Chapter 734

Superiority by a Margin Tests for Vaccine Efficacy using the Hazard Ratio (Cox's Proportional Hazards Model)

Introduction

This module provides power analysis and sample size calculation for superiority by a margin tests for vaccine efficacy (VE) using the hazard ratio as measured by Cox regression. VE is a traditional index of the protective efficacy of a vaccine. It is calculated as

$$VE = 1 - \frac{h_2}{h_1} = 1 - HR$$

where h_1 and h_2 are *hazard rates* of the disease being studied among those vaccinated (group 2) and those not vaccinated (group 1). Hence, an analysis of vaccine effectiveness reduces to an analysis of the hazard ratio of two hazard rates. Note that usually, $h_2 < h_1$, so the value of $VE < 1$.

A clinical trial may be employed to test the clinical superiority of a treatment over a control with regards to their vaccine efficacy. Cox proportional-hazards regression is often used to analyze the resulting 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, and Wang (2008) which summarizes the work of Schoenfeld (1981, 1983).

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

$$rVE = 1 - \frac{h_2}{h_1} = 1 - HR$$

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 result in the conclusion of clinical superiority when the null hypothesis is rejected is

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

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 result in the conclusion of clinical superiority when the null hypothesis is rejected is

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

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. When testing superiority by a margin, you can use b from a Cox regression or calculate the modified logrank statistic as follows

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 $(\log(HR) - \log(HR_0))\sqrt{P_1 P_2 dN}$ 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

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

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

These results are easily written in terms of vaccine efficacy since $VE = 1 - HR$.

Example 1 – Finding the Sample Size

A researcher is planning a clinical superiority trial using a parallel, two-group, equal sample allocation design to compare the survivability of a new treatment with that of the current treatment using vaccine efficacy. The clinical superiority boundary is VE0 = 0.4. The desired power is 0.80 and significance level is 0.025. VE1 will be values between 0.5 and 0.8. The probability of observing an event is estimated at 0.05 in the control group and 0.030 in the treatment group.

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: VE > VE0 or HR < HR0)**
Power..**0.8**
Alpha...**0.025**
Group Allocation ....**Equal (N1 = N2)**
Pev1 (Event Probability in Group 1)...............**0.05**
Pev2 (Event Probability in Group 2)...............**0.03**
Vaccine Efficacy Input Type...........................**Vaccine Efficacies**
VE1 (Actual Vaccine Efficacy) **0.5 0.6 0.7 0.8**
VE0 (Superiority Vaccine Efficacy) **0.4**

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
Higher Hazards Are: Worse
Hypotheses: H0: VE ≤ VE0   vs.   H1: VE > VE0

	Sample Size			Number of Events			Vaccine Efficacy		Hazard Ratio		Event Probability		
Power	N1	N2	N	E1	E2	E	Actual VE1	Superiority VE0	Actual HR1	Superiority HR0	Pev1	Pev2	Alpha
0.80000	11806	11806	23612	590.3	354.2	944.5	0.5	0.4	0.5	0.6	0.05	0.03	0.025
0.80005	2387	2388	4775	119.4	71.6	191.0	0.6	0.4	0.4	0.6	0.05	0.03	0.025
0.80009	817	817	1634	40.9	24.5	65.4	0.7	0.4	0.3	0.6	0.05	0.03	0.025
0.80027	325	326	651	16.3	9.8	26.0	0.8	0.4	0.2	0.6	0.05	0.03	0.025

|	
Power	The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N1, N2, and N	The sample sizes of the control, the treatment, and both groups, respectively.
E1, E2, and E	The number of events required in the control, the treatment, and both groups, respectively.
HR	The hazard ratio (treatment/control). HR = h2/h1.
VE	The vaccine efficacy. VE = 1 - HR.
VE1	The actual vaccine efficacy at which power is calculated.
VE0	The superiority by a margin vaccine efficacy boundary.
HR1	The actual hazard ratio at which power is calculated.
HR0	The superiority by a margin hazard ratio boundary.
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 (where higher hazard rates are considered worse) will be used to test whether the Group 2 (treatment) hazard rate is superior to the Group 1 (control) hazard rate by a margin, with a superiority vaccine efficacy of 0.4 (or hazard ratio of 0.6) (H0: VE ≤ 0.4 versus H1: VE > 0.4, VE = 1 - h2 / h1). The comparison will be made using a one-sided, two-sample Cox proportional hazards regression test (or equivalent non-inferiority logrank test) with a Type I error rate (α) of 0.025. It is anticipated that the probability of observing an event during the course of the study is 0.05 for each member of the control group and 0.03 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 vaccine efficacy (1 - h2 / h1) of 0.5 (or hazard ratio of 0.5) with 80% power, the number of needed subjects will be 11806 in Group 1 and 11806 in Group 2 (totaling 23612 subjects). The corresponding required number of events is 590.3 in Group 1 and 354.2 in Group 2 (totaling 944.5 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.
Nauta, Jozef. 2020. Statistics in Clinical and Observational Vaccine Studies, 2nd Edition. Springer. Cham, Switzerland.

These reports show the values of each of the parameters, one scenario per row.

Plots Section
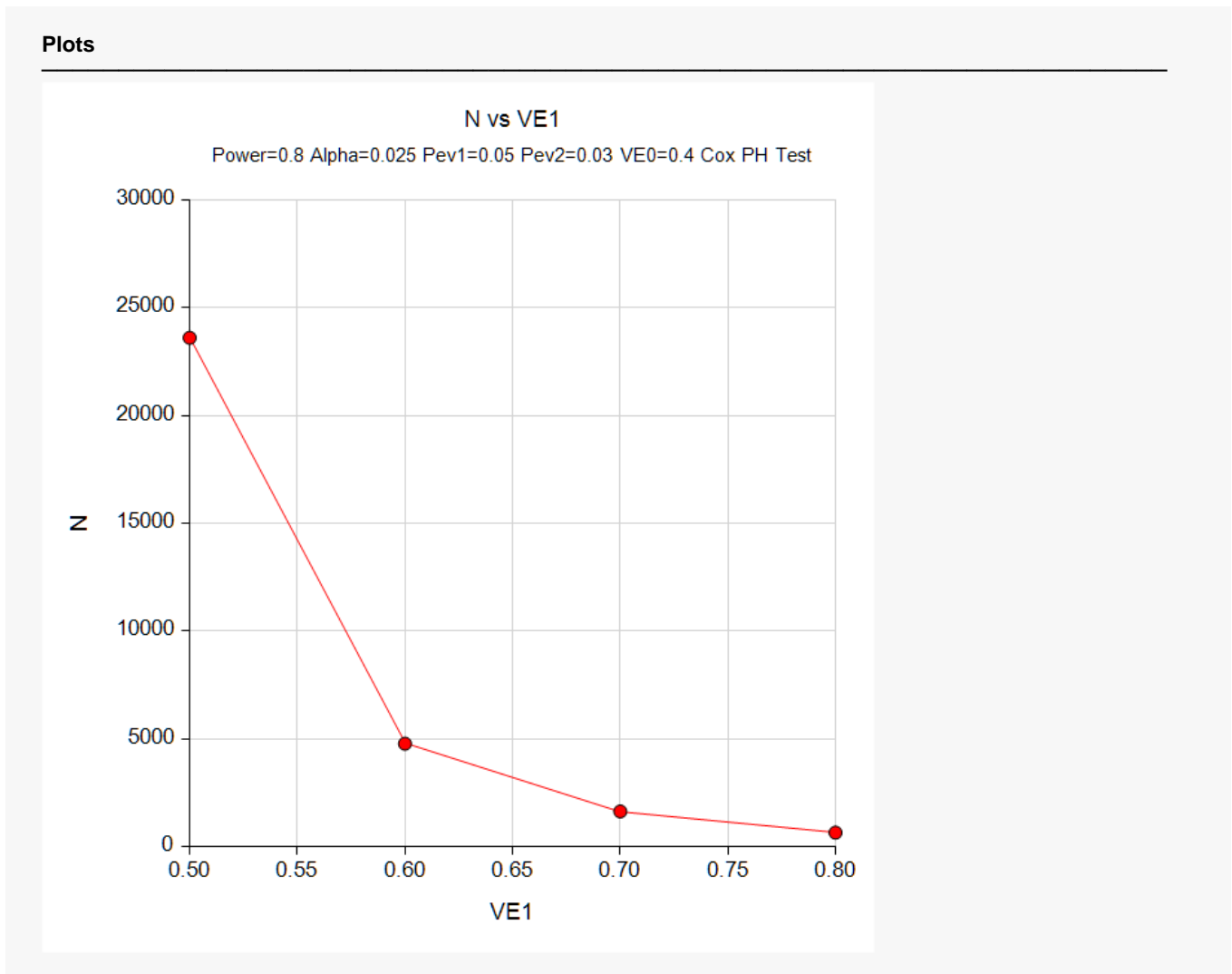
Plots

This plot shows the relationship between VE and N.

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

Chow et al. (2008) page 179 presents an example that we will use for validation. In their example, HR1 = 2, HR0 = 1.35, Pev1 = Pev2 = 0.8, alpha = 0.05, and power = 0.8. They obtained a sample size of 100 per group.

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 ....**Better (H1: VE < VE0 or HR > HR0)**	
Power..**0.8**	
Alpha...**0.05**	
Group Allocation ....**Equal (N1 = N2)**	
Pev1 (Event Probability in Group 1)...............**0.8**	
Pev2 (Event Probability in Group 2)...............**0.8**	
Vaccine Efficacy Input Type...........................**Hazard Ratios**	
HR1 (Actual Hazard Ratio) **2**	
HR0 (Superiority Hazard Ratio) **1.35**	

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
Higher Hazards Are: Better
Hypotheses: H0: VE ≥ VE0   vs.   H1: VE < VE0

	Sample Size			Number of Events			Vaccine Efficacy		Hazard Ratio		Event Probability		
Power	N1	N2	N	E1	E2	E	Actual VE1	Superiority VE0	Actual HR1	Superiority HR0	Pev1	Pev2	Alpha
0.80154	100	101	201	80	80.8	160.8	-1	-0.35	2	1.35	0.8	0.8	0.05

PASS has calculated the value of N = 201. It turns out that the exact power at N1 = N2 = 100 is slightly less than 0.8, so N2 has been increased to 101.