Chapter 393

GEE Tests for the TAD of Multiple Groups in a Repeated Measures Design (Continuous Outcome)

Introduction

This module calculates the power for testing for differences among the time-averaged responses of two or more means from **continuous**, correlated data that are analyzed using the GEE method. Such data can occur in two design types: clustered and longitudinal. This procedure provides results for the longitudinal design.

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.

Time-averaged response analysis is often used when the outcome to be measured varies with time. For example, suppose that you want to compare three treatment groups based on the means of a certain outcome such as blood pressure. It is known that a person's blood pressure depends on several instantaneous factors such as amount of sleep, excitement level, mood, exercise, etc. If only a single measurement is taken from each patient, then the comparison of mean values from the groups may be insensitive because of the large degree of variation in blood pressure levels within patients. The precision of the experiment is increased by taking multiple measurements from each individual and comparing the time-averaged response among the groups. Care must be taken in the analysis because of the correlation that is introduced when several measurements are taken from the same individual. The correlation structure may take on several forms depending on the nature of the experiment and the subjects involved.

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

Technical details are given in Ahn, Heo, and Zhang (2015), chapter 4, section 4.4.4, pages 116-119 and in Zhang and Ahn (2013).

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.

The mean of y_{kij} is modeled by

$$y_{kij} = \mu_k + \epsilon_{kij}$$

where

$\quad y_{kij} \quad$ is the jth response from subject i in group k, with variance given by σ^2,

$\quad r_k \quad$ is the proportion of subjects in group k,

$\quad \mu_k \quad$ is group-specific treatment effect (k = 1, ...,G),

$\quad \epsilon_{kij} \quad$ is a zero-mean error term with variance σ^2.

In this procedure, the primary interest is to test $H_0: \mu_1 = \cdots = \mu_G$ against the alternative that at least one mean is different.

GEE is used to estimate and test hypotheses about these group means. H_0 is rejected with a type I error α if $\boldsymbol{B'W^{-1}B} > \chi^2_{G-1,1-\alpha}$ where $\chi^2_{G-1,1-\alpha}$ is the 100(1 - α)th percentile of a chi-square distribution with G-1 degrees of freedom. The mean deviation vector $\boldsymbol{B}$ is given by

$$\boldsymbol{B} = \sqrt{N}(\hat{\mu}_1 - \hat{\mu}, \dots, \hat{\mu}_{G-1} - \hat{\mu})'$$

and $\boldsymbol{W}$ is a consistent estimate of the variance matrix based on the residuals.

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 correlation 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 ρ 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 ρ, 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 ρ 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 ρ, 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 ρ is the baseline correlation.

AR1 (Traditional)

This version of AR1 (autoregressive order 1) correlation model assumes that correlations t time periods apart are equal to ρ^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 ρ 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

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

where ρ is the baseline correlation. Note that in this pattern, the value of ρ 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

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

where ρ is the baseline correlation.

Damped Exponential (Proportional)

This version of the damped exponential 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 $\rho^{|t_j-t_k|^\theta}$. That is

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

where ρ 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, *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

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

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

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 κ_j. The proportion non-missing at a particular time point is $\phi_j = 1 - \kappa_j$. We will refer to ϕ_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

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

As explained above, GEE is used to estimate the regression coefficients. Under the alternative hypothesis, as N approaches infinity, the test statistic $B'\widehat{W}^{-1}B$ is approximately distributed as a noncentral chi-square random variable with $G-1$ degrees of freedom and noncentrality parameter $U = N\boldsymbol{\eta}'\boldsymbol{W}^{-1}\boldsymbol{\eta}$

where

$$\boldsymbol{\eta}' = (\mu_1 - \bar{\mu}, \dots, \mu_{G-1} - \bar{\mu})$$

$$\bar{\mu} = \sum_{k=1}^{G} r_i \mu_i$$

$$\boldsymbol{\eta}'\boldsymbol{W}^{-1}\boldsymbol{\eta} = \frac{\bar{m}^2}{s}\left[\sum_{k=1}^{G-1} r_k \eta_k^2 + \frac{1}{r_G}\left(\sum_{k=1}^{G-1} r_k \eta_k\right)^2\right]$$

$$\bar{m} = \sum_{k=1}^{G} \phi_k$$

$$s = \sigma^2 \sum_{j=1}^{m} \sum_{j'=1}^{m} \phi_{jj'} \rho_{jj'}$$

This noncentral distribution can be used to calculate the power using the following

$$Power = Pr\left(\chi_{G-1}'^2(U) > \chi_{G-1,1-\alpha}^2\right)$$

Using this power function, the sample size can be determined using a simple binary search.

Example 1 – Determining Sample Size

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 doses of only one drug, two days apart. The researchers want a sample size large enough to detect a time-averaged difference of 5 between the highest and lowest time-averaged heart rates. They will use the means of 65, 60, and 60 to represent this difference.

Similar studies have had a standard deviation of the residuals within a subject across time of between 5 and 7. These studies also 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 split 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.

Design Tab

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's Input Type ....**μ1, μ2, ..., μG**
μ1, μ2, ..., μG...**65 60 60**
σ (Standard Deviation)...................................**5 6 7**
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**

Output

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

Numeric Reports

Numeric Results

Solve For: Sample Size
Measurement Times: Equally spaced
Correlation: AR1: $\rho(j,k) = \rho^{|j-k|}$
Missing Pattern: Range of missing proportions
Observant Proportions: Assume independence
Number of Groups: 3

Power	Total Sample Size N	Group Allocation Proportions ri	Number of Measurement Times M	Time-Averaged Responses µi	Standard Deviation Group Means σm	Standard Deviation Responses σ	Base Correlation ρ	First Row of Correlation Matrix	Missing Data Proportions	Measurement Times	Alpha
0.9060	36	ri(1)	4	µi(1)	2.36	5	0.6	ρ1(1)	Ms1(1)	T(1)	0.05
0.9131	42	ri(1)	4	µi(1)	2.36	5	0.7	ρ2(1)	Ms1(1)	T(1)	0.05
0.9148	48	ri(1)	4	µi(1)	2.36	5	0.8	ρ3(1)	Ms1(1)	T(1)	0.05
0.9012	51	ri(1)	4	µi(1)	2.36	6	0.6	ρ1(1)	Ms1(1)	T(1)	0.05
0.9109	60	ri(1)	4	µi(1)	2.36	6	0.7	ρ2(1)	Ms1(1)	T(1)	0.05
0.9015	66	ri(1)	4	µi(1)	2.36	6	0.8	ρ3(1)	Ms1(1)	T(1)	0.05
0.9118	72	ri(1)	4	µi(1)	2.36	7	0.6	ρ1(1)	Ms1(1)	T(1)	0.05
0.9085	81	ri(1)	4	µi(1)	2.36	7	0.7	ρ2(1)	Ms1(1)	T(1)	0.05
0.9020	90	ri(1)	4	µi(1)	2.36	7	0.8	ρ3(1)	Ms1(1)	T(1)	0.05

Item	Values
ri(1)	0.333, 0.333, 0.333
µi(1)	65, 60, 60
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	The Group Allocation Proportions 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	The Time-Averaged Responses gives the name of the set containing the time-averaged responses for each group.
σm	Standard Deviation of Group Means. The population standard deviation of the group means.
σ	The standard deviation of a response.
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 period.
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.

Summary Statements

A 3-group repeated measures design (with a continuous response and with 4 measurements for each subject) will be used to test whether there is a group difference in time-averaged response between any of the 3 groups. The test will be performed by collectively comparing the GEE estimates of the time-averaged group means using a Chi-square test with 2 degrees of freedom, with a Type I error rate (α) 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: $\rho(j,k) = \rho^{|j-k|}$). The residual (zero-mean) standard deviation for all 3 groups is assumed to be 5. To detect time-averaged group means of 65, 60, 60 with 90% power, the total number of needed subjects is 36 (divided into the 3 groups according to the proportions: 0.333, 0.333, 0.333).

References

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

Zhang, S. and Ahn, C. 2013. Sample Size Calculations for Comparing Time-Averaged Responses in K-Group Repeated-Measurement Studies. Computational Statistics and Data Analysis. Vol 58(1). Pages 283-291.

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

Plots Section

Plots
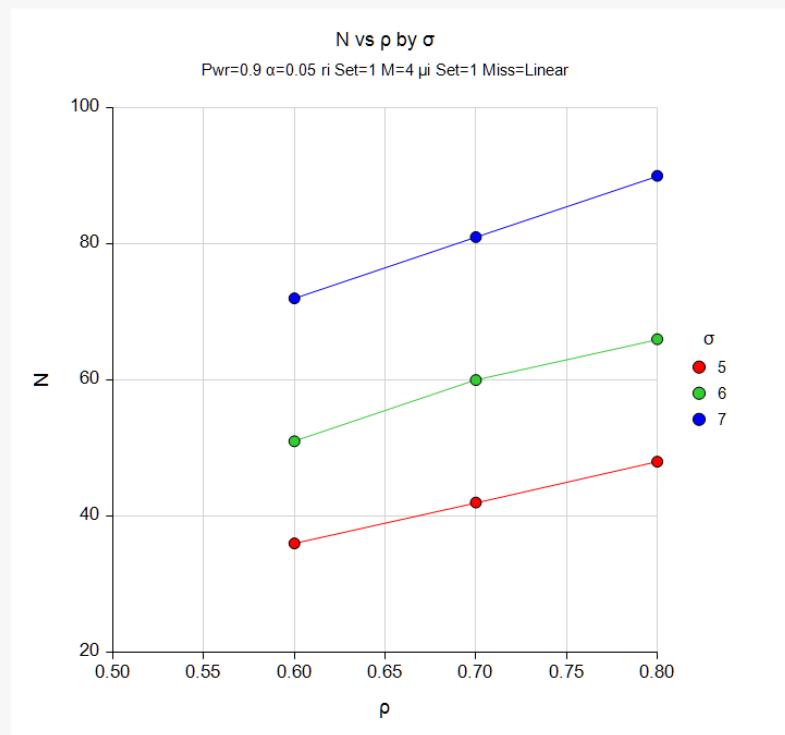
393-10
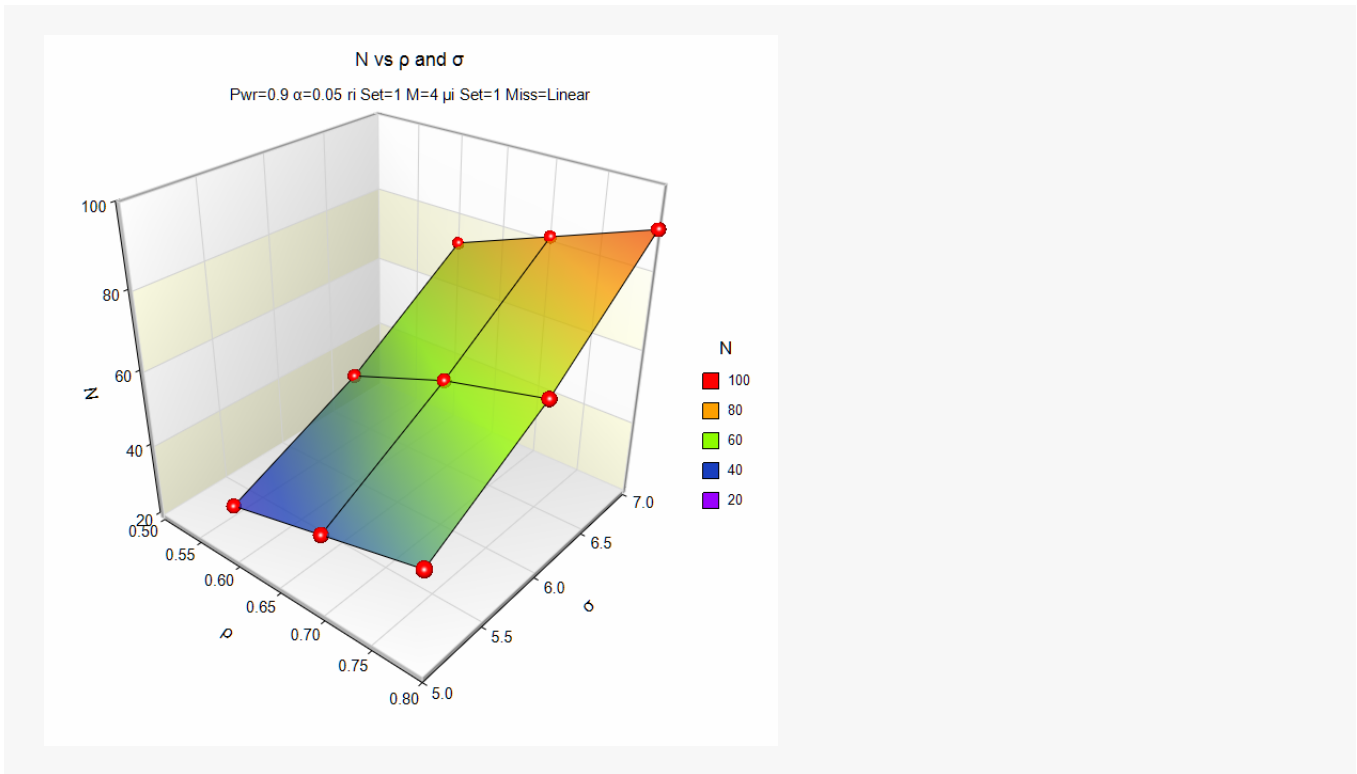
These charts show the relationship among the design parameters.

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

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(More Reports Follow)

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 5 to 40 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.

Design Tab

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)............................**5 to 40 by 5**
Measurement Time Input Type ....**Equally Spaced Measurement Times**
M (Number of Measurement Times) **4**
μi's Input Type ....**μ1, μ2, ..., μG**
μ1, μ2, ..., μG...**65 60 60**
σ (Standard Deviation)..................................**6**
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**

Output

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

Numeric Results
_____

Solve For: Power
Measurement Times: Equally spaced
Correlation: AR1: $\rho(j,k) = \rho^{\wedge}|j-k|$
Missing Pattern: Range of missing proportions
Observant Proportions: Assume independence
Number of Groups: 3
_____

| | | | | | Standard Deviation | | | | | | |
Power	Total Sample Size N	Group Sample Sizes ni	Number of Measurement Times M	Time-Averaged Responses μi	Group Means σm	Responses σ	Base Correlation ρ	First Row of Correlation Matrix ρ1(1)	Missing Data Proportions	Measurement Times	Alpha
0.3484	15	ni(1)	4	μi(1)	2.36	6	0.7	ρ1(1)	Ms1(1)	T(1)	0.05
0.6255	30	ni(2)	4	μi(1)	2.36	6	0.7	ρ1(1)	Ms1(1)	T(1)	0.05
0.8091	45	ni(3)	4	μi(1)	2.36	6	0.7	ρ1(1)	Ms1(1)	T(1)	0.05
0.9109	60	ni(4)	4	μi(1)	2.36	6	0.7	ρ1(1)	Ms1(1)	T(1)	0.05
0.9611	75	ni(5)	4	μi(1)	2.36	6	0.7	ρ1(1)	Ms1(1)	T(1)	0.05
0.9839	90	ni(6)	4	μi(1)	2.36	6	0.7	ρ1(1)	Ms1(1)	T(1)	0.05
0.9936	105	ni(7)	4	μi(1)	2.36	6	0.7	ρ1(1)	Ms1(1)	T(1)	0.05
0.9976	120	ni(8)	4	μi(1)	2.36	6	0.7	ρ1(1)	Ms1(1)	T(1)	0.05

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Item	Values
ni(1)	5, 5, 5
ni(2)	10, 10, 10
ni(3)	15, 15, 15
ni(4)	20, 20, 20
ni(5)	25, 25, 25
ni(6)	30, 30, 30
ni(7)	35, 35, 35
ni(8)	40, 40, 40
μi(1)	65, 60, 60
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

Plots
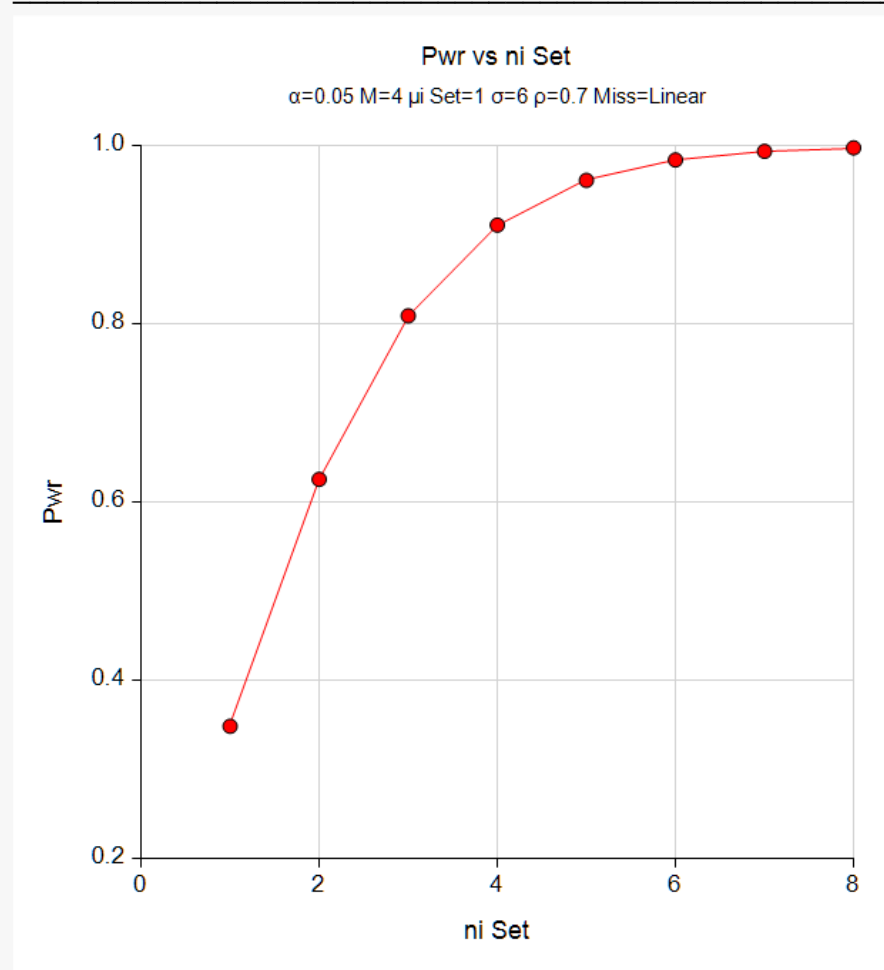
Note that the horizontal axis is scaled according to the *ni* set index. Hence, 1 is for *ni(1)*, 2 is for *ni(2)*, and so on. The same is true for the *μi's* and the *Linear Miss* in the subtitle.

Example 3 – Comparing Various Effect Sizes

Continuing with Examples 1 and 2, the researchers want to compare the various sets of mean time-averaged responses on the sample size. To do this, they will compare the four sets of means 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 Time-Averaged Responses

C1	C2	C3	C4
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.

Design Tab

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's Input Type ....**Columns containing sets of μi's**
Columns Containing Sets of μi's **C1-C4**
σ (Standard Deviation)..................................**6**
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**

Input Spreadsheet Data

Row	C1	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

Solve For: Sample Size
Measurement Times: Equally spaced
Correlation: AR1: $\rho(j,k) = \rho^{|j-k|}$
Missing Pattern: Range of missing proportions
Observant Proportions: Assume independence
Number of Groups: 3

Power	Total Sample Size N	Group Allocation Proportions ri	Number of Measurement Times M	Time-Averaged Responses μi	Standard Deviation Group Means σm	Standard Deviation Responses σ	Base Correlation ρ	First Row of Correlation Matrix	Missing Data Proportions	Measurement Times	Alpha
0.9109	60	ri(1)	4	C1(1)	2.36	6	0.7	ρ1(1)	Ms1(1)	T(1)	0.05
0.9086	93	ri(1)	4	C2(2)	1.89	6	0.7	ρ1(1)	Ms1(1)	T(1)	0.05
0.9026	162	ri(1)	4	C3(3)	1.41	6	0.7	ρ1(1)	Ms1(1)	T(1)	0.05
0.9013	363	ri(1)	4	C4(4)	0.94	6	0.7	ρ1(1)	Ms1(1)	T(1)	0.05

Item	Values
ri(1)	0.333, 0.333, 0.333
C1(1)	65, 60, 60
C2(2)	65, 61, 61
C3(3)	65, 62, 62
C4(4)	65, 63, 63
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

Plots
_____

Note that the horizontal axis gives the index of the means footnotes. Thus, '1.0' is column C1, '2.0' is column C2, and so on.

Example 4 – Validation of Sample Size Calculation using Zhang and Ahn (2013)

Zhang and Ahn (2013) presents an example which we will use to validate this procedure. Their example uses G = 4, m = 3, σ = 1.43178, ρ = 0.45, α = 0.05, power = 0.9, compound symmetry correlation pattern, equal group sample sizes, missing proportions of 0.02, 0.14, 0.23, measurement times at 1 week, 3 weeks, and 6 weeks, and group means of 1.99, 1.99, 1.99, 1.0. The resulting sample size was computed as 108 (27 per group).

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.

Design Tab

Solve For .... **Sample Size**
Power.. **0.90**
Alpha.. **0.05**
G (Number of Groups) **4**
Group Allocation Input Type .... **Equal (n1 = n2 = ··· = nG = n)**
Measurement Time Input Type .... **List of Measurement Time Proportions**
Measurement Time Proportions..................... **0 0.6 1**
μi's Input Type .... **μ1, μ2, ..., μG**
μ1, μ2, ..., μG... **1.99 1.99 1.99 1**
σ (Standard Deviation)................................. **1.43178**
Pattern of ρ's Across Time........................... **Compound Symmetry (All ρ's Equal)**
ρ (Base Correlation)..................................... **0.45**
Missing Input Type....................................... **List**
Pairwise Missing Pattern.............................. **Independent (Ind)**
List of Missing Proportions (Ind) **0.02 0.14 0.23**

Output

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

Numeric Results

Solve For: Sample Size
Measurement Times: List of proportions of max time: {0 0.6 1}
Correlation: Compound symmetry (all ρ's equal)
Missing Pattern: List of missing proportions
Observant Proportions: Assume independence
Number of Groups: 4

	Total Sample Size N	Group Allocation Proportions ri	Number of Measurement Times M	Time-Averaged Responses μi	Standard Deviation Group Means σm	Standard Deviation Responses σ	Base Correlation ρ	First Row of Correlation Matrix	Missing Data Proportions	Measurement Times	
Power											Alpha
0.9007	108	ri(1)	3	μi(1)	0.43	1.43	0.45	ρ1(1)	Ms(1)	T(1)	0.05

Item	Values
ri(1)	0.25, 0.25, 0.25, 0.25
μi(1)	1.99, 1.99, 1.99, 1
ρ1(1)	1, 0.45, 0.45
Ms(1)	0.02, 0.14, 0.23
T(1)	0, 0.6, 1

The sample size of 108 matches Zhang and Ahn (2013) exactly.

Example 5 – 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.

This example uses G = 4, M = 6, σ = 14.3, α = 0.05, and power = 0.9. The correlation pattern is Linear Exponential Decay with a base correlation of 0.8, 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 means are 5, 5, 7, 10. The per group sample size is 120.

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.

Design Tab

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)............................**120**
Measurement Time Input Type ....**Columns of Measurement Time Proportions**
Columns of Time Proportions **Tm1-Tm5**
μi's Input Type ....**μ1, μ2, ..., μG**
μ1, μ2, ..., μG..**5 5 7 10**
σ (Standard Deviation)..................................**14.3**
Pattern of ρ's Across Time............................**Linear Exponential Decay**
ρ (Base Correlation)......................................**0.8**
Base Time Proportion **0.2**

Emax (Max Decay Exponent) **4**
Missing Input Type..**Linear (Steady Change)**
Pairwise Missing Pattern...............................**Independent (Ind)**
First Missing Proportion (Ind).........................**0**
Last Missing Proportion (Ind).........................**0.30**

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	0.8	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

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

					Standard Deviation							
Power	Total Sample Size N	Group Sample Sizes ni	Number of Measurement Times M	Time-Averaged Responses μi	Group Means σm	Responses σ	Base Correlation ρ	First Row of Correlation Matrix	Missing Data Proportions	Measurement Times	Alpha
0.8783	480	ni(1)	6	μi(1)	2.05	14.3	0.8	ρ1(Tm1)	Ms1(Tm1)	Tm1(1)	0.05
0.8629	480	ni(1)	6	μi(1)	2.05	14.3	0.8	ρ1(Tm2)	Ms1(Tm2)	Tm2(2)	0.05
0.8588	480	ni(1)	6	μi(1)	2.05	14.3	0.8	ρ1(Tm3)	Ms1(Tm3)	Tm3(3)	0.05
0.8867	480	ni(1)	6	μi(1)	2.05	14.3	0.8	ρ1(Tm4)	Ms1(Tm4)	Tm4(4)	0.05
0.8550	480	ni(1)	6	μi(1)	2.05	14.3	0.8	ρ1(Tm5)	Ms1(Tm5)	Tm5(5)	0.05

Item	Values
ni(1)	120, 120, 120, 120
μi(1)	5, 5, 7, 10
ρ1(Tm1)	1, 0.8, 0.6767, 0.5724, 0.4842, 0.4096
ρ1(Tm2)	1, 0.5724, 0.5265, 0.4842, 0.4453, 0.4096
ρ1(Tm3)	1, 0.8698, 0.8, 0.7358, 0.6767, 0.4096
ρ1(Tm4)	1, 0.8698, 0.8, 0.4842, 0.4453, 0.4096
ρ1(Tm5)	1, 0.649, 0.6224, 0.5969, 0.5724, 0.4096
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(1)	0, 0.2, 0.4, 0.6, 0.8, 1
Tm2(2)	0, 0.6, 0.7, 0.8, 0.9, 1
Tm3(3)	0, 0.1, 0.2, 0.3, 0.4, 1
Tm4(4)	0, 0.1, 0.2, 0.8, 0.9, 1
Tm5(5)	0, 0.45, 0.5, 0.55, 0.6, 1

Plots
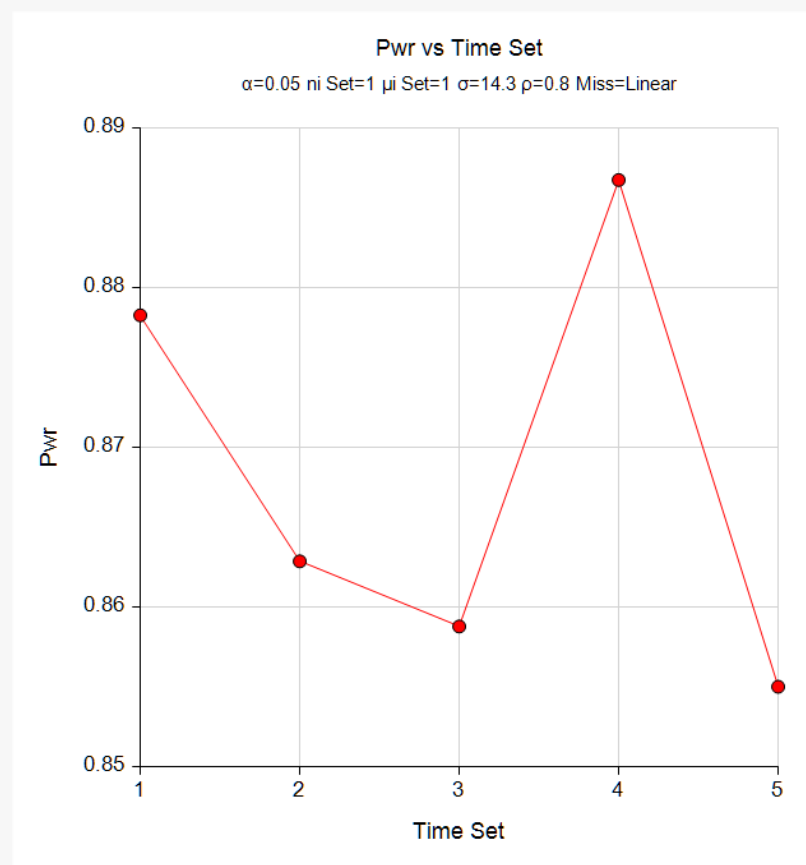
The horizontal axis, *Time Set*, gives the sequence number of the measurement columns. Thus, 1 is Tm1(1), 2 is Tm2(2), and so on.

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

Patterns Tm2, Tm3, and Tm5 are nearly tied for achieving the low powers. Tm1, the equally-spaced measurement scenario, is near the top.

Example 6 – Entering a Correlation Matrix

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

This example uses G = 4, M = 4, σ = 14.3, α = 0.05, and power = 0.9. The missing input type will be set to Linear from 0 to 30% and the pairwise missing assumption is independent. Group means are 5, 5, 7, 10. The per group sample sizes range from 50 to 150. A correlation matrix (shown below) is available from a previous study.

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

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.

Design Tab
_____

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)..............................**50 to 150 by 10**
Measurement Time Input Type ....**Equally Spaced Measurement Times**
M (Number of Measurement Times) **4**
μi's Input Type ....**μ1, μ2, ..., μG**
μ1, μ2, ..., μG...**5 5 7 10**
σ (Standard Deviation)...................................**14.3**
Pattern of ρ's Across Time.............................**Matrix on Spreadsheet**
Columns Containing the ρjk's **C1-C4**
Missing Input Type...**Linear (Steady Change)**
Pairwise Missing Pattern................................**Independent (Ind)**
First Missing Proportion (Ind).........................**0**
Last Missing Proportion (Ind).........................**0.30**

Input Spreadsheet Data

Row	C1	C2	C3	C4
1	1.000	0.70	0.49	0.343
2	0.700	1.00	0.70	0.490
3	0.490	0.70	1.00	0.700
4	0.343	0.49	0.70	1.000

Output

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

Numeric Results

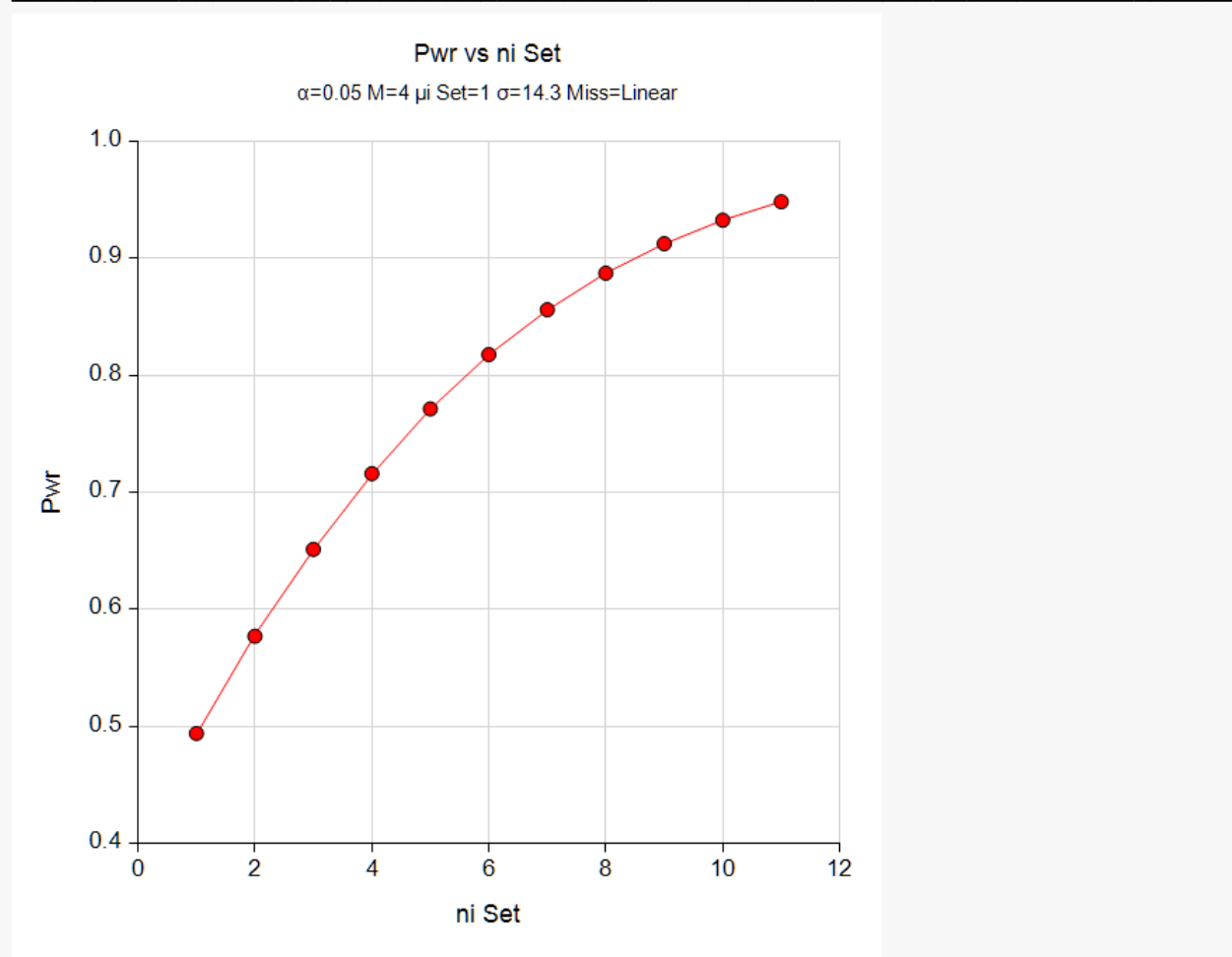| Solve For:	Power
Measurement Times:	Equally spaced
Correlation:	Matrix stored on spreadsheet in columns C1-C4
Missing Pattern:	Range of missing proportions
Observant Proportions:	Assume independence
Number of Groups:	4

					Standard Deviation						
Power	Total Sample Size N	Group Sample Sizes ni	Number of Measurement Times M	Time-Averaged Responses μi	Group Means σm	Responses σ	Base Correlation ρ	First Row of Correlation Matrix	Missing Data Proportions	Measurement Times	Alpha
0.4939	200	ni(1)	4	μi(1)	2.05	14.3	N/A	ρ1(1)	Ms1(1)	T(1)	0.05
0.5770	240	ni(2)	4	μi(1)	2.05	14.3	N/A	ρ1(1)	Ms1(1)	T(1)	0.05
0.6513	280	ni(3)	4	μi(1)	2.05	14.3	N/A	ρ1(1)	Ms1(1)	T(1)	0.05
0.7160	320	ni(4)	4	μi(1)	2.05	14.3	N/A	ρ1(1)	Ms1(1)	T(1)	0.05
0.7713	360	ni(5)	4	μi(1)	2.05	14.3	N/A	ρ1(1)	Ms1(1)	T(1)	0.05
0.8178	400	ni(6)	4	μi(1)	2.05	14.3	N/A	ρ1(1)	Ms1(1)	T(1)	0.05
0.8561	440	ni(7)	4	μi(1)	2.05	14.3	N/A	ρ1(1)	Ms1(1)	T(1)	0.05
0.8874	480	ni(8)	4	μi(1)	2.05	14.3	N/A	ρ1(1)	Ms1(1)	T(1)	0.05
0.9126	520	ni(9)	4	μi(1)	2.05	14.3	N/A	ρ1(1)	Ms1(1)	T(1)	0.05
0.9327	560	ni(10)	4	μi(1)	2.05	14.3	N/A	ρ1(1)	Ms1(1)	T(1)	0.05
0.9485	600	ni(11)	4	μi(1)	2.05	14.3	N/A	ρ1(1)	Ms1(1)	T(1)	0.05

Item	Values
ni(1)	50, 50, 50, 50
ni(2)	60, 60, 60, 60
ni(3)	70, 70, 70, 70
ni(4)	80, 80, 80, 80
ni(5)	90, 90, 90, 90
ni(6)	100, 100, 100, 100
ni(7)	110, 110, 110, 110
ni(8)	120, 120, 120, 120
ni(9)	130, 130, 130, 130
ni(10)	140, 140, 140, 140
ni(11)	150, 150, 150, 150
μi(1)	5, 5, 7, 10
ρ1(1)	1, 0.7, 0.49, 0.343
Ms1(1)	0, 0.1, 0.2, 0.3
T(1)	0, 0.33, 0.67, 1

Plots

Pwr vs ni Set

α=0.05 M=4 µi Set=1 σ=14.3 Miss=Linear

Autocorrelation Matrix for Report Row 1

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

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(More Reports Follow)

Note that the horizontal axis corresponds to the sequence number of the ni set. Hence, 1 is ni(1), 2 is ni(2), and so on.

Example 7 – Entering an Observant Probabilities Matrix

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

This example uses G = 4, M = 4, σ = 14.3, and α = 0.05. The per group sample sizes range from 50 to 150. Group means are 5, 5, 7, 10. The correlation pattern will be Linear Exponential Decay with a base correlation of 0.8, Base Time Proportion of 0.1, and Emax set to 4.

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

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

Design Tab

Solve For ....**Power**
Alpha..**0.05**
G (Number of Groups) **4**
Group Allocation Input Type ....**Equal (n1 = n2 = ··· = nG = n)**
n (Sample Size Per Group)............................**50 to 150 by 20**
Measurement Time Input Type ....**Equally Spaced Measurement Times**
M (Number of Measurement Times) **4**
μi's Input Type ....**μ1, μ2, ..., μG**
μ1, μ2, ..., μG...**5 5 7 10**
σ (Standard Deviation)..................................**14.3**
Pattern of ρ's Across Time............................**Linear Exponential Decay**
ρ (Base Correlation)......................................**0.8**
Base Time Proportion **0.1**
Emax (Max Decay Exponent) **4**
Missing Input Type..**Pairwise Observed Proportions on Spreadsheet**
Columns of Pairwise Observed......................**C1-C4**

Input Spreadsheet Data

Row	C1	C2	C3	C4
1	1.0	0.90	0.80	0.70
2	0.9	0.90	0.72	0.63
3	0.8	0.72	0.80	0.56
4	0.7	0.63	0.56	0.70

Output

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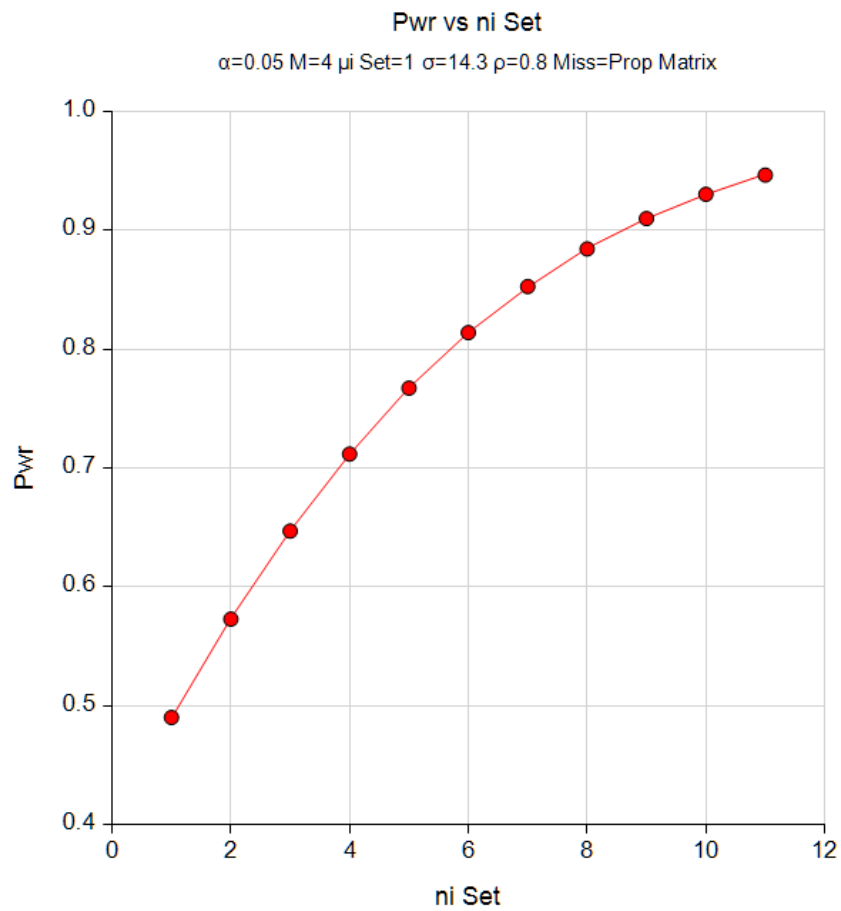
Numeric Results

Solve For:	Power
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.
Number of Groups:	4

					Standard Deviation						
Power	Total Sample Size N	Group Sample Sizes ni	Number of Measurement Times M	Time-Averaged Responses μi	Group Means σm	Responses σ	Base Correlation ρ	First Row of Correlation Matrix	Missing Data Proportions	Measurement Times	Alpha
0.4901	200	ni(1)	4	μi(1)	2.05	14.3	0.8	ρ1(1)	N/A	T(1)	0.05
0.5729	240	ni(2)	4	μi(1)	2.05	14.3	0.8	ρ1(1)	N/A	T(1)	0.05
0.6470	280	ni(3)	4	μi(1)	2.05	14.3	0.8	ρ1(1)	N/A	T(1)	0.05
0.7118	320	ni(4)	4	μi(1)	2.05	14.3	0.8	ρ1(1)	N/A	T(1)	0.05
0.7673	360	ni(5)	4	μi(1)	2.05	14.3	0.8	ρ1(1)	N/A	T(1)	0.05
0.8141	400	ni(6)	4	μi(1)	2.05	14.3	0.8	ρ1(1)	N/A	T(1)	0.05
0.8528	440	ni(7)	4	μi(1)	2.05	14.3	0.8	ρ1(1)	N/A	T(1)	0.05
0.8844	480	ni(8)	4	μi(1)	2.05	14.3	0.8	ρ1(1)	N/A	T(1)	0.05
0.9100	520	ni(9)	4	μi(1)	2.05	14.3	0.8	ρ1(1)	N/A	T(1)	0.05
0.9304	560	ni(10)	4	μi(1)	2.05	14.3	0.8	ρ1(1)	N/A	T(1)	0.05
0.9466	600	ni(11)	4	μi(1)	2.05	14.3	0.8	ρ1(1)	N/A	T(1)	0.05

Item	Values
ni(1)	50, 50, 50, 50
ni(2)	60, 60, 60, 60
ni(3)	70, 70, 70, 70
ni(4)	80, 80, 80, 80
ni(5)	90, 90, 90, 90
ni(6)	100, 100, 100, 100
ni(7)	110, 110, 110, 110
ni(8)	120, 120, 120, 120
ni(9)	130, 130, 130, 130
ni(10)	140, 140, 140, 140
ni(11)	150, 150, 150, 150
μi(1)	5, 5, 7, 10
ρ1(1)	1, 0.6725, 0.5249, 0.4096
T(1)	0, 0.33, 0.67, 1

Plots
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The standard reports are displayed.