Chapter 358

Non-Inferiority Tests for Vaccine Efficacy using the Ratio of Two Negative Binomial Rates

Introduction

This module provides power analysis and sample size calculation for non-inferiority tests for vaccine efficacy (VE) using the ratio of two negative binomial incidence rates.

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

$$VE = \frac{\lambda_1 - \lambda_2}{\lambda_1} = 1 - \frac{\lambda_2}{\lambda_1}$$

where λ_2 and λ_1 are *incidence rates* of the disease being studied among those vaccinated with a new vaccine and those not vaccinated with the new vaccine. An incidence rate is the average number of events per subject per unit of time. An analysis of vaccine effectiveness reduces to an analysis of the ratio of two incidence rates.

Note that because $\lambda_2 < \lambda_1$ (because lower rates are better), the value of $VE < 1$.

The calculation details are found in Zhu (2017). Some of the details are summarized below.

Technical Details

Definition of Terms

The following table presents the various terms that are used.

Group	**1 (Control)**	**2 (Treatment)**
Sample size	N_1	N_2
Individual event rates	λ_1	λ_2

Dispersion parameter: φ (Negative binomial dispersion)

Average exposure time: μ_t

Non-inferiority margin ratio: R_0 ($R_0 < 1$)

Non-inferiority VE boundary: VE_0 ($VE_0 < 1$)

Sample size ratio: $\theta = N_2/N_1$

Hypotheses

When higher rates are worse, the non-inferiority test hypotheses are

$$H_0: \frac{\lambda_2}{\lambda_1} \geq R_0 \quad \text{vs.} \quad H_1: \frac{\lambda_2}{\lambda_1} < R_0$$

where $R_0 < 1$.

In terms of *VE*, the statistical hypothesis tested by the non-inferiority test can be written as

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

Note that $VE_0 = 1 - R_0$.

Sample Size and Power Calculations

Sample Size Calculation

Zhu (2017) bases the sample size calculations on a non-inferiority test derived from a *negative binomial regression* model. The sample size calculation is

$$N_1 \geq \frac{\left(z_\alpha \sqrt{V_0} + z_\beta \sqrt{V_1}\right)^2}{(\log(R_0) - \log(\lambda_2/\lambda_1))^2}$$

$$N_2 = \theta N_1$$

where

$$V_1 = \frac{1}{\mu_t}\left(\frac{1}{\lambda_1} + \frac{1}{\theta\lambda_2}\right) + \frac{(1+\theta)\varphi}{\theta}$$

$$R_0 = 1 - VE_0$$

and V_0 may be calculated in any of 3 ways.

V_0 Calculation Method 1 (using assumed true rates)

$$V_{01} = \frac{1}{\mu_t}\left(\frac{1}{\lambda_1} + \frac{1}{\theta\lambda_2}\right) + \frac{(1+\theta)\varphi}{\theta}$$

Using Method 1, V_0 and V_1 are equal.

V_0 Calculation Method 2 (fixed marginal total)

$$V_{02} = \frac{(1 + R_0\theta)^2}{\mu_t R_0 \theta(\lambda_1 + \theta\lambda_2)} + \frac{(1+\theta)\varphi}{\theta}$$

V_0 Calculation Method 3 (restricted maximum likelihood estimation)

$$V_{03} = \frac{2a}{\mu_t\left(-b - \sqrt{b^2 - 4ac}\right)}\left(1 + \frac{1}{\theta R_0}\right) + \frac{(1+\theta)\varphi}{\theta}$$

where

$$a = -\varphi\mu_t R_0(1+\theta),$$

$$b = \varphi\mu_t(\lambda_1 R_0 + \theta\lambda_2) - (1 + \theta R_0),$$

$$c = \lambda_1 + \theta\lambda_2$$

Zhu (2017) did not give a recommendation regarding whether Method 1, 2, or 3 should be used, except to say that "for many scenarios, Methods 1 and 2 gave the smallest and largest sample sizes, respectively, while the sample sizes given by Method 3 were between the other two methods and had the closest simulated power values to the targeted power."

Power Calculation

The corresponding power calculation to the sample size calculation above is

$$Power \geq 1 - \Phi\left(\frac{\sqrt{N_1}(\log(R_0) - \log(\lambda_2/\lambda_1)) - z_\alpha\sqrt{V_0}}{\sqrt{V_1}}\right)$$

Example 1 – Calculating Sample Size

Researchers wish to determine whether the average negative binomial rate of those receiving a new vaccine is not inferior to the current control. The average exposure time for all subjects is 1 year. The incidence rate of the control group is 0.1 events per year. Overdispersion is not anticipated. The desired power is 0.8 and the significance level will be 0.025. The variance calculation method used will be the restricted MLE.

How large of a sample is needed to detect a change in vaccine efficacy from -0.5 to 0.1, 0.3, 0.5?

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**
Variance Calculation Method	**Restricted Maximum Likelihood Estimation**
Power	**0.90**
Alpha	**0.025**
μ(t) (Average Exposure Time)	**1**
Group Allocation	**Equal (N1 = N2)**
Vaccine Efficacy Input Type	**Enter VE0 and VE1**
VE0 (Non-Inferiority Vaccine Efficacy)	**-0.5**
VE1 (Actual Vaccine Efficacy)	**0.5 0.3 0.1**
λ1 (Control Group Incidence Rate)	**0.1**
φ (Dispersion)	**1**

Output

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

Numeric Reports

Numeric Results

Solve For:	Sample Size
Variance Calculation Method:	Restricted Maximum Likelihood
Groups:	1 = Control, 2 = Vaccine
Higher Event Rates Are:	Worse
Hypotheses:	H0: VE ≤ VE0 vs. H1: VE > VE0

	Sample Size			Average Exposure Time	Incidence Rate			Vaccine Efficacy			
						Vaccine					
Power	N1	N2	N	μ(t)	Control λ1	Non-Inferiority λ2.0	Actual λ2.1	Non-Inferiority VE0	Actual VE1	Dispersion φ	Alpha
0.90026	949	949	1898	1	0.1	0.15	0.09	-0.5	0.1	1	0.025
0.90038	477	477	954	1	0.1	0.15	0.07	-0.5	0.3	1	0.025
0.90032	266	266	532	1	0.1	0.15	0.05	-0.5	0.5	1	0.025

Power	The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N1 and N2	The number of subjects in groups 1 and 2, respectively.
N	The total sample size. N = N1 + N2.
μ(t)	The average exposure (observation) time across subjects in both groups.
λ1	The event rate per time unit in Group 1 (control).
λ2.0	The incidence rate per unit in the vaccine group under the null hypothesis. This may be thought of as a non-inferiority bound for the incidence rate.
λ2.1	The incidence rate per unit in the vaccine group under the alternative hypothesis.
VE1	The vaccine efficacy under the alternative hypothesis. VE1 = 1 - λ2.1 / λ1.
VE0	The vaccine efficacy under the null hypothesis. This may be thought of as the non-inferiority bound for vaccine efficacy.
φ	The negative binomial dispersion parameter. Overdispersion is modelled by setting φ > 1.
Alpha	The probability of rejecting a true null hypothesis.

Summary Statements

A parallel two-group design (with the assumption that higher event rates are worse) will be used to test whether the Group 2 (vaccine) Negative Binomial rate (λ2) is non-inferior to the Group 1 (control) Negative Binomial rate (λ1), by testing whether the vaccine efficacy (VE = 1 - λ2 / λ1) is greater than -0.5 (H0: VE ≤ -0.5 versus H1: VE > -0.5). The comparison will be made using a one-sided, negative binomial regression coefficient test with the restricted maximum likelihood estimation variance calculation method, with a Type I error rate (α) of 0.025. The incidence rate of the control group (λ1) is assumed to be 0.1. The dispersion coefficient is assumed to be 1. The average exposure (or observation) time across subjects in both groups is assumed to be 1. To detect a vaccine efficacy of 0.1 (or treatment group incidence rate of 0.09) with 90% power, the number of subjects needed will be 949 in the control group and 949 in the vaccine 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%	949	949	1898	1187	1187	2374	238	238	476
20%	477	477	954	597	597	1194	120	120	240
20%	266	266	532	333	333	666	67	67	134

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, 1187 subjects should be enrolled in Group 1, and 1187 in Group 2, to obtain final group sample sizes of 949 and 949, respectively.

References

Zhu, H. 2017. 'Sample Size Calculation for Comparing Two Poisson or Negative Binomial Rates in Non-Inferiority or Equivalence Trials.' Statistics in Biopharmaceutical Research, 9(1), 107-115, doi:10.1080/19466315.2016.1225594.

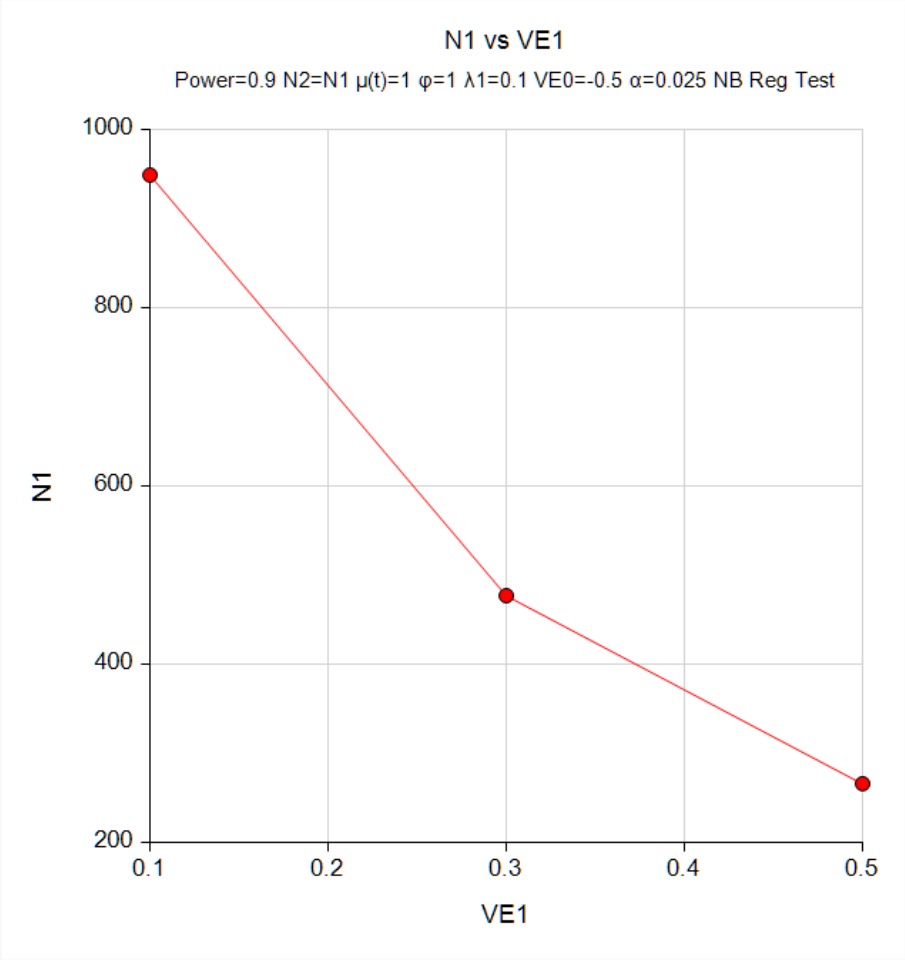
Machin, D., Campbell, M., Tan, S.B., and Tan, S.H. 2009. Sample Size Tables for Clinical Studies, 3rd Edition. Wiley-Blackwell. Chichester, UK.

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

This report shows the sample sizes for the indicated scenarios.

Plots Section

Plots



This plot presents the required sample sizes for various values of VE1.

Example 2 – Validation using Zhu (2017)

Zhu (2017) presents an example of solving for sample size where lower negative binomial rates are better, the event rates are both 1.5, the dispersion is 0.24, the average duration is 0.85, the non-inferiority ratio is 1.1, the power is 0.9, and the Type I error rate is 0.025. These rates translate to VE0 = -0.1 and VE1 = 0.

Using the restricted MLE variance method, the sample size in each group is found to be 2372.

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**
Variance Calculation Method	**Restricted Maximum Likelihood Estimation**
Power	**0.9**
Alpha	**0.025**
μ(t) (Average Exposure Time)	**0.85**
Group Allocation	**Equal (N1 = N2)**
Vaccine Efficacy Input Type	**Enter VE0 and VE1**
VE0 (Non-Inferiority Vaccine Efficacy)	**-0.1**
VE1 (Actual Vaccine Efficacy)	**0**
λ1 (Control Group Incidence Rate)	**1.5**
φ (Dispersion)	**0.24**

Output

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

Numeric Results

Solve For:	Sample Size
Variance Calculation Method:	Restricted Maximum Likelihood
Groups:	1 = Control, 2 = Vaccine
Higher Event Rates Are:	Worse
Hypotheses:	H0: VE ≤ VE0 vs. H1: VE > VE0

	Sample Size			Average Exposure Time	Incidence Rate			Vaccine Efficacy			
						Vaccine					
Power	N1	N2	N	μ(t)	Control λ1	Non-Inferiority λ2.0	Actual λ2.1	Non-Inferiority VE0	Actual VE1	Dispersion φ	Alpha
0.90006	2372	2372	4744	0.85	1.5	1.65	1.5	-0.1	0	0.24	0.025

The value of N1 = 2372 matches the previous procedure, so this procedure is validated.