Chapter 104

Superiority by a Margin Tests for Vaccine Efficacy with Extremely Low Incidence

Introduction

This module provides power analysis and sample size calculation for superiority by a margin 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 0.002. 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 reduced to at least 0.0015. That is, they want to show that the efficacy of the new vaccine is at least 1 – 0.0015/0.002 = 0.25.

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, superiority-by-a-margin hypotheses in terms of VE may be written as

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

An equivalent test about θ is

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

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

$$Power = 1 - \Phi\left(\frac{z_{1-\alpha}\sqrt{\theta_0(1 - \theta_0)} - \sqrt{N_1 P_1 + N_2 P_2}(\theta_0 - \theta)}{\sqrt{\theta(1 - \theta)}}\right)$$

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 better than a control. The disease rate in the control group is 0.004. The superiority boundary is set at 0.003. The disease rate in the treatment group is anticipated to be between 0.001 and 0.002. 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	**0.8**
Alpha	**0.025**
Group Allocation	**Equal (N1 = N2)**
Vaccine Efficacy Input Type	**Enter P1.0, P1.1, and P2**
P1.0 (Superiority Vaccine Event Prob)	**0.003**
P1.1 (Actual Vaccine Event Prob)	**0.001 0.0015 0.002**
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	Superiority	Actual	Superiority	Actual	
Target	Actual	N1	N2	N	P2	P1.0	P1.1	VE0	VE1	Alpha
0.8	0.80006	6536	6536	13072	0.004	0.003	0.0010	0.25	0.750	0.025
0.8	0.80001	13538	13538	27076	0.004	0.003	0.0015	0.25	0.625	0.025
0.8	0.80000	34321	34321	68642	0.004	0.003	0.0020	0.25	0.500	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 smallest value of the event probability for vaccinated group that still yields a superiority 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 superiority 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 vaccine efficacy by a margin, with a superiority 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, superiority-by-a-margin Z-test, with a Type I error rate (α) of 0.025. The vaccine and control group event probabilities are assumed to be 0.001 and 0.004, respectively. The vaccine group event probability at the superiority limit is 0.003. To detect a vaccine efficacy of 0.75 with 80% power, the number of subjects needed will be 6536 in the vaccine group, and 6536 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%	6536	6536	13072	8170	8170	16340	1634	1634	3268
20%	13538	13538	27076	16923	16923	33846	3385	3385	6770
20%	34321	34321	68642	42902	42902	85804	8581	8581	17162

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, 8170 subjects should be enrolled in Group 1, and 8170 in Group 2, to obtain final group sample sizes of 6536 and 6536, 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.

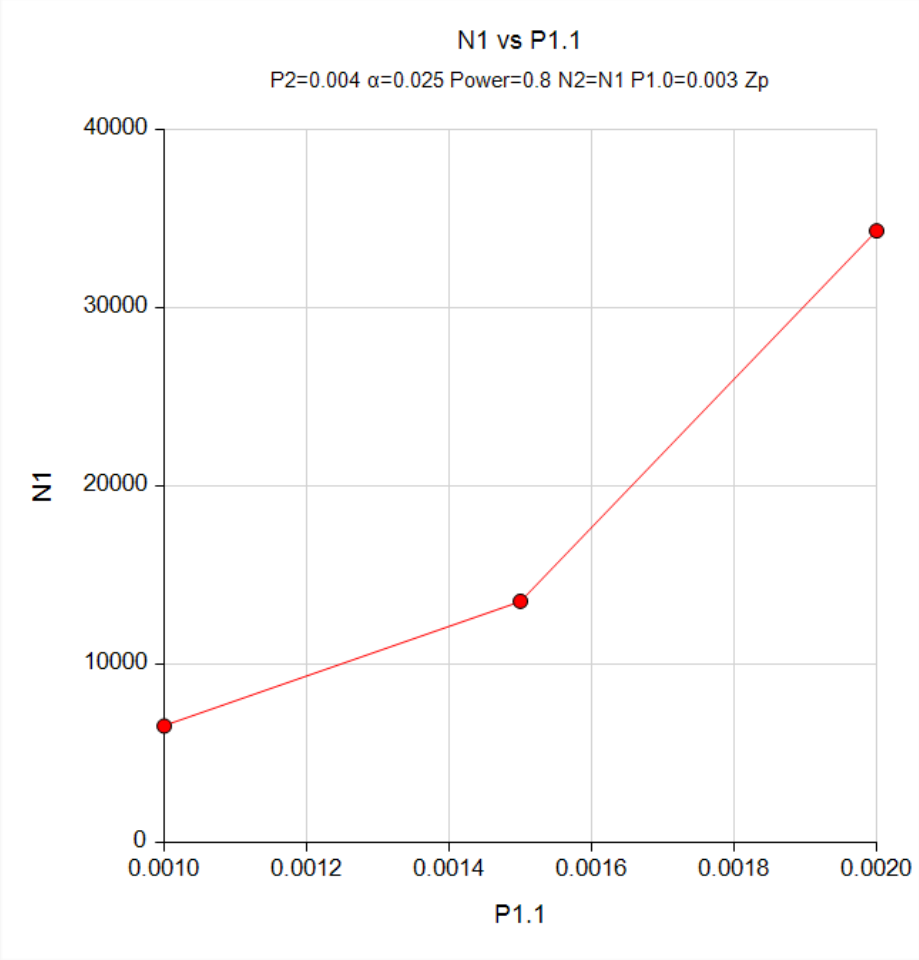
Blackwelder, William C. 1993. 'Sample Size and Power for Prospective Analysis of Relative Risk.' Statistics in Medicine, Vol. 12, 691-698.

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 various values of P1.1.

Example 2 – Validation using Hand Calculations

We could not find a validation example in the literature so we will validate the procedure using hand calculations. A two-arm parallel study is being planned to substantiate that a new vaccine controls a certain disease better than a control. The disease rate in the control group is 0.004. The superiority boundary is set at 0.003. The disease rate in the treatment group is anticipated to be 0.001. The significance level of the test is 0.025 and the power is 0.80. The sample size per group is 6536.

We will validate this procedure by calculating the power and showing that the power is indeed 0.80.

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

$$= 1 - \Phi\left(\frac{1.959964\sqrt{0.428571(0.571429)} - \sqrt{6536(0.001 + 0.004)}(0.428571 - 0.2)}{\sqrt{0.2(1-0.2)}}\right)$$

$$= 1 - \Phi\left(\frac{0.969931 - 1.306659}{0.4}\right)$$

$$= 1 - \Phi(-0.84182)$$

$$= 0.80006$$

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	**6536**
Vaccine Efficacy Input Type	**Enter P1.0, P1.1, and P2**
P1.0 (Superiority Vaccine Event Prob)	**0.003**
P1.1 (Actual Vaccine Event Prob)	**0.001**
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	Superiority P1.0	Actual P1.1	Superiority VE0	Actual VE1	Alpha
0.80006	6536	6536	13072	0.004	0.003	0.001	0.25	0.75	0.025

PASS has also calculated the power as 0.80006, so the procedure is validated.