Chapter 730

Tests for Two Survival Curves using Cox's Proportional Hazards Model

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.

Technical Details

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

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

$$H_0: b = 0 \quad \text{vs.} \quad H_1: b \neq 0$$

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^{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 distribution of L is approximately normal with mean $b\sqrt{P_1P_2dN}$ 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, $N_2 = N(P_2)$

Pev_1 is probability of the event of interest in the control group

Pev_2 is probability of the event of interest in the treatment group

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 the statistical test of b is given by

$$\Phi\left(b\sqrt{P_1P_2dN} - z_{1-\alpha/2}\right)$$

or equivalently

$$\Phi\left(\log(HR_1)\sqrt{P_1P_2dN} - z_{1-\alpha/2}\right)$$

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

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 (h1 = 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 (h2 = 0.288). Hence, HR1 = 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 HR1 on the sample size, so they would like to look at a range of possible values for 0.3 to 0.7.

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**
Alternative Hypothesis	**Ha: HR ≠ 1**
Power	**0.8 0.9**
Alpha	**0.05**
Group Allocation	**Equal (N1 = N2)**
Pev1 (Probability of a Control Event)	**0.5**
Pev2 (Probability of a Treatment Event)	**0.25**
HR1 (Actual Hazard Ratio to Detect)	**0.3 0.4 0.4156 0.5 0.6 0.7**

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: HR = 1 vs. Ha: HR ≠ 1

	Sample Size			Percent	Number of Events			Hazard	Probability of an Event		
Power	N	N1	N2	Group 1 %N1	E	E1	E2	Ratio HR1	Pev1	Pev2	Alpha
0.8016	58	29	29	50	21.8	14.5	7.3	0.300	0.5	0.25	0.05
0.8011	100	50	50	50	37.5	25.0	12.5	0.400	0.5	0.25	0.05
0.8002	109	54	55	50	40.8	27.0	13.8	0.416	0.5	0.25	0.05
0.8009	175	87	88	50	65.5	43.5	22.0	0.500	0.5	0.25	0.05
0.8014	322	161	161	50	120.8	80.5	40.3	0.600	0.5	0.25	0.05
0.8003	659	329	330	50	247.0	164.5	82.5	0.700	0.5	0.25	0.05
0.9025	78	39	39	50	29.3	19.5	9.8	0.300	0.5	0.25	0.05
0.9011	134	67	67	50	50.3	33.5	16.8	0.400	0.5	0.25	0.05
0.9012	146	73	73	50	54.8	36.5	18.3	0.416	0.5	0.25	0.05
0.9009	234	117	117	50	87.8	58.5	29.3	0.500	0.5	0.25	0.05
0.9003	430	215	215	50	161.3	107.5	53.8	0.600	0.5	0.25	0.05
0.9003	882	441	441	50	330.8	220.5	110.3	0.700	0.5	0.25	0.05

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 groups 1 and 2, respectively.
%N1	The percent of the total sample that is in group 1, the control group.
E, E1, and E2	The number of events required in both groups and groups 1 and 2, respectively.
HR1	The actual hazard ratio at which power is calculated. HR = h2/h1.
Pev1 and Pev2	The probabilities of an event in the control and the treatment groups, respectively.
Alpha	The probability of rejecting a true null hypothesis.

Summary Statements

A parallel, two-group design will be used to test whether the Group 2 (treatment) hazard rate is different from the Group 1 (control) hazard rate (H0: HR = 1 versus Ha: HR ≠ 1, HR = h2 / h1). The comparison will be made using a two-sided, two-sample Cox proportional hazards regression test (or equivalent logrank test) with a Type I error rate (α) of 0.05. It is anticipated that the probability of observing an event during the course of the study is 0.5 for each member of the control group and 0.25 for each member of the treatment group. The calculations are based on the assumption that the hazard ratio is constant throughout the study. To detect a hazard ratio (h2 / h1) of 0.3 with 80% power, the number of needed subjects will be 29 in Group 1 and 29 in Group 2 (totaling 58 subjects). The corresponding required number of events is 14.5 in Group 1 and 7.3 in Group 2 (totaling 21.8 events).

References

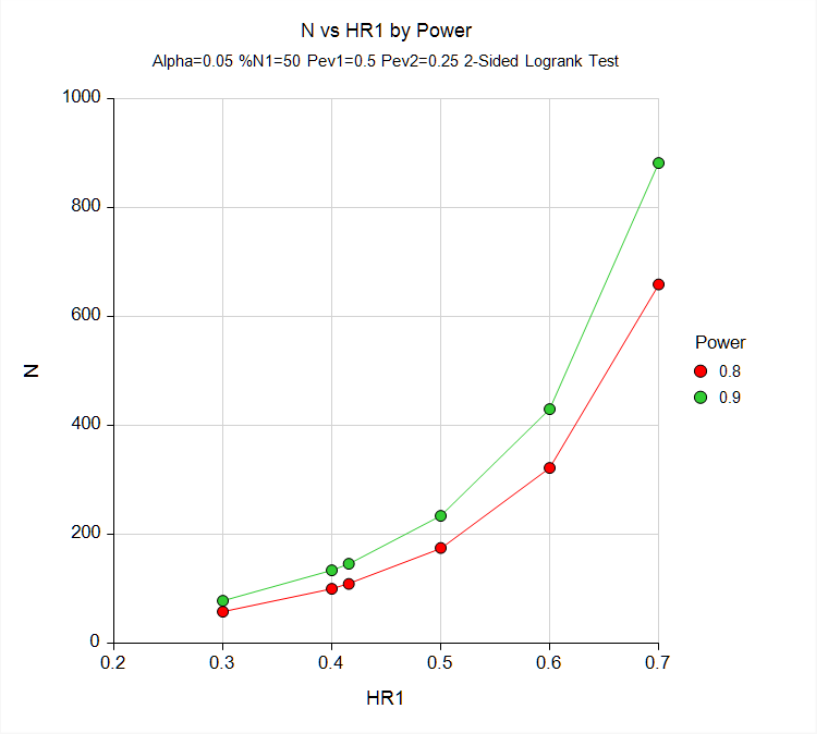
Chow, S.C., Shao, J., Wang, H. 2008. Sample Size Calculations in Clinical Research, 2nd Edition. Chapman & Hall/CRC.

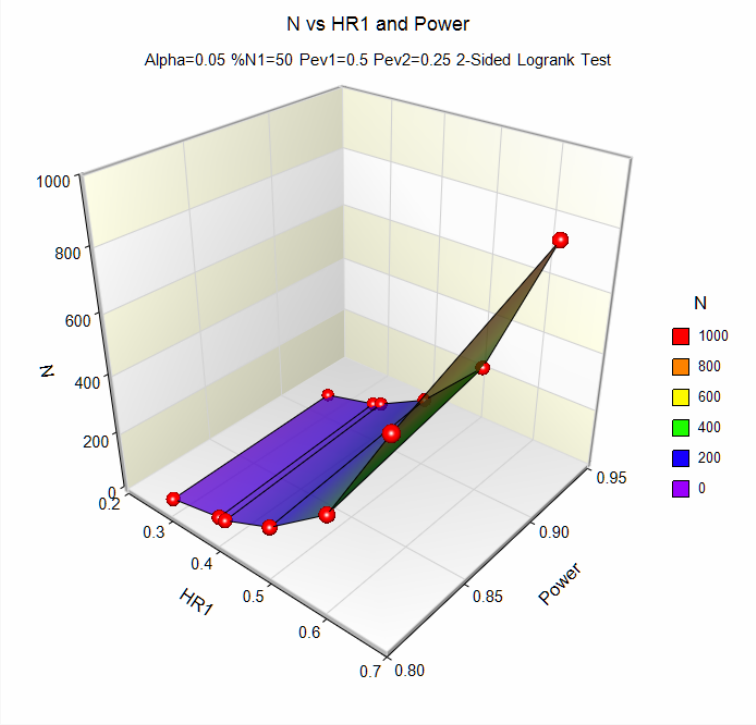
Schoenfeld, David A. 1983. 'Sample Size Formula for the Proportional-Hazards Regression Model', Biometrics, Volume 39, Pages 499-503.

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

Plots





This plot shows the relationship between HR1 and sample size.

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

Chow et al. (2008) page 179 presents 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

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: HR ≠ 1**
Power	**0.80**
Alpha	**0.05**
Group Allocation	**Equal (N1 = N2)**
Pev1 (Probability of a Control Event)	**0.8**
Pev2 (Probability of a Treatment Event)	**Pev1**
HR1 (Actual Hazard Ratio to Detect)	**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: HR = 1 vs. Ha: HR ≠ 1

	Sample Size			Percent Group 1	Number of Events			Hazard Ratio	Probability of an Event		
Power	N	N1	N2	%N1	E	E1	E2	HR1	Pev1	Pev2	Alpha
0.8015	82	41	41	50	65.6	32.8	32.8	2	0.8	0.8	0.05

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