Chapter 531

GEE Tests for Two Means in a Cluster-Randomized Design

Introduction

This module calculates the power for testing the difference between two means obtained from a cluster-randomized design. The mean come from continuous, correlated data that are analyzed using the GEE method. Such data occur in two design types: clustered and longitudinal. This procedure is specific to cluster-randomized designs. A companion procedure power analyzes data from a repeated measures design.

GEE is different from mixed models in that it does not require the full specification of the joint distribution of the clustered measurements, as long as the marginal mean model is correctly specified. Estimation consistency is achieved even if the correlation matrix is incorrect. Also, the correlation matrix of the responses is specified directly, rather than using an intermediate, random effects model as is the case in mixed models. For clustered designs, GEE often uses a *compound symmetric* (CS) correlation structure.

Time-averaged difference analysis is often used when the outcome varies with time. However, in this case, the observations are treated as if they were repeated measurements from a subject (cluster). Each cluster is randomized either in the treatment or the control group.

Making these assumptions, the data may be analyzed using the GEE TAD methodology. This procedure performs a power analysis and sample size calculation for data obtained and analyzed in this manner.

Missing Values

This procedure allows you to specify a proportion of the subjects that are missing from each cluster.

Technical Details

Theory and Notation

Technical details are given in Ahn, Heo, and Zhang (2015), chapter 4, section 4.4.1, pages 110-116.

Suppose we have $K1$ clusters in group 1 (treatment) and $K2$ clusters in group 2 (control) for a total of K clusters. The average cluster size (number of subjects per cluster) is M. The mean of y_{ij} is modeled by

$$\mu_{ij} = \beta_1 + \beta_2 r_i$$

where

y_{ij}	is the response of the j^{th} subject from cluster i, with variance σ^2
μ_{ij}	is expectation of y_{ij}
r_i	is the cluster treatment indicator with 0 for control and 1 for treatment
β_1	is the regression coefficient giving the intercept of the control group
β_2	is the regression coefficient giving the TAD between the two groups

In this procedure, the primary interest is on β_2.

This mean model is reparametrized as

$$\mu_{ij} = b_1 + b_2(r_i - \bar{r})$$

where

$$b_1 = \beta_1 + \bar{r}\beta_2$$

$$b_2 = \beta_2$$

The vector of covariates is given by $x_{ij} = (1, r_i - \bar{r})'$.

GEE is used to estimate and test hypotheses about $\boldsymbol{b}$ with $\hat{\boldsymbol{b}}$.

Correlation Matrix Structure

In a cluster-randomized design with *K* clusters, each containing *M* subjects, observations within a particular cluster are correlated. The pattern of those correlations is assumed to be compound symmetric, with a single correlation, ρ.

A compound symmetry correlation model assumes that all correlations are equal, and all diagonal elements are one. That is

$$[\rho_{jj'}] = \begin{bmatrix} 1 & \rho & \rho & \rho & \cdots & \rho \\ \rho & 1 & \rho & \rho & \cdots & \rho \\ \rho & \rho & 1 & \rho & \cdots & \rho \\ \rho & \rho & \rho & 1 & \cdots & \rho \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ \rho & \rho & \rho & \rho & \cdots & 1 \end{bmatrix}_{M\times M}$$

Sample Size Calculations

The details of the calculation of sample size and power is given in Ahn, Heo, and Zhang (2015), Chapter 4, page 113. These are summarized here.

As explained above, GEE is used to estimate the regression coefficients $\boldsymbol{b}$ with $\hat{\boldsymbol{b}}$. The significance of b_4, the coefficient associated with the difference between the control and treatment slopes, is tested using a Wald statistic from which the following sample size formula is derived

$$K = \frac{\sigma^2\eta_0\left(z_{1-\frac{\alpha}{h}} + z_{1-\gamma}\right)^2}{\delta^2\mu_0^2\sigma_r^2}$$

where

K = number of clusters

M = average cluster size

h = 1 (one-sided test) or 2 (two-sided test)

γ = 1 – power

α = significance level

$\delta = \beta_2 =$ the mean difference

$\kappa =$ proportion missing within a cluster

$\mu_0 = M(1-\ \kappa)$

$\eta_0 = [M^2\rho + (1-\rho)](1-\ \kappa)$

$\sigma_r^2 = \bar{r}(1-\bar{r})$

$\rho =$ the intracluster correlation coefficient, ICC

The above formula is easily rearranged to obtain a formula for power.

Example 1 – Determining Sample Size

Researchers are planning a cluster-randomized study to compare a new drug with the standard drug for the treatment of a certain disease. The researchers want to investigate what happens when the cluster size is between 10 and 40 patients. The outcome will be the change in heart rate.

The study will be powered to detect a difference of 4. Similar studies have found a standard deviation between 8.0 and 10.0. These studies had an ICC of 0.2. The two-sided test will be conducted at the 0.05 significance level and at 90% power. They are planning on dividing the subjects equally between the treatment and control groups. The researchers anticipate the proportion missing will be 0.10.

How many clinics will be required for this study?

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	**K1 (Number of Group 1 Clusters)**
Alternative Hypothesis	**Two-Sided**
Power	**0.90**
Alpha	**0.05**
K2 (Number of Group 2 Clusters)	**K1**
M (Average Cluster Size)	**10 20 30 40**
δ (Mean Difference = μ1 - μ2)	**4**
σ (Standard Deviation)	**8 9 10**
ρ (Intracluster Correlation, ICC)	**0.2**
Missing Input Type	**Constant**
Missing Proportion	**0.1**

Output

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

Numeric Reports

Numeric Results

Solve For: K1 (Number of Group 1 Clusters)
Groups: 1 = Treatment, 2 = Control
Difference: δ = μ1 - μ2
Alternative Hypothesis: Two-Sided

		Number of Clusters										
Power	Number of Subjects N	Group 1 K1	Group 2 K2	Total K	Allocation Ratio K1 / K2	Average Cluster Size M	Mean Difference δ	Standard Deviation σ	ICC ρ	Alpha	Missing Proportion
0.9088	540	27	27	54	1	10	4	8	0.2	0.05	0.1
0.9075	680	34	34	68	1	10	4	9	0.2	0.05	0.1
0.9010	820	41	41	82	1	10	4	10	0.2	0.05	0.1
0.9072	920	23	23	46	1	20	4	8	0.2	0.05	0.1
0.9061	1160	29	29	58	1	20	4	9	0.2	0.05	0.1
0.9076	1440	36	36	72	1	20	4	10	0.2	0.05	0.1
0.9106	1320	22	22	44	1	30	4	8	0.2	0.05	0.1
0.9022	1620	27	27	54	1	30	4	9	0.2	0.05	0.1
0.9076	2040	34	34	68	1	30	4	10	0.2	0.05	0.1
0.9061	1680	21	21	42	1	40	4	8	0.2	0.05	0.1
0.9104	2160	27	27	54	1	40	4	9	0.2	0.05	0.1
0.9076	2640	33	33	66	1	40	4	10	0.2	0.05	0.1

Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N The total number of subjects in the study.
K1, K2, and K The number of clusters in groups 1, 2, and both, respectively.
K1 / K2 The allocation ratio. The smallest sample size occurs when it is 1.0.
M The average cluster size. That is, it is the number of subjects per cluster.
δ The mean (or time-averaged) difference (TAD) at which the power is calculated. It is in the same scale as σ. δ = μ1 - μ2.
σ The standard deviation of a response.
ρ The intracluster correlation coefficient or ICC. It is the correlation between any two subjects within a cluster.
Alpha The probability of rejecting a true null hypothesis.
Missing Proportion The missing proportion. This is the proportion of subjects that are not expected to complete the study.

Summary Statements

A parallel, two-group cluster-randomized design will be used to test whether the Group 1 (treatment) mean (μ1) is different from the Group 2 (control) mean (μ2). The comparison will be made using a two-sided generalized estimating equation (GEE) regression coefficient test (Wald-type), with a Type I error rate (α) of 0.05. The standard deviation of responses (assumed to be constant across all clusters) is anticipated to be 8. The intracluster correlation coefficient (ICC) is assumed to be 0.2. The anticipated proportion missing is 0.1. To detect a difference (μ1 - μ2) of 4 with 90% power, with an average cluster size of 10 subjects per cluster, the total number of needed clusters is 54 (27 in Group 1 and 27 in Group 2, for a total sample size of 540 subjects).

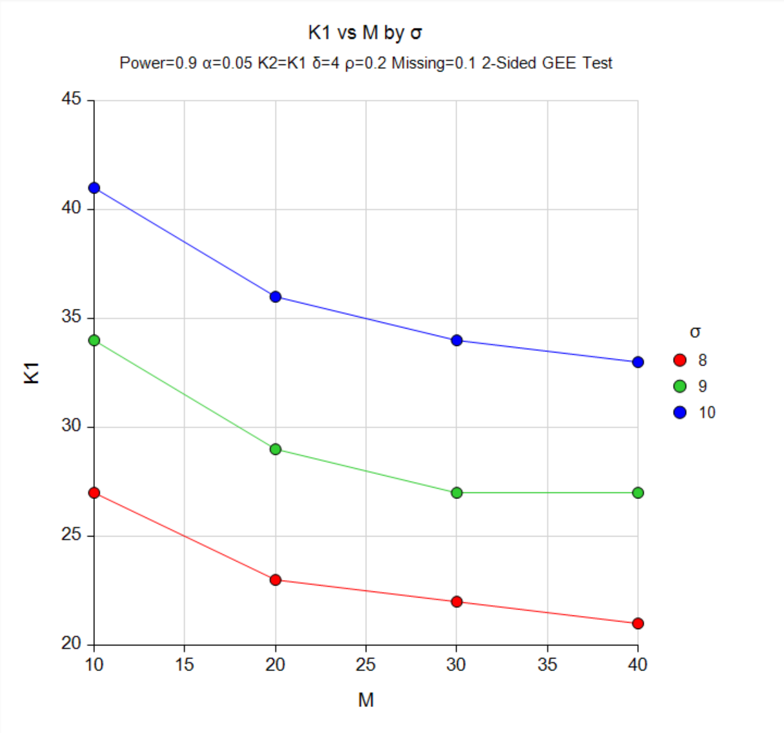
References

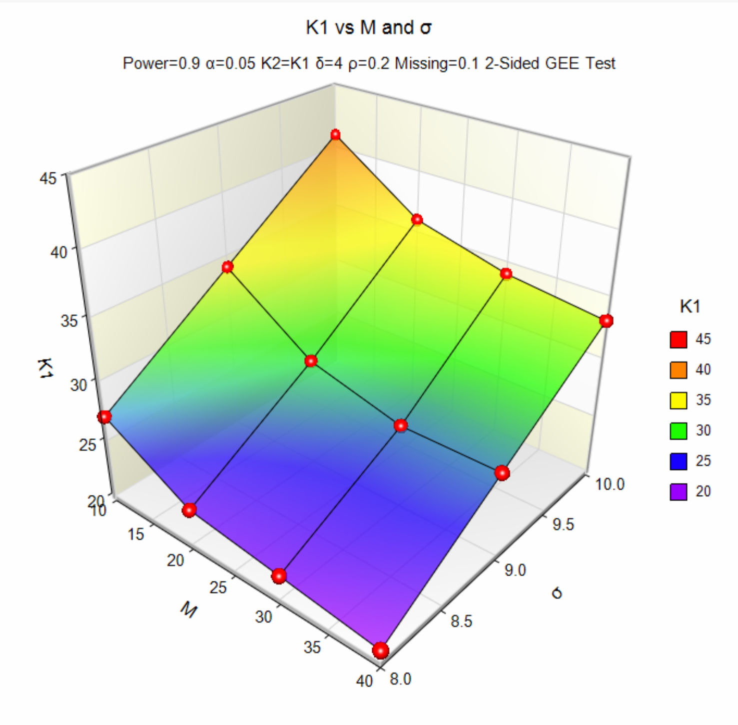
Ahn, C., Heo, M., and Zhang, S. 2015. Sample Size Calculations for Clustered and Longitudinal Outcomes in Clinical Research. CRC Press. New York. See page 113.

This report gives the necessary cluster count for each value of the other parameters.

Plots Section

Plots





These plots show the relationship among the parameters varied.

Example 2 – Finding the Power

Continuing with Example 1, the researchers want to determine the power corresponding to K1 values ranging from 20 to 40 and a standard deviation of 9.

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**
Alpha.. **0.05**
K1 (Number of Group 1 Clusters) **20 30 40**
K2 (Number of Group 2 Clusters) **K1**
M (Average Cluster Size)............................... **10 20 30 40**
δ (Mean Difference = μ1 - μ2)....................... **4**
σ (Standard Deviation).................................. **9**
ρ (Intracluster Correlation, ICC)..................... **0.2**
Missing Input Type.. **Constant**
Missing Proportion **0.1**

Output

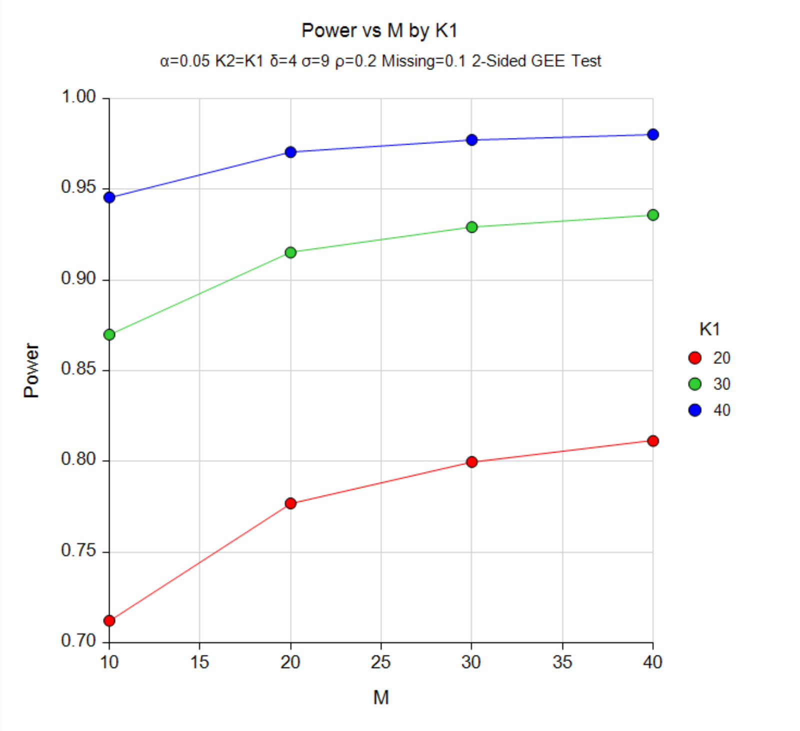
Click the Calculate button to perform the calculations and generate the following output.

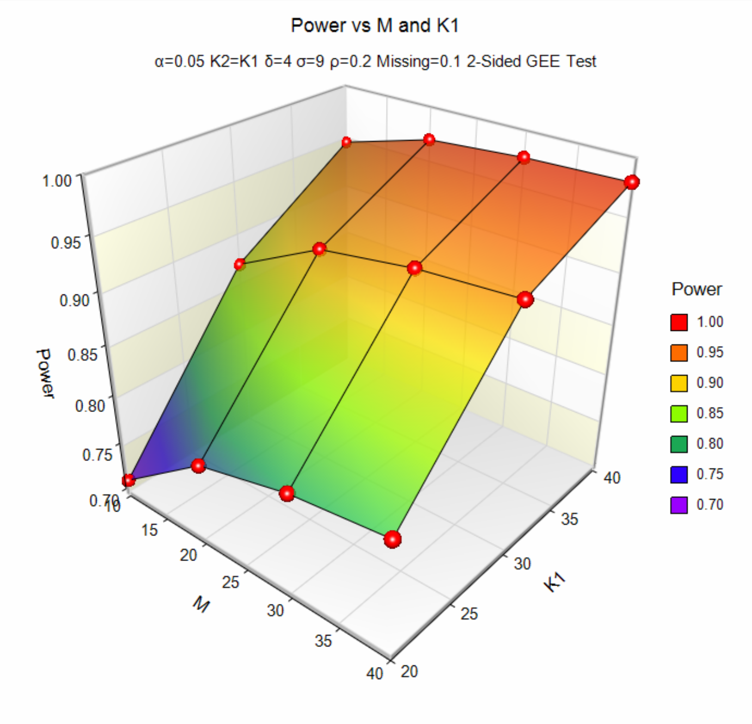
Numeric Results

Solve For: Power
Groups: 1 = Treatment, 2 = Control
Difference: δ = μ1 - μ2
Alternative Hypothesis: Two-Sided

		Number of Clusters									
Power	Number of Subjects N	Group 1 K1	Group 2 K2	Total K	Allocation Ratio K1 / K2	Average Cluster Size M	Mean Difference δ	Standard Deviation σ	ICC ρ	Alpha	Missing Proportion
0.7122	400	20	20	40	1	10	4	9	0.2	0.05	0.1
0.7769	800	20	20	40	1	20	4	9	0.2	0.05	0.1
0.7997	1200	20	20	40	1	30	4	9	0.2	0.05	0.1
0.8113	1600	20	20	40	1	40	4	9	0.2	0.05	0.1
0.8699	600	30	30	60	1	10	4	9	0.2	0.05	0.1
0.9152	1200	30	30	60	1	20	4	9	0.2	0.05	0.1
0.9292	1800	30	30	60	1	30	4	9	0.2	0.05	0.1
0.9359	2400	30	30	60	1	40	4	9	0.2	0.05	0.1
0.9456	800	40	40	80	1	10	4	9	0.2	0.05	0.1
0.9706	1600	40	40	80	1	20	4	9	0.2	0.05	0.1
0.9773	2400	40	40	80	1	30	4	9	0.2	0.05	0.1
0.9803	3200	40	40	80	1	40	4	9	0.2	0.05	0.1

Plots





The report and plot show the power for each scenario.

Example 3 – Validation using Ahn, Heo, and Zhang (2015)

Ahn, Heo, and Zhang (2015) do not present any numerical examples for this procedure. However, on page 115 they give a simplified formula for the compound symmetry case. We will calculate a result by hand using this formula and then calculate with the program to validate this procedure.

The simplified sample size formula is

$$K = \frac{4\sigma^2[1+(M-1)\rho]\left(z_{1-\frac{\alpha}{h}} + z_{1-\gamma}\right)^2}{\delta^2 M}$$

Using M = 5, σ = 3, ρ = 0.5, δ = 1.5, α = 0.05, and power = 0.9, we obtain

$$\begin{aligned} K &= \text{ceiling}\left(\frac{4(3^2)[1+(5-1)0.5](1.96+1.28)^2}{1.5^2(5)}\right) \\ &= \text{ceiling}(100.78) \\ &= 101 \end{aligned}$$

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 3** 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	**K1 (Number of Group 1 Clusters)**
Alternative Hypothesis	**Two-Sided**
Power	**0.90**
Alpha	**0.05**
K2 (Number of Group 2 Clusters)	**K1**
M (Average Cluster Size)	**5**
δ (Mean Difference = μ1 - μ2)	**1.5**
σ (Standard Deviation)	**3**
ρ (Intracluster Correlation, ICC)	**0.5**
Missing Input Type	**Constant = 0**

Output

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

Numeric Results

Solve For: K1 (Number of Group 1 Clusters)
Groups: 1 = Treatment, 2 = Control
Difference: δ = μ1 - μ2
Alternative Hypothesis: Two-Sided

		Number of Clusters									
Power	Number of Subjects N	Group 1 K1	Group 2 K2	Total K	Allocation Ratio K1 / K2	Average Cluster Size M	Mean Difference δ	Standard Deviation σ	ICC ρ	Alpha	Missing Proportion
0.9031	510	51	51	102	1	5	1.5	3	0.5	0.05	0

The number of clusters of 102 matches the above calculations very closely. Actually, the hand calculations of 101 clusters did not take into account that we wanted K1 = K2, which require an even number. PASS gave us the desired even number by increasing the number of clusters from 101 to 102.