Chapter 623

Non-Inferiority Tests for Two Survival Curves using Cox's Proportional Hazards Model in a Cluster-Randomized Design

Introduction

This procedure calculates power and sample size for testing the non-inferiority of a treatment hazard rate compared to a control hazard rate using Cox's proportional hazards regression when the data are obtained in a cluster-randomized design. 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, Wang, and Lokhnygina (2018) and Machin, Campbell, Tan, and Tan (2018) which are based on the work of Schoenfeld (1981, 1983).

Cluster-randomized designs are those in which whole clusters of subjects (classes, hospitals, communities, etc.) are randomized into the treatment or control groups. In this design, the survival curves of the two groups, made up of K_i clusters of M_{ij} individuals each, are to be tested using a regression coefficient from a Cox regression.

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 one-sided, statistical hypothesis testing survival non-inferiority is a test of whether b is different from a constant value. This hypothesis is stated as

$$H_0: b \geq b_0 \quad \text{vs.} \quad H_1: b < b_0$$

Non-Inferiority Hypothesis

Higher Hazards Worse

Assuming that lower hazard rates are better, non-inferiority means that the treatment hazard rate is at most, only slightly higher than the control hazard rate. We find it more convenient to state the hypotheses in terms of the hazard ratio, *HR*, rather than the Cox regression coefficient, *b*. Remembering that $b = \log(HR)$ and assuming that $HR_0 > 1$, non-inferiority requires that $HR < HR_0$. Here, HR_0 is the boundary of clinical insignificance or the non-inferiority boundary.

The statistical hypotheses that result in the conclusion of non-inferiority when the null hypothesis is rejected are of the form

$$H_0: \log(HR) \geq \log(HR_0) \quad \text{vs.} \quad H_1: \log(HR) < \log(HR_0)$$

Higher Hazards Better

Assuming that higher hazard rates are better, non-inferiority means that the treatment hazard rate is at most, only slightly lower than the control hazard rate. We find it more convenient to state the hypotheses in terms of the hazard ratio, *HR*, rather than the Cox regression coefficient, *b*. Remembering that $b = \log(HR)$ and assuming that $HR_0 < 1$, non-inferiority requires that $HR > HR_0$. Here, HR_0 is called the boundary of clinical insignificance or the non-inferiority boundary.

The statistical hypotheses that result in the conclusion of non-inferiority when the null hypothesis is rejected are of the form

$$H_0: \log(HR) \leq \log(HR_0) \quad \text{vs.} \quad H_1: \log(HR) > \log(HR_0)$$

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

$$L = \frac{\sum_{k=1}^{K}\left(I_k - \frac{Y_{1i}HR_0}{Y_{1i}HR_0 + Y_{2i}}\right)}{\left[\sum_{k=1}^{K}\left(\frac{Y_{1i}Y_{2i}HR_0}{(Y_{1i}HR_0 + Y_{2i})^2}\right)\right]^{-\frac{1}{2}}}$$

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

The distribution of L is approximately normal with mean $\left(\log(HR) - \log(HR_0)\right)\sqrt{P_1 P_2 dN}$ 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, $N_2 = N(P_2)$
>
> 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, $d = Pev_1 P_1 + Pev_2 P_2$
>
> HR is the observed hazard ratio
>
> HR_0 is the superiority boundary (limit) of the hazard ratio

Cluster-Randomized Designs

Denote an observation by Y_{ijk} where i = 1, 2 gives the group, j = 1, 2, ..., K_i gives the cluster within group i, and k = 1, 2, ..., m_{ij} denotes an individual in cluster j of group i. In this chapter, we will assume that group 1 is the control group and group 2 is the treatment group.

Let ρ denote the intracluster correlation coefficient (ICC) among individuals from the same cluster. <u>This correlation is the correlation of censor indicator variable</u>. Also let COV denote the coefficient of variation of the cluster sizes. Machin *et al.* (2018) page 101 shows that the number of events, e, that are needed to obtain a given power of 1 – β and a one-sided significance level of α to detect a hazard ratio of HR (h_2 / h_1) is given by

$$e = \frac{(1+r)^2}{r}\left[\frac{(z_{1-\alpha} + z_{1-\beta})^2}{(\log HR_1 - \log HR_0)^2}\right]$$

where $r = N_2 / N_1$ and $z_x = \Phi(x)$ is the standard normal distribution function.

The number of subjects in a regular design can be determined using

$$N = N_1 + N_2 = \frac{e}{F}$$

where

$$F = \frac{(Pev_1 + r(Pev_2))}{1 + r}$$

Design Effect

When using a cluster-randomized design Machin *et al*. (2018) page 202 show that the above formula is modified using a quantity that is known as the *design effect* (DE). The version of DE that is used in **PASS** is given as formula 12.7 on page 197 of Machin *et al*. (2018) which is

$$DE = 1 + \{[CV^2 + 1]\bar{M} - 1\}\rho$$

where $\bar{M}$ is the average cluster size of all clusters given by

$$\bar{M} = \frac{K_1 M_1 + K_2 M_2}{K_1 + K_2}$$

CV is the coefficient of variation of cluster sizes of all clusters in the study and ρ is the ICC as defined above.

The resulting sample size formula in terms of cluster counts and size is

$$N = K_1 M_1 + K_2 M_2 = DE \left(\frac{e}{F}\right)$$

Power Calculations

The power of this test is given by

$$\Phi\left(\left(\log(HR_1) - \log(HR_0)\right)\sqrt{P_1 P_2 dN} - z_{1-\alpha}\right)$$

where HR_1 is the actual value of the hazard ratio under the alternative hypothesis and N is defined as above.

Example 1 – Showing Impact of ICC and COV on K1 and K2

This example will not only show how to find the sample size but will also show how ICC and COV impact the sample size.

Suppose a cluster-randomized study is being planned in which higher hazards are worse; *HR1* = 1; *HR0* = 1.25; *Pev1* = 0.7; *Pev2* = 0.5; *ρ* = 0.00, 0.01, 0.05; *M1* and *M2* = 20; *alpha* = 0.05; *power* = 0.90; *COV* = 0.0, 0.6; and *K1* = *K2*. Sample size (number of clusters) is desired.

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 ....**Number of Clusters**
Higher Hazards Are ....**Worse (H1: HR < HR0)**
Power...**0.90**
Alpha...**0.05**
M1 (Average Cluster Size)............................**20**
K2 (Number of Clusters) **K1**
M2 (Average Cluster Size)............................**M1**
COV of Cluster Sizes....................................**0 0.6**
Pev1 (Probability of a Control Event)............**0.7**
Pev2 (Probability of a Treatment Event) **0.5**
HR0 (Non-Inferiority Hazard Ratio)...............**1.25**
HR1 (Actual Hazard Ratio) **1**
ρ (Intracluster Correlation) **0 0.01 0.05**

Output

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

Numeric Reports

Numeric Results

Solve For: Number of Clusters
Higher Hazards Are: Worse
Groups: 1 = Control, 2 = Treatment
Hypotheses: H0: HR ≥ HR0   vs.   H1: HR < HR0

		Sample Size Ni	Number of Events Ei	Number of Clusters Ki	Cluster Size Average Mi	Cluster Size COV	Probability of an Event Pevi	Hazard Ratio Non-Inferiority HR0	Hazard Ratio Actual HR1	Intracluster Correlation ρ	Alpha
Group	Power										
1: Control		580	406.0	29	20	0.0	0.7			0.00	
2: Treatment	0.90296	580	290.0	29	20	0.0	0.5	1.25	1	0.00	0.05
Total		1160	696.0	58							
1: Control		700	583.1	35	20	0.0	0.7			0.01	
2: Treatment	0.90649	700	416.5	35	20	0.0	0.5	1.25	1	0.01	0.05
Total		1400	999.6	70							
1: Control		1120	1528.8	56	20	0.0	0.7			0.05	
2: Treatment	0.90048	1120	1092.0	56	20	0.0	0.5	1.25	1	0.05	0.05
Total		2240	2620.8	112							
1: Control		580	406.0	29	20	0.6	0.7			0.00	
2: Treatment	0.90296	580	290.0	29	20	0.6	0.5	1.25	1	0.00	0.05
Total		1160	696.0	58							
1: Control		740	653.7	37	20	0.6	0.7			0.01	
2: Treatment	0.90570	740	466.9	37	20	0.6	0.5	1.25	1	0.01	0.05
Total		1480	1120.7	74							
1: Control		1340	2166.8	67	20	0.6	0.7			0.05	
2: Treatment	0.90300	1340	1547.7	67	20	0.6	0.5	1.25	1	0.05	0.05
Total		2680	3714.5	134							

Group   The group to which the results on this line belong. Group 1 is the control group and group 2 is the treatment group.
          The first (Total) line shows the total when appropriate.
Power   The probability of rejecting a false null hypothesis for this hazard ratio. This is the power calculated at HR1.
Ni   The number of items (subjects) in the ith group. The total sample size is shown as the last row of each three-row set.
Ei   The number of events in the ith group required to achieve the power indicated.
Ki   The number of clusters in the ith group. The total number of clusters is reported in the last row of each three-row set.
Mi   The average number of items per cluster (or average cluster size) in the ith group.
COV   The coefficient of variation of the cluster sizes of the clusters within the group. This value is used for both groups.
Pevi   The average probability that a subject in the ith group will have an event during the study. This probability includes
          the impact of various kinds of censoring.
HR0   The non-inferiority hazard ratio boundary used to declare whether a treatment is non-inferior to the control.
HR1   The hazard ratio of the treatment group and the control group. HR1 = h2 / h1. The subscript '1' indicates that this
          hazard ratio value is used for the alternative hypothesis, H1.
ρ   The intracluster correlation (ICC) between any two observations from within a cluster. This statistic has two common
          interpretations: (1) the proportion of variation related to the between-cluster variation or (2) the correlation between
          two subjects from the same cluster.
Alpha   The probability of rejecting a true null hypothesis.

Summary Statements
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A parallel, two-group cluster-randomized design (where higher hazard rates are considered worse) will be used to test whether the Group 2 (treatment) hazard rate is non-inferior to the Group 1 (control) hazard rate, with a non-inferiority hazard ratio of 1.25 (H0: HR ≥ 1.25 versus H1: HR < 1.25, HR = h2 / h1). The comparison will be made using a one-sided, two-sample Cox proportional hazards regression coefficient 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 0.7 for each member of the control group and 0.5 for each member of the treatment group. The coefficient of variation of the cluster sizes within a group is assumed to be 0. The intracluster correlation coefficient of responses within a particular cluster is assumed to be 0. The calculations are based on the assumption that the hazard ratio is constant throughout the study. To detect a hazard ratio (h2 / h1) of 1, with average cluster sizes of 20 subjects per cluster in Group 1 and 20 subjects per cluster in Group 2, with 90% power, the number of needed clusters is 29 for Group 1 (control) (totaling 580 subjects) and 29 for Group 2 (treatment) (totaling 580 subjects). The corresponding required number of events is 406 in Group 1 and 290 in Group 2 (totaling 696 events).

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References
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Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. 2018. Sample Size Calculations in Clinical Research, 3rd Edition. Chapman & Hall/CRC. Boca Raton, FL. Pages 86-88.
Donner, A. and Klar, N. 2000. Design and Analysis of Cluster Randomization Trials in Health Research. Arnold. London.
Machin, D., Campbell, M.J., Tan, S.B, and Tan, S.H. 2018. Sample Sizes for Clinical, Laboratory, and Epidemiology Studies, 4th Edition. Wiley Blackwell.
Schoenfeld, David A. 1983. 'Sample Size Formula for the Proportional-Hazards Regression Model', Biometrics, Volume 39, Pages 499-503.

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This report shows the sample size for each of the scenarios. Note each scenario requires three report lines.

Plots Section

Plots
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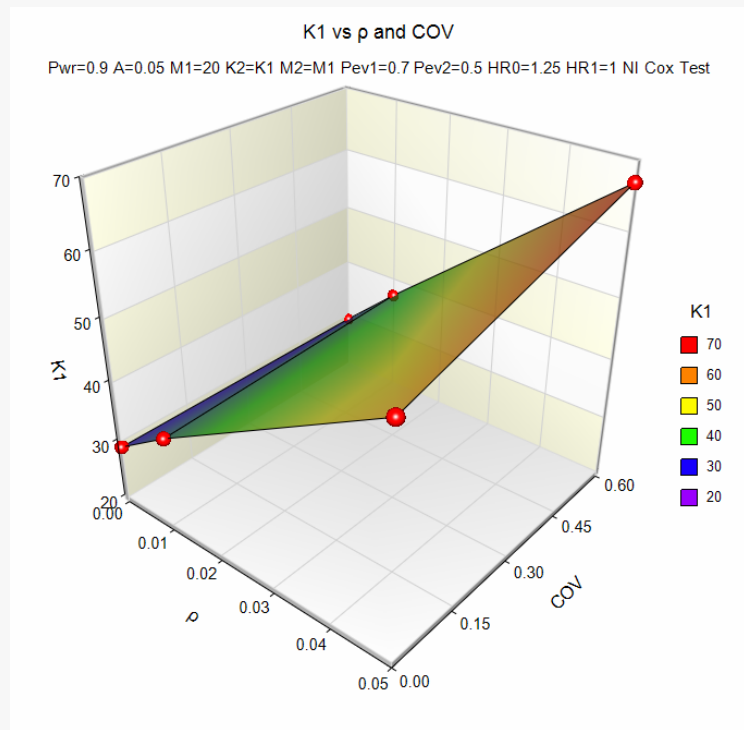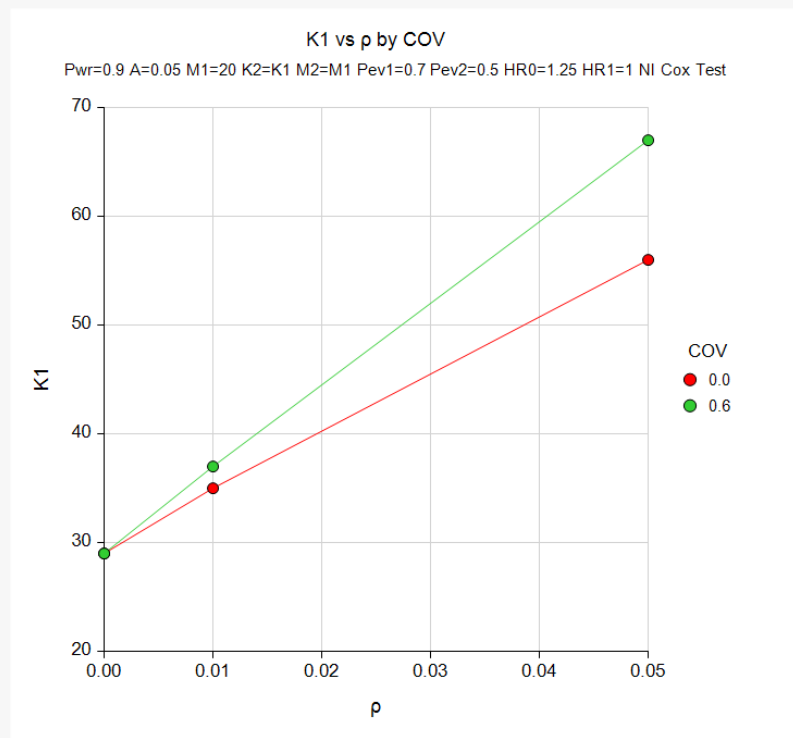
These plots show the relationship between the number of clusters, COV, and ICC.

Example 2 – Validation using a Previously Validated Procedure

We could not find a validation result in the statistical literature, so we will use a previously validated **PASS** procedure (**Non-Inferiority Tests for Two Survival Curves using Cox's Proportional Hazards Model**) to produce the results for the following example.

The parameters for this procedure are as follows: M = 4.1, COV = 0.6, ρ = 0.05, $alpha$ = 0.05, $power$ = 0.8, $HR0$ = 2, $HR1$ = 1.36, $Pev1$ = 0.8; and $Pev2$ = 0.8. Higher hazards are worse. Solve for sample size using equal allocation. Note that the parameters COV, M, and ρ relate to cluster-randomization and so they are not used in this procedure.

The **Non-Inferiority Tests for Two Survival Curves using Cox's Proportional Hazards Model** procedure is set up as follows.

Design Tab

Solve For ....**Sample Size**
Higher Hazards Are ....**Worse (Ha: HR < HR0)**
Power..**0.80**
Alpha...**0.05**
Group Allocation ....**Equal (N1 = N2)**
Pev1 (Event Probability in Group 1)..............**0.8**
Pev2 (Event Probability in Group 2)..............**Pev1**
HR1 (Actual Hazard Ratio) **1.36**
HR0 (Non-Inferiority Hazard Ratio)...............**2**

This set of options generates the following report.

Numeric Results

Solve For: Sample Size
Groups: 1 = Control, 2 = Treatment
Hypotheses: H0: HR ≥ HR0   vs.   Ha: HR < HR0

| | | | | | | | | Hazard Ratio | | Event Probability | | |
| | Sample Size | | | Percent | Number of Events | | | Non-Inferiority | Actual | | | |
Power	N	N1	N2	Group 1 %N1	E	E1	E2	HR0	HR1	Pev1	Pev2	Alpha
0.8003	208	104	104	50	166.4	83.2	83.2	2	1.36	0.8	0.8	0.05

The result is $N1 = N2$ = 104.

Next, we calculate DE by hand. The formula for DE is

$$DE = 1 + \{[CV^2 + 1]\bar{M} - 1\}\rho$$

Plugging in we will now set COV = 0.6 and ρ = 0.05. the above values for COV and ρ

$$DE = 1 + \{[0.36 + 1]4.1 - 1\}(0.05) = 1.2288$$

Multiplying 1.2288 times 104 gives 127.7952 which rounds up to 128 for *N1* and *N2* in the CR (cluster-randomized) design. Finally, we divide 128 by 4.1 to obtain the number of clusters per group as 31.2195. This could be rounded to 31 or 32 clusters. We find that the appropriate power (0.8) is obtained when K1 and K2 are both 31.

The next step is to run the CR routine and determine if the number of clusters match.

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 ....**Number of Clusters**
Higher Hazards Are ....**Worse (H1: HR < HR0)**
Power...**0.8**
Alpha..**0.05**
M1 (Average Cluster Size).............................**4.1**
K2 (Number of Clusters) **K1**
M2 (Average Cluster Size).............................**M1**
COV of Cluster Sizes....................................**0.6**
Pev1 (Probability of a Control Event)............**0.8**
Pev2 (Probability of a Treatment Event) **Pev1**
HR0 (Non-Inferiority Hazard Ratio)................**2**
HR1 (Actual Hazard Ratio) **1.36**
ρ (Intracluster Correlation) **0.05**

Output

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

Numeric Results
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Solve For: Number of Clusters
Higher Hazards Are: Worse
Groups: 1 = Control, 2 = Treatment
Hypotheses: H0: HR ≥ HR0   vs.   H1: HR < HR0
_____

| | | | | Cluster Size | | | Hazard Ratio | | | |
Group	Power	Sample Size Ni	Number of Events Ei	Number of Clusters Ki	Average Mi	COV	Probability of an Event Pevi	Non-Inferiority HR0	Actual HR1	Intracluster Correlation ρ	Alpha
1: Control		128	125.8	31	4.1	0.6	0.8			0.05	
2: Treatment	0.80083	128	125.8	31	4.1	0.6	0.8	2	1.36	0.05	0.05
Total		256	251.7	62							
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PASS also calculates K1 = K2 = 31 which validates the procedure.