

## Chapter 383

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

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### 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 a 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.

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### 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.

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- $T_{ij}$  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  $i^{\text{th}}$  cluster the is distributed as  $N(0, \sigma_u^2)$ .
- $e_{ij}$  is a random effect for the  $j^{\text{th}}$  subject in the  $i^{\text{th}}$  cluster that is distributed as  $N(0, \sigma_e^2)$ .
- $\sigma_u^2$  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

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

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

## Procedure Options

This section describes the options that are specific to this procedure. These are located on the Design tab. For more information about the options of other tabs, go to the Procedure Window chapter.

## Design Tab

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

### Solve For

#### Solve For

This option specifies the parameter to be solved for from the other parameters. The parameters that may be selected are  $\delta$ ,  $Power$ ,  $KI$ , and  $M$ .

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Under most situations, you will select either *Power* to calculate power or *K1* to calculate the number of subjects. Note that the value selected here always appears as the vertical axis on the charts.

The program is set up to calculate power directly. To find appropriate values of the other parameters, a binary search is made using an iterative procedure until an appropriate value is found. This search considers integer values of M only.

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### Power and Alpha

#### Power

This option specifies one or more values for power. Power is the probability of rejecting a false null hypothesis, and is equal to one minus Beta. Beta is the probability of a type-II error, which occurs when a false null hypothesis is not rejected.

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 or a range of values such as *0.8 to 0.95 by 0.05* may be entered.

If your only interest is in determining the appropriate sample size for a confidence interval, set power to 0.5.

#### 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.

Values must be between zero and one. Usually, the value of 0.05 is used for alpha and this has become a standard. This means that about one test in twenty will falsely reject the null hypothesis. You should pick a value for alpha that represents the risk of a type-I error you are willing to take in your experimental situation.

You may enter a range of values such as *0.01 0.05 0.10* or *0.01 to 0.10 by 0.01*.

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### Sample Size – Subjects and Measurements – Number of Subjects

#### K1 (Group 1 Subjects)

This is the number of subjects (level-two units) in group 1 (treatment group).

This value must be a positive number greater than 1.

You can enter a list of values such as "10 20 30". A separate analysis will be run for each element in the list.

#### K2 (Group 2 Subjects)

This is the number of subjects in group 2 (control group).

This value must be a positive number greater than 1.

#### Using Multiples of K1

If you simply want a multiple of the value for group one, you would enter the multiple followed by "K1", with no blanks. If you want to use K1 directly, you do not have to enter the leading "1". For example, all of the following are valid entries:

10K1 2K1 0.5K1 K1.

You can use a list of values such as "10 20 30" or "K1 2K1 3K1".

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## Sample Size – Subjects and Measurements – Measurements Per Subject

### M (Measurements Per Subject)

This is the number of measurements (time points) per subject. It is assumed that these measurements are equally spaced through time.

This value must be a positive integer that is at least 2.

### List

You can use a list of values such as "4 6 8". A separate analysis will be run for each element in the list.

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## Effect Size

### Slope Input Type

Select the input type for entering the difference in slopes. Two options are available: ( $\mu_1 - \mu_2$ ) and  $\delta$ .

- **$\mu_1 - \mu_2$  (Mean Difference)**

Enter the difference in means at the final time point. The difference in slopes will then be calculated from this value. This option is provided because this is a value that can be easily interpreted and should be readily available.

- **$\delta$  (Slope Difference)**

Enter values for  $\delta$  directly. This option requires you to determine appropriate values for  $\delta$  which will often be difficult.

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

Enter one or more values for the mean difference where  $\mu_1$  is the mean of group 1 at the final measurement and  $\mu_2$  is the mean of group 2 at the final measurement. This mean difference is used to calculate the difference in slopes ( $\delta$ ) using the formula:

$$\delta = (\mu_1 - \mu_2) / (M - 1).$$

This formula comes from the group-by-time interaction term in the mixed model which is  $\delta_{XT}$ . Here, X indicates whether the subject is a member of group 1 or not, and T is the time. Since this procedure assumes that the times are 0, 1, 2, ..., (M-1), the value of T at the last measurement point is (M-1). Thus,  $\delta_{XT} = \delta_{X(M-1)}$  at the last time point. This leads to the above formula.

The subject slopes are assumed to be random from a normal distribution with different group means.

The power is the probability of detecting a  $\delta$  of at least this amount. This value is not necessarily the true difference. Rather, it is the difference you want to detect.

The difference,  $\mu_1 - \mu_2$ , can be any non-zero value (positive or negative). Since this procedure uses a two-sided test statistic, you will get the same result with either positive or negative values.

### Syntax

You can enter a single value such as 1 or a series of values such as 1 2 3 or 1 to 2 by 0.2.

When a series of values is entered, **PASS** will generate a separate calculation result for each value of the series.

**Mixed Models Tests for the Slope Difference in a 2-Level Hierarchical Design with Random Slopes** **$\delta$  (Slope Difference)**

Enter one or more values for  $\delta$  which is the difference between the group 1 and 2 slopes of the outcome over time. This difference equates to the difference in means at the final measurement if the means at the first measurement are equal (which is often the case for randomized trials).

The formula of the relationship between the group means at the final measurement is  $(\mu_1 - \mu_2) = \delta (M - 1)$ .

The slopes of the measurements across time are assumed to be a random. These slopes are distributed normally with different mean slopes for the two groups. The power is the probability of detecting a difference of at least this amount between the two average slopes. This value is not necessarily the true difference. Rather, it is the difference you want to detect.

Range:  $\delta$  can be any non-zero value (positive or negative). Since this procedure uses a two-sided test statistic, you will get the same result with either positive or negative values.

You can enter a single value such as 1 or a series of values such as 1 2 3 or 1 to 2 by 0.2. When a series of values is entered, PASS will generate a separate calculation result for each value of the series.

 **$\sigma$  (Standard Deviation)**

Enter the standard deviation of Y. This standard deviation applies for both groups. A good estimate of this value is the average squared residual from a previous study.

Note that  $\sigma$  must be a positive number. You can enter a single value such as 5 or a series of values such as 1 3 5 7 9 or 1 to 9 by 2.

Press the small 'σ' button to the right to obtain calculation options for estimating the standard deviation.

 **$r_T$  (Random Slope Variance/ $\sigma^2$ )**

Enter the ratio of the variance of subject-specific, random slopes to the sum of the other variances,  $\sigma^2$ .

Possible values range from 0 (for a fixed-slope model) to any positive value.

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

When a series of values is entered, PASS will generate a separate calculation result for each value of the series.

 **$\rho$  (Within Subject Correlation)**

This is the value of the within-subject correlation coefficient. It may be interpreted as the correlation between any two observations on the same subject.

Possible values are from 0 to just below 1. Typical values are between 0.0001 and 0.5.

You may enter a single value or a list of values.

## 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 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

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Mixed Models Tests for the Slope Difference in a 2-Level Hierarchical Design with Random Slopes** procedure window. You may then make the appropriate entries as listed below, or open **Example 1** by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
<b>Design Tab</b>	
Solve For .....	<b>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>

### Annotated Output

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

### Numeric Results

Numeric Results for a Two-Level, Longitudinal Model

	Total Subjects	Group 1 Subjects	Group 2 Subjects	Measure- ments /Subject	Mean Difference	Standard Deviation	V( $\beta_i$ ) / $\sigma^2$	Correlation Within a Subject	Alpha
Power	K	K1	K2	M	$\mu_1 - \mu_2$	$\sigma$	$r_T$	$\rho$	
0.2098	10	5	5	4	9.00	9.20	0.100	0.500	0.050
0.3709	20	10	10	4	9.00	9.20	0.100	0.500	0.050
0.5147	30	15	15	4	9.00	9.20	0.100	0.500	0.050
0.6353	40	20	20	4	9.00	9.20	0.100	0.500	0.050
0.7317	50	25	25	4	9.00	9.20	0.100	0.500	0.050
0.3362	10	5	5	4	12.00	9.20	0.100	0.500	0.050
0.5847	20	10	10	4	12.00	9.20	0.100	0.500	0.050

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0.7588	30	15	15	4	12.00	9.20	0.100	0.500	0.050
0.8674	40	20	20	4	12.00	9.20	0.100	0.500	0.050
0.9302	50	25	25	4	12.00	9.20	0.100	0.500	0.050
0.4847	10	5	5	4	15.00	9.20	0.100	0.500	0.050
0.7756	20	10	10	4	15.00	9.20	0.100	0.500	0.050
0.9144	30	15	15	4	15.00	9.20	0.100	0.500	0.050
0.9702	40	20	20	4	15.00	9.20	0.100	0.500	0.050
0.9903	50	25	25	4	15.00	9.20	0.100	0.500	0.050

References

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

Report Definitions

Power is the probability of rejecting a false null hypothesis. It should be close to one.

K is the total number of subjects.

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

M is the number of equally-spaced measurement times.

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

$\sigma$  is the standard deviation of the response.

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

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

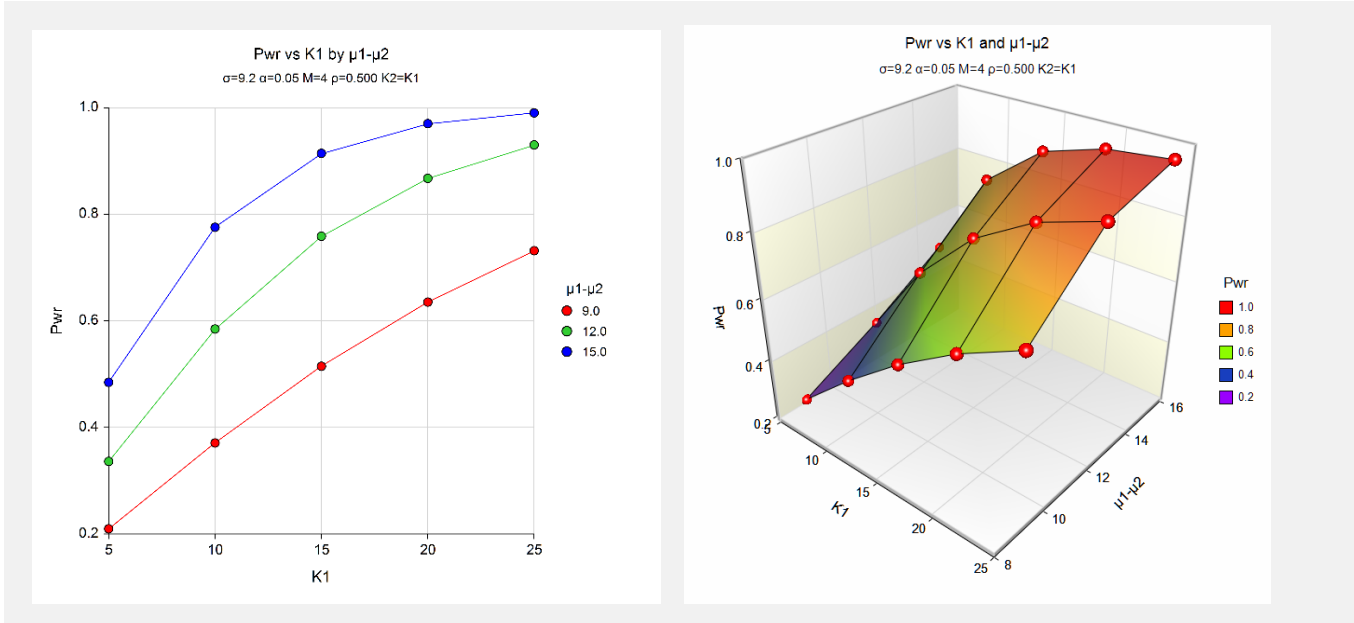
Alpha is the probability of rejecting a true null hypothesis, that is, rejecting when the slopes are actually equal.

Summary Statements

A total of 10 subjects, obtained as 5 in group one and 5 in group two, were each measured at 4 time points. The study achieves 21% power to detect a difference between the (fixed) group means at the last time of 9.00. The standard deviation is 9.20. The ratio of the subject-specific slope variance to  $\sigma^2$  is 0.100. The correlation between measurements within a subject is 0.500. The test based on a mixed-model regression analysis uses a significance level of 0.050.

This report shows the power for each of the scenarios.

Plots Section



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

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Mixed Models Tests for the Slope Difference in a 2-Level Hierarchical Design with Random Slopes** procedure window. You may then make the appropriate entries as listed below, or open **Example 2** by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
<b>Design Tab</b>	
Solve For .....	<b>K1 (Group 1 Subjects)</b>
Power.....	<b>0.90</b>
Alpha.....	<b>0.05</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>

### Output

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

### Numeric Results

	Total Subjects	Group 1 Subjects	Group 2 Subjects	Measurements /Subject	Mean Difference	Standard Deviation	V( $\beta_i$ ) / $\sigma^2$	Correlation Within a Subject	Alpha
Power	K	K1	K2	M	$\mu_1 - \mu_2$	$\sigma$	$r_T$	$\rho$	
0.8062	60	30	30	4	9.00	9.20	0.100	0.500	0.050
0.8091	34	17	17	4	12.00	9.20	0.100	0.500	0.050
0.8133	22	11	11	4	15.00	9.20	0.100	0.500	0.050

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

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Mixed Models Tests for the Slope Difference in a 2-Level Hierarchical Design with Random Slopes** procedure window. You may then make the appropriate entries as listed below, or open **Example 3** by going to the **File** menu and choosing **Open Example Template**.

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

### Output

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

### Numeric Results

Numeric Results for a Two-Level, Longitudinal Model										
	Total Subjects	Group 1 Subjects	Group 2 Subjects	Measure- ments /Subject	Difference in Slopes	Standard Deviation	V( $\beta_i$ ) / $\sigma^2$	Correlation Within a Subject		
Power	K	K1	K2	M	$\delta$	$\sigma$	$r_T$	$\rho$	Alpha	
0.8010	598	299	299	5	0.40	4.00	0.100	0.100	0.050	

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