Chapter 121

Tests for Vaccine Efficacy with Composite Efficacy Measure using the Ratio of Two Means

Introduction

This module provides power analysis and sample size calculation for inequality tests of vaccine efficacy (VE) when one is interested in both the incidence and severity of an infection. The burden-of-illness (BOI) score allows investigation of both disease incidence rates and disease severity and duration. See Chang et al. (1994) and Callegaro et al. (2020) for more details.

The BOI method requires that a severity-of-illness score X > 0 be assigned to individuals who develop the disease and a severity score of 0 be assigned to those not infected. Thus, a binary incidence variable and a continuous severity variable are combined to form a single burden-of-illness measurement.

Technical Details

This routine is based on Callegaro et al. (2020).

In the discussion that follows, the subscripts 1 and 2 refer to the new vaccine group and the control (or placebo) group, respectively. Let N_1 and N_2 be the sample sizes of the two groups.

A post-infection variable *X* records a BOI score. If a subject is not infected, their BOI score is 0. The BOI score measures various attributes of the infection such as amount of pain, duration, etc. Often, *X* is an ordinal variable taking on values from 1 to 7 or 1 to 10.

Test Statistics

A reasonable composite index of is the following vaccine efficacy statistic

$$\widehat{VE}_{BOI} = 1 - \frac{\bar{X}_1}{\bar{X}_2}$$

where $\bar{X}_1$ and $\bar{X}_2$ are the group means of *X*.

In a fixed-time design, which is terminated after a preset elapsed time, the following results are obtained.

$$\mathrm{E}(\bar{X}_j) = P_j\mu_j, \qquad j = 1,2$$

$$\mathrm{V}(\bar{X}_j) = P_j\{\sigma_j^2 + (1-P_j)\mu_j^2\}/N_j$$

where P_j is the probability of infection, μ_j is the expectation of X of those infected in group j, σ_j is the standard deviation of X for those infected in group j.

It follows from the delta method that

$$Var\left(\frac{\bar{X}_1}{\bar{X}_2}\right) = \left(\frac{P_1\mu_1}{P_2\mu_2}\right)^2\left(\frac{P_1\{\sigma_1^2 + (1-P_1)\mu_1^2\}}{N_1(P_1\mu_1)^2} + \frac{P_2\{\sigma_2^2 + (1-P_2)\mu_2^2\}}{N_2(P_2\mu_2)^2}\right)$$

Using this result, a test statistic Z is developed as follows

$$Z = \frac{\log(\widehat{RR})}{\sqrt{\widehat{\mathrm{Var}}\left(\log(\widehat{RR})\right)}}$$

where $\widehat{RR} = \left(\frac{\bar{X}_1}{\bar{X}_2}\right)$. Note that $VE_{BOI} = 1 - RR$, with $RR = \left(\frac{P_1\mu_1}{P_2\mu_2}\right)$.

This leads to

$$E(Z) = \frac{\log(RR)}{\sqrt{\frac{P_1\{\sigma_1^2 + (1-P_1)\mu_1^2\}}{N_1(P_1\mu_1)^2} + \frac{P_2\{\sigma_2^2 + (1-P_2)\mu_2^2\}}{N_2(P_2\mu_2)^2}}}$$

Power Calculation

The asymptotic power of this test statistic for a two-sided inequality test is given by

$$Power = \Phi\left(E(Z) - z_{1-\alpha/2}\right)$$

Sample Size Calculation

Sample size is found using a binary search with this power formula.

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 0.003. The disease rate in the treatment group is anticipated to be between 0.001 and 0.0015. The significance level of the test is 0.05.

Previous trials have obtained an average BOI score in the control group of 11.9 and standard deviation of 1.87. Three BOI scores in the vaccine group will be considered: 9, 10, and 11. Their standard deviation will be set to 1.7.

The sample sizes will be equal in each arm. The current analysis is to determine the required sample size to achieve a power of 0.80 when using a two-sided test.

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**
Alternative Hypothesis	**Two-Sided**
Power	**0.8**
Alpha	**0.05**
Group Allocation	**Equal (N1 = N2)**
P1 (Vaccine Event Prob|H1)	**0.001 0.0015**
P2 (Control Event Probability)	**0.003**
μ1 (Mean of Vaccine Group)	**9 10 11**
μ2 (Mean of Control Group)	**11.9**
Std Dev Input Type	**Unequal**
σ1 (Std Dev of Vaccine Group)	**1.7**
σ2 (Std Dev of Control Group)	**1.87**

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
Hypothesis: Two-Sided

				Event Probability		Burden-of-Illness (BOI) Scores: Mean | Infected			Burden-of-Illness (BOI) Scores: Standard Deviation		Vaccine Efficacy		
	Sample Size							Adjusted			BOI	Event	
Power	N1	N2	N	Vaccine P1	Control P2	Vaccine μ1	Control μ2	Ratio RR	Vaccine σ1	Control σ2	Scores VE_{BOI}	Probability VE	Alpha
0.8001	5686	5686	11372	0.0010	0.003	9	11.9	0.252	1.7	1.87	0.748	0.667	0.05
0.8000	6633	6633	13266	0.0010	0.003	10	11.9	0.280	1.7	1.87	0.720	0.667	0.05
0.8000	7722	7722	15444	0.0010	0.003	11	11.9	0.308	1.7	1.87	0.692	0.667	0.05
0.8000	8549	8549	17098	0.0015	0.003	9	11.9	0.378	1.7	1.87	0.622	0.500	0.05
0.8000	10706	10706	21412	0.0015	0.003	10	11.9	0.420	1.7	1.87	0.580	0.500	0.05
0.8000	13469	13469	26938	0.0015	0.003	11	11.9	0.462	1.7	1.87	0.538	0.500	0.05

Power	The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N1 and N2	The sample sizes of the vaccine group and the control group, respectively.
N	The total sample size. N = N1 + N2.
P1	The event probability of the vaccine group assumed by H1.
P2	The event probability (attack rate) of the control group.
μ1	The mean BOI score of those infected in the vaccine group.
μ2	The mean BOI score of those infected in the control group.
RR	The ratio of the adjusted BOI means. RR = (P1 × μ1) / (P2 × μ2).
σ1	The standard deviation of the BOI scores of those infected in the vaccine group.
σ2	The standard deviation of the BOI scores of those infected in the control group.
VE_{BOI}	The BOI score vaccine efficacy assumed by the alternative hypothesis, H1. VE_{BOI} = 1 - (P1 × μ1) / (P2 × μ2) = 1 - RR.
VE	The vaccine efficacy assumed by the alternative hypothesis, H1. VE = 1 - 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 with a composite efficacy measure. The comparison will be made using a two-sided Z-test based on the ratio of the means, with a Type I error rate (α) of 0.05. The means of the vaccine and control groups are assumed to be 9 and 11.9, respectively. The standard deviations of the vaccine and control groups are assumed to be 1.7 and 1.87, respectively. The event probabilities of the vaccine and control groups are assumed to be 0.001 and 0.003, respectively. To detect a burden-of-illness (BOI) vaccine efficacy of 0.748 with 80% power, the number of subjects needed will be 5686 in the vaccine group, and 5686 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%	5686	5686	11372	7108	7108	14216	1422	1422	2844
20%	6633	6633	13266	8292	8292	16584	1659	1659	3318
20%	7722	7722	15444	9653	9653	19306	1931	1931	3862
20%	8549	8549	17098	10687	10687	21374	2138	2138	4276
20%	10706	10706	21412	13383	13383	26766	2677	2677	5354
20%	13469	13469	26938	16837	16837	33674	3368	3368	6736

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 (as entered by the user). 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. 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, 7108 subjects should be enrolled in Group 1, and 7108 in Group 2, to obtain final group sample sizes of 5686 and 5686, respectively.

References

Callegaro, A., Curran, D., and Matthews, S. 2020. 'Burden-of-illness vaccine efficacy'. Pharmaceutical Statistics. Volume 19, Issue 5. Pages 636-645. https://doi.org/10.1002/pst.2020

Chang, M.N., Guess, H.A., and Heyse, J.F. 1994. 'Reduction in Burden of Illness: A New Efficacy Measure for Prevention Trials'. Statistics in Medicine. Vol 13. Pages 1807-1814. https://doi.org/10.1002/sim.4780131803

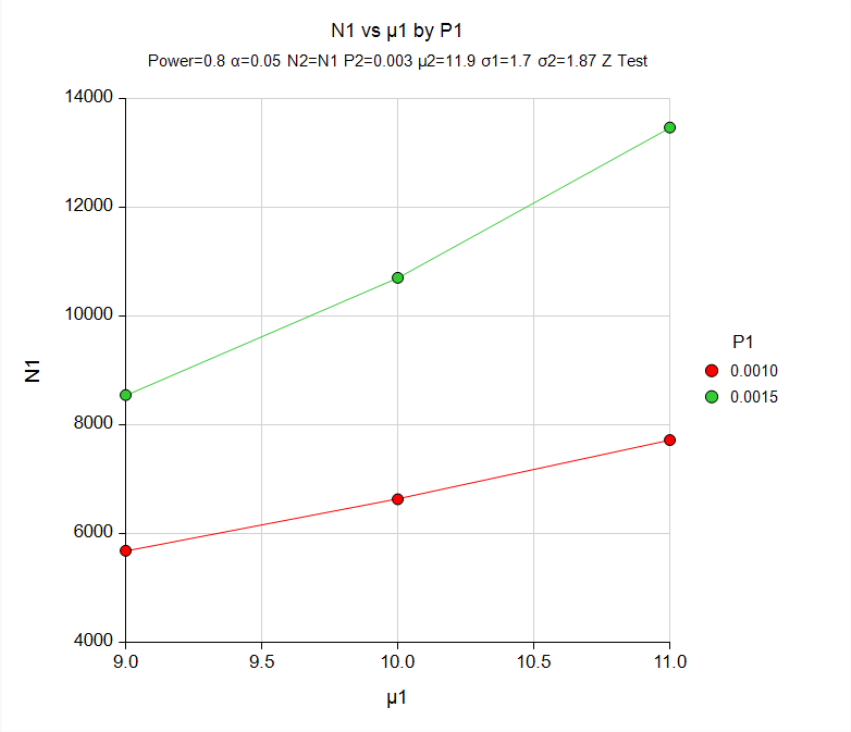
Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. 2018. Sample Size Calculations in Clinical Research, Third Edition. Taylor & Francis/CRC. Boca Raton, Florida.

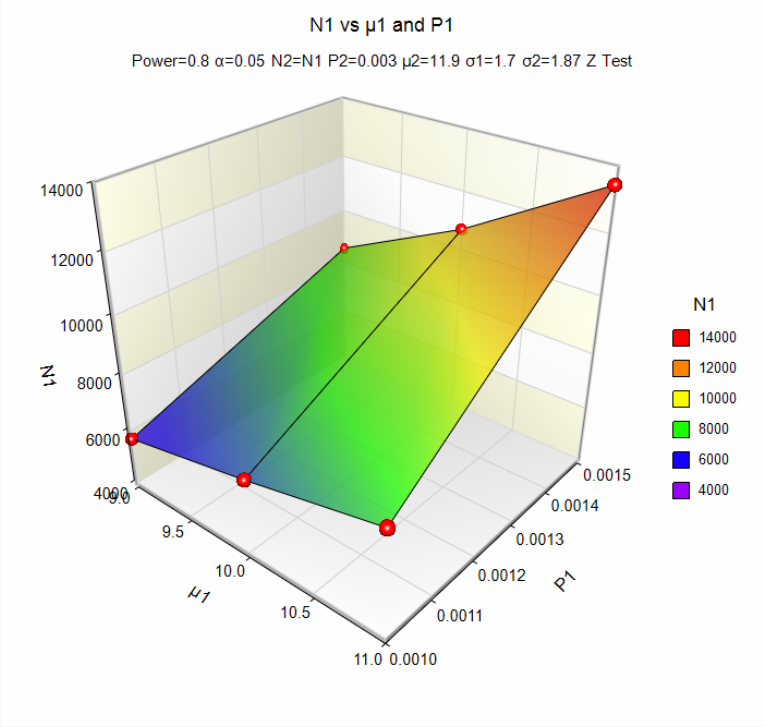
Nauta, Jozef. 2020. Statistics in Clinical and Observational Vaccine Studies, 2nd Edition. Springer. Cham, Switzerland.

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 μ1 and P1.

Example 2 – Validation using Callegaro et al. (2020)

Callegaro et al. (2020) Table 5 presents the results of an extensive simulation study. We will use the ninth row of this table to validate this procedure. Note that since this is a simulation study, our analytic results will not match those from the article exactly.

The settings for this example are N1 = N2 = 858, P1 = 0.105, P2 = 0.15, μ1 = 3.7, μ2 = 4.5, σ = 1.5, and α= 0.05 (two-sided). The resulting power is 0.980.

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**
Alternative Hypothesis	**Two-Sided**
Alpha	**0.05**
Group Allocation	**Equal (N1 = N2)**
Sample Size Per Group	**858**
P1 (Vaccine Event Prob|H1)	**0.105**
P2 (Control Event Probability)	**0.15**
μ1 (Mean of Vaccine Group)	**3.7**
μ2 (Mean of Control Group)	**4.5**
Std Dev Input Type	**Equal**
σ (Std Dev of Both Groups)	**1.5**

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
Hypothesis: Two-Sided

	Sample Size			Event Probability		Burden-of-Illness (BOI) Scores: Mean | Infected			Burden-of-Illness (BOI) Scores: Standard Deviation		Vaccine Efficacy		
Power	N1	N2	N	Vaccine P1	Control P2	Vaccine μ1	Control μ2	Adjusted Ratio RR	Vaccine σ1	Control σ2	BOI Scores VE_{BOI}	Event Probability VE	Alpha
0.9785	858	858	1716	0.105	0.15	3.7	4.5	0.576	1.5	1.5	0.424	0.3	0.05

PASS has calculated the power as 0.9785 which is close to the simulated value of 0.980. Thus, the procedure is validated.