

## Chapter 730

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

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### Introduction

A clinical trial is often employed to test the equality of survival distributions of two treatment groups. 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 works 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

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

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

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

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

The two-sided, statistical hypothesis testing survival equality is a test of whether  $b$  is zero. This hypothesis is stated as

$$H_0 : b = 0 \quad \text{versus} \quad H_a : b \neq 0$$

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### 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 shown next.

### Logrank Test

The logrank test statistic is

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

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

The distribution of  $L$  is approximately normal with mean  $b\sqrt{P_1 P_2 dN}$  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

$d$  is the overall probability of an event,  $d = Pe_{v1}P_1 + Pe_{v2}P_2$

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

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### Power Calculations

The power of the statistical test of  $b$  is given by

$$\Phi(b\sqrt{P_1 P_2 dN} - z_{1-\alpha/2})$$

or equivalently

$$\Phi(\log(HR_1)\sqrt{P_1 P_2 dN} - z_{1-\alpha/2})$$

where  $HR_1$  is the actual assumed value of the hazard ratio under the alternative hypothesis.

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## 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.

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### Design Tab

The Design tab contains most of the parameters and options that you will be concerned with.

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#### 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.

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#### Test Direction

##### Alternative Hypothesis

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

HR stand for the hazard ratio of groups 2 (Treatment) and 1 (Control).

The two-sided test ( $H_a: HR \neq 1$ ) is the standard. Only use a one-sided test under special circumstances. If you do use a one-sided test, be sure that the alternative hypothesis matches the values HR. That is, if you have set  $HR = 2$ , and you want to analyze a one-sided test, the Alternative Hypothesis should be ' $H_a: HR > 1$ '.

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#### 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.

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## 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.

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

### 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  $\geq Y$ .

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 - 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 x 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 x N2.

#### Range

$$0 < Pev2 < 1$$

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## Effect Size

### HR1 (Actual Hazard Ratio to Detect)

Specify one or more hazard ratios at which the power is calculated. *HR* is defined as the treatment hazard rate (*h2*) divided by the control hazard rate (*h1*). *HR1* represents the assumed value at which the power of rejecting  $H_0$  is calculated. When  $H_0$  is rejected, you conclude that the hazard ratio is different from one, but not that it is actually equal to this hazard ratio.

The null hypothesis is  $H_0: HR = 1$ . The two-sided alternative hypothesis is  $H_a: HR \neq 1$ . The one-sided alternative hypotheses are  $H_a: HR < 1$  or  $H_a: HR > 1$ .

### Range

If  $H_a: HR \neq 1$  then the range is  $HR1 > 0$ . Typical values are from 0.25 to 4.0, except 1.

If  $H_a: HR < 1$  then the range is  $0 < HR1 < 1$ . Typical values are from 0.25 up to 1.0.

If  $H_a: HR > 1$  then the range is  $HR1 > 1$ . Typical values are between 1.0 and 4.0.

Press the "Survival Parameter Conversion Tool" button to estimate reasonable values based on median survival times, hazard rates, or the proportion surviving.

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

## Example 1 – Finding the Sample Size

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 ( $h_1 = 0.693$ ). The power of the test procedure will be calculated for the case when the proportion surviving after the new treatment is 0.75 ( $h_2 = 0.288$ ). Hence,  $HR_1 = 0.288/0.693 = 0.4156$ .

The probability of an event is 0.50 in the control group and 0.25 in the treatment group. The researcher decides to use a two-sided test at the 0.05 significance level and a power of either 0.8 or 0.90.

The researchers would like to study the influence of  $HR_1$  on the sample size, so they would like to look at a range of possible values for 0.3 to 0.7.

### 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 Two Survival Curves Using Cox's Proportional Hazards Model** procedure window by expanding **Survival**, then **Two Survival Curves**, then clicking **Test (Inequality)**, and then clicking on **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>
Alternative Hypothesis .....	<b>Ha: HR ≠ 1</b>
Power .....	<b>0.8 0.9</b>
Alpha .....	<b>0.05</b>
Group Allocation .....	<b>Equal (N1 = N2)</b>
Pev1 (Probability of a Control Event) .....	<b>0.5</b>
Pev2 (Probability of a Treatment Event).....	<b>0.25</b>
HR1 (Actual Hazard Ratio to Detect).....	<b>0.3 0.4 0.4156 0.5 0.6 0.7</b>

### Annotated Output

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

### Numeric Results

Numeric Results												
Hypotheses: H0: HR = 1 vs. Ha: HR ≠ 1												
Power	Total Sample Size	Control Sample Size	Trtmnt Sample Size	Percent Control %N1	Actual Hazard Ratio HR1	Control Prob Event Pev1	Trtmnt Prob Event Pev2	Control Events E1	Trtmnt Events E2	Alpha	Beta	
0.8016	58	29	29	50.0	0.300	0.500	0.250	14.5	7.3	0.050	0.2000	
0.8011	100	50	50	50.0	0.400	0.500	0.250	25.0	12.5	0.050	0.2000	
0.8002	109	54	55	50.0	0.416	0.500	0.250	27.0	13.8	0.050	0.2000	
0.8009	175	87	88	50.0	0.500	0.500	0.250	43.5	22.0	0.050	0.2000	
0.8014	322	161	161	50.0	0.600	0.500	0.250	80.5	40.3	0.050	0.2000	
0.8003	659	329	330	50.0	0.700	0.500	0.250	164.5	82.5	0.050	0.2000	
0.9025	78	39	39	50.0	0.300	0.500	0.250	19.5	9.8	0.050	0.1000	
0.9011	134	67	67	50.0	0.400	0.500	0.250	33.5	16.8	0.050	0.1000	
<b>0.9012</b>	<b>146</b>	<b>73</b>	<b>73</b>	<b>50.0</b>	<b>0.416</b>	<b>0.500</b>	<b>0.250</b>	<b>36.5</b>	<b>18.3</b>	<b>0.050</b>	<b>0.1000</b>	
0.9009	234	117	117	50.0	0.500	0.500	0.250	58.5	29.3	0.050	0.1000	
0.9003	430	215	215	50.0	0.600	0.500	0.250	107.5	53.8	0.050	0.1000	
0.9003	882	441	441	50.0	0.700	0.500	0.250	220.5	110.3	0.050	0.1000	



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

### 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

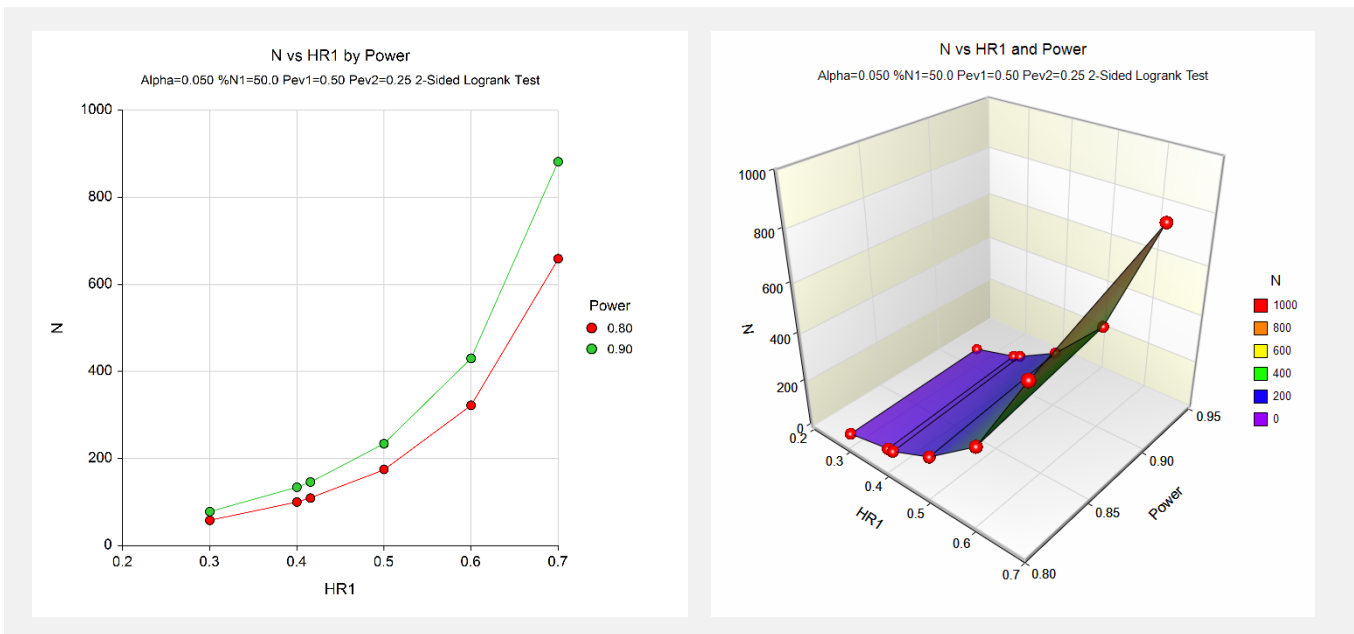
Power is the probability of rejecting a false null hypothesis. Power should be close to one.  
 N is the total sample size.  
 N1 and N2 are the sample sizes of the control and treatment groups, respectively.  
 %N1 is the percent of the total sample that is in group 1, the control group.  
 HR =  $h_2/h_1$  is the hazard ratio.  
 HR1 is the actual hazard ratio at which power is calculated.  
 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 rejecting a true null hypothesis.  
 Beta is the probability of failing to reject a false null hypothesis.

### Summary Statements

A two-sided test of whether the hazard ratio is one with an overall sample size of 58 subjects (of which 29 are in the control group and 29 are in the treatment group) achieves 80% power at a 0.050 significance level when the hazard ratio is actually 0.300. The number of events required to achieve this power is 21.8. It is anticipated that proportions of subjects having the event during the study is 0.500 for the control group and 0.250 for the treatment group. These results assume that the hazard ratio is constant throughout the study and that Cox proportional hazards regression is used to analyze the data.

These reports show the values of each of the parameters, one scenario per row. We have bolded the row that was of particular interest to the researchers.

## Plots Section



This plot shows the relationship between HR1 and sample size.

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

Chow et al. (2008) page 179 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 sample size when  $HR1 = 2$ . They further assume that about 80% of the patients will show the event of interest (infection) during the study. Alpha is set to 0.05 and power is 0.80.

They should have obtained a value of about 41 per group (We have found that the sample size in their example was doubled).

### 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 Two Survival Curves Using Cox's Proportional Hazards Model** procedure window by expanding **Survival**, then **Two Survival Curves**, then clicking **Test (Inequality)**, and then clicking on **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>
Alternative Hypothesis .....	<b>Ha: HR ≠ 1</b>
Power .....	<b>0.80</b>
Alpha .....	<b>0.05</b>
Group Allocation .....	<b>Equal (N1 = N2)</b>
Pev1 (Probability of a Control Event) .....	<b>0.8</b>
Pev2 (Probability of a Treatment Event).....	<b>Pev1</b>
HR1 (Actual Hazard Ratio to Detect).....	<b>2</b>

### Output

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

### Numeric Results

Numeric Results												
Hypotheses: H0: HR = 1 vs. Ha: HR ≠ 1												
	Total Sample Size	Control Sample Size	Trtmnt Sample Size	Percent Control	Actual Hazard Ratio	Control Prob Event	Trtmnt Prob Event	Control Events	Trtmnt Events	Alpha	Beta	
Power	N	N1	N2	%N1	HR1	Pev1	Pev2	E1	E2			
0.8015	82	41	41	50.0	2.000	0.800	0.800	32.8	32.8	0.050	0.2000	

PASS also calculates the value of  $N1 = N2 = 41$ .