Chapter 350

Multi-Arm Superiority by a Margin Tests for Vaccine Efficacy using Treatment vs. Control Hazard Ratios (Cox's Proportional Hazards Model)

Introduction

This module computes power and sample size for multiple superiority by a margin tests for vaccine efficacy (VE) of treatment versus control survival curves (or logrank tests). VE is a traditional index of the protective efficacy of a vaccine. It is calculated as

$$VE_i = 1 - \frac{h_i}{h_C} = 1 - HR_i$$

where h_i and h_C are hazard rates of the disease being studied among those vaccinated and those not vaccinated. Hence, an analysis of vaccine effectiveness reduces to an analysis of the hazard ratio.

This multiple comparison procedure is 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 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.

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.

Multi-Arm Sup. by a Margin Tests for Vaccine Efficacy using Treat. vs. Control Hazard Ratios (Cox's Prop. Hazards Model)

Relative Vaccine Efficacy

Often, the goal of the study is to show that the attack rate of a new vaccine is better than that of the current standard vaccine. The trial is conducted to show that the new vaccine is an attractive replacement for the standard vaccine because it is better by a non-trivial amount. In this case, the control group does not receive a placebo. Rather, it receives the standard vaccine. In this case, the quantity of interest is called the *relative vaccine efficacy (rVE)*. It is calculated as

$$rVE_i = 1 - \frac{h_i}{h_C} = 1 - HR_i$$

Technical Details

Suppose you have k treatment groups with hazard ratios HR_i of size N_i and one control group with size N_c . The total sample size is $N = N_1 + N_2 + ... + N_k + N_c$.

Assuming that lower hazard rates are better, superiority means that the treatment hazard rate is at least a non-trivial amount lower than the control hazard rate. We may 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 $HR_0 < 1$, superiority requires that $HR < HR_0$. Here, HR_0 is the boundary of clinical insignificance or the superiority boundary.

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

$$H_0: \log(HR) \ge \log(HR_0)$$
 vs. $H_a: \log(HR) < \log(HR_0)$

The k one-sided superiority tests are

$$H_{0i}: VE_i \leq VE_0$$
 vs. $H_{1i}: VE_i > VE_0$ for $i = 1, 2, ..., k$

Note that if lower hazard rates are better, as is usually the case when the studying disease prevention, $VE_0 < 1$.

For convenience, these hypotheses are collectively referred to as

$$H_0: VE \leq VE_0$$
 vs. $H_1: VE > VE_0$

These hypotheses may be restated in terms of hazard ratios as

$$H_0: HR \ge HR_0$$
 vs. $H_1: HR < HR_0$

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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

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

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

Logrank Test

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.

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 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 $(\log(HR) - \log(HR_0))\sqrt{P_1P_2dN}$ 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, $N_2 = N(P_2)$

Pev₁ is probability of the event of interest in the control group

Pev₂ is probability of the event of interest in the treatment group

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

HR is the observed hazard ratio

 HR_0 is the clinical superiority boundary (limit) of the hazard ratio

Multi-Arm Sup. by a Margin Tests for Vaccine Efficacy using Treat. vs. Control Hazard Ratios (Cox's Prop. Hazards Model)

Power Calculations

The power of this test is given by

$$\Phi\left(\left(\log(HR_1)-\log(HR_0)\right)\sqrt{P_1P_2dN}-z_{1-\alpha}\right)$$

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 i^{th} 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).

Multi-Arm Sup. by a Margin Tests for Vaccine Efficacy using Treat. vs. Control Hazard Ratios (Cox's Prop. Hazards Model)

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.

Suppose the superiority hazard ratio is set at 0.80. Hence its superiority vaccine efficacy is 0.20. The researchers want to determine the sample size necessary to detect the situation when the vaccine efficacy of any of the new treatment increases to 0.40. This equates to a hazard ratio of 0.60 for all three treatments.

The researchers would like to study the influence of the value of *HR* on the sample size, so they would like to look at a range of possible values: 0.5 to 0.7. For planning purposes, they decide that the probability of an event is 0.75 in all groups. The researchers decide to 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.

Solve For	Sample Size
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	Pev
Control Sample Size Allocation	1.732
Set A Number of Groups	3
Set A Hazard Ratio	0.5 0.6 0.7
Set A Probability of an Event	Pev
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

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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 Cox Proportional Hazards Regression

Hypotheses: H0: $VE \le VE0$ vs. H1: VE > VE0 or H0: $HR \ge HR0$ vs. H1: HR < HR0

Number of Groups: 4

Bonferroni Adjustment: Standard Bonferroni (Divisor = 3)

	р.	Power		Sample Size		Vaccine Efficacy		Hazard Ratio		Doob ob ilitor	Alpha	
Comparison				Allocation	Events Ei	Superiority VE0	Actual VEi	Superiority HR0	Actual HRi	Probability of an Event Pevi	Overall	Bonferroni- Adjusted
Control			173	1.732	129.8					0.75		
vs A1	0.8	0.80129	100	1.000	75.0	0.2	0.5	0.8	0.5	0.75	0.025	0.00833
vs A2		0.80129	100	1.000	75.0	0.2	0.5	0.8	0.5	0.75	0.025	0.00833
vs A3		0.80129	100	1.000	75.0	0.2	0.5	0.8	0.5	0.75	0.025	0.00833
Total			473		354.8							
Control			461	1.732	345.8					0.75		
vs A1	0.8	0.80003	266	1.000	199.5	0.2	0.4	0.8	0.6	0.75	0.025	0.00833
vs A2	0.8	0.80003	266	1.000	199.5	0.2	0.4	0.8	0.6	0.75	0.025	0.00833
vs A3 Total	8.0	0.80003	266 1259	1.000	199.5 944.3	0.2	0.4	0.8	0.6	0.75	0.025	0.00833
Control			2139	1.732	1604.3					0.75		
vs A1	0.8	0.80005		1.000	926.3	0.2	0.3	0.8	0.7	0.75	0.025	0.00833
vs A2		0.80005		1.000	926.3	0.2	0.3	0.8	0.7	0.75	0.025	0.00833
vs A3		0.80005		1.000	926.3	0.2	0.3	0.8	0.7	0.75	0.025	0.00833
Total			5844		4383.0							
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Multi-Arm Sup. by a Margin Tests for Vaccine Efficacy using Treat. vs. Control Hazard Ratios (Cox's Prop. Hazards Model)

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 (hi) is superior to the control group hazard rate (hc) by a margin, with a superiority hazard ratio limit of 0.8 (H0: HR \geq 0.8 versus H1: HR < 0.8, HR = hi / hc), or, equivalently, whether the vaccine efficacy for each treatment group (VEi = 1 - hi / hc) is superior by a margin, with a superiority vaccine efficacy limit of 0.2 (H0: VE \leq 0.2 versus H1: VE > 0.2). In this study, lower hazard rates are considered to be better. 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 0.75, 0.75, 0.75, and 0.75. To detect the treatment to control hazard ratios 0.5, 0.5, and 0.5 with at least 80% power for each test, the control group sample size needed will be 173 and the number of needed subjects for the treatment groups will be 100, 100, and 100 (totaling 473 subjects overall). The corresponding total number of events is 354.8. The treatment vaccine efficacies that correspond to the detectable hazard ratios 0.5, 0.5, and 0.5 are 0.5, 0.5, and 0.5. 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.

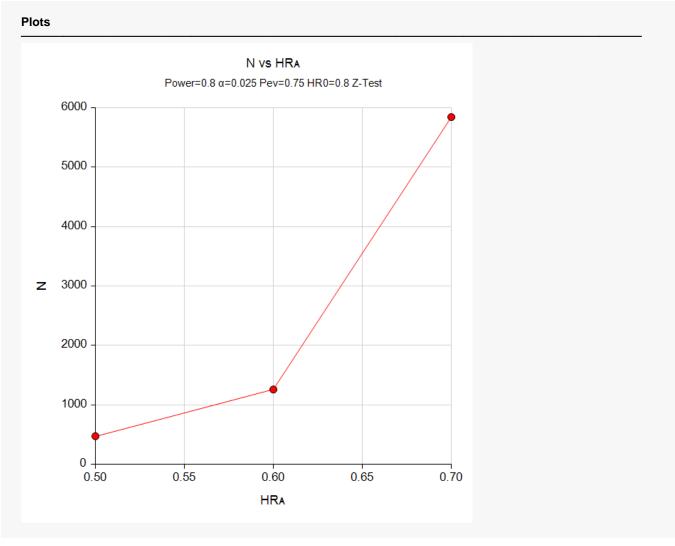
Schoenfeld, David A. 1983. 'Sample Size Formula for the Proportional-Hazards Regression Model', Biometrics, Volume 39, Pages 499-503.

Nauta, Jozef. 2020. Statistics in Clinical and Observational Vaccine Studies, 2nd Edition. Springer. Cham, Switzerland.

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.

Multi-Arm Sup. by a Margin Tests for Vaccine Efficacy using Treat. vs. Control Hazard Ratios (Cox's Prop. Hazards Model)

Plots Section



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 0.9 to 1.0.

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 Vaccine Efficacy Using the Hazard Ratio (Cox's Proportional Hazards Model)) to produce the results for the following example.

Suppose the superiority hazard ratio is set at 0.80. Hence its superiority vaccine efficacy is 0.20. The researchers want to determine the sample size necessary to detect the situation when the vaccine efficacy of any of the new treatment increases to 0.40. This equates to a hazard ratio of 0.60 for all three treatments.

For planning purposes, they decide that the probability of an event is 0.75 in all groups. The researchers decide to use a 0.025/3 = 0.00833 significance level and a power of 0.8.

The sample sizes of all groups will be equal.

The Superiority by a Margin Tests for Vaccine Efficacy Using the Hazard Ratio (Cox's Proportional Hazards Model) procedure is set up as follows

Solve For	Sample Size
Higher Hazards Are	Worse (H1: VE > VE0 or HR < HR0)
Power	0.8
Alpha	0.00833 (which is Alpha / k)
Group Allocation	Equal (N1 = N2)
Pev1 (Event Probability in Group 1)	0.75
Pev2 (Event Probability in Group 2)	0.75
Vaccine Efficacy Input Type	Hazard Ratios
HR1 (Actual Hazard Ratio)	0.6
HR0 (Superiority Hazard Ratio)	0.8

This set of options generates the following report.

Solve For Groups: Higher Ha Hypothes	azards <i>l</i>	1 Are: W	/orse	Size ol, 2 = Tre VE0 vs.		> VE0							
							Vacci	ne Efficacy	Haz	ard Ratio		ent	
	9.	mnla S	izo	Mun	hor of E	ionte							
	Sa	ample S	ize	Num	ber of E	ents	Actual	Superiority	Actual	Superiority	Prob	ability	
Power	N1	Mple S	Size N	Nun E1	iber of Ev E2	ents E	Actual VE1	Superiority VE0	Actual HR1	Superiority HR0	Prob Pev1	Pev2	Alpha

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 338 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.

Multi-Arm Sup. by a Margin Tests for Vaccine Efficacy using Treat. vs. Control Hazard Ratios (Cox's Prop. Hazards Model)

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.

Solve For	Sample Size
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	Pev
Set A Number of Groups	3
Set A Hazard Ratio	0.6
Set A Probability of an Event	Pev
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.

Solve For: Sample Size Group Allocation: Equal (Nc = N1 = N2 =) Test Type: Z-Test Based on Cox Proportional Hazards Regression Hypotheses: H0: $VE \le VE0$ vs. H1: $VE > VE0$ or H0: $HR \ge HR0$ vs. H1: $HR < HR0$ Number of Groups: 4 Bonferroni Adjustment: Standard Bonferroni (Divisor = 3)											
	D-		Comple		Vaccine Efficacy		Hazard Ratio		Deel elite	Alpha	
Comparison		wer Actual	Sample Size Ni	Events Ei	Superiority VE0	Actual VEi	Superiority HR0	Actual HRi	Probability of an Event Pevi	Overall	Bonferroni- Adjusted
Control			338	253.5					0.75		
vs A1	0.8	0.8009	338	253.5	0.2	0.4	0.8	0.6	0.75	0.025	0.00833
vs A2	0.8	0.8009	338	253.5	0.2	0.4	0.8	0.6	0.75	0.025	0.00833
vs A3	0.8	0.8009	338	253.5	0.2	0.4	0.8	0.6	0.75	0.025	0.00833
Total			1352	1014.0							

As you can see, the sample sizes are all 338. This matches the sample size found in the validation run above. The procedure is validated.