Chapter 122

Tests for Vaccine Efficacy with Composite Efficacy Measure using the Difference 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 score 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 Chang et al. (1994).

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

The test statistic associated with this procedure is

$$T = \bar{X}_2 - \bar{X}_1$$

where $\bar{X}_1$ and $\bar{X}_2$ are the group means of the BOI scores, *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 that $E(T)$ and $V(T)$ are

$$\mathrm{E}(T) = P_2\mu_2 - P_1\mu_1$$

$$\mathrm{V}(T) = \mathrm{V}(\bar{X}_2) + \mathrm{V}(\bar{X}_1)$$

Since under the null hypothesis $E(T) = 0$, a test statistic Z is as follows

$$Z = \frac{T}{\sqrt{\hat{\mathrm{V}}(\mathrm{T})}}$$

Power Calculation

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

$$Power = Pr\left(\frac{|T|}{\sqrt{V_0}} > z_{1-\alpha/2}\right)$$

$$= Pr\left(\frac{T}{\sqrt{V_0}} > z_{1-\alpha/2}\right) + Pr\left(\frac{T}{\sqrt{V_0}} < -z_{1-\alpha/2}\right)$$

$$= \Phi\left(\frac{-z_{1-\alpha/2}\sqrt{V_0} + (P_2\mu_2 - P_1\mu_1)}{\sqrt{V_1}}\right) + 1 - \Phi\left(\frac{z_{1-\alpha/2}\sqrt{V_0} + (P_2\mu_2 - P_1\mu_1)}{\sqrt{V_1}}\right)$$

where

$$\mathrm{V}_0 = \mathrm{W}(\mathrm{P}_2, \mu_2, \sigma_2, N_2) + \mathrm{W}(\mathrm{P}_2, \mu_2, \sigma_1, N_1)$$

$$\mathrm{V}_1 = \mathrm{W}(\mathrm{P}_2, \mu_2, \sigma_2, N_2) + \mathrm{W}(\mathrm{P}_1, \mu_1, \sigma_1, N_1)$$

$$\mathrm{W}(\mathrm{P}, \mu, \sigma, N) = P\{\sigma^2 + (1-P)\mu^2\}/N$$

Power for one-sided tests is found using either the left or right term of the two-sided expression above.

Sample Size Calculation

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

Example 1 – Finding Sample Size

A two-arm parallel study is being planned to substantiate that a new vaccine reduces the incidence rate of a certain disease more than a control. The disease rate in the control group is 0.01. The disease rate in the treatment group is anticipated to be between 0.005 and 0.007.

Previous trials have obtained an average BOI score in the control group of 1.5. Three BOI scores in the vaccine group will be considered: 1.0, 1.1, and 1.2. The standard deviations of both groups will be set to 0.9. The significance level of the test is 0.05. The sample sizes will be equal in each arm. The task is to determine the required sample size to achieve a power of 0.80 when using a two-sided test in each of the resulting scenarios.

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 (H1: δ ≠ 0)**
Power	**0.8**
Alpha	**0.05**
Group Allocation	**Equal (N1 = N2)**
P1 (Vaccine Event Prob|H1)	**0.005 0.007**
P2 (Control Event Probability)	**0.01**
μ1 (Mean of Vaccine Group)	**1.0 1.1 1.2**
μ2 (Mean of Control Group)	**1.5**
Std Dev Input Type	**Equal**
σ (Std Dev of Both Groups)	**0.9**

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
Alternative Hypothesis:	Two-Sided (H1: δ ≠ 0)

				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	Difference δ	Vaccine σ1	Control σ2	Scores VEBOI	Probability VE	Alpha
0.8000	4227	4227	8454	0.005	0.01	1.0	1.5	0.0100	0.9	0.9	0.667	0.5	0.05
0.8001	4716	4716	9432	0.005	0.01	1.1	1.5	0.0095	0.9	0.9	0.633	0.5	0.05
0.8001	5293	5293	10586	0.005	0.01	1.2	1.5	0.0090	0.9	0.9	0.600	0.5	0.05
0.8000	6757	6757	13514	0.007	0.01	1.0	1.5	0.0080	0.9	0.9	0.533	0.3	0.05
0.8000	8188	8188	16376	0.007	0.01	1.1	1.5	0.0073	0.9	0.9	0.487	0.3	0.05
0.8000	10113	10113	20226	0.007	0.01	1.2	1.5	0.0066	0.9	0.9	0.440	0.3	0.05

The severity-of-illness (SOI) score is only obtained from those subjects that were infected.
The burden-of-illness (BOI) score is obtained from all subjects. For infected subjects, BOI = SOI. For uninfected subjects, BOI = 0.

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.
δ	The difference between the adjusted BOI means of the two groups. δ = Sc2 - Sc1, where Sc1 = P1 × μ1 and Sc2 = 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.
VEBOI	The vaccine efficacy using the BOI scores assumed by H1. VEBOI = 1 - (P1 × μ1) / (P2 × μ2). VEBOI is included for reference only.
VE	The vaccine efficacy assumed by H1. VE = 1 - P1 / P2. VE is included for reference only.
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 difference of the means, with a Type I error rate (α) of 0.05. The severity score means of the vaccine and control groups are assumed to be 1 and 1.5, respectively. (Note that these severity scores correspond only to those subjects that are infected.) The severity score standard deviations of the vaccine and control groups are assumed to be 0.9 and 0.9, respectively. The event probabilities of the vaccine and control groups are assumed to be 0.005 and 0.01, respectively. To detect a difference in mean burden-of-illness (BOI) scores of 0.01 with 80% power, the number of subjects needed will be 4227 in the vaccine group, and 4227 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%	4227	4227	8454	5284	5284	10568	1057	1057	2114
20%	4716	4716	9432	5895	5895	11790	1179	1179	2358
20%	5293	5293	10586	6617	6617	13234	1324	1324	2648
20%	6757	6757	13514	8447	8447	16894	1690	1690	3380
20%	8188	8188	16376	10235	10235	20470	2047	2047	4094
20%	10113	10113	20226	12642	12642	25284	2529	2529	5058

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, 5284 subjects should be enrolled in Group 1, and 5284 in Group 2, to obtain final group sample sizes of 4227 and 4227, respectively.

References

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

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

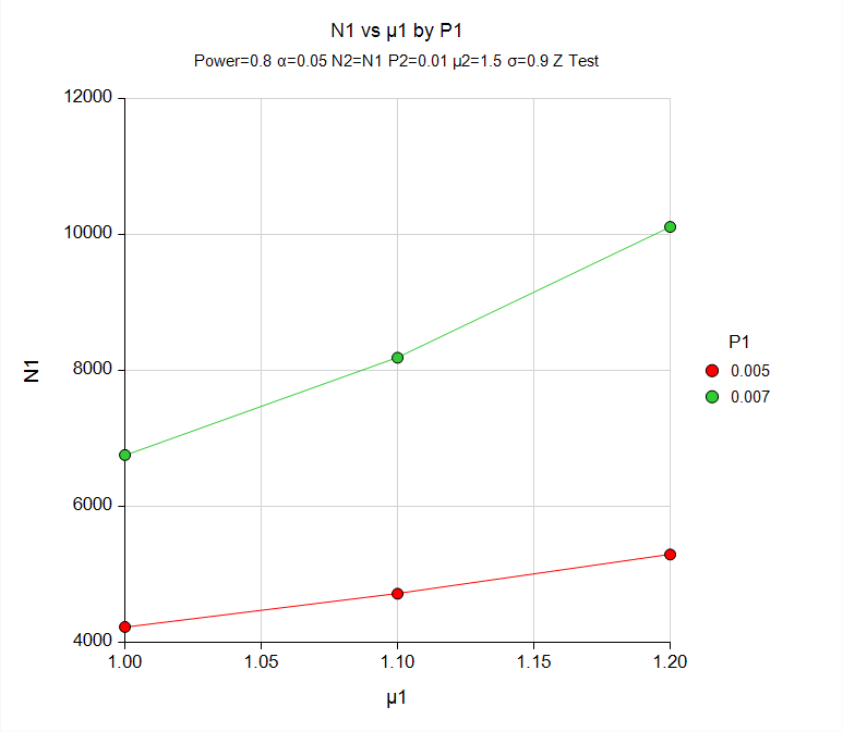
Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. 2018. Sample Size Calculations in Clinical Research, Third Edition. Taylor & Francis/CRC. Boca Raton, Florida.

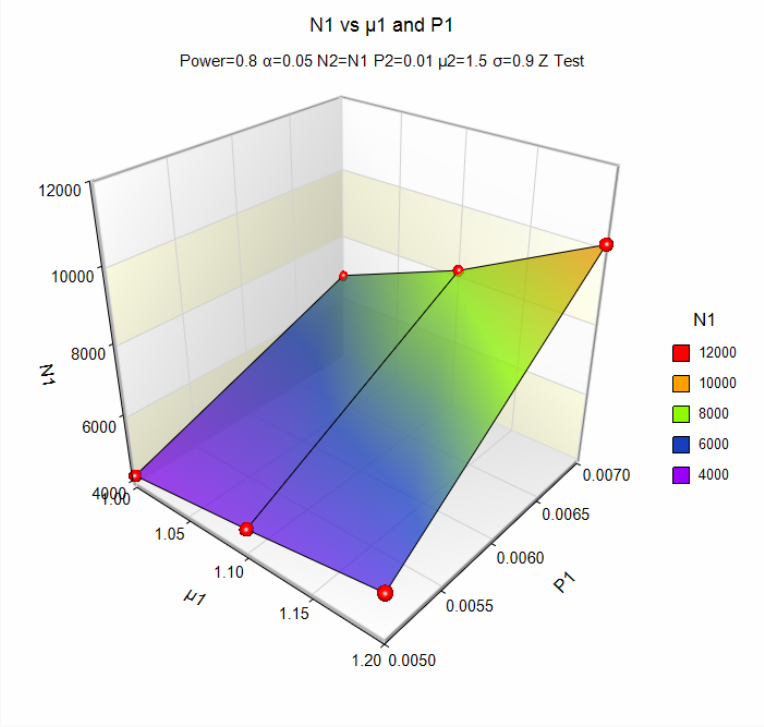
Nauta, Jozef. 2020. Statistics in Clinical and Observational Vaccine Studies, 2nd Edition. Springer. Cham, Switzerland.

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 Chang et al. (1994)

Chang, Guess, and Heyse (1994) page 1811 present an example which will be used to validate this procedure.

The settings for this example are P1 = 0.007, P2 = 0.01, μ1 = 1.05, μ2 = 1.5, σ = 0.9, α = 0.05 (two-sided), and power = 0.95. The resulting sample size was found to be 11,687 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**
Alternative Hypothesis	**Two-Sided (H1: δ ≠ 0)**
Power	**0.95**
Alpha	**0.05**
Group Allocation	**Equal (N1 = N2)**
P1 (Vaccine Event Prob|H1)	**0.007**
P2 (Control Event Probability)	**0.01**
μ1 (Mean of Vaccine Group)	**1.05**
μ2 (Mean of Control Group)	**1.5**
Std Dev Input Type	**Equal**
σ (Std Dev of Both Groups)	**0.9**

Output

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

Numeric Results

Solve For:	Sample Size
Test Statistic:	Z-Test
Groups:	1 = Vaccine, 2 = Control
Alternative Hypothesis:	Two-Sided (H1: δ ≠ 0)

				Event Probability		Burden-of-Illness (BOI) Scores: Mean | Infected			Burden-of-Illness (BOI) Scores: Standard Deviation		Vaccine Efficacy		
	Sample Size												
Power	N1	N2	N	Vaccine P1	Control P2	Vaccine μ1	Control μ2	Adjusted Difference δ	Vaccine σ1	Control σ2	BOI Scores VEBOI	Event Probability VE	Alpha
0.95	11686	11686	23372	0.007	0.01	1.05	1.5	0.00765	0.9	0.9	0.51	0.3	0.05

The severity-of-illness (SOI) score is only obtained from those subjects that were infected.
The burden-of-illness (BOI) score is obtained from all subjects. For infected subjects, BOI = SOI. For uninfected subjects, BOI = 0.

PASS has calculated the group sample size at 11,686. The difference between this and the original value of 11,687 may be attributed to rounding. Thus, the procedure is validated.