# Chapter 201

# Tests for Two Proportions in a Repeated Measures Design

## Introduction

This module calculates the power for testing the time-averaged difference (TAD) between two proportions in a *repeated measures* design. A repeated measures design is one in which subjects are observed repeatedly over time. Measurements may be taken at pre-determined intervals (e.g. weekly or at specified time points following the administration of a particular treatment), or at random times with variable intervals between repeated measurements.

This type of time-averaged difference analysis is often used when the outcome to be measured varies with time. For example, suppose that you want to compare two treatment groups based on a certain binary response variable such as the presence (or absence) of a disease. The disease status may change over time, depending on various factors unrelated to the treatment. The precision of the experiment is increased by taking multiple measurements from each individual and comparing the time-averaged difference in proportions between the two 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 covariance structure may take on several forms depending on the nature of the experiment and the subjects involved. This procedure allows you to calculate sample sizes and power using four different covariance patterns: Compound Symmetry, AR(1), Banded(1), and Simple.

This procedure can be used to calculate sample size and power for tests of pairwise contrasts in a mixed models analysis of repeated measures data. Mixed models analysis of repeated measures data is also employed to provide more flexibility in covariance specification and a greater degree of robustness in the presence of missing data, provided that the data can be assumed to be missing at random.

# Technical Details

## Two Test Statistics

This routine has the capability of calculating power and sample size for testing time-averaged difference in proportions based on two different test statistics. The first test statistic is presented in Liu and Wu (2005) and Diggle et al. (1994). The test statistic is based on the difference in proportions:

$$d = p_1 - p_2,$$

and has the form

$$z = \frac{\hat{p}_1 - \hat{p}_2}{\sqrt{\text{var}(\hat{p}_1 - \hat{p}_2)}}.$$

The second type of test statistic, presented in Brown and Prescott (2006), has application to mixed models analysis of repeated measures data where there aren't any random effects other than the subjects themselves, and is based on the difference in proportions defined on the logit link scale:

$$d = \log(OR) = \log\left(\frac{p_1}{1 - p_1}\right) - \log\left(\frac{p_2}{1 - p_2}\right) = \text{logit}(p_1) - \text{logit}(p_2),$$

and has the form

$$z = \frac{\text{logit}(\hat{p}_j) - \text{logit}(\hat{p}_h)}{\sqrt{\text{var}(\text{logit}(\hat{p}_j) - \text{logit}(\hat{p}_h))}}.$$

# Testing the Time-Averaged Difference between Two Proportions

## Theory and Notation

The following derivation is based on the results in Liu and Wu (2005). For a study with $n_1$ subjects in group 1, having success proportion $p_1$, and $n_2$ subjects in group 2, having success proportion $p_2$ (for a total of $N$ subjects), each measured $m$ times, the time-averaged difference ($d = p_1 - p_2$) in proportions between the two groups can be estimated using the following model:

$$E(y_{ij} \mid x_{ij}) = \Pr(y_{ij} = 1 \mid x_{ij}) = \beta_0 + \beta_1 x_{ij}, \quad i = 1, \cdots, N; \; j = 1, \cdots, m,$$

where

$y_{ij}$ is the $j$th binary response from subject $i$,

$\beta_0$ is the model intercept,

$\beta_1$ is the treatment effect or the time-averaged difference in proportions between groups 1 and 2 (i.e. $\beta_1 = d$),

$x_{ij}$ is a binary group assignment variable, which is equal to 1 if the $i$th subject is in group 1 and equal to 0 if the $i$th subject is in group 2.

The proportions used to find the difference might be expressed directly as $p_1$ and $p_2$, or indirectly as $p_2$ and an odds ratio

$$\psi = \frac{p_1(1 - p_1)}{p_2(1 - p_2)} = \frac{p_1 q_2}{p_2 q_1}.$$

The proportion from group 1 can then be computed as

$$p_1 = \frac{\psi p_2}{1 - p_2 + \psi p_2}.$$

Accounting for the relationship between repeated measurements, the model presented above can be written in matrix form as

$$E(\mathbf{y}_i \mid x_i) = \mathbf{X}_i'\boldsymbol{\beta},$$

where

$\mathbf{y}_i = \begin{pmatrix} y_{i1} & y_{i2} & \cdots & y_{im} \end{pmatrix}'$ is an $m \times 1$ vector of responses from subject $i$,

$$\mathbf{X}_i = \begin{pmatrix} 1 & 1 \\ 1 & 1 \\ \vdots & \vdots \\ 1 & 1 \end{pmatrix}_{m \times 2} \quad \text{if the } i^{\text{th}} \text{ subject is in group 1,}$$

$$\mathbf{X}_i = \begin{pmatrix} 1 & 0 \\ 1 & 0 \\ \vdots & \vdots \\ 1 & 0 \end{pmatrix}_{m \times 2} \quad \text{if the } i^{\text{th}} \text{ subject is in group 2, and}$$

$\boldsymbol{\beta} = \begin{pmatrix} \beta_0 \\ \beta_1 \end{pmatrix}$ is the vector of model parameters.

We can stack the data in a single vector and matrix form as follows:

$$\mathbf{y} = (\mathbf{y}_1', \mathbf{y}_2', \ldots, \mathbf{y}_N')'$$
$$\mathbf{X} = (\mathbf{X}_1', \mathbf{X}_2', \cdots, \mathbf{X}_N')'$$

and the model for the $N$ equations can be compressed into one as

$$E(\mathbf{y} \mid \mathbf{x}) = \mathbf{X}'\boldsymbol{\beta},$$

with

$$\mathbf{V} = \text{var}(\mathbf{y})$$
$$= \sigma^2 \begin{pmatrix} \mathbf{R}_1 & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \ddots & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{R}_N \end{pmatrix}$$
$$= \sigma^2 \mathbf{R}$$

as the covariance (or variance-covariance) matrix.

## Model Estimation

With $\hat{\mathbf{V}} = \hat{\sigma}^2 \hat{\mathbf{R}}$, then estimates of the regression coefficients from the above regression model are given as

$$\hat{\boldsymbol{\beta}} = \begin{pmatrix} \hat{\beta}_0 \\ \hat{\beta}_1 \end{pmatrix}$$
$$= (\mathbf{X}'\hat{\mathbf{V}}^{-1}\mathbf{X})^{-1}\mathbf{X}'\hat{\mathbf{V}}^{-1}\mathbf{y},$$

and the variance of $\hat{\boldsymbol{\beta}}$ is estimated as

$$\text{var}(\hat{\boldsymbol{\beta}}) = \begin{pmatrix} \text{var}(\hat{\beta}_0) & \text{cov}(\hat{\beta}_0, \hat{\beta}_1) \\ \text{cov}(\hat{\beta}_0, \hat{\beta}_1) & \text{var}(\hat{\beta}_1) \end{pmatrix}$$

$$= (\mathbf{X}'\hat{\mathbf{V}}^{-1}\mathbf{X})^{-1}$$

$$= \hat{\sigma}^2(\mathbf{X}'\hat{\mathbf{R}}^{-1}\mathbf{X})^{-1}.$$

Since the data are binary, the variance term $\sigma^2$ depends on the proportions $p_1$ and $p_2$. Under the null hypothesis, $H_0$, the estimate of $\sigma^2$ is

$$\hat{\sigma}_0^2 = \frac{n_1 p_1 + n_2 p_2}{n_1 + n_2}\left(1 - \frac{n_1 p_1 + n_2 p_2}{n_1 + n_2}\right)$$

$$= \frac{(n_1 p_1 + n_2 p_2)(n_1 q_1 + n_2 q_2)}{(n_1 + n_2)^2},$$

where $q_1 = 1 - p_1$ and $q_2 = 1 - p_2$. Under the alternative hypothesis, $H_1$, the estimate of $\sigma^2$ is

$$\hat{\sigma}_1^2 = \frac{n_1}{n_1 + n_2} p_1 q_1 + \frac{n_2}{n_1 + n_2} p_2 q_2$$

$$= \frac{n_1 p_1 q_1 + n_2 p_2 q_2}{n_1 + n_2}.$$

The estimated variance of $\hat{\beta}_1$ under the null hypothesis is

$$\text{var}(\hat{\beta}_1 \mid H_0) = \hat{\sigma}_{\hat{\beta}_1, H_0}^2 = \hat{\sigma}_0^2 \left[(\mathbf{X}'\hat{\mathbf{R}}^{-1}\mathbf{X})^{-1}\right]_{11},$$

and the estimated variance of $\hat{\beta}_1$ under the alternative hypothesis is

$$\text{var}(\hat{\beta}_1 \mid H_1) = \hat{\sigma}_{\hat{\beta}_1, H_1}^2 = \hat{\sigma}_1^2 \left[(\mathbf{X}'\hat{\mathbf{R}}^{-1}\mathbf{X})^{-1}\right]_{11},$$

where $[A]_{11}$ denotes the lower right-hand element of a $2 \times 2$ matrix, A.

## Hypothesis Test

A two-sided test of the null hypothesis that the time-averaged difference in proportions is equal to zero is equivalent to the test of $H_0 : \beta_1 = 0$ vs. $H_1 : \beta_1 \neq 0$. Similarly, the upper and lower one-sided tests are $H_0 : \beta_1 \leq 0$ vs. $H_1 : \beta_1 > 0$ and $H_0 : \beta_1 \geq 0$ vs. $H_1 : \beta_1 < 0$, respectively. The test can be carried out using the test statistic

$$z = \frac{\hat{\beta}_1}{\sqrt{\text{var}(\hat{\beta}_1)}} = \frac{\hat{p}_1 - \hat{p}_2}{\sqrt{\text{var}(\hat{p}_1 - \hat{p}_2)}} \rightarrow N(0,1).$$

## Power Calculations

Sample sizes for repeated measures studies are often calculated as if a simple trial with no repeated measures was planned, which results in a higher calculated sample size than would be found if the correlation between repeated measures were taken into consideration. With an idea of the correct covariance structure, and an estimate of the within-patient correlation, you can get a better estimate of the power and sample size necessary to achieve your objectives. If you have no indication of the correct covariance structure for the experiment, then the compound symmetry (program default) is likely to be adequate. If you have no previous estimate of the within-patient

correlation, then Brown and Prescott (2006) suggest using a conservative prediction of the correlation, i.e. a higher correlation than anticipated.

For a two-sided test where it is assumed that $d > 0$ (without loss of generality),

$$\text{Power} = 1 - \beta = \Pr(\text{rejecting } H_0 \mid H_1)$$

$$= \Pr\left(\left|\frac{\hat{\beta}_1}{\sqrt{\text{var}(\hat{\beta}_1)}}\right| > z_{1-\alpha/2} \mid H_1\right)$$

$$\approx \Pr\left(\frac{\hat{\beta}_1}{\sqrt{\text{var}(\hat{\beta}_1)}} > z_{1-\alpha/2} \mid H_1\right) \text{ since it is assumed that } d > 0$$

$$= \Pr\left(\frac{\hat{\beta}_1 - d}{\hat{\sigma}_{\bar{\beta}_1, H_0}} > z_{1-\alpha/2} - \frac{d}{\hat{\sigma}_{\bar{\beta}_1, H_0}} \mid H_1\right)$$

$$= \Pr\left(\frac{\hat{\beta}_1 - d}{\hat{\sigma}_{\bar{\beta}_1, H_1}} \cdot \frac{\hat{\sigma}_{\bar{\beta}_1, H_1}}{\hat{\sigma}_{\bar{\beta}_1, H_0}} > z_{1-\alpha/2} - \frac{d}{\hat{\sigma}_{\bar{\beta}_1, H_0}} \mid H_1\right)$$

$$= \Pr\left(\frac{\hat{\beta}_1 - d}{\hat{\sigma}_{\bar{\beta}_1, H_1}} > \frac{\hat{\sigma}_{\bar{\beta}_1, H_0}}{\hat{\sigma}_{\bar{\beta}_1, H_1}} \cdot z_{1-\alpha/2} - \frac{d}{\hat{\sigma}_{\bar{\beta}_1, H_1}} \mid H_1\right)$$

$$= 1 - \Phi\left(\frac{\hat{\sigma}_{\bar{\beta}_1, H_0}}{\hat{\sigma}_{\bar{\beta}_1, H_1}} \cdot z_{1-\alpha/2} - \frac{d}{\hat{\sigma}_{\bar{\beta}_1, H_1}}\right),$$

where $\Phi()$ is the standard normal density function, and $\alpha$ and $\beta$ are the probabilities of type I and type II error, respectively. For a one-sided test, $\alpha$ is used in place of $\alpha/2$.

# Testing Two Proportions using the Time-Averaged Difference defined on the Logit Link Scale (Testing Pairwise Contrasts of Fixed Effects in Mixed Models)

## Mixed Models Theory and Notation

The following derivation is based on the results in Brown and Prescott (2006) and Liu and Wu (2005). A generalized linear mixed model incorporates both fixed and random effects. Fixed effects are those effects in the model whose values are assumed constant, or unchanging. Random effects are those effects in the model that are assumed to have arisen from a distribution, resulting in another source of random variation other than residual variation. For an experiment with $N$ subjects, $p$ fixed effect parameters, and $q$ random effect parameters, the generalized linear mixed model can be expressed using matrix notation as

$$\mathbf{y}_i = \boldsymbol{\mu}_i + \boldsymbol{\varepsilon}_i, \quad i = 1, \cdots, N$$

where

$\mathbf{y}_i$ is an $n_i \times 1$ vector of responses for subject $i$,

$\boldsymbol{\mu}_i$ is an $n_i \times 1$ vector of expected means for subject $i$, and is linked to the model parameters by a link function, $g$:

$$g(\boldsymbol{\mu}_i) = \text{logit}(\boldsymbol{\mu}_i) = \begin{pmatrix} \log(\pi_i/(1-\pi_i)) \\ \log(\pi_i/(1-\pi_i)) \\ \vdots \\ \log(\pi_i/(1-\pi_i)) \end{pmatrix}_{n_i \times 1} = \mathbf{X}_i \boldsymbol{\beta} + \mathbf{Z}_i \mathbf{u}_i, \quad i = 1, \cdots, N$$

where

$\pi_i$ is the probability of success from a bernoulli distribution for individual $i$,

$\mathbf{X}_i$ is an $n_i \times p$, full-rank design matrix of fixed effects for subject $i$,

$\boldsymbol{\beta}$ is a $p \times 1$ vector of fixed effects parameters,

$\mathbf{Z}_i$ is an $n_i \times q$ design matrix of the random effects for subject $i$,

$\mathbf{u}_i$ is a $q \times 1$ vector of random effects for subject $i$ which has means of zero and scaled covariance matrix $\mathbf{G}$,

$\boldsymbol{\varepsilon}_i$ is an $n_i \times 1$ vector of errors for subject $i$ with zero mean and scaled covariance $\boldsymbol{\Sigma}_i$.

We can stack the data in a single vector and matrix form as follows:

$$\mathbf{y} = (\mathbf{y}_1, \mathbf{y}_2, \ldots, \mathbf{y}_N)'$$
$$\boldsymbol{\mu} = (\boldsymbol{\mu}_1, \boldsymbol{\mu}_2, \ldots, \boldsymbol{\mu}_N)'$$
$$\mathbf{X} = (\mathbf{X}_1, \mathbf{X}_2, \cdots, \mathbf{X}_N)'$$
$$\mathbf{Z} = \begin{pmatrix} \mathbf{Z}_1 & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \ddots & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{Z}_N \end{pmatrix}$$
$$\mathbf{u} = (\mathbf{u}_1, \mathbf{u}_2, \ldots, \mathbf{u}_N)'$$
$$\boldsymbol{\varepsilon} = (\boldsymbol{\varepsilon}_1, \boldsymbol{\varepsilon}_2, \ldots, \boldsymbol{\varepsilon}_N)'$$

and the mixed model for the $N$ equations can be compressed into one as

$$\mathbf{y} = \boldsymbol{\mu} + \boldsymbol{\varepsilon}$$

with

$$g(\boldsymbol{\mu}) = \mathrm{logit}(\boldsymbol{\mu}) = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{u}.$$

The covariance of $\mathbf{y}$, $\mathrm{var}(\mathbf{y}) = \mathbf{V}$, can then be written as

$$\mathbf{V} = \begin{pmatrix} \mathbf{V}_1 & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \ddots & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{V}_N \end{pmatrix}$$
$$= \mathrm{var}(\boldsymbol{\mu} + \boldsymbol{\varepsilon})$$
$$= \mathrm{var}(\boldsymbol{\mu}) + \boldsymbol{\Sigma}$$
$$\approx \mathbf{B}\mathbf{Z}\mathbf{G}\mathbf{Z}'\mathbf{B} + \mathbf{B}^{1/2}\mathbf{R}\mathbf{B}^{1/2},$$

where

$$\mathbf{B} = \begin{pmatrix} \pi_1(1-\pi_1) & 0 & 0 & 0 \\ 0 & \pi_2(1-\pi_2) & 0 & 0 \\ 0 & 0 & \ddots & \vdots \\ 0 & 0 & \cdots & \pi_N(1-\pi_N) \end{pmatrix}$$

$\mathbf{R}$ is the correlation matrix defined on the linear scale.

## Mixed Models Estimation

In order to fit the generalized linear mixed model, a pseudo-variable $\mathbf{z}$ must be introduced to transform $\mathbf{y}$ onto the linear scale. More specifically,

$$\begin{aligned}
\mathbf{z} &= g(\boldsymbol{\mu}) + (\mathbf{y} - \boldsymbol{\mu})\mathbf{B}^{-1} \\
&= \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{u} + (\mathbf{y} - \boldsymbol{\mu})\mathbf{B}^{-1}
\end{aligned}$$

and $\mathbf{z}$ has variance

$$\begin{aligned}
\mathbf{V_z} &= \mathrm{var}(\mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{u}) + \mathbf{B}^{-1}\,\mathrm{var}(\mathbf{y} - \boldsymbol{\mu})\mathbf{B}^{-1} \\
&= \mathbf{ZGZ'} + \mathbf{B}^{-1/2}\mathbf{R}\mathbf{B}^{-1/2}
\end{aligned}$$

If $\mathbf{ZGZ'} = \mathbf{0}$ (which is the case when no random effects are included in the model), then

$$\mathbf{V_z} = \mathbf{B}^{-1/2}\mathbf{R}\mathbf{B}^{-1/2}.$$

Estimates of the variance components are found using maximum likelihood (ML) or restricted/residual maximum likelihood (REML) methods. The fixed effects are then estimated as

$$\hat{\boldsymbol{\beta}} = (\mathbf{X'}\hat{\mathbf{V}}_{\mathbf{z}}^{-1}\mathbf{X})^{-1}\mathbf{X'}\hat{\mathbf{V}}_{\mathbf{z}}^{-1}\mathbf{y}$$

with the variance estimated as

$$\mathrm{var}(\hat{\boldsymbol{\beta}}) = (\mathbf{X'}\hat{\mathbf{V}}_{\mathbf{z}}^{-1}\mathbf{X})^{-1}$$

These estimation equations are nearly identical to the TAD estimation equations presented earlier, except for the fact that $\boldsymbol{\beta}$ may contain more than two parameters, i.e. a parameter for each fixed effect being modeled. In the TAD model presented above, $\beta_1$ represents the difference between two treatment proportions. In the generalized mixed model formulation presented here, $\beta_1$, $\beta_2$, etc. represent individual proportions defined on the logit link scale.

## Testing Fixed Effects

Significance tests for fixed or random effects can be done using tests based on the $t$ distribution. We can define tests of fixed and random effects as contrasts

$$\mathbf{C} = \mathbf{L'}\hat{\boldsymbol{\beta}} = \mathbf{0},$$

respectively. For example, in a trial containing three treatments A, B, and C, a pairwise comparison of treatments A and C is given by the contrast

$$\mathbf{C}_{AC} = \mathbf{L'}\hat{\boldsymbol{\beta}} = (0 \quad 1 \quad 0 \quad -1)\hat{\boldsymbol{\beta}} = \hat{\beta}_A - \hat{\beta}_C,$$

where the first term in $\boldsymbol{\beta}$ is the intercept term, and the other three terms are the treatment effects.

For a single comparison, the Wald test statistic is given by

$$\begin{aligned}
z &= \frac{\mathbf{L'}\hat{\boldsymbol{\beta}}}{\sqrt{\mathrm{var}(\mathbf{L'}\hat{\boldsymbol{\beta}})}} \\
&= \frac{\hat{\beta}_j - \hat{\beta}_h}{\sqrt{\mathrm{var}(\hat{\beta}_j - \hat{\beta}_h)}} \\
&= \frac{\mathrm{logit}(\hat{p}_j) - \mathrm{logit}(\hat{p}_h)}{\sqrt{\mathrm{var}(\mathrm{logit}(\hat{p}_j) - \mathrm{logit}(\hat{p}_h))}} \rightarrow N(0,1),
\end{aligned}$$

where $\hat{\beta}_j$ and $\hat{\beta}_h$ ($j \neq h$) are estimated treatment effects defined on the logit link scale and $p_j$ and $p_h$ are the proportions from groups $j$ and $h$, respectively.

Since the data are binary, $\text{var}(\hat{\beta}_j - \hat{\beta}_h)$ depends on the proportions $p_j$ and $p_h$. Under the null hypothesis, $H_0$, the estimate of $\text{var}(\hat{\beta}_j - \hat{\beta}_h)$ is

$$
\begin{aligned}
\text{var}(\hat{\beta}_j - \hat{\beta}_h \mid H_0) &= \hat{\sigma}^2_{\hat{\beta}_j - \hat{\beta}_h, H_0} \\
&= \mathbf{L}'(\mathbf{X}'\hat{\mathbf{V}}_{\mathbf{z}}^{-1}\mathbf{X})^{-1}\mathbf{L} \\
&= \frac{(n_j + n_h)^2}{(n_j p_j + n_h p_h)(n_j q_j + n_h q_h)}\mathbf{L}'(\mathbf{X}'\hat{\mathbf{R}}^{-1}\mathbf{X})^{-1}\mathbf{L},
\end{aligned}
$$

where $q_k = 1 - p_k$. Under the alternative hypothesis, $H_1$, the estimate of $\text{var}(\hat{\beta}_j - \hat{\beta}_h)$ is

$$
\begin{aligned}
\text{var}(\hat{\beta}_j - \hat{\beta}_h \mid H_1) &= \hat{\sigma}^2_{\hat{\beta}_j - \hat{\beta}_h, H_1} \\
&= \mathbf{L}'(\mathbf{X}'\hat{\mathbf{V}}_{\mathbf{z}}^{-1}\mathbf{X})^{-1}\mathbf{L} \\
&= \frac{n_j + n_h}{n_j p_j q_j + n_h p_h q_h}\mathbf{L}'(\mathbf{X}'\hat{\mathbf{R}}^{-1}\mathbf{X})^{-1}\mathbf{L},
\end{aligned}
$$

In practice, the test is often performed using software containing generalized linear models capability, such as SAS® PROC GLIMMIX or SAS® PROC GENMOD with a REPEATED statement. The test of the difference in proportions is generated with an estimation statement such as

```
ESTIMATE 'A-C' treat 1 0 -1;  or  LSMEANS treat/ PDIFF;
```

The latter statement would produce tests of all pairwise comparisons of the levels of the treatment variable, defined on the logit link scale. The former would only test the difference between groups A and C. Of course, these comparison statements must be used in conjunction with appropriate model and class statements.

## Power Calculations

Sample sizes for repeated measures studies are often calculated as if a simple trial with no repeated measures was planned, which results in a higher calculated sample size than would be found if the correlation between repeated measures were taken into consideration. With an idea of the correct covariance structure, and an estimate of the within-patient correlation, you can get a better estimate of the power and sample size necessary to achieve your objectives. If you have no indication of the correct covariance structure for the experiment, then the compound symmetry (program default) is likely to be adequate. If you have no previous estimate of the within-patient correlation, then Brown and Prescott (2006) suggest using a conservative prediction of the correlation, i.e. a higher correlation than anticipated.

For a two-sided test where it is assumed that $\hat{\beta}_j - \hat{\beta}_h > 0$ (without loss of generality),

$$\text{Power} = 1 - \beta = \Pr(\text{rejecting } H_0 \mid H_1)$$

$$= \Pr\left(\left|\frac{\hat{\beta}_j - \hat{\beta}_h}{\sqrt{\text{var}(\hat{\beta}_j - \hat{\beta}_h)}}\right| > z_{1-\alpha/2} \mid H_1\right)$$

$$\approx \Pr\left(\frac{\hat{\beta}_j - \hat{\beta}_h}{\sqrt{\text{var}(\hat{\beta}_j - \hat{\beta}_h)}} > z_{1-\alpha/2} \mid H_1\right) \text{ since it is assumed that } d > 0$$

$$= \Pr\left(\frac{\hat{\beta}_1 - d}{\hat{\sigma}_{\hat{\beta}_j - \hat{\beta}_h, H_0}} > z_{1-\alpha/2} - \frac{d}{\hat{\sigma}_{\hat{\beta}_j - \hat{\beta}_h, H_0}} \mid H_1\right)$$

$$= \Pr\left(\frac{\hat{\beta}_j - \hat{\beta}_h - d}{\hat{\sigma}_{\hat{\beta}_j - \hat{\beta}_h, H_1}} \cdot \frac{\hat{\sigma}_{\hat{\beta}_j - \hat{\beta}_h, H_1}}{\hat{\sigma}_{\hat{\beta}_j - \hat{\beta}_h, H_0}} > z_{1-\alpha/2} - \frac{d}{\hat{\sigma}_{\hat{\beta}_j - \hat{\beta}_h, H_0}} \mid H_1\right)$$

$$= \Pr\left(\frac{\hat{\beta}_1 - d}{\hat{\sigma}_{\hat{\beta}_j - \hat{\beta}_h, H_1}} > \frac{\hat{\sigma}_{\hat{\beta}_j - \hat{\beta}_h, H_0}}{\hat{\sigma}_{\hat{\beta}_j - \hat{\beta}_h, H_1}} \cdot z_{1-\alpha/2} - \frac{d}{\hat{\sigma}_{\hat{\beta}_j - \hat{\beta}_h, H_1}} \mid H_1\right)$$

$$= 1 - \Phi\left(\frac{\hat{\sigma}_{\hat{\beta}_j - \hat{\beta}_h, H_0}}{\hat{\sigma}_{\hat{\beta}_j - \hat{\beta}_h, H_1}} \cdot z_{1-\alpha/2} - \frac{d}{\hat{\sigma}_{\hat{\beta}_j - \hat{\beta}_h, H_1}}\right),$$

where $\Phi()$ is the standard normal density function, and $\alpha$ and $\beta$ are the probabilities of type I and type II error, respectively. For a one-sided test, $\alpha$ is used in place of $\alpha/2$.

## Covariance Patterns

In a repeated measures design with $N$ subjects, each measured $m$ times, observations from a single subject may be correlated and a pattern for their covariance is specified. In this case, $\mathbf{V}$ will have a block-diagonal form and can be written as

$$\mathbf{V} = \sigma^2 \mathbf{R} = \begin{pmatrix} \mathbf{V}_1 & \mathbf{0} & \mathbf{0} & \cdots & \mathbf{0} \\ \mathbf{0} & \mathbf{V}_2 & \mathbf{0} & \cdots & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{V}_3 & \cdots & \mathbf{0} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \mathbf{0} & \mathbf{0} & \mathbf{0} & \cdots & \mathbf{V}_N \end{pmatrix}$$

where $\mathbf{V}_i$ are $m \times m$ covariance matrices corresponding to the $i^{\text{th}}$ subject. The $\mathbf{0}$'s represent $m \times m$ matrices of zeros giving zero covariances for observations on different subjects. This routine allows the specification of four different covariance matrix types: Compound Symmetry, AR(1), Banded(1), and Simple.

## Compound Symmetry

A compound symmetry covariance model assumes that all covariances are equal, and all variances on the diagonal are equal. That is

$$
\mathbf{V}_i = \sigma^2 \begin{pmatrix}
1 & \rho & \rho & \rho & \cdots & \rho \\
\rho & 1 & \rho & \rho & \cdots & \rho \\
\rho & \rho & 1 & \rho & \cdots & \rho \\
\rho & \rho & \rho & 1 & \cdots & \rho \\
\vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\
\rho & \rho & \rho & \rho & \cdots & 1
\end{pmatrix}_{m \times m}
$$

where $\sigma^2 = \mathrm{var}(y_{ij})$ and $\rho$ is the correlation between observations on the same subject.

## AR(1)

An AR(1) (autoregressive order 1) covariance model assumes that all variances on the diagonal are equal and that covariances $t$ time periods apart are equal to $\sigma^2 \rho^t$. That is

$$
\mathbf{V}_i = \sigma^2 \begin{pmatrix}
1 & \rho & \rho^2 & \rho^3 & \cdots & \rho^{m-1} \\
\rho & 1 & \rho & \rho^2 & \cdots & \rho^{m-2} \\
\rho^2 & \rho & 1 & \rho & \cdots & \rho^{m-3} \\
\rho^3 & \rho^2 & \rho & 1 & \cdots & \rho^{m-4} \\
\vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\
\rho^{m-1} & \rho^{m-2} & \rho^{m-3} & \rho^{m-4} & \cdots & 1
\end{pmatrix}_{m \times m}
$$

where $\sigma^2 = \mathrm{var}(y_{ij})$ and $\rho$ is the correlation between observations on the same subject.

## Banded(1)

A Banded(1) (banded order 1) covariance model assumes that all variances on the diagonal are equal, covariances for observations one time period apart are equal to $\sigma^2 \rho$, and covariances for measurements greater than one time period apart are equal to zero. That is

$$
\mathbf{V}_i = \sigma^2 \begin{pmatrix}
1 & \rho & 0 & 0 & \cdots & 0 \\
\rho & 1 & \rho & 0 & \cdots & 0 \\
0 & \rho & 1 & \rho & \cdots & 0 \\
0 & 0 & \rho & 1 & \cdots & 0 \\
\vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\
0 & 0 & 0 & 0 & \cdots & 1
\end{pmatrix}_{m \times m}
$$

where $\sigma^2 = \mathrm{var}(y_{ij})$ and $\rho$ is the correlation between observations on the same subject.

## Simple

A simple covariance model assumes that all variances on the diagonal are equal and that all covariances are equal to zero. That is

$$\mathbf{V}_i = \sigma^2 \begin{pmatrix} 1 & 0 & 0 & 0 & \cdots & 0 \\ 0 & 1 & 0 & 0 & \cdots & 0 \\ 0 & 0 & 1 & 0 & \cdots & 0 \\ 0 & 0 & 0 & 1 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & 1 \end{pmatrix}_{m \times m}$$

where $\sigma^2 = \mathrm{var}(y_{ij})$.

# 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 the parameters associated with this test such as the proportions, sample sizes, alpha, and power. This chapter covers two procedures, each of which has different options. This section documents options that are common to both procedures. Later, unique options for each procedure will be documented.

## 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 beta criterion you have specified for each of the terms. The "solve for" parameter is displayed on the vertical axis of the plot.

## Test

### Test Statistic Based On

This option specifies the type of test statistic for which power is calculated. This routine has the capability of calculating power and sample size for testing time-averaged differences for binary data based on two different test statistics. The options are as follows:

- **Difference: P1-P2**

  This option calculates the power for the test statistic based on the difference in proportions:

$$z = \frac{\hat{p}_1 - \hat{p}_2}{\sqrt{\mathrm{var}(\hat{p}_1 - \hat{p}_2)}}.$$

## Tests for Two Proportions in a Repeated Measures Design

- **Log(OR): logit(P1)-logit(P2)**

  This option calculates the power for the test statistic based on the difference defined on the logit link scale:

  $$z = \frac{\text{logit}(\hat{p}_j) - \text{logit}(\hat{p}_h)}{\sqrt{\text{var}(\text{logit}(\hat{p}_j) - \text{logit}(\hat{p}_h))}} \; .$$

## Alternative Hypothesis

This option specifies the alternative hypothesis. This implicitly specifies the direction of the hypothesis test. The null hypothesis is always $H_0 : \beta_1 = 0$.

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 $H_1 : \beta_1 > 0$ or $H_1 : \beta_1 < 0$.

- **Two-Sided**

  This is the most common selection. It yields the *two-tailed* test. Use this option when you are testing whether the means are different, but you do not want to specify beforehand which mean is larger.

## 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 means when in fact the means 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 means when in fact the means 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*.

## Sample Size (When Solving for Sample Size)

### Group Allocation

Select the option that describes the constraints on *N1* or *N2* or both.

The options are

- **Equal (N1 = N2)**

  This selection is used when you wish to have equal sample sizes in each group. Since you are solving for both sample sizes at once, no additional sample size parameters need to be entered.

- **Enter N2, solve for N1**

  Select this option when you wish to fix *N2* at some value (or values), and then solve only for *N1*. Please note that for some values of *N2*, there may not be a value of *N1* that is large enough to obtain the desired power.

- **Enter R = N2/N1, solve for N1 and N2**

  For this choice, you set a value for the ratio of *N2* to *N1*, and then PASS determines the needed *N1* and *N2*, with this ratio, to obtain the desired power. An equivalent representation of the ratio, *R*, is

  $$N2 = R * N1.$$

- **Enter percentage in Group 1, solve for N1 and N2**

  For this choice, you set a value for the percentage of the total sample size that is in Group 1, and then PASS determines the needed *N1* and *N2* with this percentage to obtain the desired power.

### N2 (Sample Size, Group 2)

*This option is displayed if Group Allocation = "Enter N2, solve for N1"*

*N2* is the number of items or individuals sampled from the Group 2 population.

*N2* must be $\geq 2$. You can enter a single value or a series of values.

### R (Group Sample Size Ratio)

*This option is displayed only if Group Allocation = "Enter R = N2/N1, solve for N1 and N2."*

*R* is the ratio of *N2* to *N1*. That is,

$$R = N2 / N1.$$

Use this value to fix the ratio of *N2* to *N1* while solving for *N1* and *N2*. Only sample size combinations with this ratio are considered.

*N2* is related to *N1* by the formula:

$$N2 = [R \times N1],$$

where the value *[Y]* is the next integer $\geq Y$.

For example, setting *R* = 2.0 results in a Group 2 sample size that is double the sample size in Group 1 (e.g., *N1* = 10 and *N2* = 20, or *N1* = 50 and *N2* = 100).

*R* must be greater than 0. If *R* < 1, then *N2* will be less than *N1*; if *R* > 1, then *N2* will be greater than *N1*. You can enter a single or a series of values.

**Tests for Two Proportions in a Repeated Measures Design**

## Percent in Group 1

*This option is displayed only if Group Allocation = "Enter percentage in Group 1, solve for N1 and N2."*

Use this value to fix the percentage of the total sample size allocated to Group 1 while solving for *N1* and *N2*. Only sample size combinations with this Group 1 percentage are considered. Small variations from the specified percentage may occur due to the discrete nature of sample sizes.

The Percent in Group 1 must be greater than 0 and less than 100. You can enter a single or a series of values.

## Sample Size (When Not Solving for Sample Size)

### Group Allocation

Select the option that describes how individuals in the study will be allocated to Group 1 and to Group 2.

The options are

- **Equal (N1 = N2)**

   This selection is used when you wish to have equal sample sizes in each group. A single per group sample size will be entered.

- **Enter N1 and N2 individually**

   This choice permits you to enter different values for *N1* and *N2*.

- **Enter N1 and R, where N2 = R * N1**

   Choose this option to specify a value (or values) for *N1*, and obtain *N2* as a ratio (multiple) of *N1*.

- **Enter total sample size and percentage in Group 1**

   Choose this option to specify a value (or values) for the total sample size (*N*), obtain *N1* as a percentage of *N*, and then *N2* as *N - N1*.

### Sample Size Per Group

*This option is displayed only if Group Allocation = "Equal (N1 = N2)."*

The Sample Size Per Group is the number of items or individuals sampled from each of the Group 1 and Group 2 populations. Since the sample sizes are the same in each group, this value is the value for *N1*, and also the value for *N2*.

The Sample Size Per Group must be ≥ 2. You can enter a single value or a series of values.

### N1 (Sample Size, Group 1)

*This option is displayed if Group Allocation = "Enter N1 and N2 individually" or "Enter N1 and R, where N2 = R * N1."*

*N1* is the number of items or individuals sampled from the Group 1 population.

*N1* must be ≥ 2. You can enter a single value or a series of values.

### N2 (Sample Size, Group 2)

*This option is displayed only if Group Allocation = "Enter N1 and N2 individually."*

*N2* is the number of items or individuals sampled from the Group 2 population.

*N2* must be ≥ 2. You can enter a single value or a series of values.

## R (Group Sample Size Ratio)

*This option is displayed only if Group Allocation = "Enter N1 and R, where N2 = R \* N1."*

*R* is the ratio of *N2* to *N1*. That is,

$$R = N2/N1$$

Use this value to obtain *N2* as a multiple (or proportion) of *N1*.

*N2* is calculated from *N1* using the formula:

$$N2 = [R \times N1],$$

where the value *[Y]* is the next integer $\geq Y$.

For example, setting *R* = 2.0 results in a Group 2 sample size that is double the sample size in Group 1.

*R* must be greater than 0. If *R* < 1, then *N2* will be less than N1; if *R* > 1, then *N2* will be greater than *N1*. You can enter a single value or a series of values.

## Total Sample Size (N)

*This option is displayed only if Group Allocation = "Enter total sample size and percentage in Group 1."*

This is the total sample size, or the sum of the two group sample sizes. This value, along with the percentage of the total sample size in Group 1, implicitly defines *N1* and *N2*.

The total sample size must be greater than one, but practically, must be greater than 3, since each group sample size needs to be at least 2.

You can enter a single value or a series of values.

## Percent in Group 1

*This option is displayed only if Group Allocation = "Enter total sample size and percentage in Group 1."*

This value fixes the percentage of the total sample size allocated to Group 1. Small variations from the specified percentage may occur due to the discrete nature of sample sizes.

The Percent in Group 1 must be greater than 0 and less than 100. You can enter a single value or a series of values.

## Effect Size

### Input Type

Indicate what type of values to enter to specify the effect size. Regardless of the entry type chosen, the test statistics used in the power and sample size calculations are the same. This option is simply given for convenience in specifying the effect size.

### P1 (Group 1 Proportion|H1)

*This option is displayed only if Input Type = "Proportions"*

Enter a value for the proportion of 'successes' in group 1 under the alternative hypothesis. If you know the expected odds ratio for the two treatment groups, click on the 'P' button to the right to calculate the corresponding proportions. You may enter a single value or a range of values such as *0.1 0.2 0.3* or *0.1 to 0.5 by 0.1*. The items in the list may be separated with commas or blanks.

## OR (Odds Ratio|H1 = O1/O2)

*This option is displayed only if Input Type = "Odds Ratios"*

Enter a value for the odds ratio for that is to be detected. If you know the expected proportions for the two treatment groups but do not know the odds ratio, click on the "OR" button to the right to calculate the corresponding odds ratio. The odds ratio is used along with P2 to calculate P1 using the formula: P1 = (OR*P2)/(1 - P2 + OR*P2). You may enter a single value or a range of values such as *1.5 2 2.5* or *1.5 to 2 by 0.1*. The items in the list may be separated with commas or blanks.

## Effect Size – Group 2 (Control) Proportion

### P2 (Group 2 or Control Proportion)

Enter a value for P2, the baseline proportion, or the proportion of "successes" from group 2. You may enter a single value or a range of values such as *0.1 0.2 0.3* or *0.1 to 0.3 by 0.05*. The items in the list may be separated with commas or blanks.

## Effect Size – Repeated Measurements

### M (Number of Time Points)

Enter a value for the number of time points (repeated measurements) for which each subject will be observed. You may enter a single value or a range of values such as '3 5 7' or '2 to 8 by 1'. The items in the list may be separated with commas or blanks.

## Effect Size – Covariance Structure

### Covariance Type

Select the within-subject covariance structure that will be used in the mixed models analysis. The options are:

- **Compound Symmetry**

  All variances on the diagonal of the within-subject variance-covariance matrix are equal to $\sigma^2$, and all covariances are equal to $\rho\sigma^2$.

- **AR(1)**

  All variances on the diagonal of the within-subject variance-covariance matrix are equal to $\sigma^2$, and the covariance between observations *t* time periods apart is $\rho^t\sigma^2$.

- **Banded(1)**

  All variances on the diagonal of the within-subject variance-covariance matrix are equal to $\sigma^2$, and the covariance between observations one time period apart is $\rho\sigma^2$. Covariances between observations more than one time period apart are equal to zero.

- **Simple**

  All variances are equal to $\sigma^2$, and all covariances are equal to zero.

### Rho (Autocorrelation)

Enter a value for the correlation between observations on the same subject. When no previous estimate of the within-patient correlation is available, you should use a conservative prediction of the correlation, i.e. a correlation that is higher than anticipated. You may enter a single value or a range of values such as *0.5 0.6 0.7* or *0.4 to 0.9 by 0.1*. The items the list may be separated with commas or blanks.

# Example 1 – Determining Power

A study is being planned to determine the efficacy of a prophylactic treatment for the common cold. The study will follow a treatment group and placebo control group through the winter to determine if there is an overall difference between the two treatment groups in the proportion of patients who get sick. Subjects will take the treatment (or placebo) once daily throughout the duration of the study. The study will be conducted from September to April with scheduled, monthly visits (beginning in October) to determine the patient's disease status (present or absent). Therefore, a total of seven responses will be observed for each patient. Previous studies have indicated a baseline disease rate of 60% for the common cold. The researchers want to be able to detect a treatment to control odds ratio of 0.5 (an odds ratio of 0.5 corresponds to a treatment group proportion of 0.4285714). A compound-symmetry covariance pattern with autocorrelation of 0.5 is assumed to be adequate. The test will be conducted using a mixed models analysis with an alpha level of 0.05.

What power does the study achieve over a range of possible sample sizes?

# Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Tests for Two Proportions in a Repeated Measures Design** procedure window by expanding **Proportions**, then **Two Independent Proportions**, then clicking on **Repeated Measures**, and then clicking on **Tests for Two Proportions in a Repeated Measures Design**. 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**.

| Option | Value |
|---|---|
| **Design Tab** | |
| Solve For .................................................. | **Power** |
| Test Statistic Based on ........................... | **Log(OR): logit(P1)-logit(P2)** |
| Alternative Hypothesis ............................ | **Two-Sided** |
| Alpha....................................................... | **0.05** |
| Group Allocation ..................................... | **Equal (N1 = N2)** |
| Sample Size Per Group ........................... | **10 to 100 by 10** |
| Input Type............................................... | **Proportions or Odds Ratios** |
| P1 (*If using Proportions*) ......................... | **0.4285714** |
| OR1 (*If using Odds Ratios*) .................... | **0.5** |
| P2............................................................ | **0.6** |
| M ............................................................. | **7** |
| Covariance Type..................................... | **Compound Symmetry** |
| Rho ......................................................... | **0.5** |

# Output

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

## Numeric Results

**Numeric Results**
Test Statistic Based on Log(OR): logit(P1) - logit(P2).
Two-Sided Test. Null Hypothesis: OR = 1. Alternative Hypothesis: OR ≠ 1.
Covariance Type = Compound Symmetry

| Power | N1 | N2 | N | M | P1 | P2 | OR1 | Rho | Alpha |
|---|---|---|---|---|---|---|---|---|---|
| 0.17843 | 10 | 10 | 20 | 7 | 0.429 | 0.600 | 0.500 | 0.500 | 0.050 |
| 0.30742 | 20 | 20 | 40 | 7 | 0.429 | 0.600 | 0.500 | 0.500 | 0.050 |
| 0.42768 | 30 | 30 | 60 | 7 | 0.429 | 0.600 | 0.500 | 0.500 | 0.050 |
| 0.53515 | 40 | 40 | 80 | 7 | 0.429 | 0.600 | 0.500 | 0.500 | 0.050 |
| 0.62800 | 50 | 50 | 100 | 7 | 0.429 | 0.600 | 0.500 | 0.500 | 0.050 |
| 0.70610 | 60 | 60 | 120 | 7 | 0.429 | 0.600 | 0.500 | 0.500 | 0.050 |
| 0.77040 | 70 | 70 | 140 | 7 | 0.429 | 0.600 | 0.500 | 0.500 | 0.050 |
| 0.82241 | 80 | 80 | 160 | 7 | 0.429 | 0.600 | 0.500 | 0.500 | 0.050 |
| 0.86386 | 90 | 90 | 180 | 7 | 0.429 | 0.600 | 0.500 | 0.500 | 0.050 |
| 0.89646 | 100 | 100 | 200 | 7 | 0.429 | 0.600 | 0.500 | 0.500 | 0.050 |

**References**
Brown, H., Prescott, R., 2006. Applied Mixed Models in Medicine. 2nd ed. John Wiley & Sons Ltd. Chichester,
    West Sussex, England.
Liu, H. and Wu, T., 2005. 'Sample Size Calculation and Power Analysis of Time-Averaged Difference.' Journal of
    Modern Applied Statistical Methods, Vol. 4, No. 2, pages 434-445.
Diggle, P.J., Liang, K.Y., and Zeger, S.L., 1994. Analysis of Longitudinal Data. Oxford University Press. New
    York, New York. Chapter 2.

**Report Definitions**
Power is the probability of rejecting a false null hypothesis.
N1 and N2 are the number of items sampled from each population.
N is the total sample size, N1 + N2.
M is the number of time points (repeated measurements) at which each subject is observed.
P1 and P2 are the proportions from groups 1 and 2, respectively.
OR1 is the odds ratio ((P1/(1-P1))/(P2/(1-P2))) to be detected.
Rho is the correlation between observations on the same subject.
Alpha is the probability of rejecting a true null hypothesis.

**Summary Statements**
Group sample sizes of 10 and 10 achieve 17.843% power to detect an odds ratio of 0.500 in a
design with 7 repeated measurements having a Compound Symmetry covariance structure when the
proportion from group 2 is 0.600, the correlation between observations on the same subject is
0.500, and the alpha level is 0.050.

This report gives the power for each value of the other parameters.

## Power

This is the computed power for detecting the time-averaged difference between the two group means.

## Group 1 Sample Size (N1)

The value of *N1* is the number of subjects in group 1.

## Group 2 Sample Size (N2)

The value of *N2* is the number of subjects in group 2.

## Time Points (M)

This is the number of repeated measurements taken.

## Group 1 Prop (P1) & Group 2 Prop (P2)

These are the proportions of successes in groups 1 and 2, respectively.

## Odds Ratio (OR1)

This is the value of the odds ratio under the alternative hypothesis.

## Autocorr. (Rho)

This is the correlation between observations from the same subject.

## Alpha

Alpha is the significance level of the test.

## Beta

Beta is the probability of failing to reject the null hypothesis when the alternative hypothesis is true.

# Plots Section

**Using Proportions**



**Using Odds Ratios**
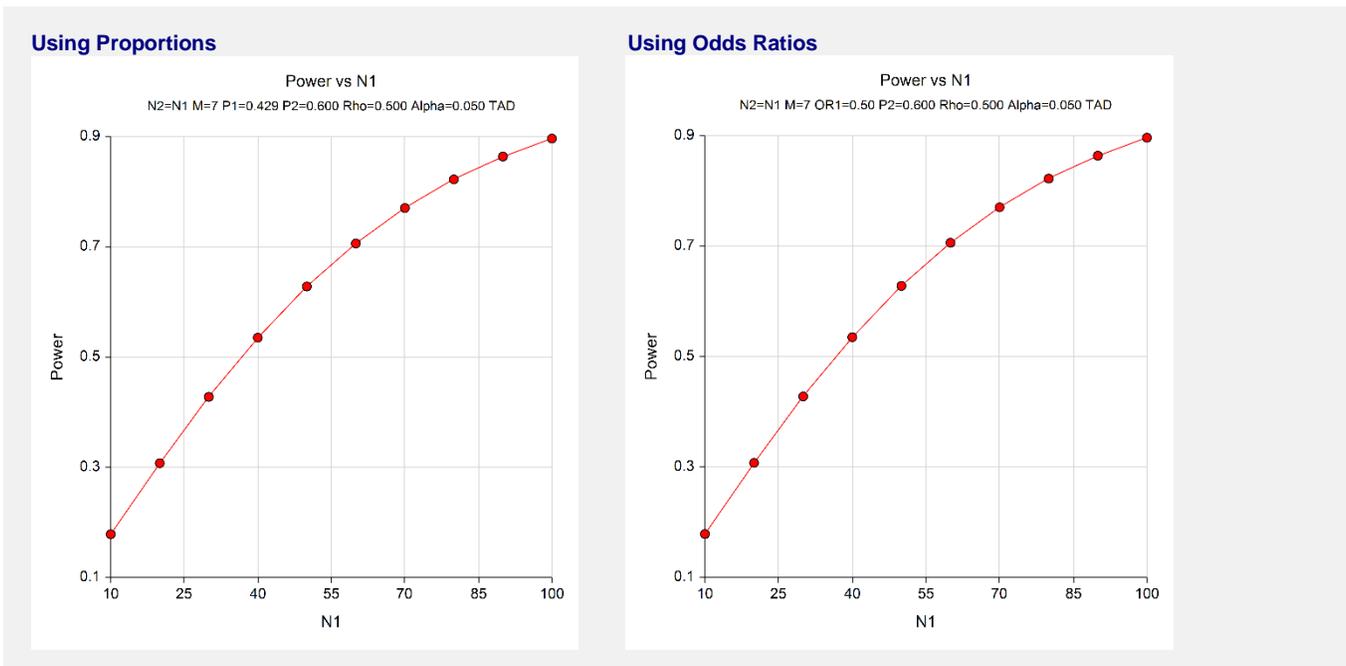


The chart shows the relationship between power and *N1* when the other parameters in the design are held constant.

# Example 2 – Finding the Sample Size

Continuing with Example 1, the researchers want to determine the exact sample size necessary to achieve at least 80% power.

## Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Tests for Two Proportions in a Repeated Measures Design** procedure window by expanding **Proportions**, then **Two Independent Proportions**, then clicking on **Repeated Measures**, and then clicking on **Tests for Two Proportions in a Repeated Measures Design**. 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**.

**Option**                                    **Value**

**Design Tab**

Solve For ................................................. **Sample Size**
Test Statistic Based on ........................... **Log(OR): logit(P1)-logit(P2)**
Alternative Hypothesis ............................ **Two-Sided**
Power ...................................................... **0.80**
Alpha ....................................................... **0.05**
Group Allocation ..................................... **Equal (N1 = N2)**
Input Type ............................................... **Proportions or Odds Ratios**
P1 (*If using Proportions*) ......................... **0.4285714**
OR1 (*If using Odds Ratios*) .................... **0.5**
P2 ............................................................ **0.6**
M .............................................................. **7**
Covariance Type ..................................... **Compound Symmetry**
Rho .......................................................... **0.5**

## Output

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

### Numeric Results

| Target Power | Actual Power | N1 | N2 | N | M | P1 | P2 | OR1 | Rho | Alpha |
|---|---|---|---|---|---|---|---|---|---|---|
| 0.80 | 0.80297 | 76 | 76 | 152 | 7 | 0.429 | 0.600 | 0.500 | 0.500 | 0.050 |

A group sample size of 76 is required to achieve at least 80% power.

# Example 3 – Varying the Odds Ratio

Continuing with Examples 1 and 2, the researchers want to evaluate the impact on power of varying the odds ratio from 0.4 to 0.8. In the output to follow, we only display the plots. You may want to display the numeric reports as well, but we do not here in order to save space.

## Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Tests for Two Proportions in a Repeated Measures Design** procedure window by expanding **Proportions**, then **Two Independent Proportions**, then clicking on **Repeated Measures**, and then clicking on **Tests for Two Proportions in a Repeated Measures Design**. 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**.

| Option | Value |
|---|---|
| **Design Tab** | |
| Solve For .................................................. | **Power** |
| Test Statistic Based on ........................... | **Log(OR): logit(P1)-logit(P2)** |
| Alternative Hypothesis ........................... | **Two-Sided** |
| Alpha......................................................... | **0.05** |
| Group Allocation ..................................... | **Equal (N1 = N2)** |
| Sample Size Per Group ........................... | **10 to 100 by 10** |
| Input Type................................................. | **Odds Ratios** |
| OR1............................................................. | **0.4 to 0.8 by 0.1** |
| P2 .............................................................. | **0.6** |
| M................................................................. | **7** |
| Covariance Type...................................... | **Compound Symmetry** |
| Rho ............................................................ | **0.5** |

## Output

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

### Plots Section
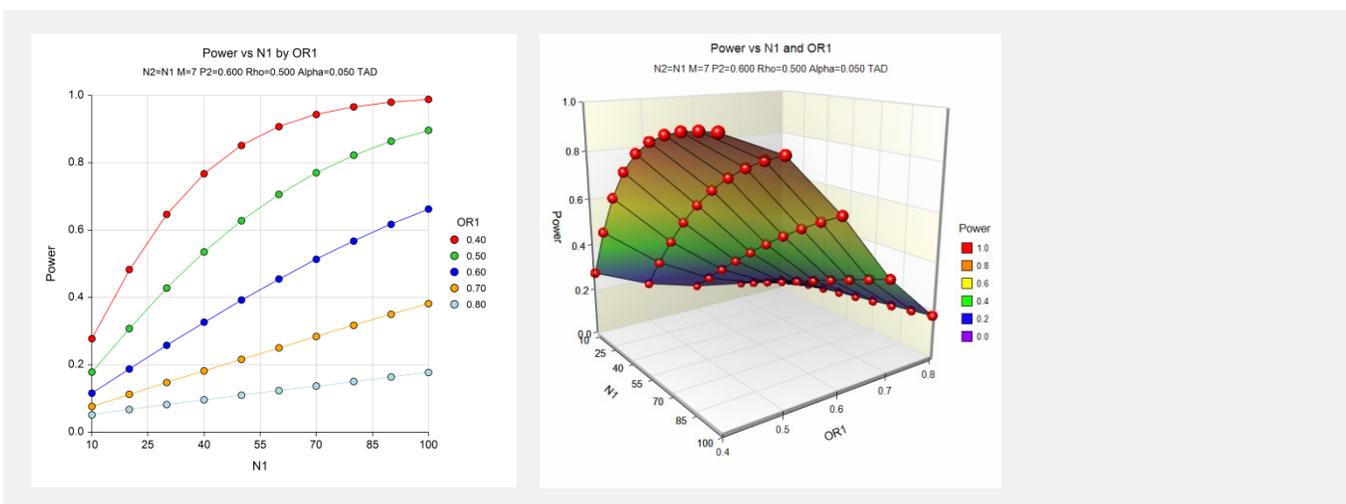


These charts show how the power depends on the odds ratio, OR1, as well as the group sample size N1.

# Example 4 – Varying the Proportions

Continuing with Examples 1 and 2, the researchers want to evaluate the impact on power of varying the group 1 proportion from 0.2 to 0.5. In the output to follow, we only display the plots. You may want to display the numeric reports as well, but we do not here in order to save space.

## Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Tests for Two Proportions in a Repeated Measures Design** procedure window by expanding **Proportions**, then **Two Independent Proportions**, then clicking on **Repeated Measures**, and then clicking on **Tests for Two Proportions in a Repeated Measures Design**. 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**.

| Option | Value |
|---|---|
| **Design Tab** | |
| Solve For .................................................. | **Power** |
| Test Statistic Based on ........................... | **Log(OR): logit(P1)-logit(P2)** |
| Alternative Hypothesis ............................ | **Two-Sided** |
| Alpha........................................................ | **0.05** |
| Group Allocation ..................................... | **Equal (N1 = N2)** |
| Sample Size Per Group ........................... | **10 to 100 by 10** |
| Input Type................................................ | **Proportions** |
| P1.............................................................. | **0.2 to 0.5 by 0.1** |
| P2 ............................................................. | **0.6** |
| M............................................................... | **7** |
| Covariance Type...................................... | **Compound Symmetry** |
| Rho ........................................................... | **0.5** |

## Output

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

### Plots Section
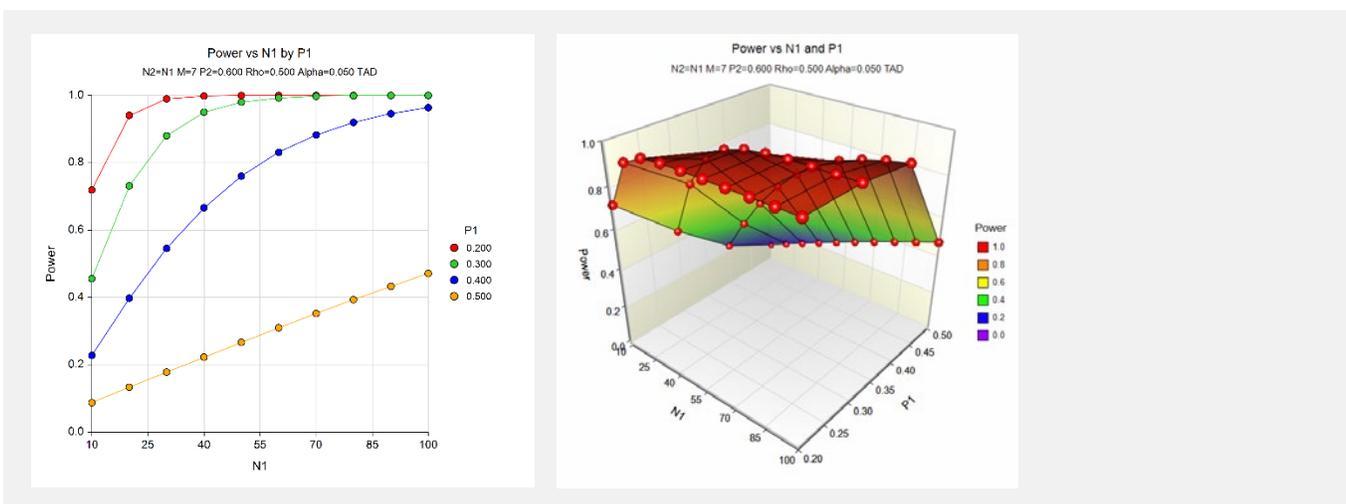


These charts show how the power depends on the proportion, P1, as well as the group sample size N1.

# Example 5 – Impact of the Number of Repeated Measurements

Continuing with Example 2, the researchers want to study the impact on the sample size if they changing the number of measurements made on each individual. Their experimental protocol calls for seven measurements. They want to see the impact of taking twice that many measurements.

## Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Tests for Two Proportions in a Repeated Measures Design** procedure window by expanding **Proportions**, then **Two Independent Proportions**, then clicking on **Repeated Measures**, and then clicking on **Tests for Two Proportions in a Repeated Measures Design**. 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**.

| Option | Value |
|---|---|
| **Design Tab** | |
| Solve For ................................................. | **Sample Size** |
| Test Statistic Based on ........................... | **Log(OR): logit(P1)-logit(P2)** |
| Alternative Hypothesis ............................. | **Two-Sided** |
| Power........................................................ | **0.80** |
| Alpha........................................................ | **0.05** |
| Group Allocation ..................................... | **Equal (N1 = N2)** |
| Input Type................................................ | **Proportions or Odds Ratios** |
| P1 (*If using Proportions*) ........................ | **0.4285714** |
| OR1 (*If using Odds Ratios*) .................... | **0.5** |
| P2 ............................................................ | **0.6** |
| M.............................................................. | **7 14** |
| Covariance Type...................................... | **Compound Symmetry** |
| Rho .......................................................... | **0.5** |

## Output

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

### Numeric Results

| Target Power | Actual Power | N1 | N2 | N | M | P1 | P2 | OR1 | Rho | Alpha |
|---|---|---|---|---|---|---|---|---|---|---|
| 0.80 | 0.80297 | 76 | 76 | 152 | 7 | 0.429 | 0.600 | 0.500 | 0.500 | 0.050 |
| 0.80 | 0.80161 | 71 | 71 | 142 | 14 | 0.429 | 0.600 | 0.500 | 0.500 | 0.050 |

Doubling the number of repeated measurements per individual decreases the group sample size by only 5 individuals. This reduction in sample size may not justify the additional seven trips to the clinic for each subject.

# Example 6 – Validation using Diggle et al. (1994)

Diggle et al. (1994) pages 31 and 32 present an example of calculating the sample size for a TAD study. They calculate the group sample sizes for the cases where the difference in proportions (P1-P2) ranges from 0.1 to 0.3, $\rho$ ranges from 0.2 to 0.8, alpha = 0.05, $p_2 = 0.5$, $M = 3$, and power = 0.8. Note that Diggle et al (1994) uses a one-sided test and the test statistic based on the difference in proportions.

To calculate the sample sizes using the odds ratio specification, we must first convert the differences to odds ratios using the formula:

$$OR = \frac{p_1/(1-p_1)}{p_2/(1-p_2)}$$

Differences of 0.1, 0.2, and 0.3 with P2 = 0.5 correspond to odds ratios of 1.5, 2.333, and 4.0, respectively.

## Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Tests for Two Proportions in a Repeated Measures Design** procedure window by expanding **Proportions**, then **Two Independent Proportions**, then clicking on **Repeated Measures**, and then clicking on **Tests for Two Proportions in a Repeated Measures Design**. 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**.

**Option**                          **Value**

**Design Tab**
Solve For ............................................... **Sample Size**
Test Statistic Based on ........................... **Difference: P1-P2**
Alternative Hypothesis ............................ **One-Sided**
Power ..................................................... **0.80**
Alpha ...................................................... **0.05**
Group Allocation ..................................... **Equal (N1 = N2)**
Input Type ............................................... **Proportions or Odds Ratios**
P1 (*If using Proportions*) ......................... **0.6 0.7 0.8**
OR1 (*If using Odds Ratios*) .................... **1.5 2.333 4**
P2 ........................................................... **0.5**
M ............................................................. **3**
Covariance Type ..................................... **Compound Symmetry**
Rho ......................................................... **0.2 0.5 0.8**

# Output

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

## Numeric Results

| Target Power | Actual Power | N1 | N2 | N | M | P1 | P2 | OR1 | Rho | Alpha |
|---|---|---|---|---|---|---|---|---|---|---|
| 0.80 | 0.80164 | 143 | 143 | 286 | 3 | 0.600 | 0.500 | 1.500 | 0.200 | 0.050 |
| 0.80 | 0.80116 | 204 | 204 | 408 | 3 | 0.600 | 0.500 | 1.500 | 0.500 | 0.050 |
| 0.80 | 0.80089 | 265 | 265 | 530 | 3 | 0.600 | 0.500 | 1.500 | 0.800 | 0.050 |
| 0.80 | 0.80870 | 35 | 35 | 70 | 3 | 0.700 | 0.500 | 2.333 | 0.200 | 0.050 |
| 0.80 | 0.80163 | 49 | 49 | 98 | 3 | 0.700 | 0.500 | 2.333 | 0.500 | 0.050 |
| 0.80 | 0.80329 | 64 | 64 | 128 | 3 | 0.700 | 0.500 | 2.333 | 0.800 | 0.050 |
| 0.80 | 0.82213 | 15 | 15 | 30 | 3 | 0.800 | 0.500 | 4.000 | 0.200 | 0.050 |
| 0.80 | 0.81509 | 21 | 21 | 42 | 3 | 0.800 | 0.500 | 4.000 | 0.500 | 0.050 |
| 0.80 | 0.81120 | 27 | 27 | 54 | 3 | 0.800 | 0.500 | 4.000 | 0.800 | 0.050 |

The sample sizes calculated by **PASS** match the results of Diggle et al. (1994) exactly.

# Example 7 – Validation using Brown and Prescott (2006)

Brown and Prescott (2006) page 270 presents an example of calculating the sample size for a future study. They calculate the group sample size to be 85 for a future study involving four post-treatment visits to detect a doubling of the odds ratio (i.e., OR1 = 2) at the 5% significance level with 80% power. They assume an autocorrelation of 0.5, and an expected rate of positives ((P1+P2)/2) of 0.4. We can calculate the corresponding values of P1, P2, and OR for use in **PASS** by solving the following system of equations for P1 and P2:

$$\frac{P1+P2}{2} = 0.4 \quad \text{and} \quad \frac{P1/(1-P1)}{P2/(1-P2)} = OR = 2.0$$

The solution to these equations occurs when P1 = 0.482255312124 and P2 = 0.317744687876. The decimal places are kept to make the solution exact.

## Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Tests for Two Proportions in a Repeated Measures Design** procedure window by expanding **Proportions**, then **Two Independent Proportions**, then clicking on **Repeated Measures**, and then clicking on **Tests for Two Proportions in a Repeated Measures Design**. 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**.

**Option**                                          **Value**

**Design Tab**
Solve For ............................................... **Sample Size**
Test Statistic Based on ........................... **Log(OR): logit(P1)-logit(P2)**
Alternative Hypothesis ........................... **Two-Sided**
Power ..................................................... **0.80**
Alpha ...................................................... **0.05**
Group Allocation .................................... **Equal (N1 = N2)**
Input Type .............................................. **Proportions or Odds Ratios**
P1 (*If using Proportions*) ........................ **0.482255312124**
OR1 (*If using Odds Ratios*) .................... **2.0**
P2 ........................................................... **0.317744687876**
M ............................................................ **4**
Covariance Type ..................................... **Compound Symmetry**
Rho ........................................................ **0.5**

## Output

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

### Numeric Results

| Target Power | Actual Power | N1 | N2 | N | M | P1 | P2 | OR1 | Rho | Alpha |
|---|---|---|---|---|---|---|---|---|---|---|
| 0.80 | 0.80080 | 86 | 86 | 172 | 4 | 0.482 | 0.318 | 2.000 | 0.500 | 0.050 |

The sample size of 86 calculated by PASS matches the results of Brown and Prescott (2006). The slight difference is due to rounding. Calculation of the sample size presented by Brown and Prescott (2006) on page 270 results in a value of 85.025337, which they round down to 85. Note that the numerical formula has a typographical error: the denominator term should be $(4 \times .693^2)$, not $(4 \times .693)^2$ (see the formula on page 269 of Brown and Prescott (2006)).