Chapter 243

# GEE Tests for Two Means in a Stratified Cluster-Randomized Design

## Introduction

This procedure calculates power and sample size for tests of two means in a stratified cluster-randomized design in which the outcome variable is continuous. It uses the work of Wang, Zhang, and Ahn (2017) which give the power in a size-stratified cluster-randomized design in which the cluster size is allowed to vary within strata. The analysis is of a simple means model fit with the GEE method.

## Technical Details

The following discussion summarizes the results in Wang, Zhang, and Ahn (2017).

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 $Y_{kji}$ be the continuous outcome of the *i*$^{th}$ $\left(i = 1, \dots, n_{kj}\right)$ subject in the *j*$^{th}$ $(j = 1, \dots, J_k)$ cluster of the *k*$^{th}$ $(k = 1, \dots, K)$ stratum. Let $X_{kj} = 0$ or $1$ depending on whether the cluster is assigned to the control (0) or treatment (1) group. Let $R = P(X_{kj} = 1) \times 100$ be the percentage of clusters assigned to the treatment group. Hence, $R = 50$ indicates balanced randomization.

Suppose the data will be analyzed using the GEE (generalized estimating equation) method. The mean model is

$$\mathrm{E}\left(Y_{kji}\right) = \beta_0 + \beta_1 X_{kj}$$

where $\beta_0 = \mu_2$ is the mean of the control group, $\mu_1$ is the mean of the treatment group, and $\beta_1 = \mu_1 - \mu_2 = \delta$ is the treatment effect.

The null hypothesis is $H0{:}\ \beta_1 = 0$ which is paired with the alternative hypothesis $H1{:}\ \beta_1 \neq 0$.

The variance matrix of $Y_{kji}$ has $\sigma^2$ on the diagonal and $\rho\sigma^2$ on the off diagonal for subjects within the same cluster. Hence $\sigma^2$ is the variance of random error and $\rho$ is the intracluster correlation coefficient (ICC).

If the GEE estimators of $\beta_0$ and $\beta_1$, found using an independent working correlation structure, are $\hat{\beta}_0$ and $\hat{\beta}_1$, then $\sqrt{N}(\hat{\beta}_1 - \beta_1)$ follows a normal distribution.

Let $\alpha$ be the type I error rate, $\delta$ be the actual, non-zero, value of the treatment effect, and

$$v_1 = \frac{\sigma^2 \sum_{k=1}^{K} J_k \theta_k^2 \left[\frac{1}{\theta_k}(1-\rho)+(1+\xi_k^2)\rho\right]}{R/100\left(\sum_{k=1}^{K} J_k \theta_k\right)^2},$$

$$v_2 = \frac{\sigma^2 \sum_{k=1}^{K} J_k \theta_k^2 \left[\frac{1}{\theta_k}(1-\rho)+(1+\xi_k^2)\rho\right]}{(1-R/100)\left(\sum_{k=1}^{K} J_k \theta_k\right)^2},$$

$\mathrm{E}(n_{kj}) = \theta_k$ (Average of cluster sizes in stratum *k*),

$\mathrm{Var}(n_{kj}) = \tau_k^2$ (Variance of cluster sizes in stratum *k*),

$\mathrm{CV}(n_{kj}) = \frac{\tau_k}{\theta_k} = \xi_k$ (Variance of cluster sizes in stratum *k*),

$N = \sum_{k=1}^{K} J_k \theta_k$ (Total number of subjects in study),

$f_k = 100\frac{(J_k \theta_k)}{N}$ (The percentage of the total sample in stratum *k*).

Three cases of statistical hypotheses are available. If $\Phi(x)$ is the standard normal cumulative distribution function, the power formula for each case is

1. $H0{:}\ \delta \geq 0$ versus $H1{:}\ \delta < 0$.

$$\text{Power} = \Phi\left(z_\alpha - \frac{\delta}{\sqrt{v_1 + v_2}}\right)$$

2. $H0{:}\ \delta \leq 0$ versus $H1{:}\ \delta > 0$.

$$\text{Power} = \Phi\left(\frac{\delta}{\sqrt{v_1 + v_2}} - z_{1-\alpha}\right)$$

3. $H0{:}\ \delta = 0$ versus $H1{:}\ \delta \neq 0$.

$$\text{Power} = \Phi\left(z_{\alpha/2} - \frac{\delta}{\sqrt{v_1 + v_2}}\right) + \Phi\left(\frac{\delta}{\sqrt{v_1 + v_2}} - z_{1-\alpha/2}\right)$$

These power formulas are used to conduct a binary search for sample size or odds ratio.

# Example 1 – Finding Sample Size

A study is being planned to investigate whether a new intervention will decrease a certain response variable. 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. Past experience has shown that clinics can be separated into small, medium, and large according to their size. They want to obtain an equal number of subjects in each stratum. The number of clinics receiving each treatment will be balanced.

The average number of subjects per clinic of the small, medium, and large strata are 6, 21, and 73, respectively.

The coefficient of variation of all strata is 0.42.

Prior studies have obtained a mean score of 80 with a standard deviation of 23 and an ICC of 0.03. The researchers want to compare the necessary sample sizes when the change is -6, -8, and -10. They also want to consider an ICC value of 0.06.

The two-sided significance level is set to 0.05 and the power is set to 0.8.

## 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 (Treatment = Control = 50%)**
δ (Mean Difference = μ1 - μ2).............................. **-6 -8 -10**
σ (Standard Deviation)........................................ **23**
ICC (Intracluster Correlation)............................... **0.03 0.06**
Cluster Size Variation Input ................................ **Coefficient of Variation**

Set 1 Number of Strata ....................................... **1**
Set 1 Percent of N in Each Stratum ..................... **33**
Set 1 Average of Cluster Sizes ............................ **6**
Set 1 Coefficient of Variation of Cluster Sizes ...... **0.42**

Set 2 Number of Strata ....................................... **1**
Set 2 Percent of N in Each Stratum ..................... **33**
Set 2 Average of Cluster Sizes ............................ **21**
Set 2 Coefficient of Variation of Cluster Sizes ...... **0.42**

Set 3 Number of Strata ........................................ **1**
Set 3 Percent of N in Each Stratum ...................... **33**
Set 3 Average of Cluster Sizes ............................ **73**
Set 3 Coefficient of Variation of Cluster Sizes ...... **0.42**

# Output

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

## Numeric Reports

**Numeric Results**

Solve For: Sample Size
Groups: 1 = Treatment, 2 = Control
Difference: δ = μ1 - μ2
Hypotheses: H0: δ = 0 vs. H1: δ ≠ 0
Number of Strata: 3

| Power | Total Sample Size N | Expected Number of Clusters | Percent Allocated to Treatment Group R | Mean Difference δ | Standard Deviation σ | Intracluster Correlation Coefficient ICC | Alpha |
|---|---|---|---|---|---|---|---|
| 0.8 | 356 | 28 | 50 | -10 | 23 | 0.03 | 0.05 |
| 0.8 | 547 | 41 | 50 | -10 | 23 | 0.06 | 0.05 |
| 0.8 | 557 | 43 | 50 | -8 | 23 | 0.03 | 0.05 |
| 0.8 | 854 | 65 | 50 | -8 | 23 | 0.06 | 0.05 |
| 0.8 | 990 | 76 | 50 | -6 | 23 | 0.03 | 0.05 |
| 0.8 | 1519 | 115 | 50 | -6 | 23 | 0.06 | 0.05 |

Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N The total sample size, i.e., the total number of subjects summed across all strata.
Expected Number of Clusters An estimate of the total number of clusters of all sizes.
R The percent of clusters in each stratum that are allocated to the treatment group.
δ The mean difference assumed by the alternative hypothesis. This is the difference at which the power is computed. δ = μ1 - μ2.
σ The standard deviation of the response. It is the standard deviation of the random error component of the GEE means model.
ICC The intracluster correlation coefficient. This is the correlation between any two responses within a particular cluster.
Alpha The probability of rejecting a true null hypothesis.

**Summary Statements**

A stratified cluster-randomized design with 3 strata will be used to test whether the Group 1 (treatment) mean (μ1) is different from the Group 2 (control) mean (μ2) (H0: δ = 0 versus H1: δ ≠ 0, δ = μ1 - μ2). The comparison will be made using a two-sided generalized estimating equation (GEE) means model test, with a Type I error rate (α) of 0.05. The standard deviation of the random error component of the GEE means model is assumed to be 23. The intracluster correlation coefficient is assumed to be 0.03. To detect a difference (μ1 - μ2) of -10 with 80% power, the total number of subjects needed will be 356, from a total of 28 clusters (with 50% of the clusters in the treatment group in each of the 3 strata).

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**References**

Wang, J., Zhang, S., and Ahn, C. 2017. 'Power analysis for stratified cluster randomisation trials with cluster size being the stratifying factor.' Statistical Theory and Related Fields, Volume 1, Number 1, pages 121-127.

## Strata-Detail Report

**Strata-Detail Report**

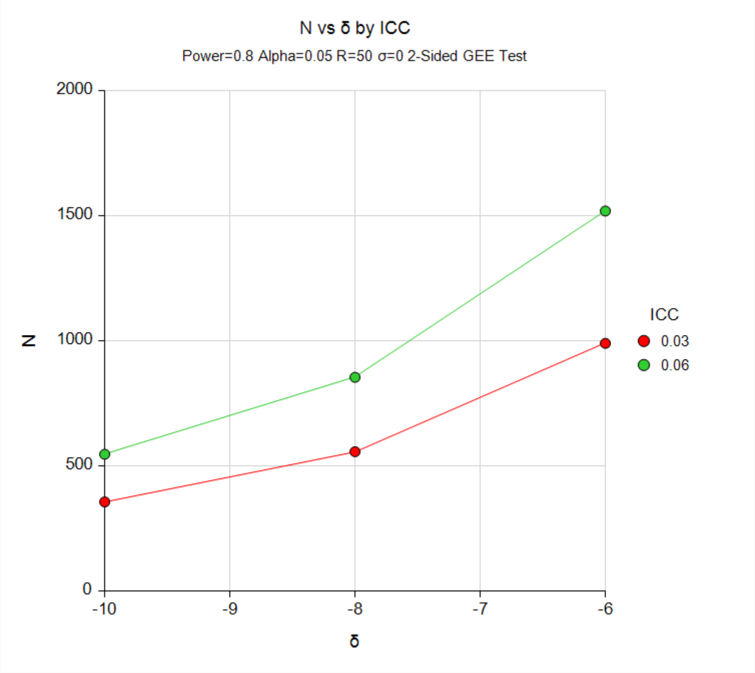
| | | | Cluster Sizes | | |
|---|---|---|---|---|---|
| Set | Number of Strata | Percent of N in Each Stratum | Average | Standard Deviation | Coefficient of Variation |
| 1 | 1 | 33.33 | 6 | 2.52 | 0.42 |
| 2 | 1 | 33.33 | 21 | 8.82 | 0.42 |
| 3 | 1 | 33.33 | 73 | 30.66 | 0.42 |

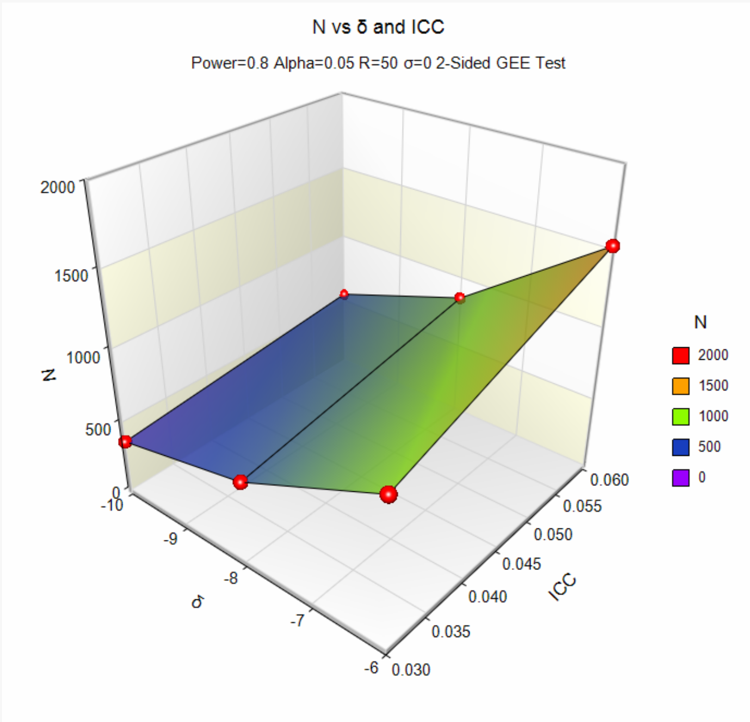
| | |
|---|---|
| Set | An identification number on the input screen. |
| Number of Strata | The number of strata defined by this set (input line). |
| Percent of N in Each Stratum | The percentage of the total sample size that is allocated to each stratum in this set. |
| Average of Cluster Sizes | The average cluster size (number of subjects) in each stratum of this set. |
| Standard Deviation of Cluster Sizes | The standard deviation of the cluster sizes in each stratum of this set. |
| Coefficient of Variation of Cluster Sizes | The coefficient of variation (CV) of the cluster sizes in each stratum of this set. CV = SD/Mean. |

This report shows the values of the individual, strata-level parameters that were used.

## Plots Section

**Plots**






The values from the Numeric Results report are displayed in these plots.

# Example 2 – Validation using Wang, Zhang, and Ahn (2017)

Wang, Zhang, and Ahn (2017) provide an example of the power analysis of a size-stratified, cluster-randomized study. We will use their results to validate this procedure.

The number of strata were 200, 510, and 1300. We will enter these values and let the program rescale them into percentages. The total number of subjects is 2010. The average number of subjects per cluster were 5, 17, and 65. The corresponding standard deviations were 2.44949, 5.00000, and 22.36068.

The mean difference to be detected is 3. The standard deviation is 12. The value of ICC is 0.05. The significance level is set to 0.05. They calculate a power of 0.8432.

## 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 ...................................................... **Power**
Alternative Hypothesis .................................. **Two-Sided (H1: δ ≠ 0)**
Alpha............................................................ **0.05**
N (Sample Size)............................................ **2010**
Group Allocation ........................................... **Equal (Treatment = Control = 50%)**
δ (Mean Difference = μ1 - μ2)....................... **3**
σ (Standard Deviation).................................. **12**
ICC (Intracluster Correlation)......................... **0.05**
Cluster Size Variation Input ........................... **Standard Deviation**

Set 1 Number of Strata ................................. **1**
Set 1 Percent of N in Each Stratum ............... **200**
Set 1 Average of Cluster Sizes ...................... **5**
Set 1 Standard Deviation of Cluster Sizes ..... **2.44949**

Set 2 Number of Strata ................................. **1**
Set 2 Percent of N in Each Stratum ............... **510**
Set 2 Average of Cluster Sizes ...................... **17**
Set 2 Standard Deviation of Cluster Sizes ..... **5.00000**

Set 3 Number of Strata ................................. **1**
Set 3 Percent of N in Each Stratum ............... **1300**
Set 3 Average of Cluster Sizes ...................... **65**
Set 3 Standard Deviation of Cluster Sizes ..... **22.36068**

# Output

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

**Numeric Results**

Solve For: Power
Groups: 1 = Treatment, 2 = Control
Difference: δ = μ1 - μ2
Hypotheses: H0: δ = 0 vs. H1: δ ≠ 0
Number of Strata: 3

| Power | Total Sample Size N | Expected Number of Clusters | Percent Allocated to Treatment Group R | Mean Difference δ | Standard Deviation σ | Intracluster Correlation Coefficient ICC | Alpha |
|---|---|---|---|---|---|---|---|
| 0.8432 | 2010 | 90 | 50 | 3 | 12 | 0.05 | 0.05 |

**Strata-Detail Report**

| | | | Cluster Sizes | | |
|---|---|---|---|---|---|
| Set | Number of Strata | Percent of N in Each Stratum | Average | Standard Deviation | Coefficient of Variation |
| 1 | 1 | 9.95 | 5 | 2.45 | 0.490 |
| 2 | 1 | 25.37 | 17 | 5.00 | 0.294 |
| 3 | 1 | 64.68 | 65 | 22.36 | 0.344 |

**PASS** has also obtained a power of 0.8432 which validates this procedure.