

## Chapter 374

# Mixed Models Tests for the Slope Difference in a 3-Level Hierarchical Design with Fixed Slopes (Level-2 Randomization)

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### Introduction

This procedure calculates power and sample size for a three-level hierarchical mixed model which is randomized at the second level. The goal of the study is to compare the two group slopes. 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 the same as testing the difference in means at the end of the study. This is a test of the time-by-treatment interaction.

The study is assumed to be longitudinal in that the third level is some type of cluster (e.g., clinic or hospital), the second level is subjects nested within the third level, and the first level is a repeated measurement at equally-spaced time points on the subjects. Ahn, Heo, and Zhang (2015) call this a *longitudinal cluster randomized design*.

The data are analyzed by considering the average trend of responses over time. These trends can be considered as fixed (this procedure) or random (a companion procedure).

### Randomization

Different models are used depending on how subjects are assigned to the intervention (treatment) groups. This procedure assumes that each subject (level-2 unit) is individually randomized to an intervention group. This is called *level-2 randomization*. A companion procedure analyzes the case of level-3 randomization.

### Fixed or Random

The subject-specific slopes of responses across the repeated measurements can be assumed to be fixed or random. In this fixed case, all subjects are assumed to share a common fixed slope with no variation. In the random case, the slopes are assumed to have a normal distribution with a modelled variance.

## Technical Details

Our formulation comes from Ahn, Heo, and Zhang (2015), chapter 6, section 6.4.2, page 206-208. The hierarchical mixed model used for the analysis is

$$Y_{ijk} = \beta_0 + \xi X_{ijk} + \tau T_{ijk} + \delta X_{ijk} T_{ijk} + u_i + u_{j(i)} + e_{ijk}$$

where

- $Y_{ijk}$  is the continuous response of the  $k^{\text{th}}$  level-1 unit of the  $j^{\text{th}}$  level-2 unit of the  $i^{\text{th}}$  level-3 unit.
- $X_{ijk}$  is an indicator variable that is 1 if  $ijk^{\text{th}}$  unit is in group 1 and 0 if it is in group 2.
- $T_{ijk}$  is an integer that represents the time period. We assume that  $T_{ijk} = T_k$  and that these time values increase from 0 (baseline measurement) to  $M - 1$  (final measurement).
- $\beta_0$  is the overall fixed intercept.
- $\xi$  is the intervention effect at baseline.
- $\tau$  is the slope of the time effect.
- $\delta$  is the treatment effect of interest. It models the difference between the two group slopes.
- $u_i$  is the level-3 random intercept effect for the  $i^{\text{th}}$  level-3 unit. It is distributed as  $N(0, \sigma_3^2)$ .
- $u_{j(i)}$  is the level-2 random intercept effect for the  $j(i)^{\text{th}}$  level-2 unit. It is distributed as  $N(0, \sigma_2^2)$ .
- $e_{ijk}$  is a random error term which is distributed as  $N(0, \sigma_e^2)$ .
- $\sigma^2$  is the variance of  $Y_{ijk}$ , where  $\sigma^2 = \sigma_e^2 + \sigma_2^2 + \sigma_3^2$ .
- $\rho$  is the correlation among level-1 units which are in a particular level-2 unit. For fixed models like this,  $\rho = \text{Corr}(Y_{ijk}, Y_{ijk'}) = (\sigma_2^2 + \sigma_3^2)/\sigma^2$ .
- $C$  is the number of level-2 units (subjects) per level-3 unit.
- $K_1$  is the number of level-2 units (clusters) assigned to group 1.
- $K_2$  is the number of level-2 units assigned to group 2.
- $M$  is the number of level-1 units per level-2 unit, i.e., the number of repeated measurements.

The test of significance of the  $X_{ijk} T_{ijk}$  interaction term in the mixed model is the test statistic of interest. It tests the difference of the two slopes.

The power is calculated using

$$\text{Power} = \Phi \left\{ \left| \frac{\delta}{\sigma} \right| \sqrt{\frac{K_2 C M \text{Var}(T)}{\left[ f_3 \left( 1 + \frac{1}{\lambda} \right) \right]}} - \Phi(1 - \alpha/2) \right\}$$

where  $\lambda = K_1/K_2$ ,  $f_3 = 1 - \rho$ , and  $\text{Var}(T) = (M - 1)(M + 1)/12$ .

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## 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.

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### Design Tab

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

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#### 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*, *C*, and *K1*.

Under most situations, you will select either *Power* to calculate power or *K1* to calculate the number of level-2 units. Occasionally, you may want to fix *K1* and *K2* and calculate *C*.

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 only integer values of *C* or *K1*.

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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

### C (Level 3 Units)

This is the number of level 3 units in group 1 (treatment group). The sample size for this group is equal to  $\text{Ceiling}(C1 * K * M)$ .

Examples of level 3 units are clinics, hospitals, or practices.

A longitudinal study might include clinics as the level 3 units, patients as the level 2 units, and repeated measurements are the level 1 units.

This value must be a positive integer.

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

### K1 (Level 2 Units Assigned to Group 1)

Enter the average number of level 2 units per level 3 unit that are assigned to group 1 (treatment group). The sample size for this group is equal to  $\text{Ceiling}(C * K1 * M)$ .

Examples of level 2 units are subjects and patients. A *longitudinal* study might include clinics as the level 3 units, patients as the level 2 units, and repeated measurements are the level 1 units.

This value must be a positive number. Decimal values such as 4.5 can be entered.

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 (Level 2 Units Assigned to Group 2)

This is the number of level 2 units per level 3 in group 2 (control group). The sample size for this group is equal to  $\text{Ceiling}(C * K2 * M)$ .

Examples of level 2 units are classrooms or patients. A longitudinal study might include clinics as the level 3 units, patients as the level 2 units, and repeated measurements are the level 1 units.

This value must be a positive number. Decimal values such as 5.7 can be entered.

### Using Multiples of K1

If you simply want a multiple of the value for group 1 (K1), 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: K1, 2K1, 0.5K1, and 1.5K1.

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

### M (Level 1 Units Per Level 2 Unit)

This is the average number of level 1 units in each level 2 unit. Examples of level 1 units are repeated measurements.

A *longitudinal* study might include clinics as the level 3 units, patients as the level 2 units, and repeated measurements are the level 1 units.

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

You can use a list of values such as "5 10 15". A separate analysis will be run for each element in the list.

## 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 fixed for all subjects within a group.

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.

The difference has the same scale as the standard deviation.

### 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.

### $\delta$ (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 slope of the measurements across time of all subjects in a group is assumed to be the same fixed value. The power is the probability of detecting a difference of at least this amount between the two means (or 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.

**Mixed Models Tests for the Slope Diff. in a 3-Level Hier. Design with Fixed Slopes (Level-2 Rand.)** **$\sigma$  (Standard Deviation)**

Enter the standard deviation of an individual observation,  $Y_{ijk}$ . 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 ‘ $\sigma$ ’ button to the right to obtain calculation options for estimating the standard deviation.

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

This is the correlation of each pair of repeated measurements within a 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

Suppose that a three-level hierarchical design is planned in which repeated measurements (level-1) will be taken on subjects (level-2) within hospitals (level-3). This analysis will calculate the power for detecting the difference in slopes of two interventions. Randomization will be at the subject (level-2) units.

The following parameter settings are used for the power analysis:  $\mu_1 - \mu_2 = 1.5$ ;  $\sigma = 2.6$ ;  $\rho = 0.1$ ;  $K_1 = 4, 6$ ;  $M = 4$ ;  $\alpha = 0.05$ ; and  $C = 4, 6$ .

### 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 Diff. in a 3-Level Hier. Design with Fixed Slopes (Level-2 Rand.)** 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>
C (Level 3 Units).....	<b>4 6</b>
K1 (Level 2 Units Assigned to Group 1) .....	<b>5 10 15 20</b>
K2 (Level 2 Units Assigned to Group 2) .....	<b>K1</b>
M (Level 1 Units Per Level 2 Unit).....	<b>4</b>
Slope Input Type.....	<b><math>\mu_1 - \mu_2</math> (Mean Difference)</b>
$\mu_1 - \mu_2$ (Mean Difference).....	<b>1.5</b>
$\sigma$ (Standard Deviation) .....	<b>2.6</b>
$\rho$ (Within Subject Correlation).....	<b>0.1</b>

### Annotated Output

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

### Numeric Results

#### Numeric Results for a Three-Level Hierarchical Mixed Model

	Total	Level 3	Group 1	Group 2	Level 1	Mean	Std	Level 1	
	N	Units	Level 2	Level 2	Units	Diff	Dev	Corr	Alpha
Power		C	Units	Units	M	$\delta$	$\sigma$	$\rho$	
0.2992	160	4	5	5	4	1.50	2.60	0.100	0.050
0.5268	320	4	10	10	4	1.50	2.60	0.100	0.050
0.6994	480	4	15	15	4	1.50	2.60	0.100	0.050
0.8177	640	4	20	20	4	1.50	2.60	0.100	0.050
0.4190	240	6	5	5	4	1.50	2.60	0.100	0.050
0.6994	480	6	10	10	4	1.50	2.60	0.100	0.050
0.8601	720	6	15	15	4	1.50	2.60	0.100	0.050
0.9396	960	6	20	20	4	1.50	2.60	0.100	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.

Mixed Models Tests for the Slope Diff. in a 3-Level Hier. Design with Fixed Slopes (Level-2 Rand.)

Report Definitions

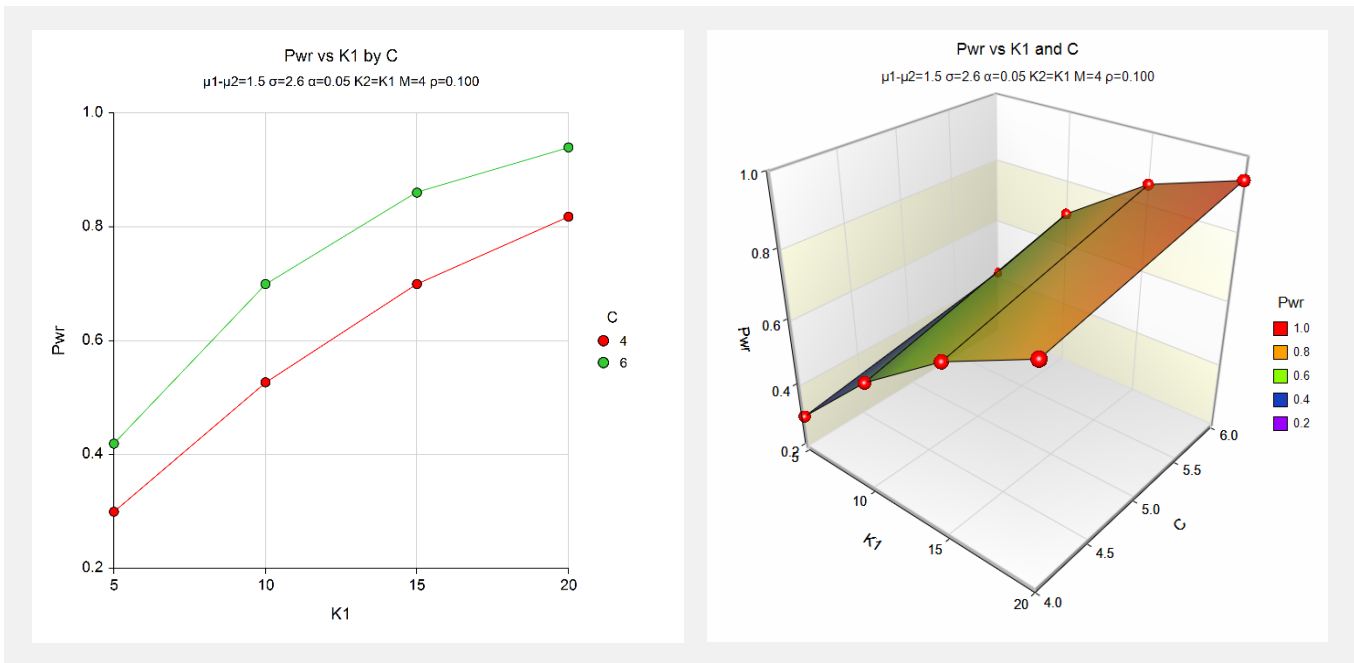
Power is the probability of rejecting a false null hypothesis. It should be close to one.  
 N is the total number of level-1 units.  
 C is the number of level-3 units.  
 K1, K2 are the average number of level-2 units per level-3 unit assigned to groups 1 and 2, respectively.  
 M is the number of level-1 units (repeated measurements) per level-2 unit (subject).  
 $\mu_1 - \mu_2$  is the difference in the two group means at the final measurement time:  $M - 1 \cdot \delta = (\mu_1 - \mu_2) / (M - 1)$ .  
 $\sigma$  is the standard deviation of the level-1 responses.  
 $\rho$  is the correlation among level-1 units in a particular level-2 unit.  
 Alpha is the probability of rejecting a true null hypothesis, that is, rejecting when the means are actually equal.

Summary Statements

The total sample size of 160, which were obtained from 4 level-3 units with 5 level-2 units in group one and 5 level-2 units in group two and 4 level-1 units (repeated measurements) per level-2 unit, achieves 30% power to detect a difference between the (fixed) group means at the last time of 1.50. The standard deviation of level-1 units is 2.60. The correlation of level-1 units within a level-2 unit is 0.100. A test based on a mixed-model analysis is anticipated at a significance level of 0.050.

This report shows the power for each of the scenarios.

Plots Section



These plots show the power versus the level-3 count for the three values of M.



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

Continuing with the last example, suppose the researchers want to determine the number of clusters needed to achieve 90% power for the values of M.

### 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 Diff. in a 3-Level Hier. Design with Fixed Slopes (Level-2 Rand.)** 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 (Number Level 2 Units Per Level 3 Unit)</b>
Power.....	<b>0.90</b>
Alpha.....	<b>0.05</b>
C (Level 3 Units) .....	<b>4 6</b>
K2 (Level 2 Units Assigned to Group 2) .....	<b>K1</b>
M (Level 1 Units Per Level 2 Unit).....	<b>4</b>
Slope Input Type.....	<b><math>\mu_1 - \mu_2</math> (Mean Difference)</b>
$\mu_1 - \mu_2$ (Mean Difference).....	<b>1.5</b>
$\sigma$ (Standard Deviation) .....	<b>2.6</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 Three-Level Hierarchical Mixed Model										
	Total	Level 3	Group 1	Group 2	Level 1	Mean	Std	Level 1		
Power	N	Units	Level 2	Level 2	Units	Diff	Dev	Corr	Alpha	
		C	Units	Units	Units	$\mu_1 - \mu_2$	$\sigma$	$\rho$		
			K1	K2	M					
0.9047	832	4	26	26	4	1.50	2.60	0.100	0.050	
0.9148	864	6	18	18	4	1.50	2.60	0.100	0.050	

This report shows the power for each of the scenarios.

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

Ahn, Heo, and Zhang (2015) page 204 provide a table in which several scenarios are reported. We will validate this procedure by the first row of the table. Actually, the table is for level-3 randomization. Following their instructions, we switch K and C to obtain results for level-2 randomization.

The following parameter settings were for the analysis: power = 0.80;  $\delta = 0.3$ ;  $\sigma = 4$ ;  $\rho = 0.1$ ;  $K1 = 8$ ;  $M = 5$ ; and  $\alpha = 0.05$ . These settings resulted in a value of C (their  $N_3^{(0)}$ ) of 32 and an attained power of 0.807.

### 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 Diff. in a 3-Level Hier. Design with Fixed Slopes (Level-2 Rand.)** 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>C (Number Level 3 Units)</b>
Power.....	<b>0.8</b>
Alpha.....	<b>0.05</b>
K1 (Level 2 Units Assigned to Group 1) .....	<b>8</b>
K2 (Level 2 Units Assigned to Group 2) .....	<b>K1</b>
M (Level 1 Units Per Level 2 Unit).....	<b>5</b>
Slope Input Type.....	<b><math>\delta</math> (Slope Difference)</b>
$\delta$ (Slope Difference).....	<b>0.3</b>
$\sigma$ (Standard Deviation) .....	<b>4</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 Hierarchical Mixed Model									
	Total	Level 3	Group 1	Group 2	Level 1	Slope	Std	Level 1	
Power	N	Units	Level 2	Level 2	Units	Diff	Dev	Corr	Alpha
0.8074	2560	C	Units	Units	M	$\delta$	$\sigma$	$\rho$	0.050
		32	K1	K2	5	0.30	4.00	0.100	
			8	8					

PASS calculates the same values of C and power: 32 and 0.807.