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 are 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

$$\begin{aligned} Power &= Pr\left(\frac{|T|}{\sqrt{V_0}} > z_{1-\alpha/2}\right) \\ &= Pr\left(\frac{T}{\sqrt{V_0}} > z_{1-\alpha/2}\right) + Pr\left(\frac{T}{\sqrt{V_0}} < -z_{1-\alpha/2}\right) \\ &= \Phi\left(\frac{-z_{1-\alpha/2}\sqrt{V_0} + (P_2\mu_2 - P_1\mu_1)}{\sqrt{V_1}}\right) + 1 - \Phi\left(\frac{z_{1-\alpha/2}\sqrt{V_0} + (P_2\mu_2 - P_1\mu_1)}{\sqrt{V_1}}\right) \end{aligned}$$

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 the 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

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**.

Option	Value
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**

Annotated Output

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

Numeric Results

Numeric Results

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

				Event Prob		Mean			Std Dev		Vaccine Efficacy		
				Vax	Cntl	Vax	Cntl	Change in BOI	Vax	Cntl	Scores	Probs	
Power	N1	N2	N	P1	P2	μ1	μ2	δ	σ1	σ2	VE$_{BOI}$	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

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.

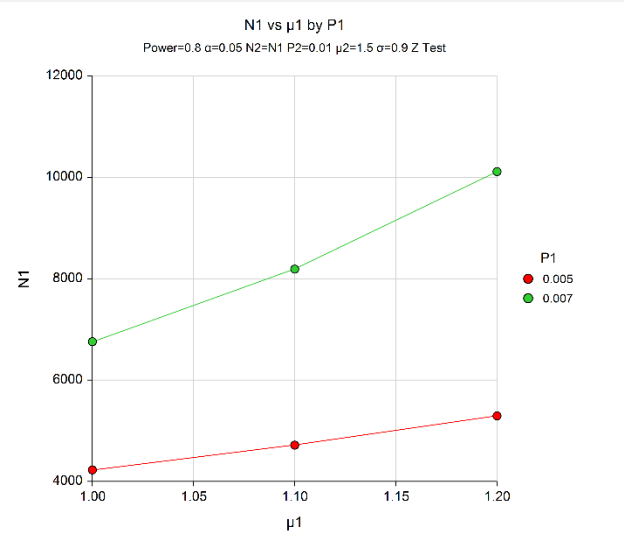
Report Definitions
The severity-of-illness (SOI) score is only obtained from those subjects that were infected.
The burden-of-illness (BOI) score is obtained from all subjects. For infected subjects, BOI = SOI. For uninfected subjects, BOI = 0.
Power is the probability of rejecting a false null hypothesis.
N1 and N2 are the sample sizes of the vaccine group and the control group, respectively.
N is the total sample size, N1 + N2.
P1 is the event probability of the vaccine group assumed by H1.
P2 is the event probability (attack rate) of the control group.
μ1 is the mean severity score of those infected in the vaccine group.
μ2 is the mean severity score of those infected in the control group.
δ change in the BOI score between the two groups. δ = Sc2 - Sc1, where Sc1 = P1(μ1) and Sc2 = P2(μ2).
σ1 is the standard deviation of the severity scores of those infected in the vaccine group.
σ2 is the standard deviation of the severity scores of those infected in the control group.
VE_{BOI} is the vaccine efficacy using the BOI scores assumed by H1. VE_{BOI} = 1 - (P1 μ1) / (P2 μ2). VE_{BOI} is included for reference only.
VE is the vaccine efficacy assumed by H1. VE = 1 - P1 / P2. VE is included for reference only.
Alpha is the probability of rejecting a true null hypothesis.

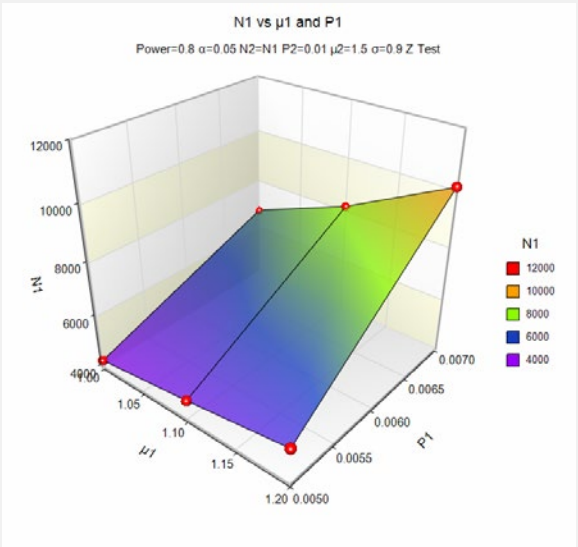
Summary Statements
Sample sizes of 4227 in the vaccine group and 4227 in the control group achieve 80% power to detect a difference in mean burden-of-illness (BOI) scores of 0.01 between the two groups. The significance level of the two-sided test is 0.05. The control group event probability is 0.01. The power is for the case when the actual vaccine group event probability is 0.005. The severity score means of the vaccine and control groups are 1 and 1.5. The severity score standard deviations of the vaccine and control groups are 0.9 and 0.9. Note that these severity scores are only obtained from those subjects that were infected. The test statistic is the two-sided Z Test.

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

Chart Section

Chart Section





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

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**.

Option	Value
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

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

				Event Prob		Mean			Std Dev		Vaccine Efficacy		
				Vax	Cntl	Vax	Cntl	Change in BOI	Vax	Cntl	Scores	Probs	
Power	N1	N2	N	P1	P2	μ1	μ2	δ	σ1	σ2	VEBOI	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

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.