

## Chapter 733

# Equivalence Tests for Two Survival Curves Using Cox's Proportional Hazards Model

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### Introduction

A clinical trial may be employed to test the equivalence of two survival distributions. Because survival times are not normally distributed and because some survival times are censored, Cox proportional-hazards regression is often used to analyze the data. The formulation for testing the significance of a Cox regression coefficient is identical to the standard logrank test. Thus the power and sample size formulas for one analysis also work for the other.

The Cox Regression model has the added benefit over the exponential model that it does not assume that the hazard rates are constant, but only that they are proportional. That is, that the hazard ratio remains constant throughout the experiment, even if the hazard rates vary.

This procedure is documented in Chow, Shao, and Wang (2008) which summarizes the work of Schoenfeld (1981, 1983). Note that there was an error in Chow, Shao, and Wang (2008) page 179 which caused the sample size to be doubled. This error has been corrected in this edition.

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### Technical Details

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#### Cox's Proportional Hazards Regression

Cox's proportional hazards regression is widely used for survival data. The regression model is

$$h(t | z) = h(t | 0) \exp(bz)$$

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where

$b$  is the regression coefficient which is equal to  $\log[h(t|1)/h(t|0)] = \log(HR)$

$z$  is a binary indicator variable of treatment group

$t$  is elapsed time

$h(t/z)$  is the hazard rate at time  $t$ , given covariate  $z$

HR is the hazard ratio  $h(t|1)/h(t|0)$

### Equivalence Hypothesis

The equivalence of two hazard rates is established by concluding that their ratio is within a clinically insignificant margin from one. The statistical hypotheses that yields this conclusion when the null hypothesis is rejected is

$$H_0 : |\log(HR)| \geq \log(HR_{eq}) \quad \text{vs} \quad H_a : |\log(HR)| < \log(HR_{eq}), \quad \text{assuming } HR_{eq} > 1$$

### Test Statistic

It can be shown that the test of  $b$  based on the partial likelihood method of Cox (1972) coincides with the common logrank test statistic. When testing equivalence, you can use  $b$  from a Cox regression or calculate the modified logrank statistic as follows

### Logrank Test

In this case, the test statistic uses two one-sided logrank tests. Define

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

where  $K$  is the number of deaths,  $Y_{ij}$  is the number of subjects at risk just prior to the  $j$ th observed event in the  $i$ th group, and  $I_k$  is a binary variable indicating whether the  $k$ th event is from group 1 or not.

The null hypothesis is rejected if  $L(HR_{eq}) < z_{\alpha}$  and  $L(1/HR_{eq}) > z_{1-\alpha}$ .

The distribution of  $L$  is approximately normal with mean  $(\log(HR) - \log(HR_{eq})) \sqrt{P_1 P_2 dN}$  and unit variance, where

$P_1$  is the proportion of  $N$  that is in the control group

$P_2$  is the proportion of  $N$  that is in the treatment group

$N$  is the total sample size

$N_1$  is the sample size from the control group,  $N_1 = N(P_1)$

$N_2$  is the sample size from the treatment group,  $N_2 = N(P_2)$

$Pe_{v1}$  is probability of the event of interest in the control group

$Pe_{v2}$  is probability of the event of interest in the treatment group

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$d$  is the overall probability of an event,  $d = Pev_1P_1 + Pev_2P_2$

$b$  is the Cox regression coefficient,  $b = \log(HR)$

### Power Calculations

The power of this test is given by

$$\Phi\left(\left\{\log(HR_{eq}) - \log(HR)\right\}\sqrt{P_1P_2dN} - z_{1-\alpha}\right) + \Phi\left(\left\{\log(HR_{eq}) + \log(HR)\right\}\sqrt{P_1P_2dN} - z_{1-\alpha}\right) - 1$$

### 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 *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.

#### 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  $\geq 2$ . 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  $\geq 2$ . 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  $\geq 2$ . 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  $\geq Y$ .

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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.

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## Sample Size – Proportion of Events Observed

### Pev1 (Probability of a Control Event)

Enter one or more values for  $Pev1$ , the average probability of an event (death) for each individual in the control group. The number of events in the control group is equal to  $Pev1 \times N1$ .

#### Range

$$0 < Pev1 < 1$$

### Pev2 (Probability of a Treatment Event)

Enter one or more values for  $Pev2$ , the average probability of an event (death) for each individual in the control group. The number of events in the control group is equal to  $Pev2 \times N2$ .

#### Range

$$0 < Pev2 < 1$$

## Hazard Ratios

### HR (Hazard Ratio = $h_2/h_1$ )

Specify one or more hazard ratios,  $HR$ , at which the power is calculated.  $HR$  is defined as the treatment hazard rate divided by the control hazard rate.  $HR$  represents the assumed value at which the power of rejecting  $H_0$  is calculated.

### Range

In equivalence tests, this ratio must be between  $1/HReq$  and  $HReq$  (assuming  $HReq > 1$ ). Usually, it is assumed to be 1.

### HReq (Equivalence Hazard Ratio)

Specify one or more values for the equivalence ratio,  $HReq$ . This value, greater than one, represents the highest that HR can be that still allows the conclusion of equivalence to be drawn.

### Range

$1 < HReq$

## Equivalence Tests for Two Survival Curves Using Cox's Proportional Hazards Model

### Example 1 – Finding the Sample Size

A researcher is planning an equivalence 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 equivalence ratio is 1.35. The desired power is 0.90 and significance level is 0.05. HR will be between 0.9 and 1.1. The probability of observing an event is 0.70 in the control group and 0.40 in the treatment group.

### Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Equivalence Tests for Two Survival Curves Using Cox's Proportional Hazards Model** procedure window by expanding **Survival**, then **Two Survival Curves**, then clicking **Equivalence**, and then clicking on **Equivalence Tests for Two Survival Curves Using Cox's Proportional Hazards 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**.

<u>Option</u>	<u>Value</u>
<b>Design Tab</b>	
Solve For .....	<b>Sample Size</b>
Power .....	<b>0.90</b>
Alpha .....	<b>0.05</b>
Group Allocation .....	<b>Equal (N1 = N2)</b>
Pev1 (Event Probability in Group 1) .....	<b>0.7</b>
Pev2 (Event Probability in Group 2) .....	<b>0.4</b>
HR (Actual Hazard Ratio = h2/h1) .....	<b>0.9 0.95 1.0 1.05 1.1</b>
HReq (Equivalence Hazard Ratio) .....	<b>1.35</b>

### Annotated Output

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

### Numeric Results

#### Numeric Results with Ha: 1/HReq < HR < HReq

Power	Total Sample Size	Control Sample Size	Trtmnt Sample Size	Prop'n Control N1/N	Hazard Ratio h2/h1	Equiv'ce Hazard Ratio HReq	Control Prob Event Pev1	Trtmnt Prob Event Pev2	Control Events E1	Trtmnt Events E2	Alpha
	N	N1	N2	P1	HR						
0.9001	1643	821	822	0.500	0.900	1.350	0.700	0.400	575	329	0.050
0.9000	1029	514	515	0.500	0.950	1.350	0.700	0.400	360	206	0.050
0.9000	874	437	437	0.500	1.000	1.350	0.700	0.400	306	175	0.050
0.9004	1014	507	507	0.500	1.050	1.350	0.700	0.400	355	203	0.050
0.9001	1486	743	743	0.500	1.100	1.350	0.700	0.400	520	297	0.050

#### References

Chow, S.C., Shao, J., Wang, H. 2008. *Sample Size Calculations in Clinical Research*, 2nd Edition. Chapman & Hall/CRC.  
 Schoenfeld, David A. 1983. 'Sample Size Formula for the Proportional-Hazards Regression Model', *Biometrics*, Volume 39, Pages 499-503.

#### 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.  
 P1 is the proportion of the total sample that is in the control group, group 1.  
 HR is the hazard ratio: h2/h1.  
 HReq is the equivalence hazard ratio.  
 Pev1 and Pev2 are the probabilities of an event in the control and the treatment groups.  
 E1 and E2 are the number of events required in the control and the treatment groups.  
 Alpha is the probability of a type one error: rejecting a true null hypothesis.



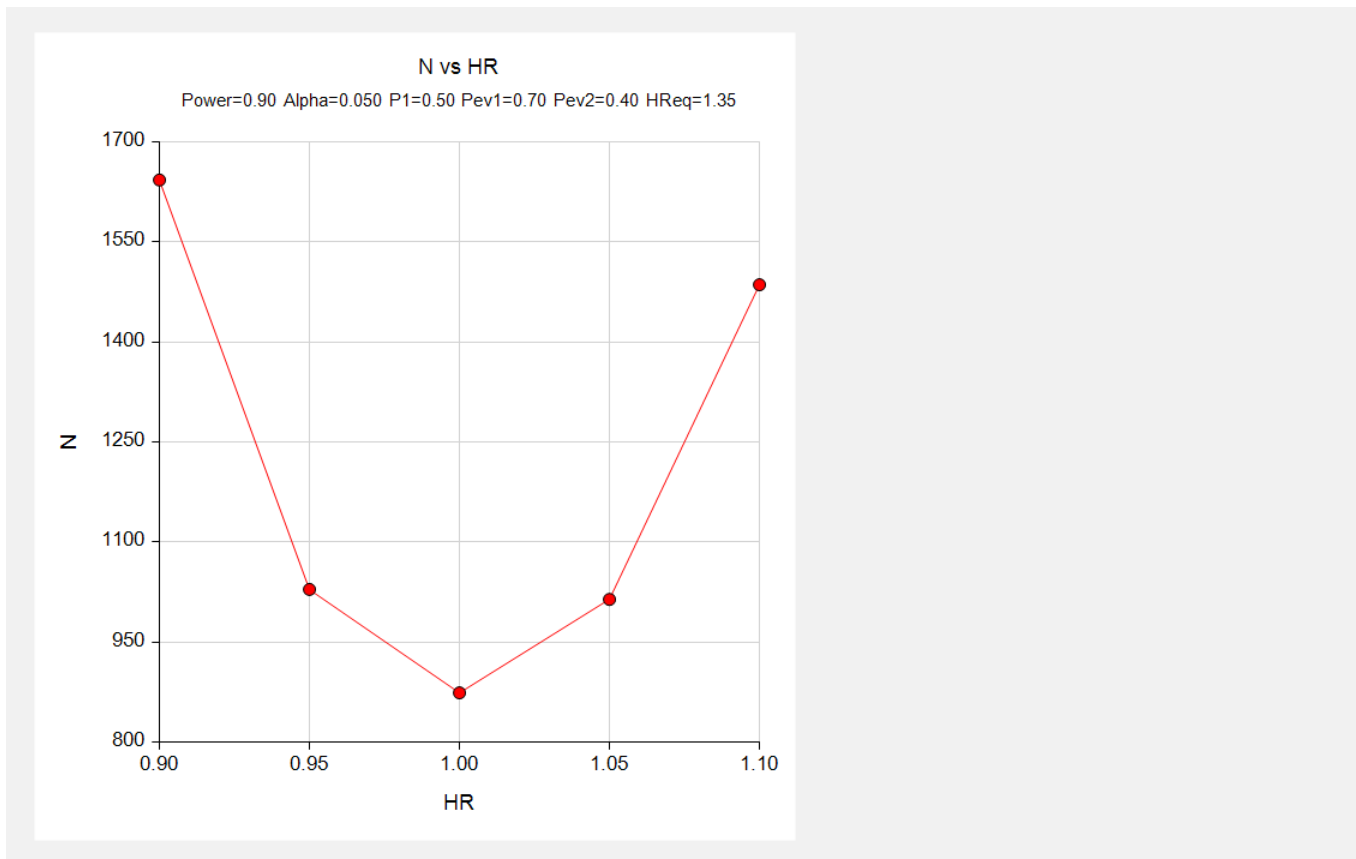
## Equivalence Tests for Two Survival Curves Using Cox's Proportional Hazards Model

### Summary Statements

An equivalence test of whether the hazard ratio with an overall sample size of 1643 subjects (of which 821 are in the control group and 822 are in the treatment group) achieves 90% power at a 0.050 significance level when the hazard ratio is actually 0.900. The equivalence ratio is 1.350. The number of events required to achieve this power is 904. It is anticipated that the proportion of subjects in which the event is observed during the study is 0.700 for the control group and 0.400 for the treatment group. These results assume that the hazard ratio is constant throughout the study and that Cox proportional hazards regression or the equivalence logrank test is used to analyze the data.

These reports show the values of each of the parameters, one scenario per row.

### Plots Section



This plot shows the relationship between HR and N.

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

Chow et al. (2008) page 179 present an example that we will use for validation. In their example,  $HR = 1$ ,  $\log(HReq) = 0.5$ ,  $Pev1 = Pev2 = 0.8$ ,  $P1 = 0.5$ ,  $\alpha = 0.05$ , and  $\text{power} = 0.8$ . They should have obtained a total sample size of about 172 (they incorrectly double their result).

### Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Equivalence Tests for Two Survival Curves Using Cox's Proportional Hazards Model** procedure window by expanding **Survival**, then **Two Survival Curves**, then clicking **Equivalence**, and then clicking on **Equivalence Tests for Two Survival Curves Using Cox's Proportional Hazards 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**.

<u>Option</u>	<u>Value</u>
<b>Design Tab</b>	
Solve For .....	<b>Sample Size</b>
Power.....	<b>0.80</b>
Alpha.....	<b>0.05</b>
Group Allocation .....	<b>Equal (N1 = N2)</b>
Pev1 (Event Probability in Group 1) .....	<b>0.8</b>
Pev2 (Event Probability in Group 2) .....	<b>0.8</b>
HR (Actual Hazard Ratio = $h2/h1$ ).....	<b>1</b>
HReq (Superiority Hazard Ratio).....	<b>1.6487</b> (which is $\exp(0.5)$ )

### Annotated Output

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

### Numeric Results

Numeric Results with $H_a: 1/HReq < HR < HReq$												
	Total Sample Size N	Control Sample Size N1	Trtmnt Sample Size N2	Prop'n Control N1/N P1	Hazard Ratio $h2/h1$ HR	Equiv'ce Hazard Ratio HReq	Control Prob Event Pev1	Trtmnt Prob Event Pev2	Control Events E1	Trtmnt Events E2	Alpha	
Power	0.8021	172	86	86	0.500	1.000	1.649	0.800	0.800	69	69	0.050

PASS also calculates the value of  $N = 172$ .