

## Chapter 397

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

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### Introduction

This module calculates the power for testing the difference between two slopes from correlated count data that are analyzed using the GEE method. Such data occur in two design types: clustered and longitudinal.

GEE does not require the full specification of the joint distribution of the repeated measurements, as long as the marginal 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 details of the calculation of sample size and power is given in Ahn, Heo, and Zhang (2015), chapter 4, section 4.7, pages 126 - 129. We will use their notation here.

Suppose we have  $n_1$  subjects in group 1 (treatment) and  $n_2$  subjects in group 2 (control) for a total of  $N$  subjects, each measured on  $M$  occasions at times  $t_j$  ( $j = 1, \dots, M$ ). For convenience, we normalize these time points to the proportion of total time so that  $t_1 = 0$  and  $t_M = 1$ . The mean event rate of the Poisson count responses  $\mu_{kij}$  is modeled by the log model

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

where

$y_{kij}$  is the  $j^{\text{th}}$  response from subject  $i$  in group  $k$ .

$\mu_{kij}$  is expectation of  $y_{kij}$  assuming the Poisson distribution,

$a_1$  is the regression coefficient giving intercept of the treatment group,

$a_2$  is the regression coefficient giving intercept of the control group,

$\beta_1$  is the regression coefficient giving slope of the treatment group,

$\beta_2$  is the regression coefficient giving slope of the control group.

This model can be expressed as

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

GEE is used to estimate and test hypotheses about the equality of the slopes  $\beta_1$  and  $\beta_2$ .

### 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 covariances are equal, and all variances on the diagonal 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.

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### Banded(1)

A Banded(1) (banded order 1) correlation model assumes that all variances on the diagonal are equal, covariances for observations one time period apart are equal to  $\rho$ , and covariances 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 all variances on the diagonal are equal, covariances for observations one time period or two periods apart are equal to  $\rho$ , and covariances 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.

### AR1 (Traditional)

This version of AR1 (autoregressive order 1) correlation model assumes that all variances on the diagonal are equal and 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 all variances on the diagonal are equal and that correlations  $|t_j - t_k|$  time periods apart are equal to  $\rho^{|t_j - t_k|}$ . That is

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

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  $|t_j - t_k| = 1$ .

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### Dampened Exponential

A dampened 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

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

where  $\rho$  is the baseline correlation.

### Dampened Exponential (Proportional)

This version of the dampened 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

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

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  $t_j = 0$  and  $t_k = 1$ , so  $|t_j - t_k| = 1$ .

### 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,  $E_{max}$ . The resulting pattern looks similar to the dampened 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,  $\rho = 0.5$ ,  $E_{max} = 3$ , 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

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

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,  $0.5^{1.5} = 0.35355339 \approx 0.3536$ .

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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

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

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

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

### Missing Input Type

There 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.

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- **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 Ahn, Heo, and Zhang (2015), Chapter 4. These are summarized here.

GEE is used to estimate the regression coefficients  $\beta_1$  and  $\beta_2$ . The significance of  $\beta_1 - \beta_2$ , the coefficient associated with the difference between the treatment and control group slopes, is tested using a Wald statistic for which the following sample size formula is derived

$$n = \frac{\left(\frac{v_1^2}{r_1} + \frac{v_2^2}{r_2}\right) \left(z_{1-\frac{\alpha}{h}} + z_{1-\gamma}\right)^2}{\delta^2}$$

where

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

$\gamma = 1 - \text{power}$

$\alpha = \text{significance level}$

$$v_k^2 = \frac{s_k^2 + c_k^2}{s_k^4}$$

$$\delta = \beta_1 - \beta_2$$

$$s_k^2 = \sum_{j=1}^M \phi_j \mu_{kj} (t_j - \tau_k)^2$$

$$c_k^2 = \sum_{j \neq j'}^M \sum_{j'} \phi_{jj'} \rho_{jj'} \sqrt{\mu_{kj} \mu_{kj'}} (t_j - \tau_k) (t_{j'} - \tau_k)$$

$$\tau_k = \frac{\sum_{j=1}^M \phi_j \mu_{kj} t_j}{\sum_{j=1}^M \phi_j \mu_{kj}}$$

$$r_k = n_k / N$$

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$\phi_j = 1 - \kappa_j$ , where  $\kappa_j$  = proportion missing at the  $j^{\text{th}}$  time point

$\rho_{jj'}$  is the corresponding element from within-subject correlation matrix

$\phi_{jj'}$  is the joint observant probability of observing both  $y_{ij}$  and  $y_{ij'}$  for every subject  $i$

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

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

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

Mixture:  $\phi_{jj'} = W(\text{Independent}) + (1 - W)(\text{Monotonic})$  for weighting factor  $W$ .

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

## 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, go to the Procedure Window chapter.

## Design Tab

The Design tab contains most of the parameters and options that you will be concerned with.

### Solve For

#### Solve For

This option specifies the parameter to be solved for. When you choose to solve for *Sample Size*, the program searches for the lowest sample size that meets the alpha and power criterion you have specified. The *Solve For* parameter is displayed on the vertical axis of the plot.

### Test

#### Alternative Hypothesis

This option specifies the alternative hypothesis. The null hypothesis is always  $H_0: \beta_1 - \beta_2 = 0$

Note that the alternative hypothesis enters into power calculations by specifying the rejection region of the hypothesis test. Its accuracy is critical.

Possible selections are:

- **One-Sided**

This option yields a *one-tailed* test. Use it for testing the alternative hypotheses  $H_1: \beta_1 - \beta_2 < 0$  or  $H_1: \beta_1 - \beta_2 > 0$ .

- **Two-Sided**

This is the most common selection. Use it for testing the alternative hypotheses  $H_1: 0 \neq \beta_1 - \beta_2$ .

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### Power and Alpha

#### Power

This option specifies one or more values for power. Power is the probability of rejecting a false null hypothesis, and is equal to one minus Beta. Beta is the probability of a type-II error, which occurs when a false null hypothesis is not rejected. In this procedure, a type-II error occurs when you fail to reject the null hypothesis of equal slopes when in fact the slopes are different.

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 also 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. In this procedure, a type-I error occurs when you reject the null hypothesis of equal slopes when in fact the slopes are equal.

Values must be between zero and one. Historically, the value of 0.05 has been used for alpha. This means that about one test in twenty will falsely reject the null hypothesis. 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*.

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### Sample Size and Group 1 Allocation Percentage

#### N (Subjects)

Enter a value for the sample size, N, the number of subjects in the study. Each subject is measured  $m$  times, where  $m > 1$ .

You may enter a single value, such as '42'; a range of values, such as '10 to 100 by 10'; or a list of values, such as '10 30 80 90'.

#### R (Group 1 Allocation %)

Enter one or more values for the percentage of the subjects that are (or will be) in group 1, the treatment group. The usual entry is 50 for 50%. The valid range is from 1 to 99. However, a more reasonable range is from 10 to 90. Usually, the treatment group allocation is 50%.

You can enter a single value such as '50' or a series of values such as '40 50 60' or '40 to 70 by 5'.

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### Measurement Times Schedule

#### Measurement Time Input Type

Specify how you want to enter the information about the measurement proportion times.

- **Equally Spaced Measurement Times**

Enter one or more values for M, the number of measurements per subject. Equally-spaced measurement time proportions will automatically be generated.

- **List of Measurement Time Proportions**

Enter a list of measurement time proportions in the box below, one for each time point. The number of measurement times, M, is set equal to the number of items in this list.



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- **Columns of Measurement Time Proportions**

Select one or more columns of the spreadsheet that contain a set of measurement time proportions. Each column is analyzed separately. The number of measurement times,  $M$ , is equal to the number of rows in the active column.

### **M (Measurements)**

Specify one or more values for  $M$ , the total number of measurements scheduled for each subject. It is assumed that these measurements are made at identical time points or under the same conditions.

At least one value must be entered. If multiple values are entered, a separate analysis is run for each value.

The value must be an integer greater than 1. A reasonable range is from 2 to 50.

Some examples are

3

3 4 5

3 to 10 by 1

### **Measurement Time Proportions**

Enter a set of measurement time proportions, one for each time point. The number of measurements,  $M$ , is the number of items in the list. Each entry in the list is the proportion that that time is of the maximum time.

For example, suppose a 24-month study is planned with anticipated measurements at the beginning and then after each six-month period. Hence, the five measurement times are 0, 6, 12, 18, and 24 months. The entry must be proportions of 24, so the actual entry would be '0, 0.25, 0.50, 0.75, 1.0'.

$M$ , the number of repeated measurements, is set to the number of items in the list.

Once  $M$  is set here, it must match its implicit value in the Correlations and Missing Proportions.

### **Auto Rescaling**

You can enter any increasing series that is convenient and it will be rescaled so that each entry is a proportion of the maximum. In the example above, you could have entered '0, 6, 12, 18, 24' or even '1, 2, 3, 4, 5' and the program would have rescaled the values into proportions beginning at 0 and ending at 1.

### **Valid Entries**

Since the numbers are automatically rescaled, the only requirement is that the series be strictly increasing.

### **Examples**

0 0.25 0.50 0.75 1.0

0 10 50 90 100

0 0.20 0.40 0.90 0.95 1.0

1 2 3 4 5

0 10 20 40

### **Column(s) of Time Proportions**

Enter one or more spreadsheet columns containing lists of measurement time proportions.

Press the Spreadsheet icon (directly to the right) to select the columns and then enter the values. Press the Input Spreadsheet icon (to the right and slightly up) to view/edit the spreadsheet. Also note that you can obtain the spreadsheet by selecting *Tools*, then *Input Spreadsheet*, from the menus. On the spreadsheet, the measurement times are entered going down.

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### Examples

C1	C2	C3
0.0	1	0.1
0.2	2	0.4
0.4	3	0.5
0.6	4	
0.8		
1.0		

### Definition of a Single Column

Each column gives one list of time proportions. Each column results in a new scenario. Different columns are not connected and may be of different lengths.

Each entry in the list is the proportion that that time is of the maximum time. For example, suppose a 24-month study is planned with anticipated measurements at the beginning and then after each six-month period. Hence, the five measurement times are 0, 6, 12, 18, and 24 months. The entry must be proportions of 24, so the actual entry would be '0, 0.25, 0.50, 0.75, 1.0' (entered vertically in a particular column).

### Auto Rescaling

You can enter any increasing series that is convenient and it will be rescaled so that each entry is a proportion of the maximum. In the example above, you could have entered '0 6 12 18 24', or even '1 2 3 4 5', going down the column and the program would have rescaled the values into proportions beginning at 0 and ending at 1.

### Valid Entries

Since the numbers are automatically rescaled, the only requirement is that the series be strictly increasing.

### Notes

M, the number of repeated measurements, is set to the number of items in the active column.

Once M is set here, it must match its implicit value in the Correlations and Missing Proportions.

The column names (C1, C2, ...) can be changed by clicking on them in the spreadsheet.

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## Effect Size

### $\mu_1(0)$ and $\mu_2(0)$ Input Type

Indicate whether the two event rates will be equal or different at the first measurement (time proportion = 0).

The choices are

- **$\mu_1(0) = \mu_2(0)$**   
Enter one or more values that will be used for both  $\mu_1(0)$  and  $\mu_2(0)$ . In a trial in which a measurement is taken before the treatment is applied, it is quite reasonable to make this assumption.
- **Enter  $\mu_1(0)$  and  $\mu_2(0)$  Separately**  
Individual entry boxes will appear for  $\mu_1(0)$  and  $\mu_2(0)$  separately allowing different values. Note that this assumes that the intercepts of the regression equations will be different making the interpretation of the slopes problematic.

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### $\mu_1(0)$ and $\mu_2(0)$

Enter values for the event rates in group 1 and 2 at the beginning of the study. We assume that group 1 is the 'treatment' group and group 2 is the 'control or reference' group.

Values must be greater than 0.

You can enter a single value such as *1* or a series of values such as *0.2 0.3* or *1 to 5 by 1*.

### $\mu_1(1)$ Input Type

Indicate what type of values to enter to specify  $\mu_1(1)$ , the group 1 event rate at the last measurement. Regardless of the entry type chosen, the same test statistic used in the power and sample size calculations. This option is simply given for convenience in specifying the  $\mu_1(1)$ .

The choices are

- **$\mu_1(1)$**   
Enter values for  $\mu_1(1)$  directly.
- **Difference ( $\mu_1(1) - \mu_2(1)$ )**  
Enter values for the difference ( $\mu_1(1) - \mu_2(1)$ ) and values for  $\mu_2(1)$ . The corresponding value of  $\mu_1(1)$  will be computed from these two values.
- **Ratio ( $\mu_1(1) / \mu_2(1)$ )**  
Enter values for the ratio ( $\mu_1(1) / \mu_2(1)$ ) and values for  $\mu_2(1)$ . The corresponding value of  $\mu_1(1)$  will be computed from these two values.

### $\mu_1(1)$

Enter values for the event rates of group 1 at the final measurement of the study. We assume that group 1 is the 'treatment' group and group 2 is the 'control or reference' group.

Values must be greater than 0.

You can enter a single value such as *2* or a series of values such as *1 2 3* or *1 to 5 by 1*.

### Note

This value must be different from  $\mu_2(1)$  but can be the same as  $\mu_1(0)$ .

### Difference ( $\mu_1(1) - \mu_2(1)$ )

Enter the difference between  $\mu_1(1)$  and  $\mu_2(1)$  at the final measurement. This difference is used with  $\mu_2(1)$  to calculate the value of  $\mu_1(1)$  using the formula:  $\mu_1(1) = \text{Diff} + \mu_2(1)$ .

You can enter a single value such as *0.5* or a series of values such as *0.3 0.5 1* or *0.1 to 0.9 by 0.2*.

### Range

Differences cannot be 0. The resulting value of  $\mu_1(1)$  must be greater than 0. If it is not, it is changed so that it is.

### Ratio ( $\mu_1(1) / \mu_2(1)$ )

Enter the ratio of the two rates  $\mu_1(1)$  and  $\mu_2(1)$ . This ratio is used with  $\mu_2(1)$  to calculate the value of  $\mu_1(1)$  using the formula:  $\mu_1(1) = \text{Ratio} \times \mu_2(1)$ .

You can enter a single value such as *1.5* or a series of values such as *1.5 1.6 1.7 1.8* or *1.25 to 2.0 by 0.25*.

### Range

Ratios must be greater than zero. They cannot take on the value of one. The resulting value of  $\mu_1(1)$  must be greater than 0. If it is not, it is changed so that it is.

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### $\mu_2(1)$

Enter values for the event rate in group 2 at the final measurement of the study. We assume that group 2 is the 'control or reference' group. The difference between  $\mu_1(1)$  and  $\mu_2(1)$  is a measure of the effect size.

Values must be between 0 and 1.

You can enter a single value such as *1* or a series of values such as *1 2 3* or *1 to 4 by 0.5*.

### Note

$\mu_2(1)$  must be different from  $\mu_1(1)$ . That is, you cannot have a zero effect size.

## Effect Size - $\rho$ (Correlation Between Measurements)

### Pattern of $\rho$ 's Across Time (or Space)

Specify the type of pattern for the  $\rho$ 's, the correlations between responses of an individual at two points in time or between subjects within a cluster. This pattern often depends on the measurement time proportions. Usually, the correlation shrinks as two points are further and further apart in time. The options are

- **Compound Symmetry (All  $\rho$ 's Equal)**

A single value of  $\rho$  is used for all correlations. This pattern is commonly used for cluster-randomized trials in which case  $m$  is the cluster size and  $\rho$  is the intraclass correlation.

1	$\rho$	$\rho$	$\rho$	
$\rho$	1	$\rho$	$\rho$	
$\rho$	$\rho$	1	$\rho$	
$\rho$	$\rho$	$\rho$	1	

Example first row of correlation matrix

1.0000, 0.5000, 0.5000, 0.5000, 0.5000, 0.5000

- **Banded (1 Time Period)**

This is similar to all  $\rho$ 's equal, except that all elements are set to zero after the first off-diagonal element.

1	$\rho$	0	0	
$\rho$	1	$\rho$	0	
0	$\rho$	1	$\rho$	
0	0	$\rho$	1	

Example first row of correlation matrix

1.0000, 0.5000, 0.0000, 0.0000, 0.0000, 0.0000

- **Banded (2 Time Periods)**

This is similar to all  $\rho$ 's equal, except that all elements are set to zero after the second off-diagonal element.

1	$\rho$	$\rho$	0	
$\rho$	1	$\rho$	$\rho$	
$\rho$	$\rho$	1	$\rho$	
0	$\rho$	$\rho$	1	

Example first row of correlation matrix

1.0000, 0.5000, 0.5000, 0.0000, 0.0000, 0.0000

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

- **AR1 (Traditional) 1st Order Autocorrelation**

A single value of  $\rho$  is used to generate a first order autocorrelation pattern in the correlation matrix. This pattern produces the autocorrelation at each successive step by multiplying the value at the last step by  $\rho$ . The basic formula is  $\rho_{jk} = \rho^{|j-k|}$ . Thus the pattern is  $\rho, \rho^2, \rho^3$ , etc.

1	$\rho$	$\rho^2$	$\rho^3$
$\rho$	1	$\rho$	$\rho^2$
$\rho^2$	$\rho$	1	$\rho$
$\rho^3$	$\rho^2$	$\rho$	1

Example first row of correlation matrix

1.0000, 0.5000, 0.2500, 0.1250, 0.0625, 0.0313

- **AR1 (Proportional)**

A single value of  $\rho$  is used to generate a first order autocorrelation pattern in the correlation matrix. This pattern produces the autocorrelation at each successive step by multiplying the value at the last step by  $\rho$ . The basic formula is  $\rho_{jk} = \rho^{|t_j - t_k|}$ , where  $t_j$  and  $t_k$  are time proportions at which measurements are planned. An example is

$\rho^{0/3}$	$\rho^{1/3}$	$\rho^{2/3}$	$\rho^{3/3}$
$\rho^{1/3}$	$\rho^{0/3}$	$\rho^{1/3}$	$\rho^{2/3}$
$\rho^{2/3}$	$\rho^{1/3}$	$\rho^{0/3}$	$\rho^{1/3}$
$\rho^{3/3}$	$\rho^{2/3}$	$\rho^{1/3}$	$\rho^{0/3}$

Example first row of correlation matrix when  $M = 6$  and  $\rho = 0.1$ . Note that  $\rho$  shows up at the end of the list in this case.

1.0000, 0.6310, 0.3981, 0.2512, 0.1585, 0.1000

- **Dampened Exponential (Traditional)**

This pattern is similar to the AR(1), except that the exponents are raised to the power of a second parameter which we label as  $D_{exp}$ . The formula is  $\rho_{jk} = \rho^{|j-k|^{D_{exp}}}$ .

Example first row of correlation matrix with  $D_{exp} = 1.1$

1.0000, 0.5000, 0.2012, 0.0729, 0.0245, 0.0078

- **Dampened Exponential (Proportional)**

A single value of  $\rho$  is used to generate a first order autocorrelation pattern in the correlation matrix. This pattern produces the autocorrelation at each successive step by multiplying the value at the last step by  $\rho$ . The basic formula is  $\rho_{jk} = \rho^{|t_j - t_k|^{D_{exp}}}$ , where  $t_j$  and  $t_k$  are time proportions at which measurements are planned. An example with  $D_{exp} = 1$  is

$\rho^{0/3}$	$\rho^{1/3}$	$\rho^{2/3}$	$\rho^{3/3}$
$\rho^{1/3}$	$\rho^{0/3}$	$\rho^{1/3}$	$\rho^{2/3}$
$\rho^{2/3}$	$\rho^{1/3}$	$\rho^{0/3}$	$\rho^{1/3}$
$\rho^{3/3}$	$\rho^{2/3}$	$\rho^{1/3}$	$\rho^{0/3}$

Example first row of correlation matrix when  $M = 6$ ,  $\rho = 0.1$ , and  $D_{exp} = 1$ . Note that  $\rho$  shows up at the end of the list in this case.

1.0000, 0.6310, 0.3981, 0.2512, 0.1585, 0.1000

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

- **Linear Exponential Decay**

This pattern is similar to AR(1). The formula is  $\rho_{jk} = \rho^{|t_j/P - t_k/P| * E_{max}}$ . P is called the Base Time Proportion. The exponents of  $\rho$  range from 1 at P to  $E_{max}$  at M.

Example first row of correlation matrix with  $E_{max} = 4$

1.0000, 0.5000, 0.2973, 0.1768, 0.1051, 0.0625

This pattern is particularly useful when you want to compare different values of M since the exponent only depends on the difference. That is, a difference of 0.10 in the time proportions will always result in the same exponent, no matter what the value of M. This is NOT the case for AR(1).

- **Matrix on Spreadsheet**

A symmetric matrix is entered in the spreadsheet. The number of columns selected must match M, the number of time periods.

**$\rho$  Pattern = Compound Symmetry, Banded (1 Time Period), Banded (2 Time Periods), AR(1)**

**$\rho$  (Base Correlation)**

This is the base correlation,  $\rho$ , between measurements on the same subject taken at two time points. In several cases, this value is modified according to a special formula.

At least one value must be entered. If multiple values are entered, a separate analysis is performed for each value.

**Range**

$0 < \rho < 1$  (negative values are not used). A value near 0 indicates low correlation. A value near 1 indicates high correlation.

**Recommended**

The value of this parameter depends on time or location pattern at which measurements are taken. In their book on sample size, Machin and Campbell comment that values between 0.60 and 0.75 are typical. Some authors recommend using 0.2 when nothing is known about the actual value.

**Examples**

0.5

0.5 0.6 0.7

0 to 0.9 by 0.1

**$\rho$  Pattern = Damped Exponential**

**$\rho$  (Base Correlation)**

This is the base correlation,  $\rho$ , between measurements on the same subject taken at two time points. In several cases, this value is modified according to a special formula.

At least one value must be entered. If multiple values are entered, a separate analysis is performed for each value.

**Range**

$0 < \rho < 1$  (negative values are not used). A value near 0 indicates low correlation. A value near 1 indicates high correlation.

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

### Recommended

The value of this parameter depends on time or location pattern at which measurements are taken. In their book on sample size, Machin and Campbell comment that values between 0.60 and 0.75 are typical. Some authors recommend using 0.2 when nothing is known about the actual value.

### Examples

0.5

0.5 0.6 0.7

0 to 0.9 by 0.1

### Dexp (Dampening Exponent)

This exponent is applied to the AR(1) formula so that the resulting correlations are reduced faster. The formula become  $\rho_{jk} = \rho^{|j-k|^{Dexp}}$ .

Range

The valid range is  $Dexp > 0$ . The typical range is 1 to 3.

### $\rho$ Pattern = Linear Exponential Decay

#### $\rho$ (Base Correlation)

This is the base correlation,  $\rho$ , between measurements on the same subject taken at two time points. In several cases, this value is modified according to a special formula.

At least one value must be entered. If multiple values are entered, a separate analysis is performed for each value.

#### Range

$0 < \rho < 1$  (negative values are not used). A value near 0 indicates low correlation. A value near 1 indicates high correlation.

### Recommended

The value of this parameter depends on time or location pattern at which measurements are taken. In their book on sample size, Machin and Campbell comment that values between 0.60 and 0.75 are typical. Some authors recommend using 0.2 when nothing is known about the actual value.

### Examples

0.5

0.5 0.6 0.7

0 to 0.9 by 0.1

### Base Time Proportion

The base time proportion is used by the Linear Exponential Decay formula to specify the time proportion at which the correlation exponent is one. Thus, at this proportion the base correlation is reproduced.

#### Range

$0 < \text{Time} < 0.5$ .

#### Typical Value

1/M

#### Note

When you are comparing values of M, choose a value for M near the smallest value of 1/M.

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

### Emax (Max Decay Exponent)

This specifies the exponent of the base correlation when the time proportion is 1. Thus, the exponents go linearly from 1 at the base time to Emax at the maximum time.

#### Range

$E_{max} > 0$ .

#### Typical

Typical values of Emax are between 1 and 10.

### $\rho$ Pattern = Matrix on Spreadsheet

#### Columns Containing the $\rho$ 's

Select a set of  $M$  columns from the spreadsheet that contain a correlation matrix. Each column represents a column of the correlation matrix so it must contain  $M$  rows.

Since this is a correlation matrix, the diagonal elements must be set to one and the absolute values of the off-diagonal elements must be less than one. Also, the matrix must be symmetric.

---

## Missing Proportions Across Measurement Times

### Missing Input Type

Specify the way in which you want to specify the pattern of missing values.

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.



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

- **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 x 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

**Missing Input Type = Constant Additional Options****Constant Missing Proportion**

Enter one or more values of the missing value proportion that is to be used for all time points.

If multiple values are entered, a separate analysis is performed for each value.

**Range**

$0 \leq \text{Missing Proportion} < 1.$

**Examples**

0.2

0.1 0.2 0.4

0 to 0.4 by 0.1

**Missing Input Type = Piecewise Constant on Spreadsheet Additional Options****Pairwise Missing Pattern**

See the Pairwise Missing Pattern section of above.

**Column of Missing Proportions (Pairwise)**

Enter the column name on the spreadsheet containing a column of missing proportions, one for each segment. The program assigns this missing proportion to all time points in this time segment. The number of segments is arbitrary and determined by the number of rows.

Note that the usual pattern is to have the missing proportions increase over time.

Press the Spreadsheet icon (directly to the right) to select the column and then enter the missing proportion values.

Press the Input Spreadsheet icon (to the right and slightly up) to view/edit the spreadsheet. Note that you can obtain also the spreadsheet window by selecting "Tools", then "Input Spreadsheet", from the menus.

**(Pairwise)**

This refers to the two types of pairwise missing patterns: Ind(ependent) and Mon(otonic).

**Example**

Suppose that 'C1' is selected for the Missing column and 'C2' is selected for the Time column. Suppose that these columns contain the following values:

<b>C1</b>	<b>C2</b>
0.1	0.2
0.3	0.5
0.35	0.75
0.4	0.9
0.6	1.0

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

This would be interpreted by the program as

<b>Time Interval</b>	<b>Missing</b>
$0 \leq t \leq 0.2$	0.1
$0.2 < t \leq 0.5$	0.3
$0.5 < t \leq 0.75$	0.35
$0.75 < t \leq 0.9$	0.4
$0.9 < t \leq 1.0$	0.6

**Column of Time Proportions (Pairwise)**

Enter the column name on the spreadsheet containing a column of Upper Limit Time Proportions, one for each segment. The program assigns the missing proportion to all time points in the time segment defined by this upper limit. The number of segments is arbitrary and determined by the number of rows. Note that the final upper limit must be 1.

Press the Spreadsheet icon (directly to the right) to select the column and then enter the missing proportion values.

Press the Input Spreadsheet icon (to the right and slightly up) to view/edit the spreadsheet. Note that you can obtain also the spreadsheet window by selecting "Tools", then "Input Spreadsheet", from the menus.

**(Pairwise)**

This refers to the two types of pairwise missing patterns: Ind(ependent) and Mon(otonic).

**Example**

Suppose that 'C1' is selected for the Missing column and 'C2' is selected for the Time column. Suppose that these columns contain the following values:

<b>C1</b>	<b>C2</b>
0.1	0.2
0.3	0.5
0.35	0.75
0.4	0.9
0.6	1.0

This would be interpreted by the program as

<b>Time Interval</b>	<b>Missing</b>
$0 \leq t \leq 0.2$	0.1
$0.2 < t \leq 0.5$	0.3
$0.5 < t \leq 0.75$	0.35
$0.75 < t \leq 0.9$	0.4
$0.9 < t \leq 1.0$	0.6

**Missing Input Type = Linear (Steady Change) Additional Options****Pairwise Missing Pattern**

See the Pairwise Missing Pattern section of above.

**First (or Last) Missing Proportion (Pairwise)**

Specify a set of  $M$  missing proportions by entering only the first and last values of the list. A straight-line formula will be used to calculate the missing proportions for each time point in the interval.

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

### Range

$$0 \leq \text{First} \leq \text{Last}$$

$$\text{First} \leq \text{Last} < 1$$

### Example

Suppose a study is being planned with 5, evenly spaced, measurements. Further suppose that the missing data proportions are anticipated to be 0.1 initially and increase to 0.6 at the end of the study, with the missing proportions in between arranged linearly. If  $M = 5$ ,  $\text{First} = 0.1$ , and  $\text{Last} = 0.6$ , then the resulting Missing Proportions will be 0.1, 0.225, 0.35, 0.475, and 0.60. Note that these proportions are evenly spaced between the two boundaries.

Note that using this option allows the value of  $M$  to be varied and reasonable comparisons in power and sample size to be made.

### **Missing Input Type = Piecewise Linear on Spreadsheet Additional Options**

#### Pairwise Missing Pairwise

See the Pairwise Missing Pairwise section of above.

#### Column of Missing (or Time) Proportions (Pairwise)

These options let you easily define separate missing proportions for various time intervals of a study.

Select the column name on the spreadsheet of a column containing missing proportions. Also select the column name of the corresponding measurement time proportions. The program calculates a straight-line defined by each successive pair of points (see example below). This set of connected line segments becomes a prediction equation for the missing proportion based on the corresponding time proportion.

The number of line segments is arbitrary and determined from the number of rows in the selected columns. The number of rows does not have to match  $M$ , the number of time points.

#### (Pairwise)

This designates which of the two types of pairwise missing patterns, Ind(ependent) or Mon(otonic), is being entered in this option.

#### Notes

The usual pattern is to for the missing proportions to increase over time. The time value of the **first row of the time column must be 0**. The time value of the **last row of the time column must be 1**.

#### Shortcuts

Press the Spreadsheet icon (directly to the right) to select the column and then enter the missing proportion values. Press the Input Spreadsheet icon (to the right and slightly up) to view/edit the spreadsheet. Note that you can obtain also the spreadsheet window by selecting "Tools", then "Input Spreadsheet", from the menus.

### Example

Suppose that you have enter data in two columns on the spreadsheet labeled *Miss* and *Time* as follows.

Miss	Time
0.5	0
0.1	0.2
0.3	0.5
0.35	0.75
0.4	0.9
0.6	1

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

Now suppose that *Miss* is selected for the Missing column and *Time* is selected for the Time column. This would be interpreted by the program as the following segmented-prediction equation.

Time Interval	Slope	Intercept
$0 \leq T \leq 0.2$	$0.25 = (0.1 - 0.05) / (0.2 - 0)$	$0.1 - 0.2 * 0.25 = 0.05$
$0.2 < T \leq 0.5$	$0.67 = (0.3 - 0.1) / (0.5 - 0.2)$	$0.3 - 0.5 * 0.67 = -0.0333$
$0.5 < T \leq 0.75$	$0.2 = (0.35 - 0.3) / (0.75 - 0.5)$	$0.35 - 0.75 * 0.2 = 0.2$
$0.75 < T \leq 0.9$	$0.33 = (0.4 - 0.35) / (0.9 - 0.75)$	$0.4 - 0.9 * 0.33 = 0.1$
$0.9 < T \leq 1$	$2 = (0.6 - 0.4) / (1 - 0.9)$	$0.6 - 1 * 2 = -1.4$

A Missing Proportion would then be calculated using the formula

$$\text{Missing} = \text{Intercept} + \text{Slope} * \text{Time}$$

For example, using the above values, the missing proportions at time points 0, 0.1, 0.3, 0.8, and 1.0 would be found as follows:

Time	Equation	Resulting Missing Proportion
0	$0.05 + 0.25(0)$	0.05
0.1	$0.05 + 0.25(0.1)$	0.075
0.3	$-0.0333 + 0.67(0.3)$	0.1667
0.8	$0.1 + 0.33(0.8)$	0.3667
1.0	$-1.4 + 2(1)$	0.6

**Missing Input Type = List Additional Options****Pairwise Missing Pairwise**

See the Pairwise Missing Pairwise section of above.

**List of Missing Proportions (Pairwise)**

These options let you easily define separate missing proportions for various time intervals of a study.

Select the column name on the spreadsheet of a column containing missing proportions. Also select the column name of the corresponding measurement time proportions. The program calculates a straight-line defined by each successive pair of points (see example below). This set of connected line segments becomes a prediction equation for the missing proportion based on the corresponding time proportion.

**Missing Input Type = Multiple Lists on Spreadsheet Additional Options****Pairwise Missing Pairwise**

See the Pairwise Missing Pairwise section of above.

**Columns of Missing Proportions (Pairwise)**

Enter lists of missing value proportions by first entering them on the spreadsheet and then selecting those columns here. The missing value proportions are entered down the rows of a column, one for each time point. Each value is the anticipated proportion of missing responses at the corresponding time point.

Although you can enter any pattern you want, the usual pattern is that the proportion missing increases over time.

When you specify more than *M* values in a list (where *M* is specified in the Measurement Times section), the extra values are ignored. When you specify too few values, the last value you specify is copied forward.

Press the Spreadsheet icon (directly to the right) to select the column and then enter the missing proportion values.

Press the Input Spreadsheet icon (to the right and slightly up) to view/edit the spreadsheet. Note that you can obtain also the spreadsheet window by selecting "Tools", then "Input Spreadsheet", from the menus.

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

This designates which of the two types of pairwise missing patterns, Ind(ependent) or Mon(otonic), is being entered in this option.

**Range**

$0 \leq \text{missing proportion} < 1$ .

**Missing Input Type = Pairwise Observed Proportions on Spreadsheet Additional Options****Columns of Pairwise Observed**

Enter an M-by-M matrix of pairwise observed proportions on the spreadsheet and then select it by selecting those M columns here. Each entry gives the proportion (or probability) that the corresponding row and column time point values are both observed (non-missing). The diagonal elements of this matrix contain the probability that an observation is observed at that point (marginal probability).

**Range**

$0 < \text{each value} \leq 1$ .

**Note**

In other missing entries, you enter the proportion missing. This is the only case that requires the proportion observed.

## Example 1 – Determining Sample Size

Researchers are planning a study to assess the effectiveness of a new anti-epileptic drug which is administered with the standard drug. They want to compare subjects who take the new drug with subjects who only take the standard drug. Their experimental protocol calls for a baseline measurement, followed by administration of the drug therapies, followed by five additional measurements one week apart. They want to detect a difference of 1 in the final response rates. They also want a sensitivity analysis by considering a range of possible differences from 0.5 to 1.5.

Similar studies have found that the average baseline rate is 2.5 which is reduced to 1.75 at the end of the treatment period with the standard drug.

Previous studies showed an autocorrelation between adjacent measurements on the same individual of 0.7, so they want to try autocorrelations of 0.6, 0.7, and 0.8. The researchers assume that first-order autocorrelation adequately represents the autocorrelation pattern. A two-sided Wald test will be conducted at the 0.05 significance level and at 90% power. The subjects will be divided equally between the treatment and control groups.

The researchers anticipate that the missing data pattern across time will begin at 0% missing and increase steadily to 40% at the sixth measurement. They assume that the pairwise missing probabilities are *independent*.

What are the sample size requirements for this study?

### Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **GEE Tests for the Slope of Two Groups in a Repeated Measures Design (Count Outcome)** procedure window. 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**.

<u>Option</u>	<u>Value</u>
<b>Design Tab</b>	
Solve For .....	<b>Sample Size</b>
Alternative Hypothesis .....	<b>Two-Sided</b>
Power .....	<b>0.90</b>
Alpha .....	<b>0.05</b>
R (Group 1 Allocation %) .....	<b>50</b>
Measurement Time Input Type .....	<b>Equally Spaced Measurement Times</b>
M (Number of Measurements) .....	<b>6</b>
$\mu_1(0)$ and $\mu_2(0)$ Input Type .....	<b><math>\mu_1(0) = \mu_2(0)</math></b>
$\mu_1(0)$ and $\mu_2(0)$ .....	<b>2.5</b>
$\mu_1(1)$ Input Type .....	<b>Difference (<math>\mu_1(1) - \mu_2(1)</math>)</b>
Difference ( $\mu_1(1) - \mu_2(1)$ ) .....	<b>0.5, 1, 1.5</b>
$\mu_2(1)$ .....	<b>1.75</b>
Pattern of $\rho$ 's Across Time .....	<b>AR1 (Traditional)</b>
$\rho$ (Base Correlation) .....	<b>0.6, 0.7, 0.8</b>
Missing Input Type .....	<b>Linear (Steady Change)</b>
Pairwise Missing Pattern .....	<b>Independent (Ind)</b>
First Missing Proportion (Ind) .....	<b>0</b>
Last Missing Proportion (Ind) .....	<b>0.4</b>

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

## Annotated Output

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

#### Numeric Results for the Test of Slope-Difference in Count Data using GEE

Measurement Times: Equally spaced  
 Correlation: AR(1):  $\rho(j,k) = \rho^{|j-k|}$   
 Missing Pattern: Range of missing proportions  
 Observant Proportions: Assume independence  
 $\mu_k(t)$ : Event rate of group k (1=treatment, 2=control) at time proportion t

Power	Group 1 Alloc Pct			M	$\mu_1(0)$	$\mu_2(0)$	$\mu_1(1)$	$\mu_2(1)$	Diff	Base Corr $\rho$	First Row of Corr Matrix	Alpha	Missing	Time
	N	R	M											
0.9001	703	50	6	2.500	2.500	2.250	1.750	0.500	0.600	$\rho_1(T1)$	0.050	M1(T1)	T1	
0.9003	654	50	6	2.500	2.500	2.250	1.750	0.500	0.700	$\rho_2(T1)$	0.050	M1(T1)	T1	
0.9002	553	50	6	2.500	2.500	2.250	1.750	0.500	0.800	$\rho_3(T1)$	0.050	M1(T1)	T1	
0.9006	208	50	6	2.500	2.500	2.750	1.750	1.000	0.600	$\rho_1(T1)$	0.050	M1(T1)	T1	
0.9000	193	50	6	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_2(T1)$	0.050	M1(T1)	T1	
0.9014	164	50	6	2.500	2.500	2.750	1.750	1.000	0.800	$\rho_3(T1)$	0.050	M1(T1)	T1	
0.9004	107	50	6	2.500	2.500	3.250	1.750	1.500	0.600	$\rho_1(T1)$	0.050	M1(T1)	T1	
0.9018	100	50	6	2.500	2.500	3.250	1.750	1.500	0.700	$\rho_2(T1)$	0.050	M1(T1)	T1	
0.9030	85	50	6	2.500	2.500	3.250	1.750	1.500	0.800	$\rho_3(T1)$	0.050	M1(T1)	T1	

#### Footnotes

T1: 0.00, 0.20, 0.40, 0.60, 0.80, 1.00  
 M1(T1): 0.00, 0.08, 0.16, 0.24, 0.32, 0.40  
 $\rho_1(T1)$ : 1.000, 0.600, 0.360, 0.216, 0.130, 0.078  
 $\rho_2(T1)$ : 1.000, 0.700, 0.490, 0.343, 0.240, 0.168  
 $\rho_3(T1)$ : 1.000, 0.800, 0.640, 0.512, 0.410, 0.328

#### References

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

#### Report Definitions

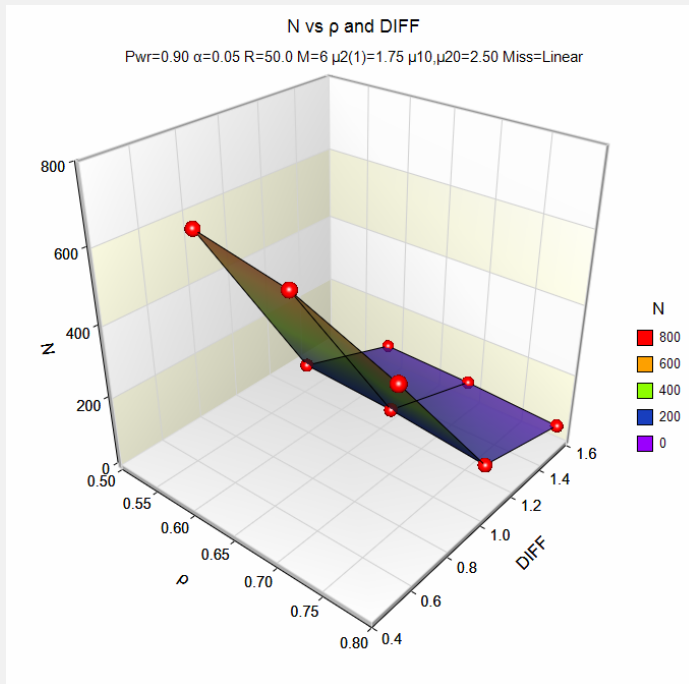
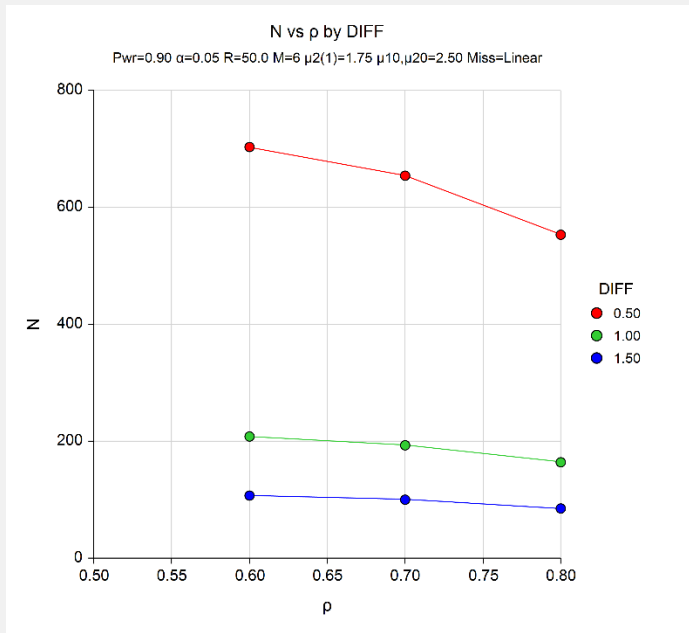
Power is the probability of rejecting a false null hypothesis.  
 N is the total number of subjects in the study.  
 R is the treatment group allocation proportion. It is the proportion of subjects that are in the treatment group.  
 M is the number of time points at which each subject is measured.  
 Diff =  $(\mu_1(1) - \mu_2(1))$  is the difference between the treatment and control event rates at the final measurement time.  
 $\mu_k(t)$  is the mean event rate of group k (1=treatment, 2=control) at the measurement time proportion t.  
 $\rho$  is the base correlation between two responses on the same subject. It may be transformed based on the correlation pattern.  
 Alpha is the significance level of the test. The probability of rejecting the null hypothesis when the null hypothesis is true.  
 Missing gives the name of the footnote containing the missing value proportions across time.  
 Time gives the name of the footnote containing the time proportions. The time values represent the proportion of the total study time that has elapsed just before the measurement.

#### Summary Statements

A sample of 703 subjects, each scheduled to be measured 6 times, achieve a power of 0.9001 when using a two-sided Wald test from a GEE analysis to test whether a  $\mu_1(1)$  of 2.250 differs from a  $\mu_2(1)$  of 1.750 at a significance level of 0.050. The value of  $\mu_1(1)$  was calculated from a difference  $(\mu_1(1) - \mu_2(1))$  of 0.500.  $\mu_1(0)$  and  $\mu_2(0)$  are assumed to be 2.500. The subjects are randomly split between a treatment group and a control group, with 50% of the subjects assigned to the treatment group. The measurements of each subject will be made at the following times expressed as proportions of the total study time: {0.00, 0.20, 0.40, 0.60, 0.80, 1.00}. Missing values are assumed to occur completely at random (MCAR). These missing value proportions will be combined to form the pairwise observant probabilities using the Independent method. The anticipated proportions missing at each measurement time are {0.00, 0.08, 0.16, 0.24, 0.32, 0.40}. The first row of the autocorrelation matrix of the responses within a subject is assumed to be {1.000, 0.600, 0.360, 0.216, 0.130, 0.078}. Other rows follow the same pattern.

This report gives the sample size for each value of the other parameters. The definitions of each of the items is given in the Reports Definitions section at the end of the report.

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



These charts show the relationship between sample size, difference, and  $\rho$  when the other parameters in the design are held constant.

**Autocorrelation Matrix for Report Row 1**

Time	T(0.00)	T(0.20)	T(0.40)	T(0.60)	T(0.80)	T(1.00)
T(0.00)	1.000	0.600	0.360	0.216	0.130	0.078
T(0.20)	0.600	1.000	0.600	0.360	0.216	0.130
T(0.40)	0.360	0.600	1.000	0.600	0.360	0.216
T(0.60)	0.216	0.360	0.600	1.000	0.600	0.360
T(0.80)	0.130	0.216	0.360	0.600	1.000	0.600
T(1.00)	0.078	0.130	0.216	0.360	0.600	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 sample sizes ranging from 50 to 300 for the main cases of the other parameters.

### Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **GEE Tests for the Slope of Two Groups in a Repeated Measures Design (Count Outcome)** procedure window. 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>
<b>Design Tab</b>	
Solve For .....	<b>Power</b>
Alternative Hypothesis .....	<b>Two-Sided</b>
Alpha.....	<b>0.05</b>
N (Subjects) .....	<b>50 to 300 by 50</b>
R (Group 1 Allocation %) .....	<b>50</b>
Measurement Time Input Type.....	<b>Equally Spaced Measurement Times</b>
M (Number of Measurements).....	<b>6</b>
$\mu_1(0)$ and $\mu_2(0)$ Input Type.....	<b><math>\mu_1(0) = \mu_2(0)</math></b>
$\mu_1(0)$ and $\mu_2(0)$ .....	<b>2.5</b>
$\mu_1(1)$ Input Type .....	<b>Difference (<math>\mu_1(1) - \mu_2(1)</math>)</b>
Difference ( $\mu_1(1) - \mu_2(1)$ ).....	<b>1</b>
$\mu_2(1)$ .....	<b>1.75</b>
Pattern of $\rho$ 's Across Time .....	<b>AR1 (Traditional)</b>
$\rho$ (Base Correlation) .....	<b>0.7</b>
Missing Input Type.....	<b>Linear (Steady Change)</b>
Pairwise Missing Pattern .....	<b>Independent (Ind)</b>
First Missing Proportion (Ind) .....	<b>0</b>
Last Missing Proportion (Ind).....	<b>0.4</b>

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

**Output**

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

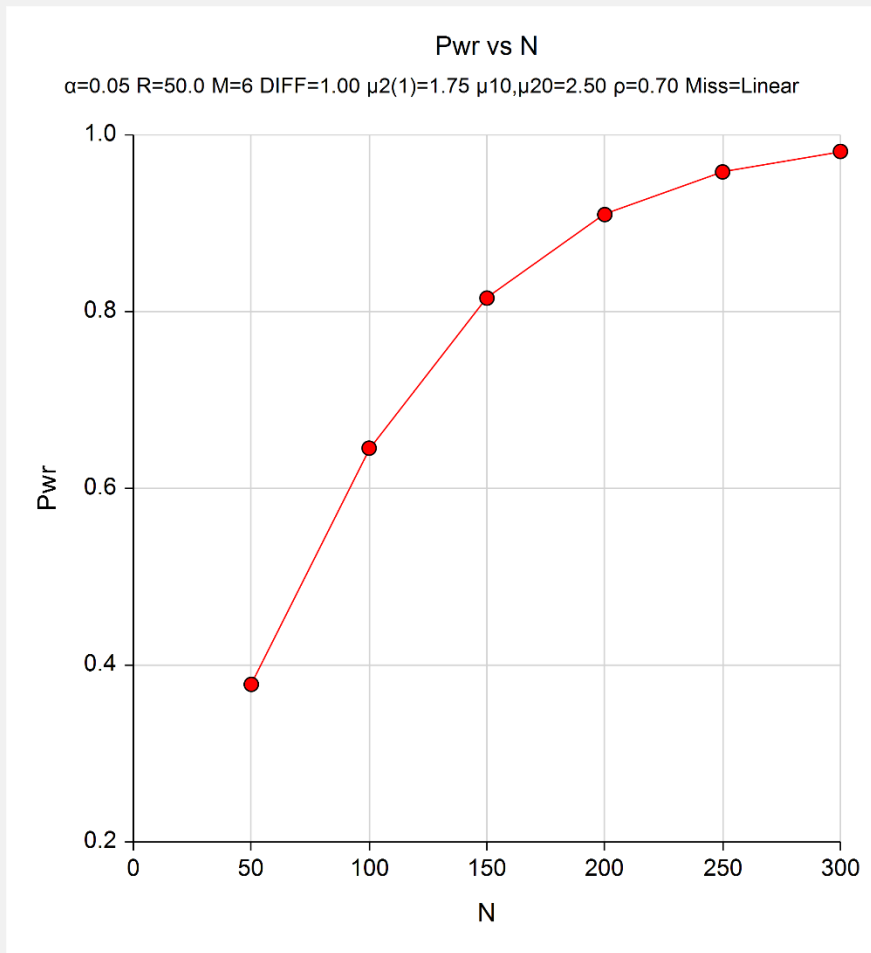
**Numeric Results for the Test of Slope-Difference in Count Data using GEE**

Measurement Times: Equally spaced  
 Correlation: AR(1):  $\rho(j,k) = \rho^{|j-k|}$   
 Missing Pattern: Range of missing proportions  
 Observant Proportions: Assume independence  
 $\mu_k(t)$ : Event rate of group k (1=treatment, 2=control) at time proportion t

Power	Group 1			$\mu_1(0)$	$\mu_2(0)$	$\mu_1(1)$	$\mu_2(1)$	Diff	Base Corr $\rho$	First Row of Corr Matrix	Alpha	Missing	Time
	N	R	M										
0.3783	50	50	6	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T1)$	0.050	M1(T1)	T1
0.6456	100	50	6	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T1)$	0.050	M1(T1)	T1
0.8153	150	50	6	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T1)$	0.050	M1(T1)	T1
0.9099	200	50	6	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T1)$	0.050	M1(T1)	T1
0.9581	250	50	6	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T1)$	0.050	M1(T1)	T1
0.9813	300	50	6	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T1)$	0.050	M1(T1)	T1

**Footnotes**

T1: 0.00, 0.20, 0.40, 0.60, 0.80, 1.00  
 M1(T1): 0.00, 0.08, 0.16, 0.24, 0.32, 0.40  
 P1(T1): 1.000, 0.700, 0.490, 0.343, 0.240, 0.168



The reports and plot indicate the power for each value of N.

## Example 3 – Impact of the Number of Repeated Measurements

Continuing with Examples 1 and 2, the researchers want to study the impact on the sample size of changing the number of measurements made on each individual. Their experimental protocol calls for 6 measurements. They want to see the impact of reducing the number of measurements to 3.

### Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **GEE Tests for the Slope of Two Groups in a Repeated Measures Design (Count Outcome)** procedure window. You may then make the appropriate entries as listed below, or open **Example 3** by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
<b>Design Tab</b>	
Solve For .....	<b>Power</b>
Alternative Hypothesis .....	<b>Two-Sided</b>
Alpha.....	<b>0.05</b>
N (Subjects) .....	<b>50 to 300 by 50</b>
R (Group 1 Allocation %) .....	<b>50</b>
Measurement Time Input Type.....	<b>Equally Spaced Measurement Times</b>
M (Number of Measurements).....	<b>3 6</b>
$\mu_1(0)$ and $\mu_2(0)$ Input Type.....	<b><math>\mu_1(0) = \mu_2(0)</math></b>
$\mu_1(0)$ and $\mu_2(0)$ .....	<b>2.5</b>
$\mu_1(1)$ Input Type .....	<b>Difference (<math>\mu_1(1) - \mu_2(1)</math>)</b>
Difference ( $\mu_1(1) - \mu_2(1)$ ).....	<b>1</b>
$\mu_2(1)$ .....	<b>1.75</b>
Pattern of $\rho$ 's Across Time .....	<b>AR1 (Traditional)</b>
$\rho$ (Base Correlation) .....	<b>0.7</b>
Missing Input Type.....	<b>Linear (Steady Change)</b>
Pairwise Missing Pattern .....	<b>Independent (Ind)</b>
First Missing Proportion (Ind) .....	<b>0</b>
Last Missing Proportion (Ind).....	<b>0.4</b>

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

Output

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

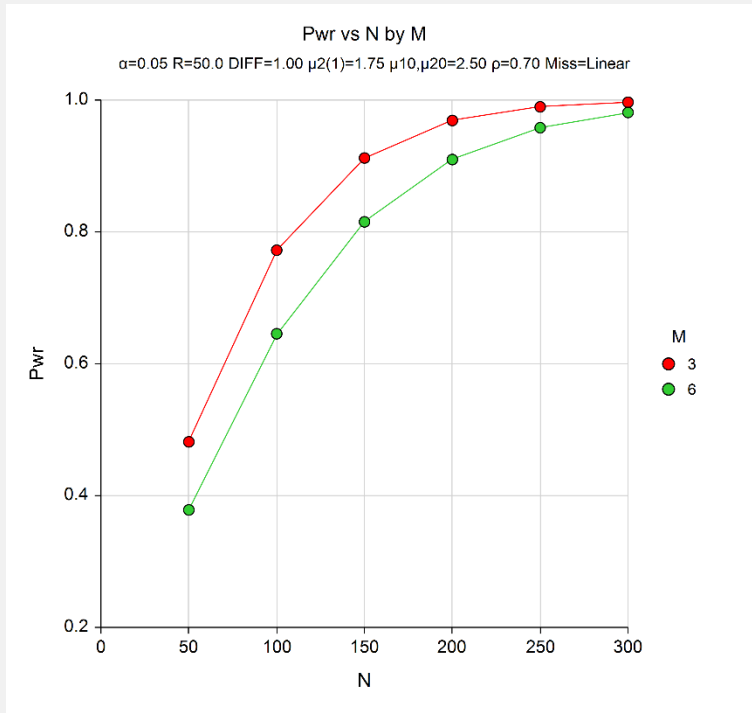
**Numeric Results for the Test of Slope-Difference in Count Data using GEE**

Measurement Times: Equally spaced  
 Correlation: AR(1):  $\rho(j,k) = \rho^{|j-k|}$   
 Missing Pattern: Range of missing proportions  
 Observant Proportions: Assume independence  
 $\mu_k(t)$ : Event rate of group k (1=treatment, 2=control) at time proportion t

Power	Group 1 Alloc Pct			$\mu_1(0)$	$\mu_2(0)$	$\mu_1(1)$	$\mu_2(1)$	Diff	Base Corr $\rho$	First Row of Corr Matrix	Alpha	Missing	Time
	N	R	M										
0.4815	50	50	3	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T1)$	0.050	M1(T1)	T1
0.3783	50	50	6	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T2)$	0.050	M1(T2)	T2
0.7723	100	50	3	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T1)$	0.050	M1(T1)	T1
0.6456	100	50	6	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T2)$	0.050	M1(T2)	T2
0.9122	150	50	3	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T1)$	0.050	M1(T1)	T1
0.8153	150	50	6	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T2)$	0.050	M1(T2)	T2
0.9691	200	50	3	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T1)$	0.050	M1(T1)	T1
0.9099	200	50	6	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T2)$	0.050	M1(T2)	T2
0.9898	250	50	3	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T1)$	0.050	M1(T1)	T1
0.9581	250	50	6	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T2)$	0.050	M1(T2)	T2
0.9968	300	50	3	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T1)$	0.050	M1(T1)	T1
0.9813	300	50	6	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T2)$	0.050	M1(T2)	T2

**Footnotes**

T1: 0.00, 0.50, 1.00  
 T2: 0.00, 0.20, 0.40, 0.60, 0.80, 1.00  
 M1(T1): 0.00, 0.20, 0.40  
 M1(T2): 0.00, 0.08, 0.16, 0.24, 0.32, 0.40  
 $\rho_1(T1)$ : 1.000, 0.700, 0.490  
 $\rho_1(T2)$ : 1.000, 0.700, 0.490, 0.343, 0.240, 0.168



Note that decreasing the number of measurements has had the surprising result of decreasing the power, probably because the assumption of the AR(1) model for the autocorrelation has changed the way in which the correlations are formed. Note from the footnotes that the final autocorrelation increases from 0.168 when M = 6 to 0.490 when M = 3. Look at the next example to see how the autocorrelations can be put on a more equal footing.

## Example 4 – Impact of Changing M with Linear Exponential Decay

We saw in Example 3 that the decreasing the number of measurements from 6 to 3 had the counter-intuitive result of increasing the power when the sample size was held constant. We surmised that this was partially due to the differing autocorrelation matrices that were used when the AR(1) model as assumed. In this example, we will leave all parameters the same, except that we will use a Linear Exponential Decay model for the autocorrelation. This will keep the autocorrelation matrices more comparable.

### Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **GEE Tests for the Slope of Two Groups in a Repeated Measures Design (Count Outcome)** procedure window. You may then make the appropriate entries as listed below, or open **Example 4** by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
<b>Design Tab</b>	
Solve For .....	<b>Power</b>
Alternative Hypothesis .....	<b>Two-Sided</b>
Alpha.....	<b>0.05</b>
N (Subjects) .....	<b>50 to 300 by 50</b>
R (Group 1 Allocation %) .....	<b>50</b>
Measurement Time Input Type.....	<b>Equally Spaced Measurement Times</b>
M (Number of Measurements).....	<b>3 6</b>
$\mu_1(0)$ and $\mu_2(0)$ Input Type .....	<b><math>\mu_1(0) = \mu_2(0)</math></b>
$\mu_1(0)$ and $\mu_2(0)$ .....	<b>2.5</b>
$\mu_1(1)$ Input Type .....	<b>Difference (<math>\mu_1(1) - \mu_2(1)</math>)</b>
Difference ( $\mu_1(1) - \mu_2(1)$ ).....	<b>1</b>
$\mu_2(1)$ .....	<b>1.75</b>
Pattern of $\rho$ 's Across Time .....	<b>Linear Exponential Decay</b>
$\rho$ (Base Correlation) .....	<b>0.7</b>
Base Time Proportion .....	<b>0.166666666</b>
E <sub>max</sub> (Max Decay Exponent) .....	<b>3</b>
Missing Input Type.....	<b>Linear (Steady Change)</b>
Pairwise Missing Pattern .....	<b>Independent (Ind)</b>
First Missing Proportion (Ind) .....	<b>0</b>
Last Missing Proportion (Ind).....	<b>0.4</b>

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

Output

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

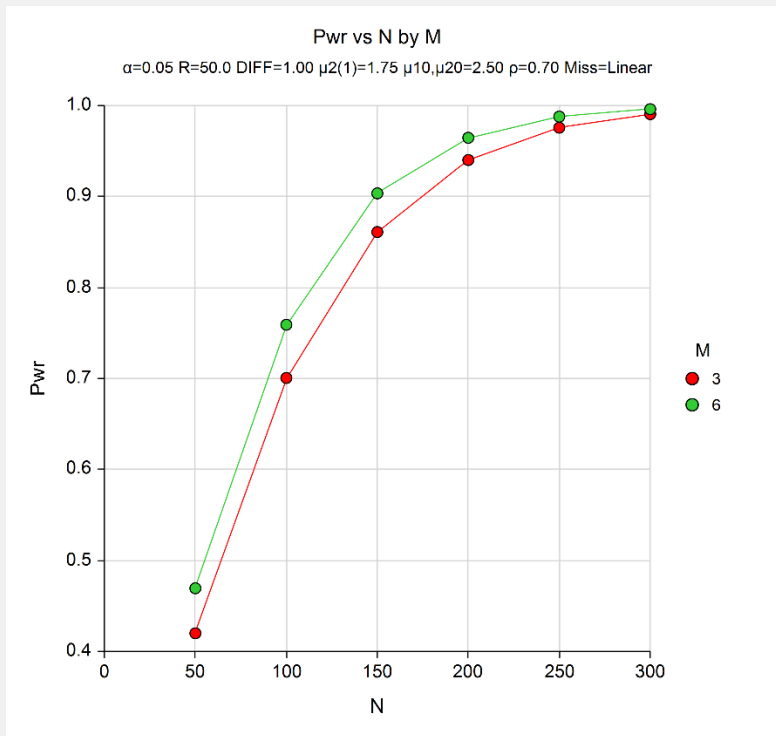
**Numeric Results for the Test of Slope-Difference in Count Data using GEE**

Measurement Times: Equally spaced  
 Correlation: AR(1):  $\rho(j,k) = \rho^{|j-k|}$   
 Missing Pattern: Range of missing proportions  
 Observant Proportions: Assume independence  
 $\mu_k(t)$ : Event rate of group k (1=treatment, 2=control) at time proportion t

Power	Group 1 Alloc Pct		M	$\mu_1(0)$	$\mu_2(0)$	$\mu_1(1)$	$\mu_2(1)$	Diff	Base Corr $\rho$	First Row of Corr Matrix	Alpha	Missing	Time
	N	R											
0.4199	50	50	3	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T1)$	0.050	M1(T1)	T1
0.4694	50	50	6	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T2)$	0.050	M1(T2)	T2
0.7005	100	50	3	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T1)$	0.050	M1(T1)	T1
0.7590	100	50	6	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T2)$	0.050	M1(T2)	T2
0.8609	150	50	3	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T1)$	0.050	M1(T1)	T1
0.9035	150	50	6	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T2)$	0.050	M1(T2)	T2
0.9401	200	50	3	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T1)$	0.050	M1(T1)	T1
0.9646	200	50	6	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T2)$	0.050	M1(T2)	T2
0.9756	250	50	3	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T1)$	0.050	M1(T1)	T1
0.9878	250	50	6	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T2)$	0.050	M1(T2)	T2
0.9905	300	50	3	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T1)$	0.050	M1(T1)	T1
0.9960	300	50	6	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T2)$	0.050	M1(T2)	T2

**Footnotes**

T1: 0.00, 0.50, 1.00  
 T2: 0.00, 0.20, 0.40, 0.60, 0.80, 1.00  
 M1(T1): 0.00, 0.20, 0.40  
 M1(T2): 0.00, 0.08, 0.16, 0.24, 0.32, 0.40  
 $\rho_1(T1)$ : 1.000, 0.526, 0.343  
 $\rho_1(T2)$ : 1.000, 0.680, 0.573, 0.483, 0.407, 0.343



Note from the footnotes that the final autocorrelation between the two models is now identical at  $0.3430 (= 0.7^3)$  when M is changed from 6 to 3. Now that the autocorrelation matrices are more comparable, the power values have increased in all cases, although only slightly. We see that increasing M has not had a huge impact on power.

## Example 5 – Validation using Hand Calculations

We could not find a published validation example, so we will create an example by hand.

In this example we set  $\mu_1(0) = 2.5$ ,  $\mu_2(0) = 2.5$ ,  $\mu_1(1) = 2.75$ ,  $\mu_2(1) = 1.75$ , the significance level = 0.05, the power = 0.90, R = 50%, M = 3, and the correlation matrix is compound symmetric with  $\rho = 0.7$ . The proportions missing at each time point are 0.0, 0.2, and 0.4.

The time values are 0, 0.5, and 1.

Taking the log values of the event rates yields

$$\text{Log}(\mu_1(0)) = 0.916291$$

$$\text{Log}(\mu_2(0)) = 0.916291$$

$$\text{Log}(\mu_1(1)) = 1.011601$$

$$\text{Log}(\mu_2(1)) = 0.559616$$

The slope and intercept for group 1 is 0.09531 and 0.916291.

The slope and intercept for group 2 is -0.35667 and 0.916291.

Using these values  $\mu_1(0.5) = 2.622022$  and  $\mu_2(0.5) = 2.09165$ .

Subtracting the missing proportions from one gives the observant proportions,  $\phi_i$ , for both groups as 1.0, 0.8, and 0.6. Using these values, we calculate  $\tau_1 = 0.431974$  and  $\tau_2 = 0.361199$ .

The observant proportions matrix,  $\phi_{ij}$ , is

1.0	0.8	0.6
0.8	0.8	0.48
0.6	0.48	0.6

Using these values and  $\rho = 0.7$ , we find  $s_1^2 = 1.008589$ ,  $s_2^2 = 0.78687$ ,  $c_1^2 = -0.55497$ , and  $c_2^2 = -0.41980$ .

These calculations lead to  $v_1^2 = 0.445926$  and  $v_2^2 = 0.592843$ .

The result is N = 106.8555 which is rounded up to 107.

## Setup

This section presents the values of each of the parameters needed to generate the upper-left-quarter of this example. First, from the PASS Home window, load the **GEE Tests for the Slope of Two Groups in a Repeated Measures Design (Count Outcome)** procedure window. You may then make the appropriate entries as listed below, or open **Example 5** by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
<b>Design Tab</b>	
Solve For .....	<b>Sample Size</b>
Alternative Hypothesis .....	<b>Two-Sided</b>
Power .....	<b>0.90</b>
Alpha .....	<b>0.05</b>
R (Group 1 Allocation %) .....	<b>50</b>
Measurement Time Input Type .....	<b>Equally Spaced Measurement Times</b>
M (Number of Measurements) .....	<b>3</b>
$\mu_1(0)$ and $\mu_2(0)$ Input Type .....	<b><math>\mu_1(0) = \mu_2(0)</math></b>
$\mu_1(0)$ and $\mu_2(0)$ .....	<b>2.5</b>
$\mu_1(1)$ Input Type .....	<b><math>\mu_1(1)</math></b>
$\mu_1(1)$ .....	<b>2.75</b>
$\mu_2(1)$ .....	<b>1.75</b>

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

Pattern of  $\rho$ 's Across Time ..... **Compound Symmetry (All  $\rho$ 's Equal)**  
 $\rho$  (Base Correlation) ..... **0.7**  
 Missing Input Type..... **Linear (Steady Change)**  
 Pairwise Missing Pattern ..... **Independent (Ind)**  
 First Missing Proportion (Ind) ..... **0**  
 Last Missing Proportion (Ind)..... **0.4**

**Output**

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

**Numeric Results for the Test of Slope-Difference in Count Data using GEE**

Measurement Times: Equally spaced  
 Correlation: Compound symmetry (all  $\rho$ 's equal)  
 Missing Pattern: Range of missing proportions  
 Observant Proportions: Assume independence  
 $\mu_k(t)$ : Event rate of group  $k$  (1=treatment, 2=control) at time proportion  $t$

Power	N	Group 1 Alloc Pct R	M	$\mu_1(0)$	$\mu_2(0)$	$\mu_1(1)$	$\mu_2(1)$	Diff	Base Corr $\rho$	First Row of Corr Matrix $\rho_1(T1)$	Alpha	Missing	Time
0.9004	107	50	3	2.500	2.500	2.750	1.750	1.000	0.700	$\rho_1(T1)$	0.050	M1(T1)	T1

**Footnotes**  
 T1: 0.00, 0.50, 1.00  
 M1(T1): 0.00, 0.20, 0.40  
 $\rho_1(T1)$ : 1.000, 0.700, 0.700

Note that the sample size is 107 which matches our hand calculations exactly.



## Example 6 – Impact of Measurement Time Distribution

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

In this example we set  $\mu_1(0) = 2.5$ ,  $\mu_2(0) = 2.5$ ,  $\mu_1(1) = 2.75$ ,  $\mu_2(1) = 1.75$ . The significance level is 0.05, the sample size ranges from 50 to 250, and R is 50%. The correlation pattern will be Linear Exponential Decay with a base correlation of 0.6, Base Time Proportion of 0.10, and Emax set to 3. The missing input type will be set to Linear from 0 to 0.30 and the pairwise missing assumption will be independent.

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

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **GEE Tests for the Slope of Two Groups in a Repeated Measures Design (Count Outcome)** procedure window. You may then make the appropriate entries as listed below, or open **Example 6** by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
<b>Design Tab</b>	
Solve For .....	<b>Power</b>
Alternative Hypothesis .....	<b>Two-Sided</b>
Alpha .....	<b>0.05</b>
N (Subjects) .....	<b>50 to 250 by 50</b>
R (Group 1 Allocation %) .....	<b>50</b>
Measurement Time Input Type .....	<b>Columns of Measurement Time Proportions</b>
Column(s) of Time Proportions .....	<b>Tm1-Tm5</b>
<i>The above table must be entered into the spreadsheet and the column names changed to Tm1 – Tm5.</i>	
<i>Press the Input Spreadsheet icon to the right to view the spreadsheet.</i>	
$\mu_1(0)$ and $\mu_2(0)$ Input Type .....	<b><math>\mu_1(0) = \mu_2(0)</math></b>
$\mu_1(0)$ and $\mu_2(0)$ .....	<b>2.5</b>
$\mu_1(1)$ Input Type .....	<b><math>\mu_1(1)</math></b>
$\mu_1(1)$ .....	<b>2.75</b>
$\mu_2(1)$ .....	<b>1.75</b>
Pattern of $\rho$ 's Across Time .....	<b>Linear Exponential Decay</b>
$\rho$ (Base Correlation) .....	<b>0.6</b>
Base Time Proportion .....	<b>0.1</b>
Emax (Max Decay Exponent) .....	<b>3</b>
Missing Input Type .....	<b>Linear (Steady Change)</b>

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

Pairwise Missing Pattern ..... **Independent (Ind)**

First Missing Proportion (Ind) ..... **0**

Last Missing Proportion (Ind)..... **0.3**

## Output

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

**Numeric Results for the Test of Slope-Difference in Count Data using GEE**

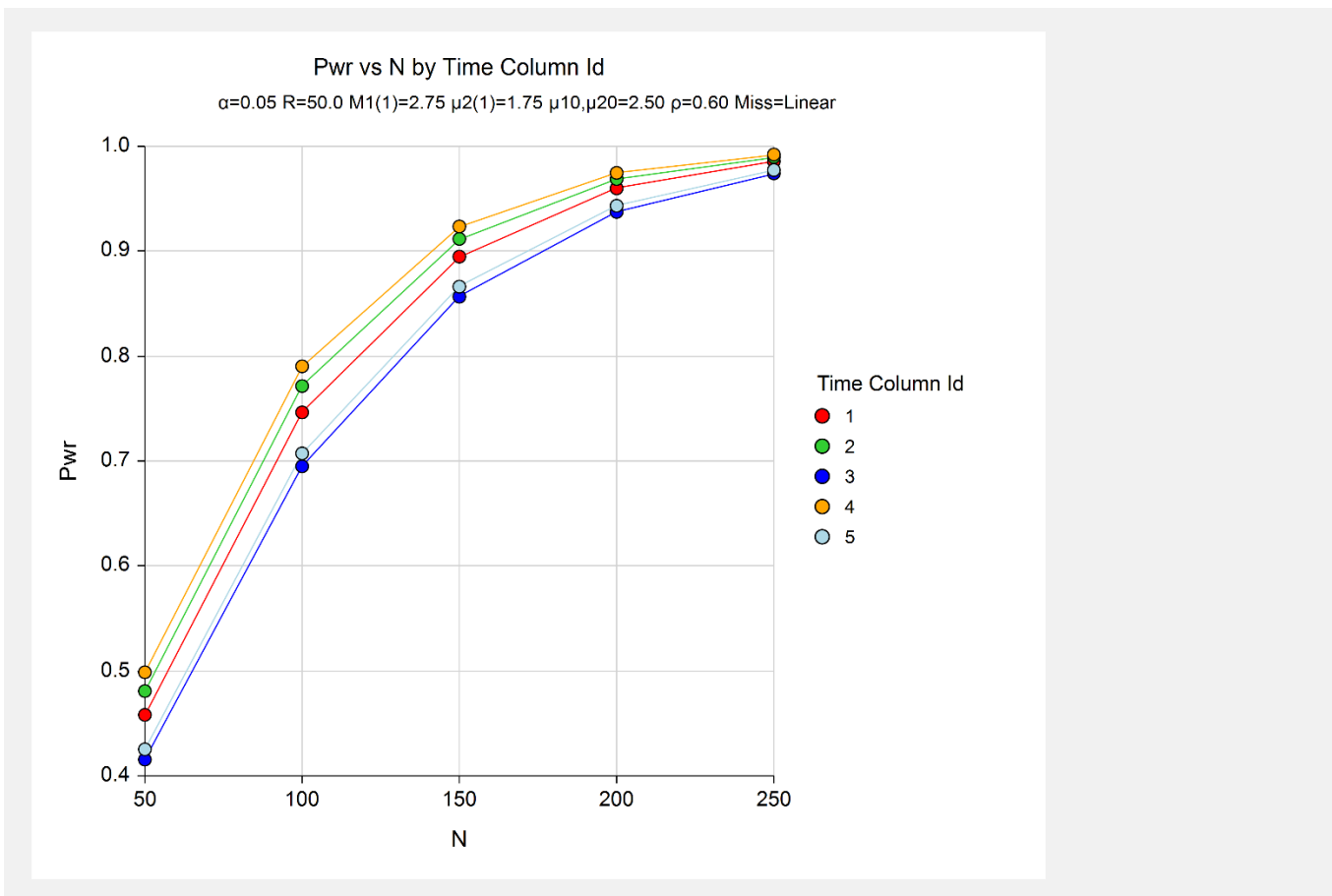
Measurement Times: Lists in spreadsheet columns: {TM1-TM5}  
 Correlation: Linear exponential decay, with Emax = 3 and Base Time Prop = 0.1  
 Missing Pattern: Range of missing proportions  
 Observant Proportions: Assume independence  
 $\mu k(t)$ : Event rate of group k (1=treatment, 2=control) at time proportion t

Power	Group 1 Alloc Pct			M	$\mu 1(0)$	$\mu 2(0)$	$\mu 1(1)$	$\mu 2(1)$	Diff	First Base Row of Corr		Alpha	Missing	Time
	N	R								$\rho$	Matrix			
0.4582	50	50	6	2.500	2.500	2.750	1.750	1.000	0.600	$\rho 1(Tm1)$	0.050	M1(Tm1)	Tm1	
0.4808	50	50	6	2.500	2.500	2.750	1.750	1.000	0.600	$\rho 1(Tm2)$	0.050	M1(Tm2)	Tm2	
0.4155	50	50	6	2.500	2.500	2.750	1.750	1.000	0.600	$\rho 1(Tm3)$	0.050	M1(Tm3)	Tm3	
0.4988	50	50	6	2.500	2.500	2.750	1.750	1.000	0.600	$\rho 1(Tm4)$	0.050	M1(Tm4)	Tm4	
0.4253	50	50	6	2.500	2.500	2.750	1.750	1.000	0.600	$\rho 1(Tm5)$	0.050	M1(Tm5)	Tm5	
0.7464	100	50	6	2.500	2.500	2.750	1.750	1.000	0.600	$\rho 1(Tm1)$	0.050	M1(Tm1)	Tm1	
0.7715	100	50	6	2.500	2.500	2.750	1.750	1.000	0.600	$\rho 1(Tm2)$	0.050	M1(Tm2)	Tm2	
0.6950	100	50	6	2.500	2.500	2.750	1.750	1.000	0.600	$\rho 1(Tm3)$	0.050	M1(Tm3)	Tm3	
0.7903	100	50	6	2.500	2.500	2.750	1.750	1.000	0.600	$\rho 1(Tm4)$	0.050	M1(Tm4)	Tm4	
0.7073	100	50	6	2.500	2.500	2.750	1.750	1.000	0.600	$\rho 1(Tm5)$	0.050	M1(Tm5)	Tm5	
0.8949	150	50	6	2.500	2.500	2.750	1.750	1.000	0.600	$\rho 1(Tm1)$	0.050	M1(Tm1)	Tm1	
0.9117	150	50	6	2.500	2.500	2.750	1.750	1.000	0.600	$\rho 1(Tm2)$	0.050	M1(Tm2)	Tm2	
0.8566	150	50	6	2.500	2.500	2.750	1.750	1.000	0.600	$\rho 1(Tm3)$	0.050	M1(Tm3)	Tm3	
0.9236	150	50	6	2.500	2.500	2.750	1.750	1.000	0.600	$\rho 1(Tm4)$	0.050	M1(Tm4)	Tm4	
0.8662	150	50	6	2.500	2.500	2.750	1.750	1.000	0.600	$\rho 1(Tm5)$	0.050	M1(Tm5)	Tm5	
0.9599	200	50	6	2.500	2.500	2.750	1.750	1.000	0.600	$\rho 1(Tm1)$	0.050	M1(Tm1)	Tm1	
0.9688	200	50	6	2.500	2.500	2.750	1.750	1.000	0.600	$\rho 1(Tm2)$	0.050	M1(Tm2)	Tm2	
0.9374	200	50	6	2.500	2.500	2.750	1.750	1.000	0.600	$\rho 1(Tm3)$	0.050	M1(Tm3)	Tm3	
0.9746	200	50	6	2.500	2.500	2.750	1.750	1.000	0.600	$\rho 1(Tm4)$	0.050	M1(Tm4)	Tm4	
0.9433	200	50	6	2.500	2.500	2.750	1.750	1.000	0.600	$\rho 1(Tm5)$	0.050	M1(Tm5)	Tm5	
0.9857	250	50	6	2.500	2.500	2.750	1.750	1.000	0.600	$\rho 1(Tm1)$	0.050	M1(Tm1)	Tm1	
0.9897	250	50	6	2.500	2.500	2.750	1.750	1.000	0.600	$\rho 1(Tm2)$	0.050	M1(Tm2)	Tm2	
0.9742	250	50	6	2.500	2.500	2.750	1.750	1.000	0.600	$\rho 1(Tm3)$	0.050	M1(Tm3)	Tm3	
0.9921	250	50	6	2.500	2.500	2.750	1.750	1.000	0.600	$\rho 1(Tm4)$	0.050	M1(Tm4)	Tm4	
0.9773	250	50	6	2.500	2.500	2.750	1.750	1.000	0.600	$\rho 1(Tm5)$	0.050	M1(Tm5)	Tm5	

**Footnotes**

Tm1: 0.00, 0.20, 0.40, 0.60, 0.80, 1.00  
 Tm2: 0.00, 0.60, 0.70, 0.80, 0.90, 1.00  
 Tm3: 0.00, 0.10, 0.20, 0.30, 0.40, 1.00  
 Tm4: 0.00, 0.10, 0.20, 0.80, 0.90, 1.00  
 Tm5: 0.00, 0.45, 0.50, 0.55, 0.60, 1.00  
 M1(Tm1): 0.00, 0.06, 0.12, 0.18, 0.24, 0.30  
 M1(Tm2): 0.00, 0.18, 0.21, 0.24, 0.27, 0.30  
 M1(Tm3): 0.00, 0.03, 0.06, 0.09, 0.12, 0.30  
 M1(Tm4): 0.00, 0.03, 0.06, 0.24, 0.27, 0.30  
 M1(Tm5): 0.00, 0.14, 0.15, 0.17, 0.18, 0.30  
 $\rho 1(Tm1)$ : 1.000, 0.536, 0.427, 0.340, 0.271, 0.216  
 $\rho 1(Tm2)$ : 1.000, 0.340, 0.304, 0.271, 0.242, 0.216  
 $\rho 1(Tm3)$ : 1.000, 0.600, 0.536, 0.478, 0.427, 0.216  
 $\rho 1(Tm4)$ : 1.000, 0.600, 0.536, 0.271, 0.242, 0.216  
 $\rho 1(Tm5)$ : 1.000, 0.403, 0.381, 0.360, 0.340, 0.216

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



The legend, *Time Column Id*, gives the sequence number of the measurement columns. Thus, 1.0 is Tm1, 2.0 is Tm2, and so on.

The pattern Tm4 consistently produces the highest power across all sample sizes. Remember that Tm4 put the measurements at the beginning and the end, but none in the middle.

Patterns Tm3 and Tm5 are nearly tied for achieving the lowest powers. Tm3 put most of the measurements at the beginning of the study. Tm5 put most of the measurements during the middle of the study.

Note that Tm1, the equally-spaced times, is in the middle.

## Example 7 – Entering a Correlation Matrix

This example will show how a correlation matrix can be loaded directly.

In this example we set  $\mu_1(0) = 2.5$ ,  $\mu_2(0) = 2.5$ ,  $\mu_1(1) = 2.75$ ,  $\mu_2(1) = 1.75$ . The significance level is 0.05, the sample size ranges from 50 to 250,  $M = 4$ , and  $R$  is 50%. The missing input type will be set to Linear from 0 to 0.30 and the pairwise missing assumption will be independent. A correlation matrix (shown below) is available from a previous study and is entered into the spreadsheet.

**Table of Correlations**

C1	C2	C3	C4
1.0000	0.7000	0.4900	0.3430
0.7000	1.0000	0.7000	0.4900
0.4900	0.7000	1.0000	0.7000
0.3430	0.4900	0.7000	1.0000

### Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **GEE Tests for the Slope of Two Groups in a Repeated Measures Design (Count Outcome)** procedure window. You may then make the appropriate entries as listed below, or open **Example 7** by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
<b>Design Tab</b>	
Solve For .....	<b>Power</b>
Alternative Hypothesis .....	<b>Two-Sided</b>
Alpha .....	<b>0.05</b>
N (Subjects) .....	<b>50 to 250 by 50</b>
R (Group 1 Allocation %) .....	<b>50</b>
Measurement Time Input Type .....	<b>Equally Spaced Measurement Times</b>
M (Number of Measurements) .....	<b>4</b>
$\mu_1(0)$ and $\mu_2(0)$ Input Type .....	<b><math>\mu_1(0) = \mu_2(0)</math></b>
$\mu_1(0)$ and $\mu_2(0)$ .....	<b>2.5</b>
$\mu_1(1)$ Input Type .....	<b><math>\mu_1(1)</math></b>
$\mu_1(1)$ .....	<b>2.75</b>
$\mu_2(1)$ .....	<b>1.75</b>
Pattern of $\rho$ 's Across Time .....	<b>Matrix on Spreadsheet</b>
Columns Containing the $\rho_{jk}$ 's .....	<b>C1-C4</b>
<i>You must enter the correlation table using the Spreadsheet icon to the right.</i>	
Missing Input Type .....	<b>Linear (Steady Change)</b>
Pairwise Missing Pattern .....	<b>Independent (Ind)</b>
First Missing Proportion (Ind) .....	<b>0</b>
Last Missing Proportion (Ind) .....	<b>0.30</b>

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

**Output**

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

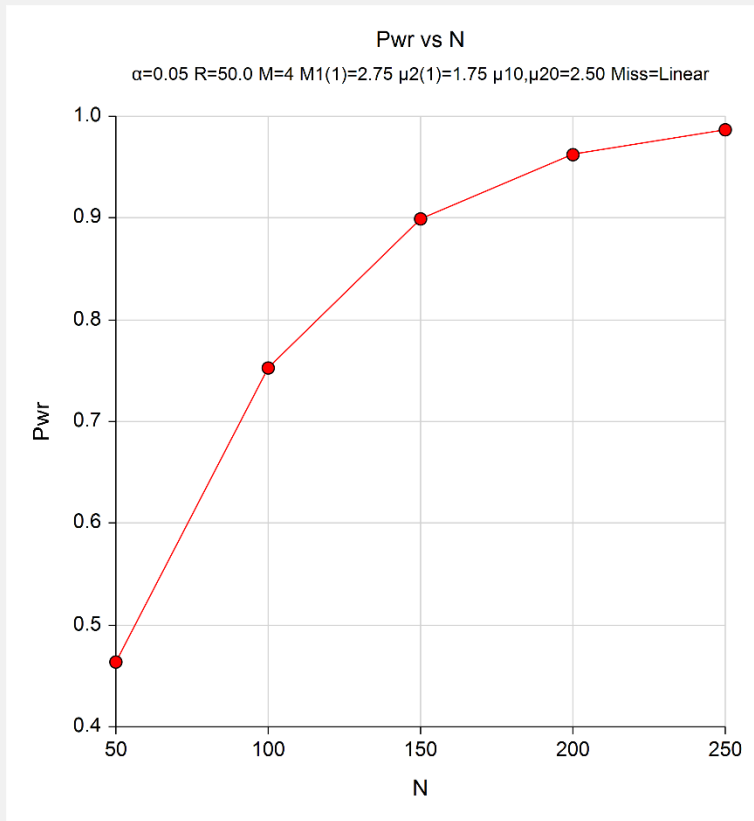
**Numeric Results for the Test of Slope-Difference in Count Data using GEE**

Measurement Times: Equally spaced  
 Correlation: Matrix stored on spreadsheet in columns C1-C4  
 Missing Pattern: Range of missing proportions  
 Observant Proportions: Assume independence  
 $\mu_k(t)$ : Event rate of group k (1=treatment, 2=control) at time proportion t

Power	Group 1			$\mu_1(0)$	$\mu_2(0)$	$\mu_1(1)$	$\mu_2(1)$	Diff	Base Corr $\rho$	First Row of Corr Matrix	Alpha	Missing	Time
	N	R	M										
0.4636	50	50	4	2.500	2.500	2.750	1.750	1.000	n/a	$\rho_1(T1)$	0.050	M1(T1)	T1
0.7526	100	50	4	2.500	2.500	2.750	1.750	1.000	n/a	$\rho_1(T1)$	0.050	M1(T1)	T1
0.8991	150	50	4	2.500	2.500	2.750	1.750	1.000	n/a	$\rho_1(T1)$	0.050	M1(T1)	T1
0.9622	200	50	4	2.500	2.500	2.750	1.750	1.000	n/a	$\rho_1(T1)$	0.050	M1(T1)	T1
0.9867	250	50	4	2.500	2.500	2.750	1.750	1.000	n/a	$\rho_1(T1)$	0.050	M1(T1)	T1

**Footnotes**

T1: 0.00, 0.33, 0.67, 1.00  
 M1(T1): 0.00, 0.10, 0.20, 0.30  
 $\rho_1(T1)$ : 1.000, 0.700, 0.490, 0.343



The standard reports are displayed.

## Example 8 – Entering an Observant Probabilities Matrix

This example will show how an observant probabilities matrix can be loaded directly.

In this example we set  $\mu_1(0) = 2.5$ ,  $\mu_2(0) = 2.5$ ,  $\mu_1(1) = 2.75$ ,  $\mu_2(1) = 1.75$ . There are to be 4 equally spaced time measurements. The significance level is 0.05, the sample size ranges from 50 to 250, and R is 50%. The correlation pattern is Linear Exponential Decay with a base correlation of 0.4, Base Time Proportion of 0.10, and Emax of 4. The significance level is 0.05, the sample size ranges from 50 to 250, and R is 50%. The missing input type will be set to Matrix of Pairwise Missing.

**Table of Observant Probabilities**

Row	C1	C2	C3	C4
1	1.00	0.90	0.80	0.70
2	0.90	0.90	0.72	0.63
3	0.80	0.72	0.80	0.56
4	0.70	0.63	0.56	0.70

This table gives the pairwise observant probabilities. That is, each entry gives the probability of obtaining a response for both the row and column time points. For example, 0.63 is the probability of observing both the second response and the fourth response.

## Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **GEE Tests for the Slope of Two Groups in a Repeated Measures Design (Count Outcome)** procedure window. You may then make the appropriate entries as listed below, or open **Example 8** by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
<b>Design Tab</b>	
Solve For .....	<b>Power</b>
Alternative Hypothesis .....	<b>Two-Sided</b>
Alpha .....	<b>0.05</b>
N (Subjects) .....	<b>50 to 250 by 50</b>
R (Group 1 Allocation %) .....	<b>50</b>
Measurement Time Input Type .....	<b>Equally Spaced Measurement Times</b>
M (Number of Measurements) .....	<b>4</b>
$\mu_1(0)$ and $\mu_2(0)$ Input Type .....	<b><math>\mu_1(0) = \mu_2(0)</math></b>
$\mu_1(0)$ and $\mu_2(0)$ .....	<b>2.5</b>
$\mu_1(1)$ Input Type .....	<b><math>\mu_1(1)</math></b>
$\mu_1(1)$ .....	<b>2.75</b>
$\mu_2(1)$ .....	<b>1.75</b>
Pattern of $\rho$ 's Across Time .....	<b>Linear Exponential Decay</b>
$\rho$ (Base Correlation) .....	<b>0.4</b>
Base Time Proportion .....	<b>0.1</b>
Emax (Max Decay Exponent) .....	<b>4</b>
Missing Input Type .....	<b>Pairwise Observed Proportions on Spreadsheet</b>
Columns of Pairwise Observed .....	<b>C1-C4</b>

*You must enter the pairwise probabilities table using the Spreadsheet icon to the right.*

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

**Output**

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

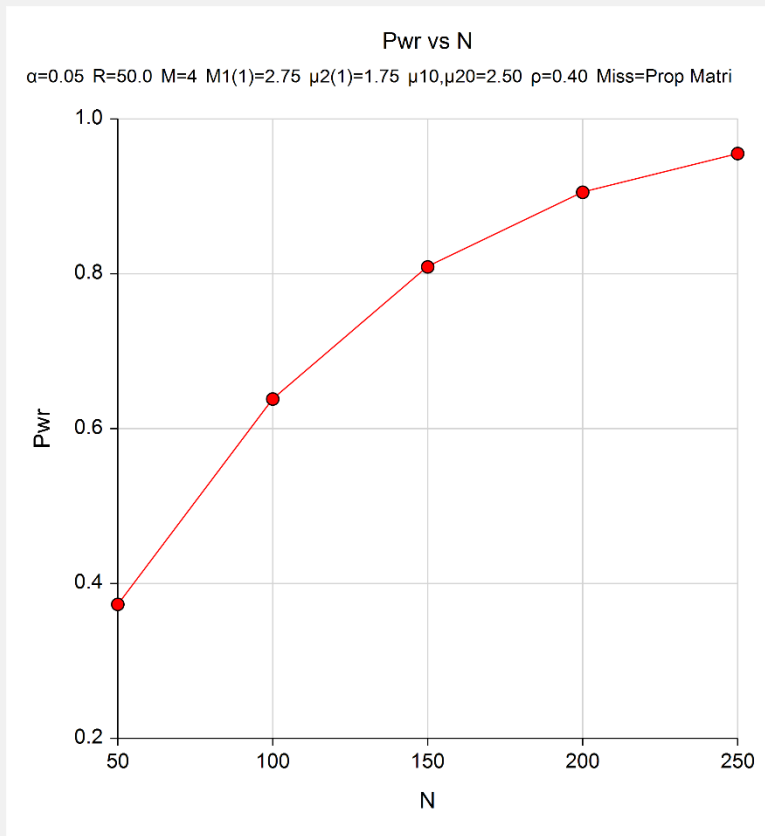
**Numeric Results for the Test of Slope-Difference in Count Data using GEE**

Measurement Times: Equally spaced  
 Correlation: Linear exponential decay, with Emax = 4 and Base Time Prop = 0.1  
 Missing Pattern: N/A. Matrix of observant probabilities entered in columns C1-C4.  
 $\mu_k(t)$ : Event rate of group k (1=treatment, 2=control) at time proportion t

Power	Group 1 Alloc Pct		M	$\mu_1(0)$	$\mu_2(0)$	$\mu_1(1)$	$\mu_2(1)$	Diff	Base Corr $\rho$	First Row of Corr Matrix	Alpha	Missing	Time
	N	R											
0.3730	50	50	4	2.500	2.500	2.750	1.750	1.000	0.400	$\rho_1(T1)$	0.050	n/a	T1
0.6382	100	50	4	2.500	2.500	2.750	1.750	1.000	0.400	$\rho_1(T1)$	0.050	n/a	T1
0.8088	150	50	4	2.500	2.500	2.750	1.750	1.000	0.400	$\rho_1(T1)$	0.050	n/a	T1
0.9052	200	50	4	2.500	2.500	2.750	1.750	1.000	0.400	$\rho_1(T1)$	0.050	n/a	T1
0.9553	250	50	4	2.500	2.500	2.750	1.750	1.000	0.400	$\rho_1(T1)$	0.050	n/a	T1

**Footnotes**

T1: 0.00, 0.33, 0.67, 1.00  
 $\rho_1(T1)$ : 1.000, 0.196, 0.071, 0.026



The standard reports are displayed.