Chapter 191

Superiority by a Margin Tests for Vaccine Efficacy using the Ratio of Two Proportions in a Cluster-Randomized Design

Introduction

This module provides power analysis and sample size calculation for superiority by a margin tests for vaccine efficacy (VE) using the ratio of two proportions in a two-sample, cluster-randomized design in which the outcome is binary.

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 and those not vaccinated. 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 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 $VE < 1$.

Cluster-randomized designs are those in which whole clusters of subjects (classes, hospitals, communities, etc.) are placed into the vaccine group or the control group. The vaccine efficacy is tested using a *z* test or a logistic regression test. Generally speaking, the larger the cluster sizes and the higher the correlation among subjects within the same cluster, the larger will be the overall sample size necessary to detect an effect with the same power.

This routine is partially based on Blackwelder (1993). It is also based on the work about how to adapt two-sample formulas to cluster-randomized designs by Donner and Klar (2000) as well as Machin et al. (2018).

Technical Details

Our formulation comes from Donner and Klar (2000). Denote a binary observation by $Y_{gkj}$where g = 1 or 2 is the group, k = 1, 2, ..., K_g is a cluster within group g, and j = 1, 2, ..., M_g is an individual in cluster k of group g.

The statistical hypothesis that is tested concerns the ratio of the two group proportions, p_1 and p_2. We assume that group 1 is the vaccine group and group 2 is the control group. With a simple modification, all of the large-sample sample size formulas that are listed in the module for testing superiority by a margin with two proportions using the ratio can be used here.

When the individual subjects are randomly assigned to one of the two groups, the variance of the sample proportion is

$$\sigma_{S,g}^2 = \frac{p_g(1-p_g)}{n_g}$$

When the randomization is by clusters of subjects, the variance of the sample proportion is

$$\sigma_{C,g}^2 = \frac{p_g(1-p_g)DE}{k_g m_g}$$

$$= \sigma_{S,g}^2 DE$$

where DE is the *design effect*. We use the following version of DE given by Machin et al. (2018) which allows for an adjustment for unequal cluster sizes.

$$DE = 1 + \left\{\left[COV(m)^2\left(\frac{K-1}{K}\right) + 1\right]\bar{m} - 1\right\}\rho$$

This formula assumes that the cluster sizes, *m*, are distributed with a mean of $\bar{m}$ and a coefficient of variation of $COV(m)$.

The Greek letter ρ is used to represent the *intracluster correlation coefficient (ICC)*. This correlation may be thought of as the simple correlation between any two subjects within the same cluster. If we stipulate that ρ is positive, it may also be interpreted as the proportion of total variability that is attributable to differences between clusters. This value is critical to the sample size calculation.

The asymptotic formula for the Farrington and Manning Likelihood Score Test that was used in comparing two proportions (see Chapter 196, "Superiority by a Margin Tests for the Ratio of Two Proportions") may be used with cluster-randomized designs as well, as long as an adjustment is made for the design effect.

Farrington and Manning's Likelihood Score Test

Farrington and Manning (1990) proposed a test statistic for testing whether the ratio is equal to a specified value ϕ_0. The regular MLE's, $\hat{p}_1$ and $\hat{p}_2$, are used in the numerator of the score statistic while MLE's $\tilde{p}_1$ and $\tilde{p}_2$, constrained so that $\tilde{p}_1 / \tilde{p}_2 = \phi_0$, are used in the denominator. A correction factor of N/(N-1) is applied to increase the variance estimate. The significance level of the test statistic is based on the asymptotic normality of the score statistic.

The formula for computing the test statistic is

$$z_{FMR} = \frac{\hat{p}_1 / \hat{p}_2 - \phi_0}{\sqrt{\left(\frac{\tilde{p}_1\tilde{q}_1}{n_1} + \phi_0^2\frac{\tilde{p}_2\tilde{q}_2}{n_2}\right)}}$$

where the estimates $\tilde{p}_1$ and $\tilde{p}_2$ are computed as in the corresponding test of Miettinen and Nurminen (1985). Note that in large samples, the Farrington and Manning statistic is substituted for the Gart and Nam statistic.

Adapting the Ratio of Two Proportions to Vaccine Efficacy Studies

A traditional index of the protective efficacy of a vaccine is called the vaccine efficacy (VE). It is calculated as

$$VE = \frac{p_2 - p_1}{p_2} = 1 - \frac{p_1}{p_2}$$

Note that VE is a simple transformation of the ratio made by subtracting it from one. Thus, methods for the ratio of two proportions can be easily adapted for vaccine efficacy studies. Blackwelder (1993) gives the details.

Power Calculations

The power for the above test statistic can be computed exactly using two binomial distributions. The following steps are taken to compute the power of these tests.

1. Find the critical value using the standard normal distribution. The critical value, $z_{critical}$, is that value of *z* that leaves exactly the target value of alpha in the appropriate tail of the normal distribution.
2. Compute the value of the test statistic, z_t, for every combination of x_{11} and x_{21}. Note that x_{11} ranges from 0 to n_1, and x_{21} ranges from 0 to n_2. A small value (around 0.0001) can be added to the zero-cell counts to avoid numerical problems that occur when the cell value is zero.
3. If $z_t > z_{critical}$, the combination is in the rejection region. Call all combinations of x_{11} and x_{21} that lead to a rejection the set *A*.
4. Compute the power for given values of $p_{1.1}$ and p_2 as

$$1 - \beta = \sum_A \binom{n_1}{x_{11}} p_{1.1}^{x_{11}} q_{1.1}^{n_1 - x_{11}} \binom{n_2}{x_{21}} p_2^{x_{21}} q_2^{n_2 - x_{21}}.$$

5. Compute the actual value of alpha achieved by the design by substituting $p_{1.0}$ for $p_{1.1}$ to obtain

$$\alpha^* = \sum_A \binom{n_1}{x_{11}} p_{1.0}^{x_{11}} q_{1.0}^{n_1 - x_{11}} \binom{n_2}{x_{21}} p_2^{x_{21}} q_2^{n_2 - x_{21}}.$$

Asymptotic Approximations

In cluster-randomized designs, a large sample approximation can be used which uses the DE adjustment shown above. The large sample approximation is made by replacing the values of $\hat{p}_1$ and $\hat{p}_2$ in the *z* statistic with the corresponding values of $p_{1.1}$ and p_2, and then computing the results based on the normal distribution. Note that in large samples, the Farrington and Manning statistic is substituted for the Gart and Nam statistic.

Example 1 – Finding Sample Size

A cluster-randomized study is being designed to establish the superiority of a new vaccine over a placebo. The researchers plan to use the Farrington and Manning likelihood score test to analyze the data. They want to find the sample size required to guarantee a power of 0.9 when the superiority vaccine efficacy is set to 0.4 and the actual vaccine efficacy is set to values of 0.5, 0.6, 0.7, 0.8, and 0.9. The event probability of the control group is 0.04. The significance level will be 0.025.

The researchers estimate that the average cluster size will be 100 and the COV of cluster sizes will be 0.65.

They want to consider three values of the intracluster correlation: 0 0.01 0.02. The value of zero lets them determine the sample size requirements if the clustering were ignored.

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 (Clusters)**
Power	**0.90**
Alpha	**0.025**
M1 (Average Cluster Size)	**100**
K2 (Clusters in Group 2)	**K1**
M2 (Average Cluster Size)	**M1**
COV of Cluster Sizes	**0.65**
Vaccine Efficacy Input Type	**Enter VE0, VE1, and P2**
VE0 (Superiority Vaccine Efficacy)	**0.4**
VE1 (Actual Vaccine Efficacy)	**0.5 0.6 0.7 0.8 0.9**
P2 (Control Group Event Probability)	**0.04**
ρ (Intracluster Correlation, ICC)	**0 0.01 0.02**

Output

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

Numeric Reports

Numeric Results

Solve For: Sample Size (Clusters)
Test Statistic: Likelihood Score Test (Farrington & Manning)
Groups: 1 = Vaccine, 2 = Control
Hypotheses: H0: VE ≤ VE0 vs. H1: VE > VE0

	Number of Clusters			Cluster Size			Total Sample Size	Event Probability: Vaccine		Event Probability: Control	Vaccine Efficacy		Intracluster Correlation	
Power	Vaccine K1	Control K2	Total K	Vaccine M1	Control M2	COV	N	Superiority P1.0	Actual P1.1	P2	Superiority VE0	Actual VE1	ρ	Alpha
0.90030	226	226	452	100	100	0.65	45200	0.024	0.020	0.04	0.4	0.5	0.00	0.025
0.90027	545	545	1090	100	100	0.65	109000	0.024	0.020	0.04	0.4	0.5	0.01	0.025
0.90022	864	864	1728	100	100	0.65	172800	0.024	0.020	0.04	0.4	0.5	0.02	0.025
0.90180	52	52	104	100	100	0.65	10400	0.024	0.016	0.04	0.4	0.6	0.00	0.025
0.90117	125	125	250	100	100	0.65	25000	0.024	0.016	0.04	0.4	0.6	0.01	0.025
0.90081	198	198	396	100	100	0.65	39600	0.024	0.016	0.04	0.4	0.6	0.02	0.025
0.90246	21	21	42	100	100	0.65	4200	0.024	0.012	0.04	0.4	0.7	0.00	0.025
0.90541	51	51	102	100	100	0.65	10200	0.024	0.012	0.04	0.4	0.7	0.01	0.025
0.90208	80	80	160	100	100	0.65	16000	0.024	0.012	0.04	0.4	0.7	0.02	0.025
0.91392	11	11	22	100	100	0.65	2200	0.024	0.008	0.04	0.4	0.8	0.00	0.025
0.90999	26	26	52	100	100	0.65	5200	0.024	0.008	0.04	0.4	0.8	0.01	0.025
0.90063	40	40	80	100	100	0.65	8000	0.024	0.008	0.04	0.4	0.8	0.02	0.025
0.90418	6	6	12	100	100	0.65	1200	0.024	0.004	0.04	0.4	0.9	0.00	0.025
0.91830	15	15	30	100	100	0.65	3000	0.024	0.004	0.04	0.4	0.9	0.01	0.025
0.90783	23	23	46	100	100	0.65	4600	0.024	0.004	0.04	0.4	0.9	0.02	0.025

Power	The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
K1, K2, and K	The number of clusters in groups 1, 2, and both, respectively.
M1 and M2	The average cluster size (number of subjects per cluster) in groups 1 and 2, respectively.
COV	The coefficient of variation of the cluster sizes. This is used for both groups.
N	The total number of subjects in the study. N = (K1 x M1) + (K2 x M2).
P1.0	The largest value of the event probability (attack rate) for the vaccinated group that still yields a superiority conclusion.
P1.1	The value of the event probability for the vaccinated group that is assumed by the alternative hypothesis, H1.
P2	The event probability of the control group.
VE0	The vaccine efficacy assumed by the null hypothesis, H0. This is the lower 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. VE1 = 1 - P1.1/P2.
ρ	The intracluster correlation.
Alpha	The probability of rejecting a true null hypothesis.

Summary Statements

A two-group cluster-randomized design will be used to test whether the Group 1 (vaccine) proportion (P1) is superior to the Group 2 (control) proportion (P2) by a margin, by testing whether the vaccine efficacy (VE = 1 - P1 / P2) is greater than 0.4 (H0: VE ≤ 0.4 versus H1: VE > 0.4). The comparison will be made using a one-sided proportion-ratio score test with a Type I error rate (α) of 0.025. The coefficient of variation of the cluster sizes is assumed to be 0.65. The intracluster correlation is assumed to be 0. The control group proportion (event probability) is assumed to be 0.04. To detect a vaccine efficacy of 0.5 (or vaccine event probability of 0.02) with 90% power, the number of clusters needed will be 226 in the vaccine group, with 100 subjects per cluster (totaling 22600 subjects), and 226 clusters in the control group, with 100 subjects per cluster (totaling 22600 subjects).

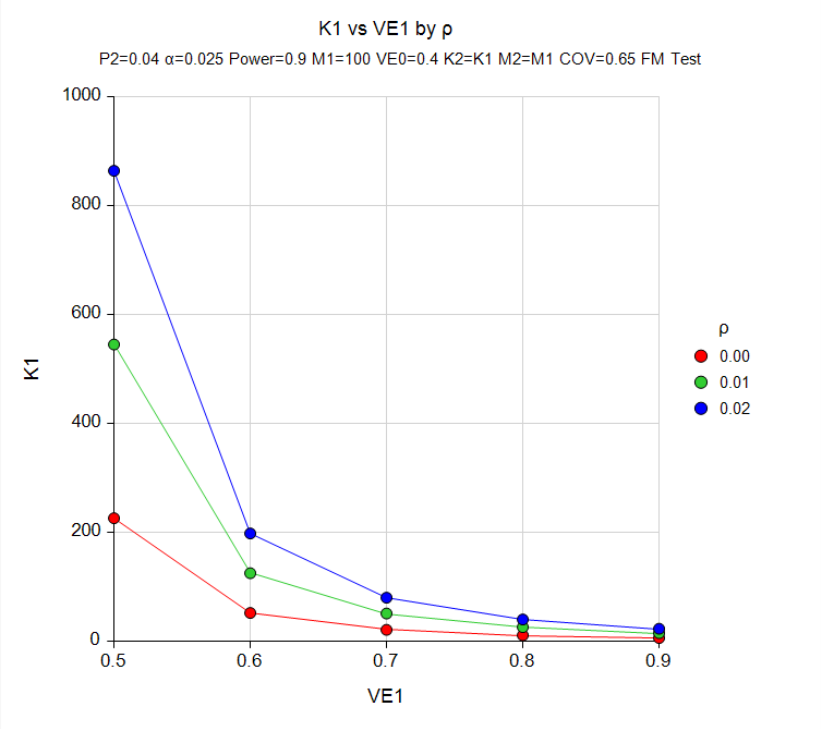
References

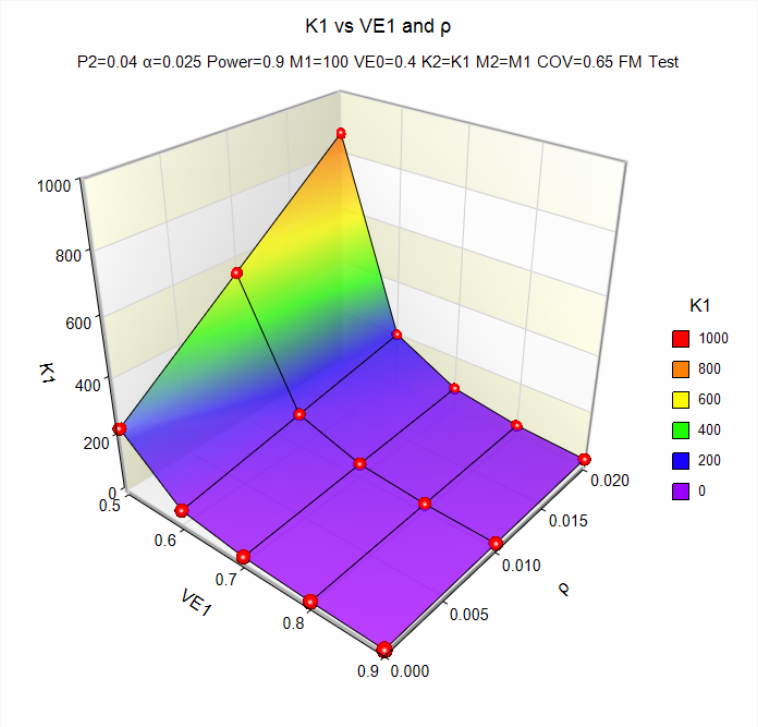
Blackwelder, W.C. 1998. 'Equivalence Trials.' In Encyclopedia of Biostatistics, John Wiley and Sons. New York. Volume 2, 1367-1372.
Campbell, M.J. and Walters, S.J. 2014. How to Design, Analyse and Report Cluster Randomised Trials in Medicine and Health Related Research. Wiley. New York.
Donner, A. and Klar, N. 2000. Design and Analysis of Cluster Randomization Trials in Health Research. Arnold. London.
Farrington, C. P. and Manning, G. 1990. 'Test Statistics and Sample Size Formulae for Comparative Binomial Trials with Null Hypothesis of Non-Zero Risk Difference or Non-Unity Relative Risk.' Statistics in Medicine, Vol. 9, pages 1447-1454.
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 values of each of the parameters, one scenario per row.

Plots Section

Plots





The values from the table are displayed on the above charts. These charts give a quick look at the sample sizes that will be required for various values of VE1.

Example 2 – Validation using Blackwelder (1993)

We could not find a direct validation example, so we will mix an example from the literature with some hand calculations to obtain a validation example.

Blackwelder (1993), page 694, presents an example in which the significance level is 0.05, power is 0.8, P2 is 0.04, VE0 is 0.7, and VE1 is 0.9. The Miettinen and Nurminen likelihood score test is used. The calculations are based on the normal approximation to the binomial. His result is 2119. **PASS** obtains N = 2120 since it forces N1 = N2. Hence, the validation result is N1 = N2 = 1060.

This example did not include adjustments for cluster randomizations, so we will add those manually. The basic adjustment is to multiply the 1060 by the design effect, DE, to obtain the adjusted sample size.

Suppose we set M1 = M2 = 10, ρ = 0.1, and COV = 0.5. Using the relationship N1 = K1 x M1, we find K1 = 106 before the other CR adjustments are made. The value of DE is computed as

$$\begin{aligned} DE &= 1 + \left\{\left[COV(m)^2\left(\frac{K-1}{K}\right) + 1\right]\bar{m} - 1\right\}\rho \\ &= 1 + \left\{\left[0.25\left(\frac{105}{106}\right) + 1\right]10 - 1\right\}0.1 \\ &= 2.1476 \end{aligned}$$

Hence, the corresponding cluster-randomized design requires $K1' = 106(2.1476) = 227.65 \approx 228$ clusters per group.

Note also that Blackwelder uses the Miettinen and Nurminen score test while this procedure uses the Farrington and Manning score test. It turns out that these two procedures give nearly identical results for large sample sizes.

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 (Clusters)**
Power	**0.8**
Alpha	**0.05**
M1 (Average Cluster Size)	**10**
K2 (Clusters in Group 2)	**K1**
M2 (Average Cluster Size)	**M1**
COV of Cluster Sizes	**0.5**
Vaccine Efficacy Input Type	**Enter VE0, VE1, and P2**
VE0 (Superiority Vaccine Efficacy)	**0.7**
VE1 (Actual Vaccine Efficacy)	**0.9**
P2 (Control Group Event Probability)	**0.04**
ρ (Intracluster Correlation, ICC)	**0.1**

Output

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

Numeric Results

Solve For: Sample Size (Clusters)
Test Statistic: Likelihood Score Test (Farrington & Manning)
Groups: 1 = Vaccine, 2 = Control
Hypotheses: H0: VE ≤ VE0 vs. H1: VE > VE0

	Number of Clusters			Cluster Size			Total Sample Size	Event Probability			Vaccine Efficacy			
								Vaccine						
Power	Vaccine K1	Control K2	Total K	Vaccine M1	Control M2	COV	N	Superiority P1.0	Actual P1.1	Control P2	Superiority VE0	Actual VE1	Intracluster Correlation ρ	Alpha
0.80059	228	228	456	10	10	0.5	4560	0.012	0.004	0.04	0.7	0.9	0.1	0.05

PASS also calculated the number of clusters per group to be 228. Thus, the procedure is validated.