0	0.5	2.5	0.165	0.165	2	2	0.05	4
0.9005	523	261	262	2	2	0	0.6	2.6	0.165	0.165	2	2	0.05	5

	Number of Events			Percent Group 1	Hazard Ratio	Variance		Report
Power	E	E1	E2	%N1	HR	σ²(h1)	σ²(h2)	Row
0.9001	4329.7	2164.4	2165.3	50	1	4.343	4.343	1
0.9000	1924.0	961.5	962.5	50	1	4.343	4.343	2
0.9003	1083.1	541.6	541.6	50	1	4.343	4.343	3
0.9004	693.5	346.3	347.2	50	1	4.343	4.343	4
0.9005	481.7	240.4	241.3	50	1	4.343	4.343	5

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 equivalence margin.
B	The upper equivalence boundary for h2. 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 will be used to test whether the Group 1 (control) hazard rate is equivalent to the Group 2 (treatment) hazard rate, with an equivalence margin of 0.2 (H0: |h2 - h1| ≥ 0.2 versus Ha: |h2 - h1| < 0.2). The comparison will be made using two one-sided, two-sample maximum likelihood estimation Z tests with an overall Type I error rate (α) of 0.05. Patients will enter the study during an accrual period of 2 time periods. 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 0 (h1 = 2, h2 = 2) with 90% power, the number of needed subjects will be 2350 in Group 1 and 2351 in Group 2 (totaling 4701 subjects). The corresponding required number of events is 2164.4 in Group 1 and 2165.3 in Group 2 (totaling 4329.7 events).

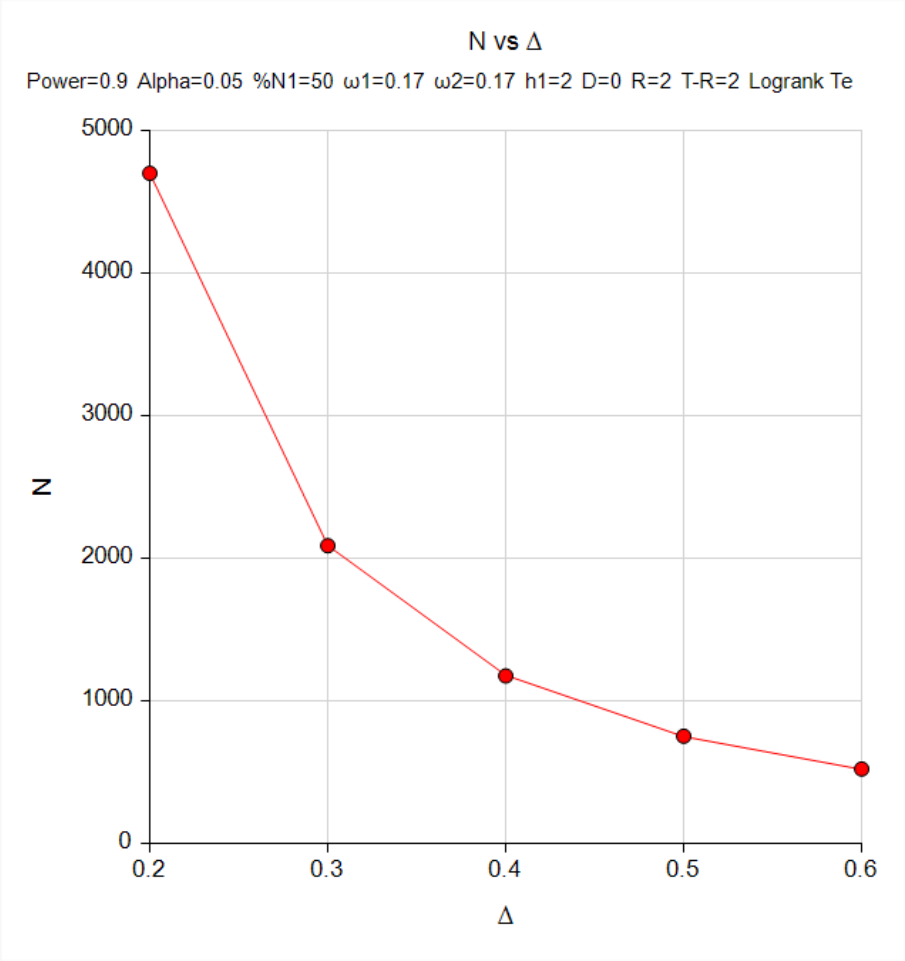
References

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



This plot shows the relationship between the equivalence margin and sample size.

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

Chow et al. (2008) page 173 presents an example of a two-group, equal sample allocation equivalence design to compare the hazard rates of a new treatment with that of the current treatment. The sample size is to be large enough to detect equivalence when h1 = 1, h2 = 1, and Δ = 0.5. 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

$$\mathrm{N1} = \left(\frac{1.64 + 1.28}{0.5 - 0}\right)^2 (0.97 + 0.97)$$

$$\approx 67$$

Note that the variance value should be 1.094, not 0.97. If this substitution is made, the per group sample size is approximately 75.

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**
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	**Differences**
h1 (Hazard Rate of Control Group)	**1**
D (Hazard Rate Difference = h2-h1)	**0**
Δ (Equivalence Margin)	**0.5**

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	Equivalence		Loss Hazard Rate		Time		
Power	N	N1	N2	h1	h2	D	Margin Δ	Boundary B	ω1	ω2	Accrual R	Follow-Up T - R	Alpha
0.8005	150	75	75	1	1	0	0.5	1.5	0	0	1	2	0.05

	Number of Events			Percent Group 1	Hazard Ratio	Variance	
Power	E	E1	E2	%N1	HR	$\sigma^2(h1)$	$\sigma^2(h2)$
0.8005	137.2	68.6	68.6	50	1	1.094	1.094

The value of N1 = 75 is close to Chow's hand calculated 67 and exactly the same as that shown above when the correct variance of 1.094 is used.