

## Chapter 383

# Mixed Models Tests for the Slope Difference in a 2-Level Hierarchical Design with Random Slopes

## Introduction

This procedure calculates power and sample size for a two-level longitudinal design in which subjects (level-two unit) are randomly assigned to one of two groups. Each subject is measured at several time points and the goal of the study is to compare the average, subject-specific slopes of the two groups. If the group means are identical at the beginning of the study (which they often are in a randomized trial), testing the difference in slopes is equivalent to testing the difference in means at the final measurement time. This is a test of the time-by-treatment interaction.

Each subject is assumed to have their own random slope. Each subject is assigned to receive one of two possible interventions.

Note that a companion procedure power analyzes the fixed-slope case in which all subjects in a group are assumed to have a common slope.

## Technical Details

Our formulation comes from Ahn, Heo, and Zhang (2015), chapter 5, section 5.4.2, pages 161-164. The longitudinal mixed model that is adopted is

$$Y_{ij} = \beta_0 + \xi X_{ij} + \tau T_{ij} + \delta X_{ij} T_{ij} + v_i T_{ij} + u_i + e_{ij}$$

where

- $Y_{ij}$  is the continuous response of the  $j^{\text{th}}$  measurement in the  $i^{\text{th}}$  subject.
- $\beta_0$  is the fixed intercept.
- $X_{ij}$  is an indicator variable that is 1 if subject  $i$  is assigned to group 1 and 0 otherwise.
- $T_{ij}$  is the time value. It is assumed that  $T_{ij} = j - 1$  for all  $i$  and  $j$ .
- $\xi$  is the intervention effect at baseline and is usually expected to be zero.
- $\delta$  is the treatment-by-time effect. It is the difference between the two treatment slopes.
- $v_i$  is subject-specific slope for the  $i^{\text{th}}$  subject which is distributed as  $N(0, \sigma_T^2)$ .
- $u_i$  is a random effect (subject-specific intercept) term for the  $i^{\text{th}}$  subject that is distributed as  $N(0, \sigma_u^2)$ .
- $e_{ij}$  is a random effect for the  $j^{\text{th}}$  measurement in the  $i^{\text{th}}$  subject that is distributed as  $N(0, \sigma_e^2)$ .

## Mixed Models Tests for the Slope Difference in a 2-Level Hierarchical Design with Random Slopes

- $\sigma_u^2$  is variance of the subject random effects.
- $\sigma_e^2$  is variance of the measurement random effects.
- $\sigma_T^2$  is variance of the subject-specific slopes.
- $\sigma^2$  is the variance of  $Y$ , where  $\sigma^2 = \sigma_e^2 / (1 - \rho)$ .
- $\rho$  is the correlation between measurements on the same subject.
- $K_1$  is the number of subjects in group 1.
- $K_2$  is the number of subjects in group 2.
- $\lambda$  is  $K_1/K_2$ .
- $M$  is the number of measurements per subject.
- $V(T)$  is  $\sum_{j=1}^M (T_j - \bar{T})^2 / M$ .
- $r_T$  is ratio of the random slope variance to the sum of the other variance terms,  $\sigma^2$ .

The test of significance of the  $X_{ij}T_{ij}$  term in the mixed model analysis is the test statistic of interest. It tests the difference of the two group slopes. The power calculations assume that the estimated value of  $\delta$ , called  $\hat{\delta}$ , has an approximate normal distribution with mean  $\delta$  and known variance.

The power is calculated using

$$Power = \Phi \left\{ \frac{\delta}{\sigma} \sqrt{K_2 MV(T) / [(1 + \lambda^{-1}) \{(1 - \rho) + r_T MV(T)\}]} - \Phi^{-1}(1 - \alpha/2) \right\}$$

The values of the other parameters when requested are found using a binary search based on this formula.

## Example 1 – Calculating Power

Researchers are planning a study of the impact of a new drug on heart rate. They want to evaluate the change in heart rate between subjects who take the new drug, and subjects who take a standard drug. Their experimental protocol calls for a baseline heart rate measurement, followed by administration of the drug, followed by three additional measurements ten minutes apart. They want to be able to detect a difference in heart rate at the final means of 12 between the two treatments. They want a sensitivity analysis by considering a range of differences from 9 to 15.

Similar studies have found a standard deviation of 9.2 and an  $r_T$  value of 0.1. These studies also showed correlation among measurements on the same individual of 0.5. The two-sided test of the slope difference parameter will be conducted at the 0.05 significance level. The desired power is 90%. They are planning on dividing subjects equally between the treatment and control groups. They want to investigate  $K1 = K2 = 5$  to 25 by 5.

### 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 .....	<b>Power</b>
Alpha.....	<b>0.05</b>
K1 (Group 1 Subjects) .....	<b>5 10 15 20 25</b>
K2 (Group 2 Subjects) .....	<b>K1</b>
M (Measurements Per Subject) .....	<b>4</b>
Slope Input Type.....	<b><math>\mu_1 - \mu_2</math> (Mean Difference)</b>
$\mu_1 - \mu_2$ (Mean Difference) .....	<b>9 12 15</b>
$\sigma$ (Standard Deviation).....	<b>9.2</b>
$r_T$ (Random Slope Variance / $\sigma^2$ ).....	<b>0.1</b>
$\rho$ (Within Subject Correlation) .....	<b>0.5</b>

## Mixed Models Tests for the Slope Difference in a 2-Level Hierarchical Design with Random Slopes

## Output

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

## Numeric Reports

## Numeric Results

Solve For: **Power**

Groups: 1 = Treatment, 2 = Control

Power	Number of Subjects			Measurements per Subject M	Mean Difference $\mu_1 - \mu_2$	Standard Deviation $\sigma$	Random Slope Variance / $\sigma^2$ rT	Within- Subject Correlation $\rho$	Alpha
	Group 1 K1	Group 2 K2	Total K						
0.2098	5	5	10	4	9	9.2	0.1	0.5	0.05
0.3709	10	10	20	4	9	9.2	0.1	0.5	0.05
0.5147	15	15	30	4	9	9.2	0.1	0.5	0.05
0.6353	20	20	40	4	9	9.2	0.1	0.5	0.05
0.7317	25	25	50	4	9	9.2	0.1	0.5	0.05
0.3362	5	5	10	4	12	9.2	0.1	0.5	0.05
0.5847	10	10	20	4	12	9.2	0.1	0.5	0.05
0.7588	15	15	30	4	12	9.2	0.1	0.5	0.05
0.8674	20	20	40	4	12	9.2	0.1	0.5	0.05
0.9302	25	25	50	4	12	9.2	0.1	0.5	0.05
0.4847	5	5	10	4	15	9.2	0.1	0.5	0.05
0.7756	10	10	20	4	15	9.2	0.1	0.5	0.05
0.9144	15	15	30	4	15	9.2	0.1	0.5	0.05
0.9702	20	20	40	4	15	9.2	0.1	0.5	0.05
0.9903	25	25	50	4	15	9.2	0.1	0.5	0.05

Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.

K The total number of subjects.

K1 and K2 The number of subjects in groups 1 and 2, respectively.

M The number of equally spaced measurement times.

$\mu_1 - \mu_2$  The difference in the two group means at the final measurement time:  $M - 1$ .  $\delta = (\mu_1 - \mu_2) / (M - 1)$ .

$\sigma$  The standard deviation of the response.

rT The ratio of the subject-specific slope variance to  $\sigma^2$ .

$\rho$  The correlation of the measurements on a subject.

Alpha The probability of rejecting a true null hypothesis, that is, rejecting when the slopes are actually equal.

## Summary Statements

A 2-group 2-level hierarchical design will have random assignment of subjects (level-2 units) to each of the 2 treatment arms (level-2 randomization), with repeated measurements (level-1 units) on each subject (over time). This design will be used to test whether the outcome trends (slopes) of the two groups are different by testing whether the 2 group means are different ( $\mu_1 - \mu_2$ ) at the final time point, using the appropriate mean difference term of the linear mixed-effects model, assuming random slopes, with a Type I error rate ( $\alpha$ ) of 0.05. The standard deviation of  $Y_{ij}$ , assuming a fixed-slope model, is assumed to be 9.2 (this standard deviation is the square-root of the fixed-slope model variance of  $Y_{ij}$  ( $\sigma^2$ ), where the fixed-slope variance is the sum of the error term variance and the level-2 random intercept variance). The ratio of the subject-specific random slope variance to  $\sigma^2$  ( $V(\tau) / \sigma^2$ ) is assumed to be 0.1 (the variance of  $Y_{ij}$ , assuming a random-slope model, is  $\sigma^2 + V(\tau) \times T[k]^2$ ). The intraclass correlation coefficient of level-1 units (repeated measurements on a subject) is assumed to be 0.5. To detect a mean difference at the final time point ( $\mu_1 - \mu_2$ ) of 9, with 5 subjects (level-2 units) in Group 1 and 5 subjects in Group 2, with 4 repeated measurements (level-1 units) obtained from each subject (level-2 unit), the power is 0.2098.

## References

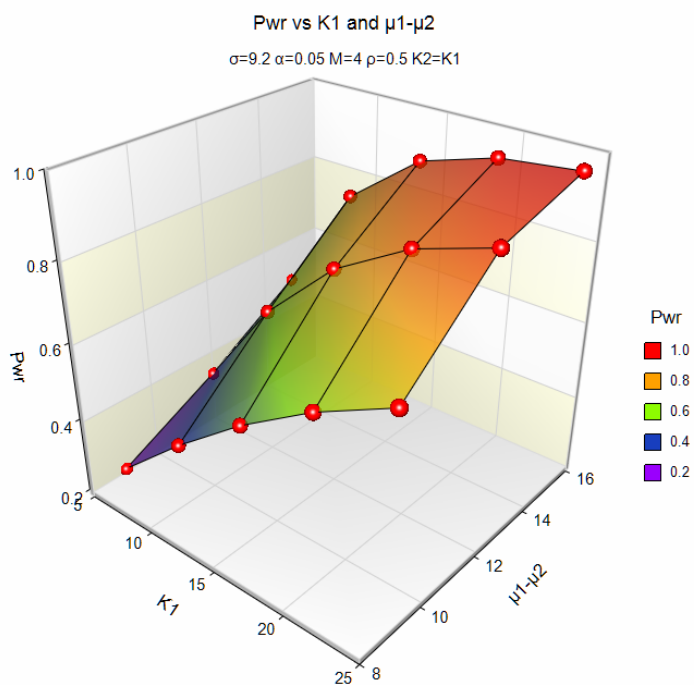
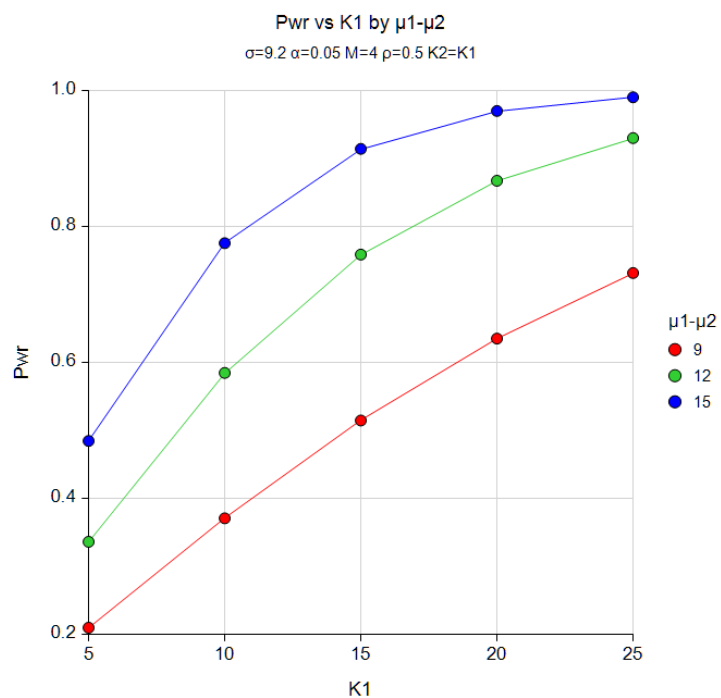
Ahn, C., Heo, M., and Zhang, S. 2015. Sample Size Calculations for Clustered and Longitudinal Outcomes in Clinical Research. CRC Press. New York.

This report shows the power for each of the scenarios.

## Mixed Models Tests for the Slope Difference in a 2-Level Hierarchical Design with Random Slopes

## Plots Section

## Plots



These plots show the power versus K1 for the various mean differences.

## Example 2 – Calculating Sample Size (Number of Subjects)

Continuing with the last example, suppose the researchers want to determine the number of subjects needed to achieve 90% power.

### 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 ..... **K1 (Group 1 Subjects)**  
 Power..... **0.90**  
 Alpha..... **0.05**  
 K2 (Group 2 Subjects) ..... **K1**  
 M (Measurements Per Subject) ..... **4**  
 Slope Input Type.....  **$\mu_1 - \mu_2$  (Mean Difference)**  
 $\mu_1 - \mu_2$  (Mean Difference) ..... **9 12 15**  
 $\sigma$  (Standard Deviation)..... **9.2**  
 $r_T$  (Random Slope Variance /  $\sigma^2$ )..... **0.1**  
 $\rho$  (Within Subject Correlation)..... **0.5**

### Output

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

#### Numeric Results

Solve For: **K1 (Group 1 Subjects)**

Groups: 1 = Treatment, 2 = Control

Power	Number of Subjects			Measurements per Subject M	Mean Difference $\mu_1 - \mu_2$	Standard Deviation $\sigma$	Random Slope Variance / $\sigma^2$ $r_T$	Within- Subject Correlation $\rho$	Alpha
	Group 1 K1	Group 2 K2	Total K						
0.8062	30	30	60	4	9	9.2	0.1	0.5	0.05
0.8091	17	17	34	4	12	9.2	0.1	0.5	0.05
0.8133	11	11	22	4	15	9.2	0.1	0.5	0.05

This report shows the number of subjects required for each of the scenarios.

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

Ahn, Heo, and Zhang (2015) page 164 provide a table in which several scenarios are reported. We will validate this procedure by duplicating the first row of their table. The following parameter settings were used: Power = 0.80;  $\delta = 0.4$ ;  $\sigma = 4$ ;  $\rho = 0.1$ ;  $M = 5$ ;  $r_T = 0.1$ ; and  $\alpha = 0.05$ . The reported value of  $K1$  is 299. The achieved power is 0.801.

### Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 3** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

#### Design Tab

Solve For ..... **K1 (Group 1 Subjects)**  
 Power..... **0.8**  
 Alpha..... **0.05**  
 K2 (Group 2 Subjects) ..... **K1**  
 M (Measurements Per Subject) ..... **5**  
 Slope Input Type.....  **$\delta$  (Slope Difference)**  
 $\delta$  (Slope Difference)..... **0.4**  
 $\sigma$  (Standard Deviation)..... **4**  
 $r_T$  (Random Slope Variance /  $\sigma^2$ )..... **0.1**  
 $\rho$  (Within Subject Correlation)..... **0.1**

### Output

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

#### Numeric Results

Solve For: **K1 (Group 1 Subjects)**

Groups: 1 = Treatment, 2 = Control

Power	Number of Subjects			Measurements per Subject M	Slope Difference $\delta$	Standard Deviation $\sigma$	Random Slope Variance / $\sigma^2$ $r_T$	Within- Subject Correlation $\rho$	Alpha
	Group 1 K1	Group 2 K2	Total K						
0.801	299	299	598	5	0.4	4	0.1	0.1	0.05

**PASS** also calculates the value of  $K1$  to be 299. The calculated power is also 0.801.