# Chapter 390

# GEE Tests for the Slope of Multiple Groups in a Repeated Measures Design (Count Outcome)

# Introduction

This module calculates the power for simultaneously testing the differences among the slopes of two or more groups of correlated count data that are analyzed using the GEE method. Such data can occur in both clustered and longitudinal designs. The slopes are measured across repeated measurements of a specific subject.

GEE is different from mixed models in that it does not require the full specification of the joint distribution of the repeated 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 MM. For clustered designs, GEE often uses a *compound symmetric* (CS) correlation structure. For longitudinal data, an *autoregressive* (AR(1)) correlation structure is often used.

# **Missing Values**

This procedure allows you to specify various patterns of incomplete (or missing) data. Subjects may miss some appointments but attend others. This phenomenon of incomplete data can be accounted for in the sample size calculation which can greatly reduce the overall sample size from that calculated by just omitting subjects with incomplete observations.

# **Technical Details**

# **Theory and Notation**

The technical details used in this procedure are given in Lou, Cao, and Ahn (2017).

Suppose we have  $n_k$  (k = 1, ..., G) subjects in each of G groups for a total of N subjects, each measured on M occasions at times  $t_j$  (j = 1, ..., M). For convenience, we normalize these time points to the proportion of total time so that  $t_1 = 0$  and  $t_M = 1$ .

Let  $y_{kij}$  be the count response of subject i in group k at time  $t_j$ . The count is modeled by the Poisson distribution

$$f(y_{kij}) = \frac{e^{-\mu_{kij}} \mu_{kij}^{y_{kij}}}{y_{kij}!}$$

GEE Tests for the Slope of Multiple Groups in a Repeated Measures Design (Count Outcome)

The mean event rate of the Poisson counts  $\mu_{kij}$  is modeled by the log model

$$\log(\mu_{kij}) = a_k + \beta_k t_j.$$

This model can also be expressed as

$$\mu_{kij} = \exp\left(a_k + \beta_k t_i\right)$$

where

 $\alpha_k$  is the intercept of group k,

 $\beta_k$  is the slope of group k,

Note that at the first scheduled time

$$\mu_{kij} = a_k$$

And at the last scheduled time

$$\mu_{kij} = a_k + \beta_k.$$

Also, since subjects are assigned randomly to the groups, it is reasonable to assume that the responses will all have the same mean at  $t_1$ . Thus, it is likely that all intercepts will be equal.

The main focus of this design is to compare the average response of each group at the final time point,  $t_m$ . The differences among the group means will thus reduce to the differences among the corresponding group slopes. That is why this test is popular.

In this procedure, the primary interest is to test  $H_0$ :  $\beta_1 = \cdots = \beta_G$  against the alternative that at least one mean is different. GEE is used to estimate and test hypotheses about these group slopes.  $H_0$  is rejected with a type I error  $\alpha$  if  $\mathbf{z}_c > z_{1-\alpha/2}$  where  $z_{1-\alpha/2}$  is the 100(1 –  $\alpha$ /2)th percentile of a standard normal distribution.

The test statistic is calculated using

$$z_c = \frac{C'b}{\sqrt{\text{Var}(C'b)}}$$

where b is the GEE estimate of  $\beta_1, ..., \beta_G$  and C is a vector of contrast coefficients with the restriction that the sum of its elements is zero. Var(C'b) is a consistent estimate of the variance based on the residuals. See Liang and Zeger (1986) for details.

# **Correlation Patterns**

In a longitudinal design with *N* subjects, each measured *M* times, observations from a single subject are correlated, and a pattern of those correlations through time needs to be specified. Several choices are available.

# **Compound Symmetry**

A compound symmetry covariance model assumes that all correlations are equal. That is

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

where  $\rho$  is the baseline correlation.

### Banded(1)

A Banded(1) (banded order 1) correlation model assumes that correlations for observations one time period apart are equal to  $\rho$ , and correlations for measurements greater than one time period apart are equal to zero. That is

$$[\rho_{jj'}] = \begin{bmatrix} 1 & \rho & 0 & 0 & \cdots & 0 \\ \rho & 1 & \rho & 0 & \cdots & 0 \\ 0 & \rho & 1 & \rho & \cdots & 0 \\ 0 & 0 & \rho & 1 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & 1 \end{bmatrix}_{M \times M}$$

where  $\rho$  is the baseline correlation.

#### Banded(2)

A Banded(2) (banded order 2) correlation model assumes that correlations for observations one time period or two periods apart are equal to p and correlations for measurements greater than one time period apart are equal to zero. That is

$$[\rho_{jj'}] = \begin{bmatrix} 1 & \rho & \rho & 0 & \cdots & 0 \\ \rho & 1 & \rho & \rho & \cdots & 0 \\ \rho & \rho & 1 & \rho & \cdots & 0 \\ 0 & \rho & \rho & 1 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & 1 \end{bmatrix}_{M \times M}$$

where  $\rho$  is the baseline correlation.

GEE Tests for the Slope of Multiple Groups in a Repeated Measures Design (Count Outcome)

#### **AR1** (Traditional)

This version of AR1 (autoregressive order 1) correlation model assumes that correlations t time periods apart are equal to  $\rho^t$ . That is

$$[\rho_{jj'}] = \begin{bmatrix} 1 & \rho & \rho^2 & \rho^3 & \cdots & \rho^{M-1} \\ \rho & 1 & \rho & \rho^2 & \cdots & \rho^{M-2} \\ \rho^2 & \rho & 1 & \rho & \cdots & \rho^{M-3} \\ \rho^3 & \rho^2 & \rho & 1 & \cdots & \rho^{M-4} \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ \rho^{M-1} & \rho^{M-2} & \rho^{M-3} & \rho^{M-4} & \cdots & 1 \end{bmatrix}_{M \times M}$$

where  $\rho$  is the baseline correlation.

# **AR1** (Proportional)

This version of AR1 (autoregressive order 1) correlation model is described in the book by Ahn et al. (2015). It assumes that correlations  $|t_j - t_k|$  time periods apart are equal to  $\rho^{|t_j - t_k|}$ . That is

$$\left[\rho_{jk}\right] = \left[\rho^{|t_j - t_k|}\right]_{M \times M}$$

where  $\rho$  is the baseline correlation. Note that in this pattern, the value of  $\rho$  is shown in the final column since in this case  $t_j = 0$  and  $t_k = 1$ , so  $|t_j - t_k| = 1$ .

# **Damped Exponential**

A damped exponential is an extension of the AR(1) correlation model in which the exponents are raised to the power Dexp ( $\theta = Dexp$  in the diagram below). This causes the resulting correlations to be reduced (dampened). Here is an example

$$[\rho_{jj'}] = \begin{bmatrix} 1 & \rho & \rho^{2\theta} & \rho^{3\theta} & \cdots & \rho^{(M-1)\theta} \\ \rho & 1 & \rho & \rho^{2\theta} & \cdots & \rho^{(M-2)\theta} \\ \rho^{2\theta} & \rho & 1 & \rho & \cdots & \rho^{(M-3)\theta} \\ \rho^{3\theta} & \rho^{2\theta} & \rho & 1 & \cdots & \rho^{(M-3)\theta} \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ \rho^{(M-1)\theta} & \rho^{(M-2)\theta} & \rho^{(M-3)\theta} & \rho^{(M-4)\theta} & \cdots & 1 \end{bmatrix}_{M \times M}$$

where  $\rho$  is the baseline correlation.

GEE Tests for the Slope of Multiple Groups in a Repeated Measures Design (Count Outcome)

# **Damped Exponential (Proportional)**

This version of the damped exponential correlation model is described in the book by Ahn et al. (2015). It assumes that all variances on the diagonal are equal and that correlations  $|t_j - t_k|$  time periods apart are equal to  $\rho^{|t_j - t_k|}^{\theta}$ . That is

$$\left[\rho_{jk}\right] = \left[\rho^{\left|t_{j} - t_{k}\right|^{\theta}}\right]_{M \times M}$$

where  $\rho$  is the baseline correlation. Note that in this pattern, the value of  $\rho^{|t_j-t_k|^{\theta}}$  turns up in the final column since in this case  $t_i = 0$  and  $t_k = 1$ , so  $|t_i - t_k| = 1$ .

# **Linear Exponential Decay**

A linear exponential decay correlation model is one in which the exponent of the correlation decays according to a linear equation from 1 at the *Base Time Proportion* to a final value, *Emax*. The resulting pattern looks similar to the damped exponential. Note that the exponents are applied to the absolute difference between the Measurement Time Proportions. This method allows you to easily construct comparable correlation matrices of different dimensions. Otherwise, differences in the resulting power would be more strongly due to differences in the correlation matrices.

Here is an example. Suppose M is 6,  $\rho$  = 0.5, Emax = 3, the  $Base\ Time\ Proportion$  is 0.20, and the Measurement Time Proportions are (0, 0.2, 0.4, 0.6, 0.8, 1). The following correlation matrix would be obtained

$$[\rho_{jj'}] = \begin{bmatrix} 1 & 0.5 & 0.3536 & 0.25 & 0.1768 & 0.125 \\ 0.5 & 1 & 0.5 & 0.3536 & 0.25 & 0.1768 \\ 0.3536 & 0.5 & 1 & 0.5 & 0.3536 & 0.25 \\ 0.25 & 0.3536 & 0.5 & 1 & 0.5 & 0.3536 \\ 0.1768 & 0.25 & 0.3536 & 0.5 & 0.3536 & 0.5 \\ 0.125 & 0.1768 & 0.25 & 0.3536 & 0.5 & 1 \end{bmatrix}_{M \times N}$$

Note that in the top row, the correlation is 0.5 for the second (0.2 - 0) time point and 0.125 ( $0.5^3$ ) at the last (1 - 0) time points. The correlations are obtained by raising 0.5 to the appropriate exponent. The linear equation from 1 to 3 results in the exponents 1, 1.5, 2, 2.5, 3 correspondent to the time proportions 0, 0.2, 0.4, 0.6, 0.8, and 1.

As a further example, note that the correlation for the 0.4 time point is,  $0.5^{1.5} = 0.35355339 \approx 0.3536$ .

This method allows you to compare various values of M while keeping the correlation matrix similar. To see what we mean, consider what the correlation matrix looks like when M is reduced to 4 and the measurement time proportions are set to (0, 0.2, 0.6, 1). It becomes

$$\left[\rho_{jj'}\right] = \begin{bmatrix} 1 & 0.5 & 0.25 & 0.125 \\ 0.5 & 1 & 0.5 & 0.25 \\ 0.25 & 0.5 & 1 & 0.5 \\ 0.125 & 0.25 & 0.5 & 1 \end{bmatrix}_{M \times M}$$

Note that the correlation at a measurement time difference of 0.6 is equal to 0.25 in both matrices.

# **Missing Data Patterns**

The problem of missing data occurs for several reasons. In longitudinal studies in which a subject is measured multiple times, missing data becomes more complicated to model because it is possible that a subject is measured only some of the time. In fact, it is probably more common for data to be incomplete than complete. The approach of omitting subjects with incomplete data during the planning phase is very inaccurate. Certainly, subjects with partial measurements are included in the analysis. This procedure provides several missing data patterns to choose from so that your sample size calculations are more realistic.

In the presentation to following, we denote the percent of subjects with a missing response at time point  $t_j$  as  $\kappa_j$ . The proportion non-missing at a particular time point is  $\phi_j = 1 - \kappa_j$ . We will refer to  $\phi_j$  as the marginal observant probability at time  $t_j$  and  $\phi_{jj'}$  as a joint observant probability at times  $t_j$  and  $t_{j'}$ .

# **Pairwise Missing Pattern**

The program provides three options for how the pairwise (joint) observant probabilities  $\phi_{jj'}$  are calculated. These are

Independent (Ind):  $\phi_{jj'} = \phi_j \phi_{j'}, \phi_{jj} = \phi_j$ 

**Monotonic (Mon)**:  $\phi_{ii'} = \phi_k$  where  $k = \max(j, j')$ 

**Mixture**:  $\phi_{ii'} = W(Ind) + (1 - W)(Mon)$  for weighting factor W.

# **Missing Input Type**

The are several ways in which the missing value pattern can be specified. Each missing value pattern is a list of missing proportions at each of the *M* time points. Each value in the list must be non-negative and less than 1. Possible input choices are

#### Constant = 0

All missing proportions are set to 0. That is, there are no missing values.

#### Constant

All missing proportions are set to constant value.

#### • Piecewise Constant on Spreadsheet

A set of missing proportions are defined for several time intervals using the spreadsheet. One column contains the missing proportions for the interval, going down the rows. Another column defines the corresponding upper limit of time proportion of the interval. The lower limit is implied by the limit given immediately above. The program assumes that the first-time interval starts at 0 percent.

#### Linear (Steady Change)

The missing proportions fall along a straight-line between 0 and 1 elapsed time. Only the first and last proportions are entered.

#### Piecewise Linear on Spreadsheet

The missing proportions fall along a set of connected straight-lines that are defined by two columns on the spreadsheet.

#### List

Enter a list of M missing proportions, one for each time point.

#### • Multiple Lists on Spreadsheet

Select multiple columns containing vertical lists of missing proportions. Each column contains a set of missing proportions in rows, one for each time point.

#### • Pairwise Observed Proportions on Spreadsheet

Enter an  $M \times M$  matrix of observant probabilities by selecting M columns. These observant probabilities are the proportion of the responses for both the row and column time points that are observed.

# **Sample Size Calculations**

The details of the calculation of sample size and power is given in Lou, Cao, and Ahn (2017). These are summarized here. The sample size formula is

$$N = \frac{(C'VC)\left(z_{1-\frac{\alpha}{2}} + z_{1-\gamma}\right)^2}{(C'\beta)^2}$$

where

 $\beta$  is a vector of anticipated GEE regression coefficients,  $\beta_1, ..., \beta_G$ 

is a vector of 2 x G contrast coefficients,  $C = (0, c_1, 0, c_2, ..., 0, c_G)$ 

y 1 – power

α significance level

 $z_{1-\alpha/2}$  is the 100(1 –  $\alpha/2$ )th percentile of a standard normal distribution

 $z_{1-\gamma}$  is the 100(1 – y)th percentile of a standard normal distribution

 $V WA^{-1}\Sigma A^{-1}W$ 

W diag  $\left(\frac{1}{\sqrt{r_1}}, \frac{1}{\sqrt{r_1}}, \dots, \frac{1}{\sqrt{r_G}}, \frac{1}{\sqrt{r_G}}\right)$ 

 $r_k$  is the proportion of subjects in group k

 $\mathsf{A} \qquad \begin{pmatrix} \sum_{j=1}^m \phi_j \, \mu_{1j} \begin{pmatrix} 1 & t_j \\ t_j & t_j^2 \end{pmatrix} & \cdots & 0 \\ \vdots & & \ddots & \vdots \\ 0 & & \cdots & \sum_{j=1}^m \phi_j \, \mu_{Gj} \begin{pmatrix} 1 & t_j \\ t_j & t_j^2 \end{pmatrix} \end{pmatrix}$ 

$$\Sigma = \begin{pmatrix} \sum_{j=1}^{m} \sum_{j'=1}^{m} \phi_{jj'} \, \rho_{jj'} \, \sqrt{\mu_{1j} \mu_{1j'}} \begin{pmatrix} 1 & t_j \\ t_j & t_j^2 \end{pmatrix} & \cdots & 0 \\ \vdots & & \ddots & \vdots \\ 0 & & \cdots & \sum_{j=1}^{m} \sum_{j'=1}^{m} \phi_{jj'} \, \rho_{jj'} \, \sqrt{\mu_{Gj} \mu_{Gj'}} \begin{pmatrix} 1 & t_j \\ t_j & t_j^2 \end{pmatrix} \end{pmatrix}$$

- $\mu_{kij} = \exp(a_k + \beta_k t_j)$
- $\phi_i$  1  $\kappa_i$ , where  $\kappa_i$  is the proportion missing at the  $j^{\text{th}}$  time point
- $ho_{ii'}$  is the corresponding element from within-subject correlation matrix
- $\phi_{ii'}$  is the joint observant probability of observing both yij and yij' for every subject i

Three possible choices are available to calculate  $\phi_{ii'}$ . These are

Independent:  $\phi_{ij'} = \phi_j \phi_{j'}$ ,  $\phi_{jj} = \phi_j$ 

*Monotonic:*  $\phi_{ii'} = \phi_k$  where  $k = \max(j, j')$ 

*Mixture*:  $\phi_{ii'} = w(Independent) + (1 - w)(Monotonic)$  for weighting factor w.

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

# Example 1 – Determining Sample Size for a Three-Arm Trial

Researchers are planning a study comparing three heart-rate medications: a standard drug and two experimental drugs. The experimental drugs appear to have about the same impact on heart rate. Each subject will receive four applications of just one drug, two days apart. The researchers want a sample size large enough to detect a slope difference of 5 between the highest and lowest slopes. They will use 65 as the initial event rate for each of the three groups. They want a sample size large enough to detect a change in the final event rates to 65, 60, and 60. They will do all sample size calculations using a contrast of 2, -1, -1.

Previous studies showed an autocorrelation between adjacent measurements on the same individual of 0.7, so they want to try values of 0.6, 0.7, and 0.8. The researchers assume that first-order autocorrelation adequately represents the autocorrelation pattern. The test will be conducted at the 0.05 significance level and powered at 90%. The subjects will be randomly assigned equally among the three groups.

The researchers anticipate that the missing pattern across time will begin at 0% missing and increase steadily to 20% at the fourth measurement. They assume that the pairwise missing is *independent*.

What are the sample size requirements 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.

Solve For	Sample Size
Power	0.90
Alpha	0.05
G (Number of Groups)	3
Group Allocation Input Type	Equal (n1 = n2 = ··· = nG = n)
Measurement Time Input Type	Equally Spaced Measurement Times
M (Number of Measurement Times)	4
μi(0)'s Input Type	µi(0) (Initial Event Rate)
μί(0) (Initial Event Rate)	65
μi(1)'s Input Type	μ1(1), μ2(1),, μG(1)
μ1(1), μ2(1),, μG(1)	65 60 60
Contrast Input Type	List of Contrast Coefficients
Contrast Coefficients	2 -1 -1
Pattern of ρ's Across Time	AR1 (Traditional)
ρ (Base Correlation)	0.6 0.7 0.8
Missing Input Type	Linear (Steady Change)
Pairwise Missing Pattern	Independent (Ind)
First Missing Proportion (Ind)	0
Last Missing Proportion (Ind)	0.2

GEE Tests for the Slope of Multiple Groups in a Repeated Measures Design (Count Outcome)

# **Output**

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

# **Numeric Reports**

#### Numeric Results for a Multi-Group Slope Comparison Test with Count Data using GEE

Sample Size Solve For: Contrast: List of Coefficients Measurement Times: Equally spaced AR1:  $\rho(j,k) = \rho^{|j-k|}$ Range of missing proportions Correlation: Missing Pattern:

Observant Proportions: Assume independence

Number of Groups:

	Total Sample	Group Allocation	Number of Measurement			Contrast	Base	First Row of			
Power	Size N	Proportions ri	Times M	First µi(0)	Last µi(1)	Coefficients Ci	Correlation ρ	Correlation Matrix	Missing Data Proportions	Measurement Times	Alpha
0.9021 0.9018 0.9040		ri(1) ri(1) ri(1)	4	μi(0,1) μi(0,1) μi(0,1)	μi(1,1)	Con(1) Con(1) Con(1)	0.6 0.7 0.8	ρ1(1) ρ2(1) ρ3(1)	Ms1(1) Ms1(1) Ms1(1)	T(1) T(1) T(1)	0.05 0.05 0.05

Item	Values
ri(1)	0.333, 0.333, 0.333
μi(0,1)	65, 65, 65
μi(1,1)	65, 60, 60
Con(1)	2, -1, -1
ρ1(1)	1, 0.6, 0.36, 0.216
ρ2(1)	1, 0.7, 0.49, 0.343
ρ3(1)	1, 0.8, 0.64, 0.512
Ms1(1)	0, 0.07, 0.13, 0.2
T(1)	0, 0.33, 0.67, 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.
ri	Group Allocation Proportions Set gives the name of the set containing group allocation proportions.
M	The number of time points at which each subject is scheduled to be measured.
μi(0)	First Event Rates gives the name of the set containing the initial event rates of each group.
μi(1)	Last Event Rates gives the name of the set containing the final event rates of each group.
Ci'	The Contrast Coefficients gives the name of the set containing the contrast coefficients that are used to form a comparison of the slopes. This comparison is the quantity that is tested.
ρ	The base correlation between two responses on the same subject. It may be transformed based on the correlation pattern.
First Row of Correlation Matrix	Presents the top row of the correlation matrix.

Missing Data Proportions

Gives the name of the set containing the individual missing value proportions for each time

**Measurement Times** 

The Measurement Times gives the name of the set containing the time proportions. The values represent the proportion of the total study time that has elapsed just before the measurement.

Alpha The probability of rejecting a true null hypothesis.

GEE Tests for the Slope of Multiple Groups in a Repeated Measures Design (Count Outcome)

#### **Summary Statements**

A 3-group repeated measures design (with a count response and with 4 measurements for each subject) will be used to test whether there is a group difference in slopes based on a contrast with group contrast coefficients 2, -1, -1. The test will be performed by comparing the contrast of the GEE estimates of the slopes to the null value zero, with a Type I error rate ( $\alpha$ ) of 0.05. The (repeated) measurements of each subject will be made at the following 4 times, expressed as proportions of the total study time: 0, 0.33, 0.67, 1. Missing values are assumed to occur completely at random (MCAR). The missing value proportions will be combined to form the pairwise observant probabilities using an independent pairwise missing pattern. The anticipated proportions missing at each measurement time are 0, 0.07, 0.13, 0.2. The first row of the autocorrelation matrix of the responses within a subject is assumed to be 1, 0.6, 0.36, 0.216, with subsequent rows following the same pattern (AR1:  $\rho(j,k) = \rho^{k}$ ). The initial (Poisson) event rates are assumed to be 65, 65, 65. To detect final event rates of 65, 60, 60 (and the corresponding slopes) with 90% power, the total number of needed subjects is 210 (divided into the 3 groups according to the proportions: 0.333, 0.333, 0.333).

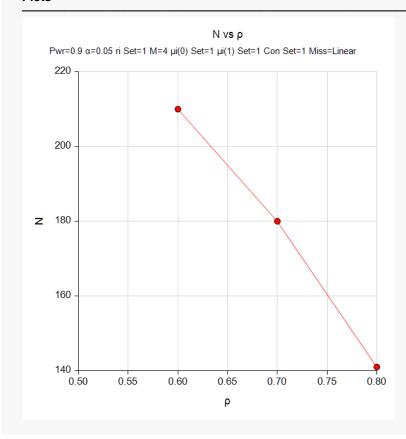
#### References

Lou, Y., Cao, J., and Ahn, C. 2017. Sample size estimation for comparing rates of change in K-group repeated count outcomes. Comm. in Statistics - Theory and Methods. Vol 46:22, Pages 11204-11213.

This report gives the sample size for each value of the other parameters.

#### **Plots Section**

#### **Plots**



This plot shows the relationship among the design parameters.

GEE Tests for the Slope of Multiple Groups in a Repeated Measures Design (Count Outcome)

# **Autocorrelation Matrices**

Autocorrelation	Matrix for	Report Row 1	

Time	T(0)	T(0.33)	T(0.67)	T(1)
T(0)	1.000	0.60	0.36	0.216
T(0.33)	0.600	1.00	0.60	0.360
T(0.67)	0.360	0.60	1.00	0.600
T(1)	0.216	0.36	0.60	1.000

### **Autocorrelation Matrix for Report Row 2**

Time	T(0)	T(0.33)	T(0.67)	T(1)
T(0)	1.000	0.70	0.49	0.343
T(0.33)	0.700	1.00	0.70	0.490
T(0.67)	0.490	0.70	1.00	0.700
T(1)	0.343	0.49	0.70	1.000

#### **Autocorrelation Matrix for Report Row 3**

Time	T(0)	T(0.33)	T(0.67)	T(1)
T(0)	1.000	0.80	0.64	0.512
T(0.33)	0.800	1.00	0.80	0.640
T(0.67)	0.640	0.80	1.00	0.800
T(1)	0.512	0.64	0.80	1.000

These reports show the autocorrelation matrix for the indicated row of the report.

# **Example 2 - Finding the Power**

Continuing with Example 1, the researchers want to determine the power corresponding to group sample sizes ranging from 30 to 80 for the middle values of the other parameters.

# 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.

Solve For	Power
Alpha	0.05
G (Number of Groups)	3
Group Allocation Input Type	Equal (n1 = n2 = ··· = nG = n)
n (Sample Size Per Group)	30 40 50 60 80
Measurement Time Input Type	Equally Spaced Measurement Times
M (Number of Measurement Times)	4
μi(0)'s Input Type	µi(0) (Initial Event Rate)
μί(0) (Initial Event Rate)	65
μi(1)'s Input Type	μ1(1), μ2(1),, μG(1)
μ1(1), μ2(1),, μG(1)	65 60 60
Contrast Input Type	List of Contrast Coefficients
Contrast Coefficients	2 -1 -1
Pattern of ρ's Across Time	AR1 (Traditional)
ρ (Base Correlation)	0.7
Missing Input Type	Linear (Steady Change)
Pairwise Missing Pattern	Independent (Ind)
First Missing Proportion (Ind)	0
Last Missing Proportion (Ind)	0.2

GEE Tests for the Slope of Multiple Groups in a Repeated Measures Design (Count Outcome)

# Output

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

#### Numeric Results for a Multi-Group Slope Comparison Test with Count Data using GEE

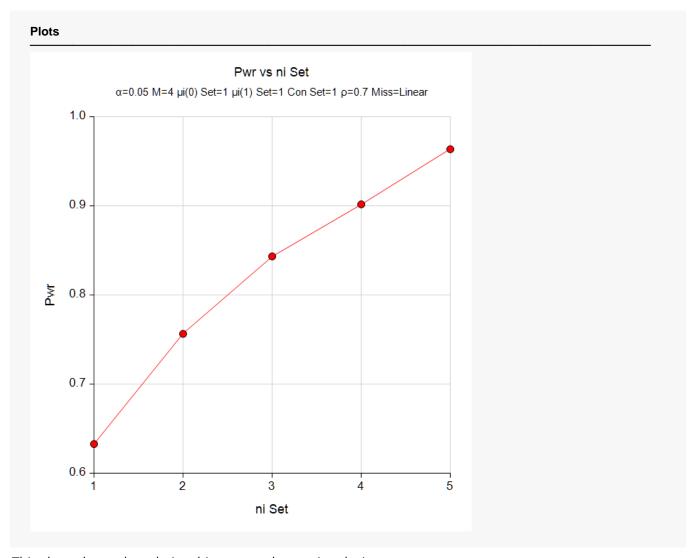
List of Coefficients Contrast: Measurement Times: Equally spaced AR1:  $\rho(j,k) = \rho^{|j-k|}$ Range of missing proportions Correlation:

Missing Pattern: Observant Proportions: Assume independence

Number of Groups:

	Total	Group	Number of Measurement		Rates	Contrast	Rase	First Row of			
Power	Size N	Sizes ni	Times M	First µi(0)	Last µi(1)	Coefficients Ci			Missing Data Proportions	Measurement Times	Alpha
0.6328	90	ni(1)	4	μi(0,1)	μi(1,1)	Con(1)	0.7	ρ1(1)	Ms1(1)	T(1)	0.05
0.7565	120	ni(2)	4	$\mu i(0,1)$	μi(1,1)	Con(1)	0.7	ρ1(1)	Ms1(1)	T(1)	0.05
0.8434	150	ni(3)	4	μi(0,1)	μi(1,1)	Con(1)	0.7	ρ1(1)	Ms1(1)	T(1)	0.05
0.9018	180	ni(4)	4	μi(0,1)	μi(1,1)	Con(1)	0.7	ρ1(1)	Ms1(1)	T(1)	0.05
0.9637	240	ni(5)	4	μi(0,1)	μi(1,1)	Con(1)	0.7	ρ1(1)	Ms1(1)	T(1)	0.05

Item	Values
ni(1)	30, 30, 30
ni(2)	40, 40, 40
ni(3)	50, 50, 50
ni(4)	60, 60, 60
ni(5)	80, 80, 80
μi(0,1)	65, 65, 65
μi(1,1)	65, 60, 60
Con(1)	2, -1, -1
ρ1(1)	1, 0.7, 0.49, 0.343
Ms1(1)	0, 0.07, 0.13, 0.2
T(1)	0, 0.33, 0.67, 1



This chart shows the relationship among the varying design parameters.

# **Example 3 - Comparing Various Effect Sizes**

Continuing with Examples 1 and 2, the researchers want to compare the impact of various sets of final event rates on sample size. To do this, they will compare the four sets of slopes shown in the following table. The first row is the standard medication. The second and third rows give the anticipated response to the experimental medications.

The values in this table must be loaded into the spreadsheet.

#### **Table of Four Sets of Final Event Rates**

<b>C</b> 1	<b>C2</b>	С3	<b>C4</b>
65	65	65	65
60	61	62	63
60	61	62	63

# 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.

Solve For	Sample Size
Power	0.90
Alpha	0.05
G (Number of Groups)	3
Group Allocation Input Type	Equal (n1 = n2 = ··· = nG = n)
Measurement Time Input Type	Equally Spaced Measurement Times
M (Number of Measurement Times)	4
μi(0)'s Input Type	µi(0) (Initial Event Rate)
μί(0) (Initial Event Rate)	65
μi(1)'s Input Type	Columns Containing Sets of μi(1)'s
Columns Containing Sets of µi(1)'s	C1-C4
Contrast Input Type	List of Contrast Coefficients
Contrast Coefficients	2 -1 -1
Pattern of ρ's Across Time	AR1 (Traditional)
ρ (Base Correlation)	0.7
Missing Input Type	Linear (Steady Change)
Pairwise Missing Pattern	Independent (Ind)
First Missing Proportion (Ind)	0
Last Missing Proportion (Ind)	0.2

GEE Tests for the Slope of Multiple Groups in a Repeated Measures Design (Count Outcome)

Row	<b>C</b> 1	C2	C3	C4
1	65	65	65	65
2	60	61	62	63
3	60	61	62	63

# **Output**

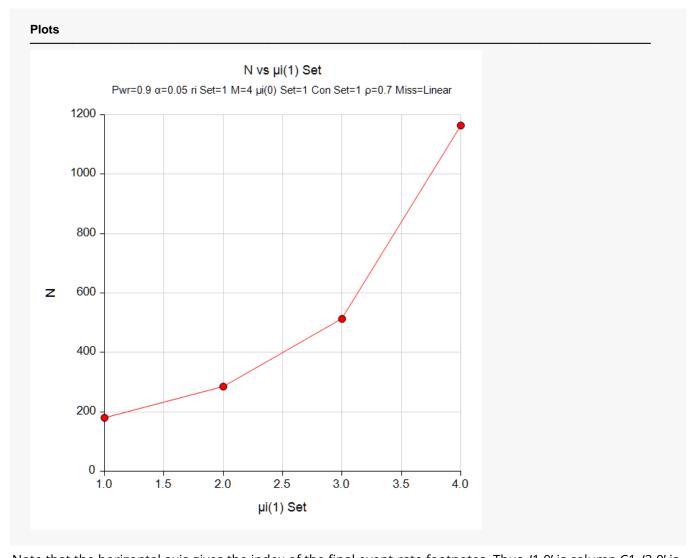
Click the Calculate button to perform the calculations and generate the following output.

#### Numeric Results for a Multi-Group Slope Comparison Test with Count Data using GEE

Number of Groups: 3

	Total Sample	Group Allocation	Number of Measurement		Rates	Contrast	Base	First Row of			
Power		Proportions	Times		Last µi(1)				Missing Data Proportions	Measurement Times	
0.9018	180	ri(1)		μi(0,1)		Con(1)	0.7	ρ1(1)	Ms1(1)	T(1)	0.05
0.9017 0.9015	285 513	ri(1) ri(1)	4	μi(0,1) μi(0,1)	C3(3)	Con(1) Con(1)	0.7 0.7	ρ1(1) ρ1(1)	Ms1(1) Ms1(1)	T(1) T(1)	0.05 0.05
0.9002	1164	ri(1)	4	μi(0,1)	C4(4)	Con(1)	0.7	ρ1(1)	Ms1(1)	T(1)	0.05

Item	Values
ri(1)	0.333, 0.333, 0.333
μi(0,1)	65, 65, 65
C1(1)	65, 60, 60
C2(2)	65, 61, 61
C3(3)	65, 62, 62
C4(4)	65, 63, 63
Con(1)	2, -1, -1
ρ1(1)	1, 0.7, 0.49, 0.343
Ms1(1)	0, 0.07, 0.13, 0.2
T(1)	0, 0.33, 0.67, 1



Note that the horizontal axis gives the index of the final event-rate footnotes. Thus, '1.0' is column C1, '2.0' is column C2, and so on. Obviously, as the event-rate values get closer together, the required sample size gets larger.

# Example 4 – Validation of Sample Size Calculation using Lou, Cao, and Ahn (2017)

Lou, Cao, and Ahn (2017) page 11209 present sample size results for several scenarios. We will validate this procedure using an entry from their Table 1. There are four groups in this example. The intercepts are all 0; the slopes are 0, 0.25, 0.25, and 0.25; the significance level is 0.05; the power is 0.80, group sizes are equal; and the number of repeated measurements per subject is 6. We will use the compound symmetry option for the correlation matrices with  $\rho$  = 0.3. The proportion missing at each time point is equal to 0, 0.05, 0.1, 0.15, 0.2, 0.25. The pairwise observant probabilities assume independence. Using these settings, the per group sample size was reported as 198. The contrast is -3, 1, 1, 1.

Note that the intercept of 0 translates to an initial event rate of 1. Similarly, the slope of 0.25 translates to a final event rate of 1.284.

# 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 4** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Solve For	Sample Size
Power	0.8
Alpha	0.05
G (Number of Groups)	4
Group Allocation Input Type	Equal (n1 = n2 = ··· = nG = n)
Measurement Time Input Type	Equally Spaced Measurement Times
M (Number of Measurement Times)	6
μi(0)'s Input Type	µi(0) (Initial Event Rate)
μί(0) (Initial Event Rate)	1
μi(1)'s Input Type	μ1(1), μ2(1),, μG(1)
μ1(1), μ2(1),, μG(1)	1 1.284 1.284 1.284
Contrast Input Type	List of Contrast Coefficients
Contrast Coefficients	3 1 1 1
Pattern of ρ's Across Time	Compound Symmetry (All ρ's Equal)
ρ (Base Correlation)	0.3
Missing Input Type	Linear (Steady Change)
Pairwise Missing Pattern	Independent (Ind)
First Missing Proportion (Ind)	0
Last Missing Proportion (Ind)	0.25

GEE Tests for the Slope of Multiple Groups in a Repeated Measures Design (Count Outcome)

# **Output**

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

Correla Missing Observ	st: ement Tir	List of the mes: Equations: Range ortions: Assume the control of t	ple Size of Coefficients ally spaced pound symm ge of missing ume independ	etry (all ρ proportio							
	Total Sample	Group	Number		nt Rates	- Contrast	Page	First Row of			
Power		Proportions ri	Tim			Coefficients	Correlation	Correlation	Missing Data Proportions	Measurement Times	
0.8003	792	ri(1)		6 µi(0,1	) µi(1,1)	Con(1)	0.3	ρ1(1)	Ms1(1)	T(1)	0.05
Item	Valu	ies		_							
ri(1)		, 0.25, 0.25,	0.25	_							
$\mu i(0,1)$											
$\mu i(1,1)$		28, 1.28, 1.2	28								
Con(1) ρ1(1)		, 1, 1 3, 0.3, 0.3, (	13 03								
Ms1(1)		05, 0.3, 0.3, 0 05, 0.1, 0.1									
T(1)		2, 0.4, 0.6, (									

The sample size of 792 (4 times 198) matches the article, so the procedure is validated. Some entries in the table differ slightly from **PASS** because **PASS** searches among only balanced designs.

# **Example 5 - Impact of Measurement Time Distribution**

This example will investigate the impact of measurement time distribution on power in this design. It will compare the power of studies in which the measurements are evenly spaced with those that take more measurements at the beginning of the study, near the middle of the study, or at the end of the study.

This example uses G = 4, m = 6,  $\alpha = 0.05$ , and power = 0.9. The correlation pattern is Linear Exponential Decay with a base correlation of 0.4, Base Time Proportion of 0.20, and Emax set to 4. The missing input type is set to Linear from 0 to 30% and the pairwise missing assumption is independent. Group slopes are 5, 5, 6, 8. The per group sample size is 30.

The measurement times for five scenarios are given in the following table.

**Table of Measurement Times in Proportion of Total Study Time** 

Tm1	Tm2	Tm3	Tm4	Tm5
0	0	0	0	0
0.20	0.60	0.10	0.10	0.45
0.40	0.70	0.20	0.20	0.50
0.60	0.80	0.30	0.80	0.55
0.80	0.90	0.40	0.90	0.60
1.00	1.00	1.00	1.00	1.00

Note that the measurements in Tm1 are evenly spaced, those in Tm2 are loaded near the end, those of Tm3 occur at the beginning, those of Tm4 occur only at the beginning and the end, and those of Tm5 occur mostly near the middle.

# 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 5** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Solve For	Power
Alpha	0.05
G (Number of Groups)	4
Group Allocation Input Type	Equal (n1 = n2 = ··· = nG = n)
n (Sample Size Per Group)	30
Measurement Time Input Type	Columns of Measurement Time Proportions
Columns of Time Proportions	Tm1-Tm5
μi(0)'s Input Type	μi(0) (Initial Event Rate)
μί(0) (Initial Event Rate)	5
μi(1)'s Input Type	μ1(1), μ2(1),, μG(1)
μ1(1), μ2(1),, μG(1)	5 5 6 8
Contrast Input Type	Linear Trend
Pattern of ρ's Across Time	Linear Exponential Decay

#### GEE Tests for the Slope of Multiple Groups in a Repeated Measures Design (Count Outcome)

#### **Input Spreadsheet Data**

Row	Tm1	Tm2	Tm3	Tm4	Tm5
1	0.0	0.0	0.0	0.0	0.00
2	0.2	0.6	0.1	0.1	0.45
3	0.4	0.7	0.2	0.2	0.50
4	0.6	0.8	0.3	0.8	0.55
5	8.0	0.9	0.4	0.9	0.60
6	1.0	1.0	1.0	1.0	1.00

# **Output**

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

#### Numeric Results for a Multi-Group Slope Comparison Test with Count Data using GEE

Solve For: Power

Measurement Times: Lists in spreadsheet columns: {TM1-TM5}

Correlation: Linear exponential decay, with Emax = 4 and Base Time Prop = 0.2

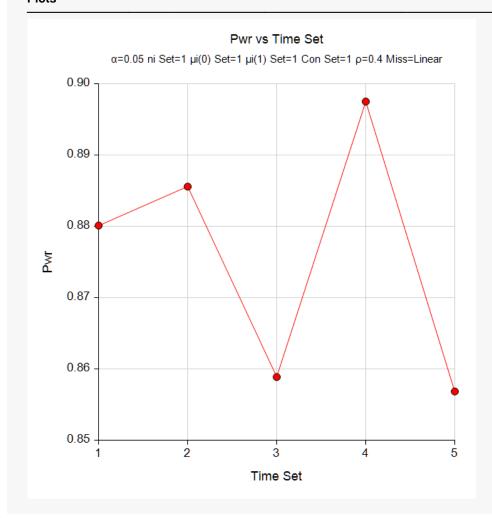
Missing Pattern: Range of missing proportions
Observant Proportions: Assume independence
Number of Groups: 4

Power	Total Sample Size N	Group Sample Sizes ni	Number of Measurement Times M		Rates Last  µi(1)	Contrast Coefficients Ci		First Row of Correlation Matrix	Missing Data	Measurement Times	Alpha
0.8801	120	ni(1)		μi(0,1)		Con(1)	0.4	ρ1(Tm1)	Ms1(Tm1)	Tm1	0.05
0.8856	120	ni(1)		μi(0,1)		Con(1)	0.4	ρ1(Tm1)	Ms1(Tm2)	Tm2	0.05
0.8589	120	ni(1)	6	μi(0,1)	μi(1,1)	Con(1)	0.4	ρ1(Tm3)	Ms1(Tm3)	Tm3	0.05
0.8975	120	ni(1)	6	μi(0,1)	μi(1,1)	Con(1)	0.4	ρ1(Tm4)	Ms1(Tm4)	Tm4	0.05
0.8568	120	ni(1)	6	μi(0,1)	μi(1,1)	Con(1)	0.4	ρ1(Tm5)	Ms1(Tm5)	Tm5	0.05

#### GEE Tests for the Slope of Multiple Groups in a Repeated Measures Design (Count Outcome)

Item	Values
ni(1)	30, 30, 30, 30
μi(0,1)	5, 5, 5, 5
μi(1,1)	5, 5, 6, 8
Con(1)	-1.5, -0.5, 0.5, 1.5
ρ1(Tm1)	1, 0.4, 0.2012, 0.1012, 0.0509, 0.0256
ρ1(Tm2)	1, 0.1012, 0.0718, 0.0509, 0.0361, 0.0256
ρ1(Tm3)	1, 0.564, 0.4, 0.2837, 0.2012, 0.0256
ρ1(Tm4)	1, 0.564, 0.4, 0.0509, 0.0361, 0.0256
ρ1(Tm5)	1, 0.1694, 0.1427, 0.1202, 0.1012, 0.0256
Ms1(Tm1)	0, 0.06, 0.12, 0.18, 0.24, 0.3
Ms1(Tm2)	0, 0.18, 0.21, 0.24, 0.27, 0.3
Ms1(Tm3)	0, 0.03, 0.06, 0.09, 0.12, 0.3
Ms1(Tm4)	0, 0.03, 0.06, 0.24, 0.27, 0.3
Ms1(Tm5)	0, 0.14, 0.15, 0.17, 0.18, 0.3
Tm1	0, 0.2, 0.4, 0.6, 0.8, 1
Tm2	0, 0.6, 0.7, 0.8, 0.9, 1
Tm3	0, 0.1, 0.2, 0.3, 0.4, 1
Tm4	0, 0.1, 0.2, 0.8, 0.9, 1
Tm5	0, 0.45, 0.5, 0.55, 0.6, 1

#### **Plots**



The horizontal axis, *Time Set*, gives the sequence number of the measurement columns. Thus, 1 is Tm1, 2 is Tm2, and so on. Note the disparity between the power for Tm4 and Tm5.

# **Example 6 – Comparing Several Sets of Contrast Coefficients**

This example will compare the power obtained by several different sets of contrast coefficients.

This example uses G = 4, m = 6,  $\alpha = 0.05$ , and power = 0.9. The correlation pattern is Linear Exponential Decay with a base correlation of 0.4, Base Time Proportion of 0.20, and Emax set to 4. The missing input type is set to Linear from 0 to 30% and the pairwise missing assumption is independent. Group slopes are 5, 5, 6, 8. The per group sample size is 30.

The measurement times for five scenarios are given in the following table.

#### **Table of Five Contrasts**

С1	C2	С3	<b>C4</b>	<b>C5</b>
-3	1	-3	1	-0.53
1	1	-1	-1	-0.53
1	1	1	-1	0.06
1	-3	3	1	1.00

Note that contrast C1 compares the first group to the rest, C2 compares the last group to the rest, C3 tests for a linear trend, C4 tests for a quadratic pattern, and C5 was found using the Maximum Power option.

# 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 6** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Solve For	Power
Alpha	0.05
G (Number of Groups)	4
Group Allocation Input Type	Equal (n1 = n2 = ··· = nG = n)
n (Sample Size Per Group)	30
Measurement Time Input Type	Equally Spaced Measurement Times
M (Number of Measurement Times)	6
μi(0)'s Input Type	μi(0) (Initial Event Rate)
μί(0) (Initial Event Rate)	5
μi(1)'s Input Type	μ1(1), μ2(1),, μG(1)
μ1(1), μ2(1),, μG(1)	5568
Contrast Input Type	Multiple Lists of Contrast Coefficients
Multiple Lists of Coefficients	C1-C5
Pattern of ρ's Across Time	Compound Symmetry (All ρ's Equal)
ρ (Base Correlation)	0.4
Missing Input Type	Linear (Steady Change)

GEE Tests for the Slope of Multiple Groups in a Repeated Measures Design (Count Outcome)

Pairwise Missing Pattern......Independent (Ind)
First Missing Proportion (Ind)......0
Last Missing Proportion (Ind).......0.3

#### **Input Spreadsheet Data**

Row	C1	C2	C3	C4	C5	
1	-3	1	-3	1	-0.53	
2	1	1	-1	-1	-0.53	
3	1	1	1	-1	0.06	
4	1	-3	3	1	1.00	

# Output

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

#### Numeric Results for a Multi-Group Slope Comparison Test with Count Data using GEE

Solve For: Power

Contrast:

Multiple Lists of Coefficients: {C1-C5}

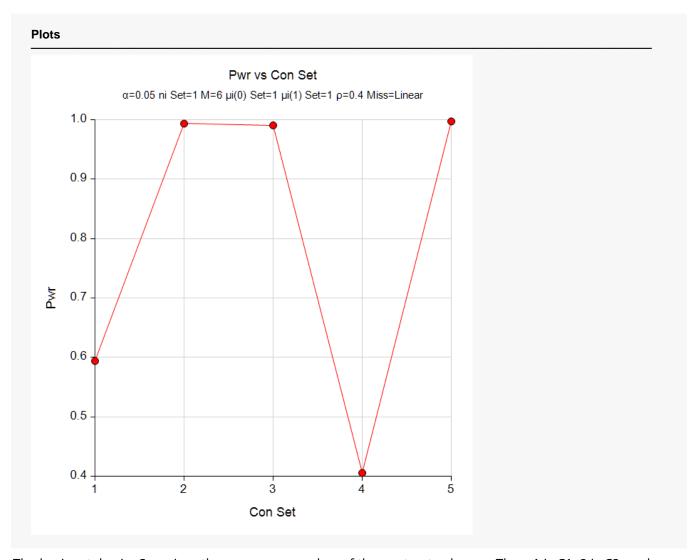
Measurement Times: Equally spaced

Correlation: Compound symmetry (all p's equal)
Missing Pattern: Range of missing proportions
Observant Proportions: Assume independence

Number of Groups: 4

	Total Sample	Group Sample	Number of Measurement		Rates	Contrast	Base	First Row of			
Power	Size N	Sizes ni	Times M	First µi(0)	Last µi(1)	Coefficients Ci	Correlation ρ	Correlation Matrix	Missing Data Proportions	Measurement Times	Alpha
0.5940	120	ni(1)	6	μi(0,1)	μi(1,1)	C1(1)	0.4	ρ1(1)	Ms1(1)	T(1)	0.05
0.9936	120	ni(1)	6	μi(0,1)	μi(1,1)	C2(2)	0.4	ρ1(1)	Ms1(1)	T(1)	0.05
0.9907	120	ni(1)	6	$\mu i(0,1)$	μi(1,1)	C3(3)	0.4	ρ1(1)	Ms1(1)	T(1)	0.05
0.4056	120	ni(1)	6	μi(0,1)	μi(1,1)	C4(4)	0.4	ρ1(1)	Ms1(1)	T(1)	0.05
0.9973	120	ni(1)	6	μi(0,1)	μi(1,1)	C5(5)	0.4	ρ1(1)	Ms1(1)	T(1)	0.05

Item	Values
ni(1)	30, 30, 30, 30
$\mu i(0,1)$	5, 5, 5, 5
μi(1,1)	5, 5, 6, 8
C1(1)	-3, 1, 1, 1
C2(2)	1, 1, 1, -3
C3(3)	-3, -1, 1, 3
C4(4)	1, -1, -1, 1
C5(5)	-0.53, -0.53, 0.06, 1
ρ1(1)	1, 0.4, 0.4, 0.4, 0.4, 0.4
Ms1(1)	0, 0.06, 0.12, 0.18, 0.24, 0.3
T(1)	0, 0.2, 0.4, 0.6, 0.8, 1



The horizontal axis, *Con*, gives the sequence number of the contrast columns. Thus, 1 is C1, 2 is C2, and so on. Note the huge impact on power that the contrast coefficients make—there is a swing from 0.4056 for C4 to 0.9973 for C5.

GEE Tests for the Slope of Multiple Groups in a Repeated Measures Design (Count Outcome)

# **Further Examples of GEE Options**

The **PASS** GEE procedures offer many options that allow you to investigate various designs in detail. These are available at the end of Chapter 399, "GEE Tests for the Slope of Two Groups in a Repeated Measures Design (Continuous Outcome)." We suggest that you take time to look through those examples.