

Chapter 735

Non-Inferiority Tests for Vaccine Efficacy using the Hazard Ratio (Cox's Proportional Hazards Model)

Introduction

This module provides power analysis and sample size calculation for non-inferiority 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 non-inferiority 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).

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 Non-Inferiority Hypothesis

Lower Hazards Better

Assuming that lower hazard rates are better, clinical non-inferiority 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 non-inferiority requires that $HR < HR_0$. Here, HR_0 is the ratio of clinical insignificance or the clinical non-inferiority ratio.

The statistical hypotheses that result in the conclusion of clinical non-inferiority 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 non-inferiority 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 non-inferiority requires that $HR > HR_0$. Here, HR_0 is called clinical non-inferiority.

The statistical hypotheses that result in the conclusion of clinical non-inferiority 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 non-inferiority, 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 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, $N_2 = N(P_2)$

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 this test is given by

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

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 non-inferiority 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 non-inferiority boundary is $VE_0 = -0.2$ (which corresponds to $HR_0 = 1.2$). VE_1 will be values between 0 and 0.5. The probability of observing an event is estimated at 0.5 in the control group and 0.30 in the treatment group. The desired power is 0.90 and significance level is 0.025.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the procedure window. You may then make the appropriate entries as listed below or open

Example 1 by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
Design Tab	
Solve For	Sample Size
Higher Hazards Are	Worse (H1: VE > VE0 or HR < HR0)
Power.....	0.9
Alpha.....	0.025
Group Allocation	Equal (N1 = N2)
Pev1 (Event Probability in Group 1)	0.5
Pev2 (Event Probability in Group 2)	0.3
Vaccine Efficacy Input Type	Vaccine Efficacies
VE1 (Actual Vaccine Efficacy)	0 to 0.5 by 0.1
VE0 (Non-Inferiority Vaccine Efficacy)	-0.2

Annotated Output

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

Numeric Results

Numeric Results

Higher Hazards are: Worse
Hypotheses: H0: $VE \geq VE_0$ vs. H1: $VE < VE_0$

Power	Sample Size			Events		Vaccine Efficacy		Hazard Ratio		Event Prob		Alpha
	Cntl	Trt	Total	Cntl	Trt	Act	N.I.	Act	N.I.	Cntl	Trt	
	N1	N2	N	E1	E2	VE1	VE0	HR1	HR0	Pev1	Pev2	
0.90009	1581	1581	3162	790.5	474.3	0.0	-0.2	1.0	1.2	0.5	0.3	0.025
0.90009	635	635	1270	317.5	190.5	0.1	-0.2	0.9	1.2	0.5	0.3	0.025
0.90039	320	320	640	160.0	96.0	0.2	-0.2	0.8	1.2	0.5	0.3	0.025
0.90025	181	181	362	90.5	54.3	0.3	-0.2	0.7	1.2	0.5	0.3	0.025
0.90006	109	110	219	54.5	33.0	0.4	-0.2	0.6	1.2	0.5	0.3	0.025
0.90187	69	69	138	34.5	20.7	0.5	-0.2	0.5	1.2	0.5	0.3	0.025

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.

Non-Inferiority Tests for Vaccine Efficacy using the Hazard Ratio (Cox's P.H. Model)

Report Definitions

Power is the probability of rejecting a false null hypothesis. Power should be close to one.
 N1 and N2 are the sample sizes of the control and treatment groups, respectively.
 N is the total sample size.
 E1 and E2 are the number of events required in the control and the treatment groups, respectively.
 $HR = h2/h1$ is the hazard ratio (treatment/control).
 $VE = 1 - HR$ is the vaccine efficacy.
 VE1 is the actual vaccine efficacy at which power is calculated.
 VE0 is the non-inferiority vaccine efficacy boundary.
 HR1 is the actual hazard ratio at which power is calculated.
 HR0 is the non-inferiority hazard ratio boundary.
 Pev1 and Pev2 are the probabilities of an event in the control and the treatment groups, respectively.
 Alpha is the probability of rejecting a true null hypothesis.

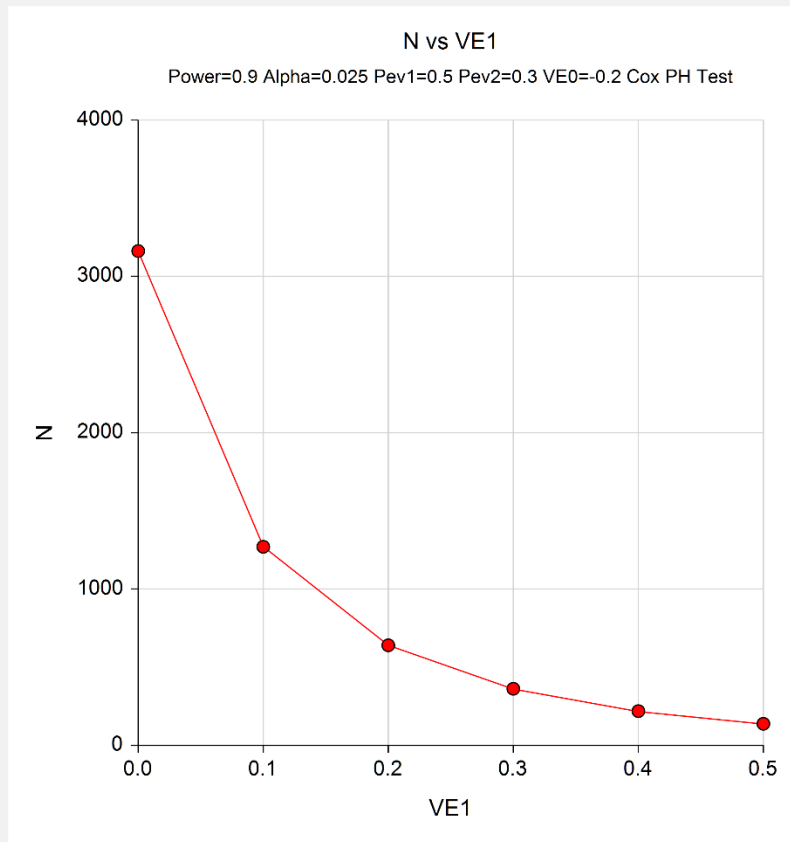
Summary Statements

A non-inferiority test of vaccine efficacy with an overall sample size of 3162 subjects (of which 1581 are in the control group and 1581 are in the treatment group) achieves 90% power at a 0.025 significance level. The non-inferiority bound of the hazard ratio is 1.2 and of the vaccine efficacy is -0.2. The actual hazard ratio is set at 1 and the actual vaccine efficacy is set at 0. The number of events required to achieve this power is 1264.8. It is anticipated that the proportion of subjects in which the event is observed during the study is 0.5 for the control group and 0.3 for the treatment group. These results assume that the hazard ratio is constant throughout the study and that Cox proportional hazards regression or the clinical non-inferiority logrank test is used to analyze the data.

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

Chart Section

Chart Section



This plot shows the relationship between VE1 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 of a superiority test, $HR1 = 2$, $HR0 = 1.35$, $Pev1 = Pev2 = 0.8$, $\alpha = 0.05$, and $power = 0.8$. We can validate the calculation for a non-inferiority test by switching $HR1$ and $HR0$. They obtained a sample size of 100 per group.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the procedure window. You may then make the appropriate entries as listed below, or open **Example 2** by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
Design Tab	
Solve For	Sample Size
Higher Hazards Are	Worse (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)	1.35
HR0 (Non-Inferiority Hazard Ratio)	2

Output

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

Numeric Results

Numeric Results												
Higher Hazards are: Worse												
Hypotheses: H0: VE ≥ VE0 vs. H1: VE < VE0												
Power	Sample Size			Events		Vaccine Efficacy		Hazard Ratio		Event Prob		Alpha
	Cntl N1	Trt N2	Total N	Cntl E1	Trt E2	Act VE1	N.I. VE0	Act HR1	N.I. HR0	Cntl Pev1	Trt Pev2	
0.80154	100	101	201	80	80.8	-0.35	-1	1.35	2	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.