

Chapter 244

Tests for the Difference Between Two Poisson Rates in a Cluster-Randomized Design with Adjustment for Varying Cluster Sizes

Introduction

This procedure calculates power and sample size for tests of two means in a cluster-randomized design in which the outcome variable is a count. It uses the work of Wang, Zhang, and Ahn (2018) which give the power for the case of varying cluster sizes. The analysis is of a simple z-test comparing the two means.

Technical Details

The following discussion summarizes the results in Wang, Zhang, and Ahn (2018).

Suppose you are interested in comparing the means of two groups (treatment and control). Further suppose that the response is known to be related to other covariates (such as age, race, or gender) and so their impact needs to be adjusted for. This may be accomplished by stratifying on the covariates and forming hypotheses about a common mean difference across all clusters and strata. Often, the stratification is based on cluster size, but this is not required.

Let Y_{jki} be the count outcome of the i th ($i = 1, \dots, n_{jk}$) subject in the k th ($k = 1, \dots, K_j$) cluster of the j th ($j = 1, 2$) group. Assuming that Y_{jki} follows a Poisson model with

$$\lambda_j = E(Y_{jki}) = \text{Var}(Y_{jki})$$

and a common intraclass correlation coefficient (ICC) $\rho = \text{corr}(Y_{jki}, Y_{jki'})$ for $i \neq i'$.

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Test Statistic

An unbiased estimator of λ_j is

$$\hat{\lambda}_j = \frac{\sum_{k=1}^{K_j} \sum_{i=1}^{n_{jk}} Y_{jki}}{\sum_{k=1}^{K_j} n_{jk}}$$

with estimated variance

$$s_j^2 = \frac{\hat{\lambda}_j \sum_{k=1}^{K_j} n_{jk} [1 + (n_{jk} - 1)\hat{\rho}]}{\left(\sum_{k=1}^{K_j} n_{jk}\right)^2}$$

Using a two-sided hypothesis $H_0: \lambda_1 = \lambda_2$ versus $H_1: \lambda_1 \neq \lambda_2$, H_0 is rejected if

$$\frac{\hat{\lambda}_1 - \hat{\lambda}_2}{\sqrt{s_1^2 + s_2^2}} > z_{1-\alpha/2}$$

Sample Size and Power

Wang, Zhang, and Ahn (2018) provide the following formula for estimating K_2 (the number of clusters in the control group) when there are an unequal number of clusters in each group.

$$K_2 = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2 \left(\frac{\lambda_1}{r} + \lambda_2\right)}{(\lambda_1 - \lambda_2)^2} \left[(1 - \rho) \frac{1}{\theta} + \rho + \rho\gamma^2 \right]$$

where $r = K_1/K_2$, $\theta = E(n_{jk})$, $\tau^2 = \text{Var}(n_{jk})$, and $\gamma = \tau/\theta$. Hence θ is the average cluster size of all clusters in the study and γ is the coefficient of variation of the cluster sizes. Note that $z_x = \Phi(x)$ is the standard normal distribution function.

This equation can easily be rearranged to provide a formula for power $(1 - \beta)$.

Procedure Options

This section describes the options that are specific to this procedure. These are located on the Design tab. For more information about the options of other tabs, refer to the Procedure Window chapter.

Design Tab

The Design tab contain most of the parameters and options of interest for this procedure.

Solve For**Solve For**

This option specifies the parameter to be solved for using the other parameters. The parameters that may be selected are δ , *Power*, or *K1 (Number of Clusters in Group 1)*. Select *K1 (Number of Clusters in Group 1)* when you want to calculate the sample size needed to achieve a given power and alpha level. Select *Power* when you want to calculate the power.

Test

Alternative Hypothesis

Specify the alternative hypothesis, H1.

- **One-Sided (H1: $\delta < 0$)**
Refers to a lower-tailed, one-sided test with alternative hypothesis H1: $\delta < 0$.
- **One-Sided (H1: $\delta > 0$)**
Refers to an upper-tailed, one-sided test with alternative hypothesis H1: $\delta > 0$.
- **Two-Sided (H1: $\delta \neq 0$)**
Refers to a two-sided test with alternative hypothesis H1: $\delta \neq 0$.

Power and Alpha

Power

Power is the probability of rejecting the null hypothesis when it is false. Power is equal to 1 - Beta, so specifying power implicitly specifies beta.

Beta is the probability of obtaining a false negative with the statistical test. That is, it is the probability of accepting a false null hypothesis.

Values must be between zero and one. Historically, the value of 0.80 (Beta = 0.20) was used for power. Now, 0.90 (Beta = 0.10) is commonly used.

A single value may be entered here or a range of values such as *0.8 to 0.95 by 0.05* may be entered.

Alpha

This option specifies one or more values for the probability of a type-I error. A type-I error occurs when a true null hypothesis is rejected. For this procedure, a type-I error occurs when you reject the null hypothesis of equal group means when in fact they are equal.

Values must be between zero and one. Historically, an alpha value of 0.05 has been recommended for two-sided tests and 0.025 for one-sided tests. You should pick a value for alpha that represents the risk of a type-I error you are willing to take in your experimental situation.

You may enter a range of values such as *0.01 0.05 0.10* or *0.01 to 0.10 by 0.01*.

Sample Size – Number of Clusters and Cluster Size

K1 (Clusters in Group 1)

Enter one or more values for the number of clusters in group 1. The number of subjects in this group is equal to the number of clusters times M, the mean cluster size.

This value must be a positive number. You can use a list of values such as *10 20 30*.

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K2 (Clusters in Group 2)

Enter one or more values for K2, the number of clusters in group 2: the control group.

If you simply want a multiple of the value for group 1, you would enter the multiple followed by “K1”, with no blanks. If you want to use K1 directly, you do not have to enter the leading “1”. For example, all of the following are valid entries: *10K1 2K1 0.5K1 K1*.

You can use a list of values such as “10 20 30” or “K1 2K1 3K1”. $K2 > 0$. K2 is an integer.

Number of Subjects

The number of subjects is computed from the number of clusters using the mean cluster size.

M (Average of Cluster Sizes)

Enter one or more values for the average cluster size (number of subjects per cluster) across all clusters. Values should be in the range $M > 1$.

This procedure lets the cluster sizes vary from cluster to cluster. The individual cluster size values are unknown at the planning stage, so it is assumed that the cluster sizes are distributed according to a discrete distribution with a certain mean and standard deviation. This option gives the mean cluster size and the next option gives the standard deviation by asking for the cluster size coefficient of variation.

CV (Coefficient of Variation of Cluster Sizes)

Enter one or more values for the coefficient of variation of the cluster sizes (the value of γ in the equation above). The coefficient of variation is the standard deviation of the cluster sizes divided by the mean cluster size.

This value can be any number greater than or equal to zero.

This procedure lets the cluster sizes vary from cluster to cluster. This results in a more accurate sample size estimate than is obtained when the cluster sizes are assumed to be a fixed number.

The individual cluster size values are unknown at the planning stage, so it is assumed that the cluster sizes are distributed according to a discrete distribution with a certain mean and standard deviation. This option gives the standard deviation by asking for the cluster size coefficient of variation.

Discrete Uniform Distribution

A reasonable choice for an approximate discrete distribution of cluster sizes is the *discrete uniform distribution* which is referred to as $DU(A,B)$ in Wang, Zhang, and Ahn (2018). Here, A and B are the lower and upper boundaries of a set of consecutive integers. The sample space consists of all integers between A and B, inclusive.

For example, the sample size of $DU(1,6)$ is the integers 1, 2, 3, 4, 5, 6, each occurring with an equal probability. This is the distribution of a single dice.

The mean of $DU(A,B)$ is $(A+B)/2$.

The variance of $DU(A,B)$ is $[(B-A+1)^2 - 1]/12$.

Hence, the CV can be easily calculated.

Here are some examples which may be easily verified.

Distribution	Mean	Variance	CV
$DU(40, 60)$	50	36.67	0.12111
$DU(25,75)$	50	216.67	0.29439
$DU(70, 130)$	100	310.00	0.17607

Effect Size

Enter λ_1 or δ

This option lets you indicate how you want to enter λ_1 .

The options are

- **λ_1 (Event Rate of Group 1)**
Enter the value of λ_1 directly.
- **δ (Difference = $\lambda_1 - \lambda_2$)**
Enter values for the difference between the means. The value of λ_1 is equal to $\lambda_2 + \delta$.

λ_1 (Mean of Group 1)

Enter a value (or range of values) for the mean count per subject in group 1, the treatment group. If Y is a random variable giving the count for a subject in this group, then $\lambda_1 = E(Y)$.

For example, Y might be the number of visits to the doctor during pregnancy, the number of cigarettes smoked, or the number misbehaviors by a child. The point to realize is that Y is a count value for a particular subject.

This value is used with λ_2 to calculate the effect size. The difference $\lambda_1 - \lambda_2$ represents the difference you want to detect with a specified power.

This value must be positive.

You can enter a single value such as "1.0" or a series of values such as "1.0 1.2 1.4" or "1 to 2 by 0.5".

λ_2 (Mean of Group 2)

Enter a value (or range of values) for the mean count per subject in group 2, the control group. If Y is a random variable giving the count for a subject in this group, then $\lambda_2 = E(Y)$.

For example, Y might be the number of visits to the doctor during pregnancy, the number of cigarettes smoked, or the number misbehaviors by a child. The point to realize is that Y is a count value for a particular subject.

This value is used with λ_1 to calculate the effect size. The difference $\lambda_1 - \lambda_2$ represents the difference you want to detect with a specified power.

This value must be positive and unequal to λ_1 .

You can enter a single value such as "1.0" or a series of values such as "1.0 1.2 1.4" or "1 to 2 by 0.5".

δ (Difference = $\lambda_1 - \lambda_2$)

Enter a value (or range of values) for the mean difference between the two groups that you want to detect.

This value must be non-zero.

You can enter a single value such as "1.0" or a series of values such as "1.0 1.2 1.4" or "1 to 2 by 0.5".

ICC (Intraclass Correlation)

Enter a value for ICC, the intraclass correlation coefficient. This may be thought of as the correlation between any two observations in the same cluster.

Note that occasionally, $ICC < 0$.

You may enter a single value or a list of values.

Since this is a correlation coefficient, it is possible for it to range from -1 to 1.

You may enter a range of values such as *0.01 0.02 0.03*.

Example 1 – Finding the Number of Clusters

A study is being planned to investigate whether a new intervention will decrease a certain response variable. This response is a count. For a number of reasons, the researchers decide to administer the intervention to whole clusters (clinics) rather than randomize the treatment to individuals within the cluster. The number of clinics receiving each treatment will be balanced.

The average number of subjects per clinic is 21. The coefficient of variation of the cluster sizes is 0.42.

Prior studies have obtained a base-line mean score of 8.4 and an ICC of 0.31. The researchers want to compare the necessary numbers of clusters when the change in the mean score is -1, -2, and -3.

The two-sided significance level is set to 0.05 and the power is set to 0.9.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load this procedure. 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	K1 (Number of Clusters in Group 1)
Alternative Hypothesis	Two-Sided (H1: $\delta \neq 0$)
Power	0.90
Alpha	0.05
K2 (Clusters in Group 2)	K1
M (Average of Cluster Sizes)	21
CV (Coeff. of Variation of Cluster Sizes)	0.42
Enter λ_1 or δ	δ (Difference = $\lambda_1 - \lambda_2$)
δ (Difference = $\lambda_1 - \lambda_2$)	-1 -2 -3
λ_2 (Mean of Group 2)	8.4
ICC (Intracluster Correlation)	0.31

Annotated Output

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

Numeric Results

Numeric Results

Hypotheses: H0: $\delta = 0$ vs. H1: $\delta \neq 0$

	Sample Size	Clus Cnt Total	Clus Cnt Grp 1	Clus Cnt Grp 2	Alloc Ratio K1/K2	Clus Size Ave M	Clus Size Coef Var CV	Mean Grp 1 λ_1	Mean Grp 2 λ_2	Mean Diff $\lambda_1 - \lambda_2$ δ	Intra-Clus Corr ICC	Alpha
Power	N	K	K1	K2	K1/K2	M	CV	λ_1	λ_2	δ	ICC	Alpha
0.9235	294	14	7	7	1.00	21	0.420	5.40	8.40	-3.00	0.310	0.050
0.9096	672	32	16	16	1.00	21	0.420	6.40	8.40	-2.00	0.310	0.050
0.9000	2772	132	66	66	1.00	21	0.420	7.40	8.40	-1.00	0.310	0.050

References

Wang, J., Zhang, S., and Ahn, C. 2018. 'Sample size calculation for count outcomes in cluster randomization trials with varying cluster sizes.' Communications in Statistics--Theory and Methods, DOI: 10.1080/03610926.2018.1532004.

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Report Definitions

Power is the probability of rejecting a false null hypothesis. It should be close to one.

N is the total sample size, i.e., the total number of subjects from all clusters.

K is the total cluster count. It is the total number of clusters.

K_1 is the number of clusters assigned to group 1, the treatment group.

K_2 is the number of clusters assigned to group 2, the control group.

K_1/K_2 is the allocation ratio. This is the number of group 1 clusters divided by the number of group 2 clusters.

M is the average cluster size. It is the average number of subjects per cluster based on all cluster sizes.

CV is the coefficient of variation of the cluster sizes. It is the standard deviation of cluster sizes divided by the average cluster size.

λ_1 is mean number of events per subject in group 1, the treatment group.

λ_2 is mean number of events per subject in group 2, the control group.

$\delta = \lambda_1 - \lambda_2$ is the mean difference assumed by the alternative hypothesis. This is the difference at which the power is computed.

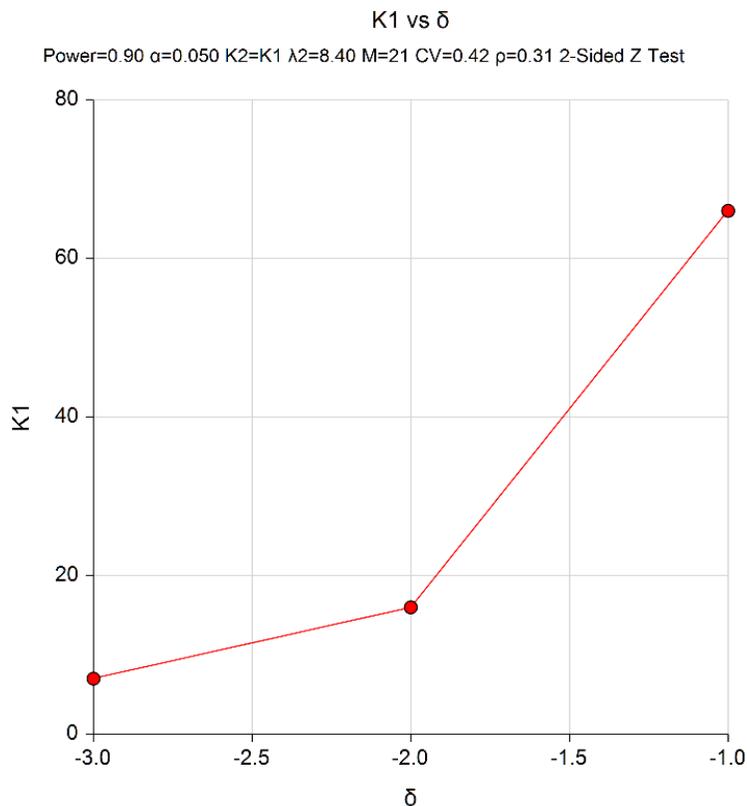
ICC is the intracluster correlation coefficient. This is the correlation between any two subjects within a particular cluster.

Alpha is the probability of rejecting a true null hypothesis.

Summary Statements

A cluster randomized design consists of 7 clusters in the treatment and 7 clusters in the control group for a grand total of 14 clusters. The number of events for each subject is the outcome (response) variable. The difference between the two group means is analyzed using a two-sided z-test. The expected sample size of 294 subjects achieves 92% power to reject the mean difference of zero assumed by the null hypothesis when the difference is actually -3.00. This difference is calculated from the treatment mean of 5.40 and the control mean of 8.40. The intracluster correlation coefficient is 0.310. The significance level of the test is 0.050. The individual cluster sizes (the number of subjects per cluster) are assumed to vary according to a discrete distribution with mean 21 and coefficient of variation 0.420.

Plots Section



The values from the Numerical Results report are displayed in this plot.

Example 2 – Validation using Wang, Zhang, and Ahn (2018)

Wang, Zhang, and Ahn (2018) provide an example of sizing a cluster-randomized study. We will use their results to validate this procedure.

The average number of subjects per cluster was expected to be 50. Three coefficients of variation were investigated: 0, 0.12111, and 0.29439. These corresponded to discrete uniform distributions of DU(50,50), DU(40,60), and DU(25,75). Note that DU(50,50) is a case in which all cluster sizes were equal to 50 and the coefficient of variation was 0.

The treatment mean was set at 4.35 and the control mean was set at 3.63. The ICC was set at 0.32. A two-sided test at a significance level of 0.05 is planned. The necessary number of clusters per group was calculated as 54, 55, and 59.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load this procedure. 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**.

<u>Option</u>	<u>Value</u>
Design Tab	
Solve For	K1 (Number of Clusters in Group 1)
Alternative Hypothesis	Two-Sided (H1: $\delta \neq 0$)
Power	0.90
Alpha	0.05
K2 (Clusters in Group 2)	K1
M (Average of Cluster Sizes)	50
CV (Coeff. of Variation of Cluster Sizes)	0 0.12111 0.29439
Enter λ_1 or δ	λ_1 (Mean Count of Group 1)
λ_1 (Mean of Group 1)	4.35
λ_2 (Mean of Group 2)	3.63
ICC (Intracluster Correlation)	0.32

Output

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

Numeric Results

Numeric Results													
Hypotheses: H0: $\delta = 0$ vs. H1: $\delta \neq 0$													
	Sample	Clus	Clus	Clus	Alloc	Clus	Clus	Mean	Mean	Mean	Intra-		
	Size	Cnt	Cnt	Cnt	Ratio	Size	Size	Grp 1	Grp 2	Diff	Clus		
Power	N	Total	Grp 1	Grp 2	K1/K2	Ave	Coef	λ_1	λ_2	δ	ICC	Alpha	
0.9002	5400	108	54	54	1.00	50	0.000	4.35	3.63	0.72	0.320	0.050	
0.9015	5500	110	55	55	1.00	50	0.121	4.35	3.63	0.72	0.320	0.050	
0.9027	5900	118	59	59	1.00	50	0.294	4.35	3.63	0.72	0.320	0.050	

PASS has obtained K1 values of 54, 55, and 59.