Chapter 111

Non-Inferiority Tests for Vaccine Efficacy with Extremely Low Incidence

Introduction

This module provides power analysis and sample size calculation for non-inferiority tests of vaccine efficacy (VE) when the disease incidence rate is extremely low. In this case, large sample sizes are required to meet power requirements. The distribution of the number of cases in each group (vaccine and control) can be approximated by a binomial random variable.

VE is a traditional index of the protective efficacy of a vaccine. It is calculated as

$$VE = \frac{P_2 - P_1}{P_2} = 1 - \frac{P_1}{P_2}$$

where P_1 and P_2 are *attack rates* of the disease being studied among those vaccinated with a new vaccine and those receiving a standard treatment or placebo. An attack rate is the probability that a subject without the disease at the beginning of the study is infected by it during the duration of the course of the study. Hence, an analysis of vaccine effectiveness reduces to an analysis of the ratio of two proportions.

Note that because $P_1 < P_2$, the value of $VE < 1$.

Perhaps an example will set the stage for the discussion of the terminology that follows. Suppose that the population of interest has a disease incidence rate of 0.004. A promising new vaccine has been developed to the point where it can be tested. The researchers wish to show that the incidence rate in a group treated with this new vaccine will be no worse than 0.005.

Relative Vaccine Efficacy

Often, the goal of the study is to show that the attack rate of a new vaccine is no worse than that of the current standard vaccine. For example, the standard vaccine might have serious side effects, be expensive to produce, etc. In this case, the trial is conducted to show that the new vaccine is an attractive replace for the standard vaccine. 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

$$rVE = \frac{p_2 - p_1}{p_2} = 1 - \frac{p_1}{p_2}$$

where now p_2 is the attack rate for those receiving the standard vaccine.

Technical Details

This procedure is based on Chow et al. (2018), pages 459 - 460.

Comparing Two Proportions with Low Incidence

Suppose you have two populations from which dichotomous (binary) responses will be recorded. The probability (or risk) of obtaining an event of interest (testing positive for a disease) in population 1 (the treatment group) is P_1 and in population 2 (the control group) is P_2.

For sufficiently large sample sizes, the number of cases in each group is given by $\lambda_1 = N_1 P_1$ and $\lambda_2 = N_2 P_2$. The number of cases is distributed approximately as Poisson random variables. The number of cases in the vaccine group given the total number of cases is approximately distributed as a binomial random variable with rate θ, where

$$\theta = \frac{\lambda_1}{(\lambda_1 + \lambda_2)} = \frac{1 - VE}{1 - VE + R}$$

with $R = N_2/N_1$ and $VE = \left(1 - \frac{P_1}{P_2}\right)$.

The one-sided, non-inferiority hypotheses in terms of VE may be written as

$$H_0: VE \leq VE_0 \text{ vs. } H_1: VE > VE_0$$

An equivalent test about θ is

$$H_0: \theta \geq \theta_0 \text{ vs. } H_1: \theta < \theta_0$$

Non-Inferiority Bound

The idea of a non-inferiority test is that a new treatment is no worse than the treatment it is being compared to. To allow the comparison to be made, you must determine a non-inferiority boundary. In this procedure, that means that p_1 can only be slightly larger than p_2. When $p_1 > p_2$, the risk ratio will be greater than one so that the value of VE will be negative. See Nauta (2020) page 94 for a discussion and example of this.

Hence, one task that will have to be completed is to determine how much worse the new vaccine can be without causing it to be rejected.

Test Statistics

A reasonable test statistic for the testing the above hypotheses is given by

$$T = \frac{\sqrt{x_1 + x_2}\left(\hat{\theta} - \theta_0\right)}{\sqrt{\theta_0(1 - \theta_0)}}$$

where

$$\hat{\theta} = x_1/(x_1 + x_2)$$

$$\theta_0 = \frac{1 - VE_0}{1 - VE_0 + R}$$

In large samples, *T* is approximately distributed as a standard normal. The null hypothesis is rejected if $T < z_{1-\alpha}$.

The power, assuming an alternative value of $P_1 < P_2$, is given by

$$Power = 1 - \Phi\left(\frac{z_{1-\alpha}\sqrt{\theta_0(1 - \theta_0)} - \sqrt{N_1P_1 + N_2P_2}(\theta_0 - \theta)}{\sqrt{\theta(1 - \theta)}}\right)$$

This power formula can be used directly for obtaining power or indirectly for obtaining sample size using a simple, binary search.

Note that the power formula given here uses the difference between the two terms in the numerator while the formula given on page 460 of Chow et al. (2018) uses the sum of these terms. This difference is most likely due to a difference in the definition of z_α here as the left-tail probability rather than the right-tail probability.

Example 1 – Finding Sample Size

A two-arm parallel study is being planned to substantiate that a new vaccine controls a certain disease no worse than a control. The disease rate in the control group is 0.004. The non-inferiority boundary is set at 0.005. The disease rate in the treatment group is anticipated to be between 0.002 and 0.003. The significance level of the test is 0.025.

The sample sizes will be equal in each arm. The researchers would like to determine the required sample size needed to achieve a power of 0.80.

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**
Power	**0.80**
Alpha	**0.025**
Group Allocation	**Equal (N1 = N2)**
Vaccine Efficacy Input Type	**Enter P1.0, P1.1, and P2**
P1.0 (Non-Inferiority Vaccine Event Prob)	**0.005**
P1.1 (Actual Vaccine Event Prob)	**0.002 0.003**
P2 (Control Event Probability)	**0.004**

Output

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

Numeric Reports

Numeric Results

Solve For: Sample Size
Test Statistic: Z-Test
Groups: 1 = Vaccine, 2 = Control
Hypotheses: H0: VE ≤ VE0 vs. H1: VE > VE0

					Event Probability					
						Vaccine		Vaccine Efficacy		
Power		Sample Size			Control	Non-Inferiority	Actual	Non-Inferiority	Actual	
Target	Actual	N1	N2	N	P2	P1.0	P1.1	VE0	VE1	Alpha
0.8	0.80002	6341	6341	12682	0.004	0.005	0.002	-0.25	0.50	0.025
0.8	0.80002	17128	17128	34256	0.004	0.005	0.003	-0.25	0.25	0.025

Target Power The desired power value. Power is the probability of rejecting a false null hypothesis.
Actual Power The calculated power obtained for the scenario on this row. Because N1 and N2 are discrete, this value is often (slightly) larger than the target power.
N1 and N2 The sample sizes of the vaccinated group and the control group, respectively.
N The total sample size. N = N1 + N2.
P1.0 The largest value of the event probability for vaccinated group that still yields a non-inferiority conclusion.
P1.1 The event probability of the vaccinated group assumed by H1.
P2 The event probability (attack rate) of the control group.
VE0 The vaccine efficacy assumed by the null hypothesis, H0. This is the non-inferiority boundary of VE. VE0 = 1 - P1.0/P2.
VE1 The vaccine efficacy assumed by the alternative hypothesis, H1. This is the VE value at which the power is calculated. VE = (P2 - P1)/P2.
Alpha The probability of rejecting a true null hypothesis.

Summary Statements

A parallel two-group design will be used to test non-inferiority of vaccine efficacy, with a non-inferiority vaccine efficacy of -0.25 (H0: VE ≤ -0.25 versus H1: VE > -0.25). The comparison will be made using a one-sided, two-sample, non-inferiority Z-test, with a Type I error rate (α) of 0.025. The vaccine and control group event probabilities are assumed to be 0.002 and 0.004, respectively. The vaccine group event probability at the non-inferiority limit is 0.005. To detect a vaccine efficacy of 0.5 with 80% power, the number of subjects needed will be 6341 in the vaccine group, and 6341 in the control group.

Dropout-Inflated Sample Size

	Sample Size			Dropout-Inflated Enrollment Sample Size			Expected Number of Dropouts		
Dropout Rate	**N1**	**N2**	**N**	**N1'**	**N2'**	**N'**	**D1**	**D2**	**D**
20%	6341	6341	12682	7927	7927	15854	1586	1586	3172
20%	17128	17128	34256	21410	21410	42820	4282	4282	8564

Dropout Rate	The percentage of subjects (or items) that are expected to be lost at random during the course of the study and for whom no response data will be collected (i.e., will be treated as "missing"). Abbreviated as DR.
N1, N2, and N	The evaluable sample sizes at which power is computed. If N1 and N2 subjects are evaluated out of the N1' and N2' subjects that are enrolled in the study, the design will achieve the stated power.
N1', N2', and N'	The number of subjects that should be enrolled in the study in order to obtain N1, N2, and N evaluable subjects, based on the assumed dropout rate. After solving for N1 and N2, N1' and N2' are calculated by inflating N1 and N2 using the formulas N1' = N1 / (1 - DR) and N2' = N2 / (1 - DR), with N1' and N2' always rounded up. (See Julious, S.A. (2010) pages 52-53, or Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. (2018) pages 32-33.)
D1, D2, and D	The expected number of dropouts. D1 = N1' - N1, D2 = N2' - N2, and D = D1 + D2.

Dropout Summary Statements

Anticipating a 20% dropout rate, 7927 subjects should be enrolled in Group 1, and 7927 in Group 2, to obtain final group sample sizes of 6341 and 6341, respectively.

References

Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. 2018. Sample Size Calculations in Clinical Research, Third Edition. Taylor & Francis/CRC. Boca Raton, Florida.

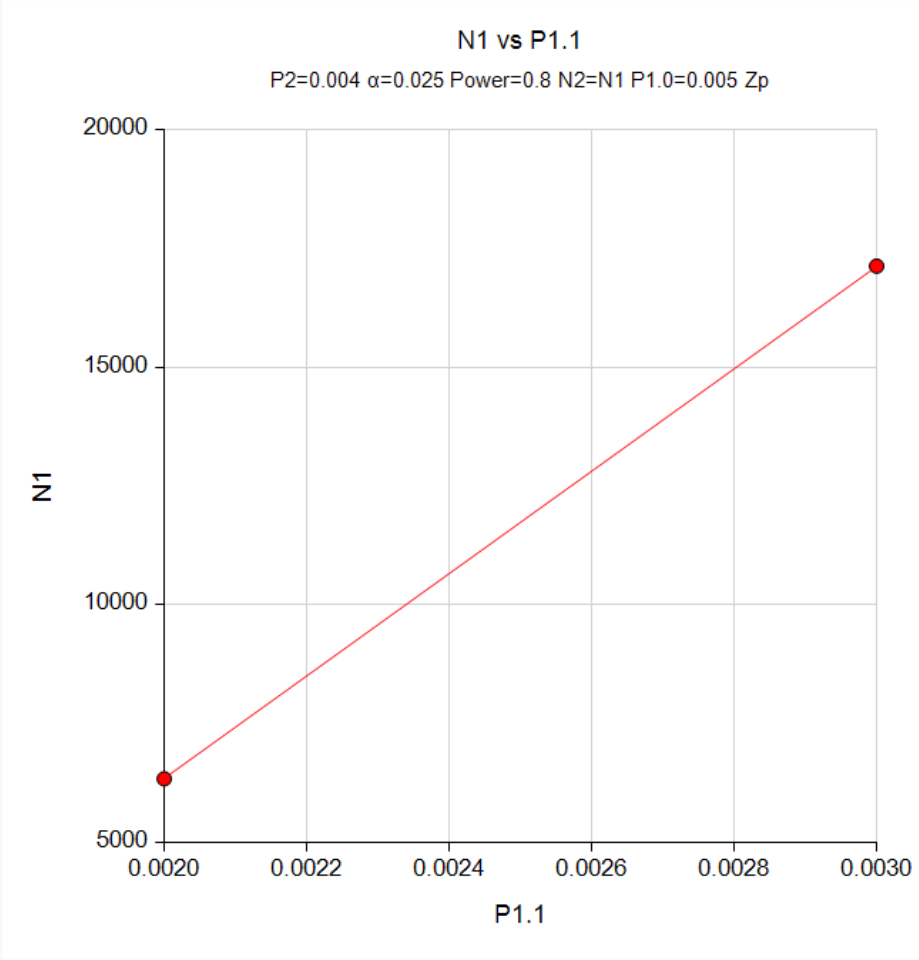
Blackwelder, William C. 1993. 'Sample Size and Power for Prospective Analysis of Relative Risk.' Statistics in Medicine, Vol. 12, 691-698.

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

This report shows the values of each of the parameters, one scenario per row.

Plots Section

Plots



The values from the table are displayed in the above chart. This chart gives a quick look at the sample sizes that are required for the two values of P1.1.

Example 2 – Validation using a Previously Validated PASS Procedure

We could not find a validation example in the literature so we will validate the procedure using the *Superiority by a Margin Tests for Vaccine Efficacy with Extremely Low Incidence* procedure. That procedure using the same power calculations as this procedure, so it can be used to validate this procedure.

Suppose a two-arm parallel study is being planned to substantiate that a new vaccine controls a certain disease no worse than a control. The disease rate in the control group is 0.004. The non-inferiority boundary is set at 0.005. The disease rate in the treatment group is anticipated to be 0.002. The significance level of the test is 0.025. Using a sample size of 6341 in each arm, the power was found to be 0.80002.

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	**Power**
Alpha	**0.025**
Group Allocation	**Equal (N1 = N2)**
Sample Size Per Group	**6341**
Vaccine Efficacy Input Type	**Enter P1.0, P1.1, and P2**
P1.0 (Non-Inferiority Vaccine Event Prob)	**0.005**
P1.1 (Actual Vaccine Event Prob)	**0.002**
P2 (Control Event Probability)	**0.004**

Output

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

Numeric Results

Solve For: Power
Test Statistic: Z-Test
Groups: 1 = Vaccine, 2 = Control
Hypotheses: H0: VE ≤ VE0 vs. H1: VE > VE0

	Sample Size			Event Probability			Vaccine Efficacy		
					Vaccine				
Power	N1	N2	N	Control P2	Non-Inferiority P1.0	Actual P1.1	Non-Inferiority VE0	Actual VE1	Alpha
0.80002	6341	6341	12682	0.004	0.005	0.002	-0.25	0.5	0.025

PASS has calculated the power as 0.80002, so the procedure is validated.