Chapter 345

Multi-Arm Superiority by a Margin Tests for Treatment and Control Survival Curves using Cox's Proportional Hazards Model

Introduction

This module computes power and sample size for multiple superiority by a margin comparisons of treatment survival curves versus a control survival curve based on the results in Machin, Campbell, Tan, and Tan (2018). In this design, there are k treatment groups and one control group. A survival curve is measured in each group. A total of k superiority by a margin hypothesis tests are anticipated, each comparing a treatment group with the common control group using a simple z-test based on a Cox proportional hazards regression coefficient.

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.

A Bonferroni adjustment of the type I error rate may be optionally made because several comparisons are being tested using the same data. Making a multiplicity adjustment is usually recommended, but not always. In fact, Saville (1990) advocates not applying it and Machin, Campbell, Tan, and Tan (2018) include omitting it as a possibility.

Background

Whether you want to test several doses of a single treatment or several types of treatments, good research practice requires that each treatment be compared with a control. For example, a popular three-arm design consists of three groups: control, treatment A, and treatment B. Two tests are run: treatment A versus control and treatment B versus the same control. This avoids having to obtain a second control group for treatment B. Besides the obvious efficiency in subjects, it may be easier to recruit subjects if their chances of receiving the new treatment are better than 50-50.

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, $h(t|1)/h(t|0)$

Clinical Superiority Hypothesis

Lower Hazards Better

Assuming that lower hazard rates are better, clinical superiority means that the treatment hazard rate is lower than the control hazard rate by a clinically significant amount. 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 $HR_0 < 1$, clinical superiority requires that $HR < HR_0$. Here, HR_0 is the ratio of clinical insignificance or the clinical superiority ratio.

The statistical hypotheses that results in the conclusion of clinical superiority when the null hypothesis is rejected is

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

Higher Hazards Better

Assuming that higher hazard rates are better, clinical superiority means that the treatment hazard rate is higher than the control hazard rate by a clinically significant amount. 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 $HR_0 > 1$, clinical superiority requires that $HR > HR_0$. Here, HR_0 is called clinical superiority.

The statistical hypotheses that results in the conclusion of clinical superiority when the null hypothesis is rejected is

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

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 clinical superiority boundary (limit) of the hazard ratio

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.

Testing Multiple Treatment Groups versus a Single Control Group

Suppose you have k treatment groups with samples of size N_i and one control group with a sample of size N_C. The total sample size is $N = N_1 + N_2 + ... + N_k + N_C$. The response for each subject is their survival time until they either exhibit the event of interest or they are censored from the study.

A Cox proportional hazards regression model is fit to the data in which one of the independent variables is a binary variable that is zero if the subject is from the control group or one if they are from the ith treatment group. Suppose that the regression coefficient associated with this independent variable is called b_i. As pointed out above, it turns out that

$$b_i = \log(HR_i)$$

where HR_i is the hazard ratio comparing the treatment and control groups. If HR_i = 1, there is no difference between the groups.

The data may be analyzed using k separate regressions each producing a superiority test of the hazard ratio comparing a treatment group to the common control group.

The power for each of the k tests can be computed using the formula given above.

Multiplicity Adjustment

Because k z-tests between treatment groups and the control group are run when analyzing the results of this study, many statisticians recommend that the Bonferroni adjustment be applied. This adjustment is easy to apply: the value of alpha that is used in the test is found by dividing the original alpha by the number of tests. For example, if the original alpha is set at 0.05 and the number of treatment (not including the control) groups is five, the individual tests will be conducted using an alpha of 0.01.

The main criticism of this procedure is that if there are many tests, the value of alpha becomes very small. To mitigate against this complaint, some statisticians recommend separating the treatment groups into those that are of primary interest and those that are of secondary interest. The Bonferroni adjustment is made by the using the number of primary treatments rather than the total number of treatments.

There are some who advocate ignoring the adjustment entirely in the case of randomized clinical trials. See for example Saville (1990) and the discussion in chapter 14 of Machin, Campbell, Tan, and Tan (2018).

Size of the Control Group

Because the control group is used over and over, some advocate increasing the number of subjects in this group. The standard adjustment is to include $\sqrt{k}$ subjects in the control group for each subject in one of the treatment groups. See Machin, Campbell, Tan, and Tan (2018, pages 231-232). Note that often, the treatment groups all have the same size.

Example 1 – Finding the Sample Size

A parallel-group, superiority trial is being designed to compare the survivability associated with three doses of a test compound against the standard (control) therapy in patients with a specific type of disease.

The proportion surviving one-year after the current treatment is 0.50 ($h_c = 0.693$). The researchers want to determine the sample size necessary to detect the situation when the proportion surviving one-year after the new treatment is 0.75 ($h_t = 0.288$). Hence, they want to compute the power when

$$HR = 0.288/0.693 = 0.4156$$

The superiority hazard ratio is 0.8. The researchers would like to study the influence of *HR* on the sample size, so they would like to look at a range of possible values: 0.4 to 0.7.

For planning purposes, they decide that the probability of an event is 0.50 in the control group and 0.25 in the three treatment groups. The researchers decide use a 0.025 significance level and a power of 0.8.

Following standard procedure, the control group multiplier will be set to $\sqrt{k} = \sqrt{3} = 1.732$ since the control group is used for three comparisons in this design.

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**	
Higher Hazards Are ....**Worse (H1: HR < HR0)**	
Power of Each Test **0.80**	
Overall Alpha **0.025**	
Bonferroni Adjustment ....**Standard Bonferroni**	
Group Allocation ....**Enter Group Allocation Pattern, solve for group sample sizes**	
Pev (Default Probability of an Event) **0.75**	
HR0 (Superiority Hazard Ratio) **0.8**	
Control Probability of an Event **0.5**	
Control Sample Size Allocation......................**1.732**	
Set A Number of Groups................................**3**	
Set A Hazard Ratio **0.4 0.5 0.6 0.7**	
Set A Probability of an Event **0.25**	
Set A Sample Size Allocation **1**	
Set B Number of Groups................................**0**	
Set C Number of Groups **0**	
Set D Number of Groups **0**	
More...**Unchecked**	

Output

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

Numeric Reports

Numeric Results

Solve For: Sample Size
Group Allocation: Enter Group Allocation Pattern, solve for group sample sizes
Test Type: Z-Test Based on the Log Hazard Ratio
Hypotheses: H0: HR ≥ HR0 vs. H1: HR < HR0
Number of Groups: 4
Bonferroni Adjustment: Standard Bonferroni (Divisor = 3)

| | Power | | Sample Size | | Events | Hazard Ratio | | Probability | Alpha | |
| | | | | | | | | of an Event | | |
Comparison	Target	Actual	Ni	Allocation	Ei	Actual HRi	Superiority HR0	Pevi	Overall	Bonferroni-Adjusted
Control			147	1.732	73.5			0.50		
vs A1	0.8	0.80424	85	1.000	21.3	0.4	0.8	0.25	0.025	0.00833
vs A2	0.8	0.80424	85	1.000	21.3	0.4	0.8	0.25	0.025	0.00833
vs A3	0.8	0.80424	85	1.000	21.3	0.4	0.8	0.25	0.025	0.00833
Total			402		137.3					
Control			317	1.732	158.5			0.50		
vs A1	0.8	0.80003	183	1.000	45.8	0.5	0.8	0.25	0.025	0.00833
vs A2	0.8	0.80003	183	1.000	45.8	0.5	0.8	0.25	0.025	0.00833
vs A3	0.8	0.80003	183	1.000	45.8	0.5	0.8	0.25	0.025	0.00833
Total			866		295.8					
Control			847	1.732	423.5			0.50		
vs A1	0.8	0.80051	489	1.000	122.3	0.6	0.8	0.25	0.025	0.00833
vs A2	0.8	0.80051	489	1.000	122.3	0.6	0.8	0.25	0.025	0.00833
vs A3	0.8	0.80051	489	1.000	122.3	0.6	0.8	0.25	0.025	0.00833
Total			2314		790.3					
Control			3928	1.732	1964.0			0.50		
vs A1	0.8	0.80015	2268	1.000	567.0	0.7	0.8	0.25	0.025	0.00833
vs A2	0.8	0.80015	2268	1.000	567.0	0.7	0.8	0.25	0.025	0.00833
vs A3	0.8	0.80015	2268	1.000	567.0	0.7	0.8	0.25	0.025	0.00833
Total			10732		3665.0					

Comparison The group that is involved in the comparison between the treatment and control displayed on this report line. The comparison is made using the hazard ratio.

Target Power The power desired. Power is probability of rejecting a false null hypothesis for this comparison. This power is of the comparison shown on this line only.

Actual Power The power actually achieved.

Ni The number of subjects in the ith group. The total sample size shown below the groups is equal to the sum of all individual group sample sizes.

Allocation The group sample size allocation ratio of the ith group. The value on each row represents the relative number of subjects assigned to the group.

Ei The number of events in the ith group required to achieve the power indicated. $E_i = P_{ev_i} \times N_i$.

HRi The hazard ratio of the ith treatment group. $HR = h_i / h_c$.

HR0 The superiority hazard ratio boundary used to declare whether a treatment is superior to the control.

Pevi The average probability that a subject the ith group will have an event during the study. Pevi also represents the proportion of individuals in the ith group that are expected to have an event during the study. This probability includes the impact of various kinds of censoring.

Overall Alpha The probability of rejecting at least one of the comparisons in this experiment when each null hypothesis is true.

Bonferroni Alpha The adjusted significance level at which each individual comparison is made.

Summary Statements
──
A parallel, 4-group design (with one control group and 3 treatment groups) will be used to test whether the hazard rate for each treatment group is superior to the control group hazard rate by a margin, with a superiority hazard ratio of 0.8 (H0: HR ≥ 0.8 versus H1: HR < 0.8, HR = treatment hazard rate i / control hazard rate). In this study, higher hazard rates are considered to be worse. The superiority-by-a-margin hypotheses will be evaluated using 3 one-sided, two-sample, Bonferroni-adjusted, Cox's proportional hazards regression term Z-tests, with an overall (experiment-wise) Type I error rate (α) of 0.025. It is anticipated that the proportions of subjects in each group that will have an event during the course of the study (beginning with the control group) will be 0.5, 0.25, 0.25, and 0.25. To detect the treatment to control hazard ratios 0.4, 0.4, and 0.4 with at least 80% power for each test, the control group sample size needed will be 147 and the number of needed subjects for the treatment groups will be 85, 85, and 85 (totaling 402 subjects overall). The corresponding total number of events is 137.3. These results assume that the hazard ratios are constant throughout the study.
──

References
──
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.
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.
──

This report shows the numeric results of this power study. Notice that the results are shown in blocks of three rows at a time. Each block represents a single design.

Plots Section

Plots

_____
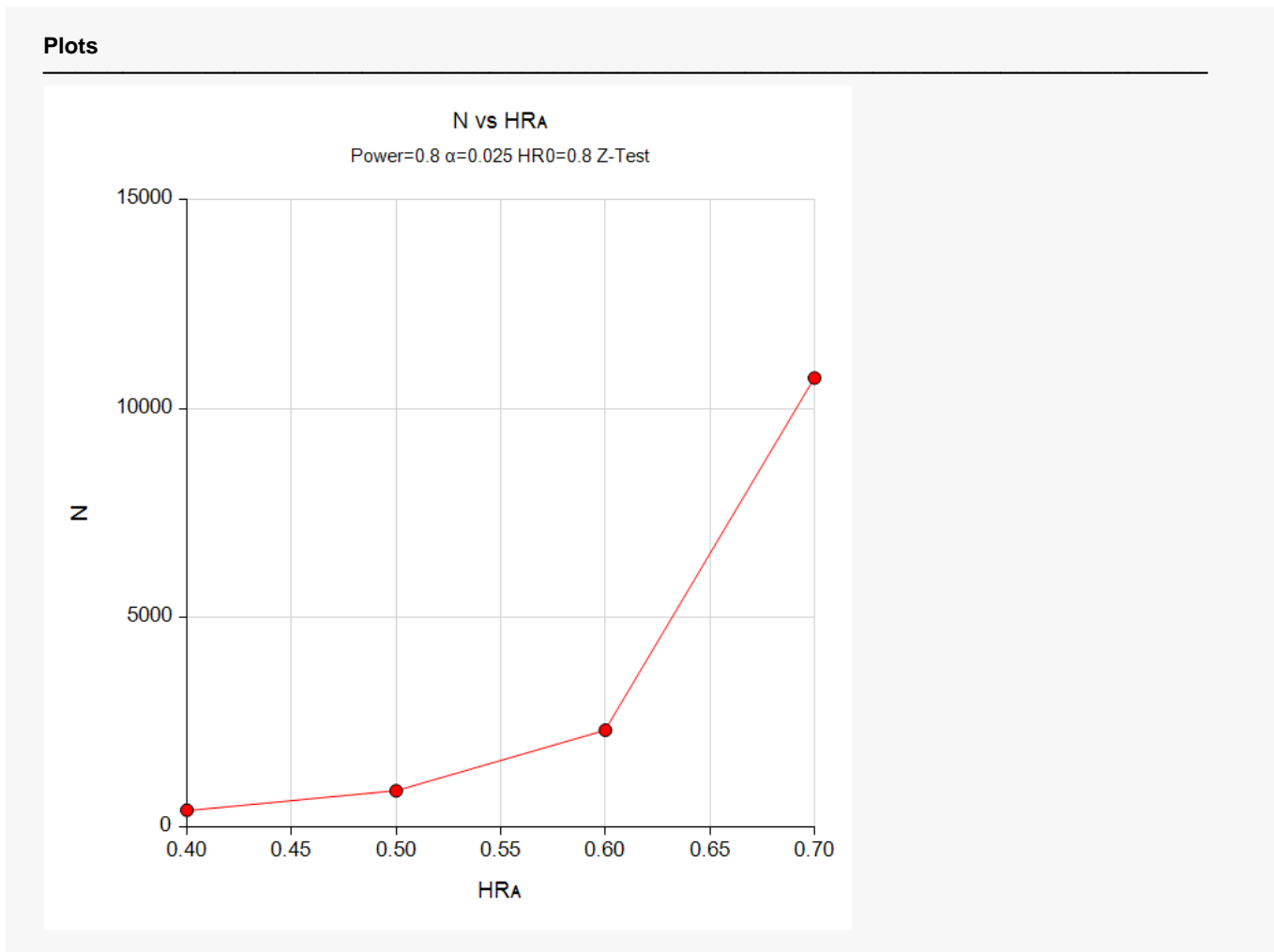
This plot gives a visual presentation to the results in the Numeric Report. We can quickly see the impact on the sample size of changing the hazard ratio from 0.4 to 0.7.

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 (**Superiority by a Margin Tests for Two Survival Curves Using Cox's Proportional Hazards Model**) to produce the results for the following example.

A parallel-group clinical trial is being designed to compare the survivability induced by three doses of a test compound against the standard (control) therapy in patients with a specific type of disease.

The hazard ratio for the power calculation is set to 0.6.

For planning purposes, they decide that the probability of an event is 0.50 in the control group and 0.25 in the three treatment groups. The researchers decide on a 0.025 significance level and a power of 0.8. Since a Bonferroni adjustment is made, the significance level is reduced to 0.025 / 3 = 0.00833.

The sample sizes of all groups will be equal.

The **Superiority by a Margin 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...**0.8**
Alpha..**0.008333** (which is Alpha / k)
Group Allocation ....**Equal (N1 = N2)**
Pev1 (Event Probability in Group 1)...............**0.5**
Pev2 (Event Probability in Group 2)...............**0.25**
HR1 (Actual Hazard Ratio) **0.6**
HR0 (Superiority Hazard Ratio) **0.8**

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
_____

	Sample Size			Percent Group 1 %N1	Number of Events			Hazard Ratio		Event Probability		
Power	N	N1	N2		E	E1	E2	Superiority HR0	Actual HR1	Pev1	Pev2	Alpha
0.80023	1350	675	675	50	506.3	337.5	168.8	0.8	0.6	0.5	0.25	0.00833

In order to maintain a power of 80% for all three groups, it is apparent that the groups will all need to have a sample size of 675 per group. This table contains the validation values. We will now run these values through the current procedure and compare the results with these values.

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**

Higher Hazards Are ....**Worse (H1: HR < HR0)**

Power of Each Test **0.80**

Overall Alpha **0.025**

Bonferroni Adjustment ....**Standard Bonferroni**

Group Allocation ....**Equal (Nc = N1 = N2 = ...)**

Pev (Default Probability of an Event) **0.75**

HR0 (Superiority Hazard Ratio) **0.8**

Control Probability of an Event **0.5**

Set A Number of Groups...............................**3**

Set A Hazard Ratio **0.6**

Set A Probability of an Event **0.25**

Set B Number of Groups...............................**0**

Set C Number of Groups **0**

Set D Number of Groups **0**

More...**Unchecked**

Output

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

Numeric Results

Solve For: Sample Size
Group Allocation: Equal (Nc = N1 = N2 = ...)
Test Type: Z-Test Based on the Log Hazard Ratio
Hypotheses: H0: HR ≥ HR0   vs.   H1: HR < HR0
Number of Groups: 4
Bonferroni Adjustment: Standard Bonferroni (Divisor = 3)

| | Power | | Sample Size | Events | Hazard Ratio | | Probability of an Event | Alpha | |
Comparison	Target	Actual	Ni	Ei	Actual HRi	Superiority HR0	Pevi	Overall	Bonferroni-Adjusted
Control			675	337.5			0.50		
vs A1	0.8	0.80023	675	168.8	0.6	0.8	0.25	0.025	0.00833
vs A2	0.8	0.80023	675	168.8	0.6	0.8	0.25	0.025	0.00833
vs A3	0.8	0.80023	675	168.8	0.6	0.8	0.25	0.025	0.00833
Total			2700	843.8					

As you can see, the sample sizes are all 675. This matches the sample size found in the validation run above. The procedure is validated.