

Chapter 371

Mixed Models Tests for Two Means at the End of Follow-Up in a 3-Level Hierarchical Design (Level-3 Randomization)

Introduction

This procedure calculates power and sample size for a three-level hierarchical design which is randomized at the third level. Each subject (level-2 unit) is measured at several time points (level-1 units) and the goal of the study is to compare the group means of at the final time point, i.e., at the end of follow-up.

The study is assumed to be longitudinal, so repeated measurements (level-1 units) are nested in patients (level-2 units) which are nested in clinics (level-3 units).

Each clinic (level-3 unit) is randomized into one of two intervention groups, e.g., treatment and control.

Technical Details

Our formulation comes from Ahn, Heo, and Zhang (2015), chapter 6, section 6.4.4, pages 209-211. The longitudinal mixed model that is adopted is a re-parameterized version of fixed-slope model

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

in which the time variable is rescaled using $S_k = T_k - T_{end}$. Therefore, the S_k become $-T_{end}, \dots, 0$.

Let $\beta'_0 = \beta_0 + \tau T_{end}$ and $\delta_e = \xi + \delta_f T_{end}$. We assume that, because of randomization, $\xi = 0$. The mixed model then becomes

$$Y_{ijk} = \beta'_0 + \delta_e X_i + \tau S_k + \delta_f X_i S_k + u_i + u_{j(i)} + e_{ij}$$

where

- Y_{ijk} is the continuous response of the k^{th} level-1 unit of the j^{th} level-2 unit of the i^{th} level-3 unit.
- β_0 is the fixed intercept.
- δ_f is the treatment-by-time interaction effect. It can be ignored since S_k is zero at the final observation because of the re-parameterization.
- δ_e is the intervention effect at the end of the study. By construction, $\delta_e = \mu_1 - \mu_2$ at the final time point. This is the term that will be tested for significance.
- X_{ijk} is an indicator variable that is 1 if j^{th} unit is in group 1 and 0 if it is in group 2.
- S_k is the rescaled time value. It is assumed that $S_k = k - (M - 1)$ for all i and j .
- ξ is the intervention effect at baseline and is assumed to be zero.

Mixed Models Tests for Two Means at the End of Follow-Up in a 3-Level Hierarchical Design (Level-3 Randomization)

- u_i is the level-3 random intercept effect for the i^{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 i^{th} level-3 unit. It is distributed as $N(0, \sigma_2^2)$.
- e_{ijk} is a random error term which is distributed as $N(0, \sigma_e^2)$.
- σ^2 is the variance of Y_{ijk} , where $\sigma^2 = \sigma_e^2 + \sigma_2^2 + \sigma_3^2$.
- ρ_1 is the correlation among level-1 units which are in a particular level-2 unit. For fixed models like this, $\rho_1 = \text{Corr}(Y_{ijk}, Y_{ijk'}) = (\sigma_2^2 + \sigma_3^2)/\sigma^2$.
- ρ_2 is the correlation among level-2 units which are in a particular level-3 unit. For fixed models like this, $\rho_2 = \text{Corr}(Y_{ijk}, Y_{ij'k'}) = (\sigma_3^2)/\sigma^2$.
- C_1 is the number of level-3 units assigned to group 1.
- C_2 is the number of level-3 units assigned to group 2.
- K is the number of level-2 units per level-3 unit.
- M is the number of level-1 units per level-2 unit.
- $V(T)$ is $\sum_{j=1}^M (T_j - \bar{T})^2 / M$. Note that $V(S) = V(T)$ and $\bar{S} = -\bar{T}$.
- $CV(S)$ is $\sqrt{V(S)}/\bar{S}$.
- $C_{(3)}$ is $1 + \frac{(1-\rho_1)}{CV(S)^2 f_3}$.

The test of significance of the X_i term in the mixed model analysis is the test statistic of interest. It tests the difference of the two group means. Since these are asymptotic results, the specific type of mixed model is not stated.

Assume that $\delta_e = \mu_1 - \mu_2$ is to be tested using a z-test (large sample). The statistical hypotheses are $H_0: \delta_e = 0$ vs. $H_a: \delta_e \neq 0$. The test statistic is the regression coefficient of the X_i term in a mixed model.

The power can be calculated using

$$\text{Power} = \Phi \left\{ \left| \frac{\delta_e}{\sigma} \right| \sqrt{\frac{C_2 KM}{[f_3 (1 + \frac{1}{\lambda}) C_{(3)}]}} - \Phi^{-1}(1 - \alpha/2) \right\}$$

where $\lambda = C_1/C_2$ and $f_3 = 1 + M(K - 1)\rho_2 + (M - 1)\rho_1$.

Example 1 – Calculating Power

Suppose that a longitudinal trial is planned in which there will be repeated measurements (level-1) which are nested in patients (level-2) which are nested in clinics (level-3). This analysis will calculate the power for detecting the difference between two interventions in heart rate. The researchers want to compare the end of follow-up heart rate of subjects who take a new drug to that of 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 of 10 in the final measurement heart rate means between the two treatments. They want a sensitivity analysis by considering a range of differences from 9 to 11.

The analysis will be a mixed model of continuous data. The following parameter settings are to be used for the power analysis: $\mu_1 - \mu_2 = 9, 10, 11$; $\sigma = 9.2$; $\rho_1 = 0.1$; $\rho_2 = 0.05$; $K = 5$; $M = 5$; $\alpha = 0.05$; and $C_1 = C_2 = 2$ to 6 by 2 .

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	Power
Alpha.....	0.05
C1 (Level 3 Units Assigned to Group 1).....	2 4 6
C2 (Level 3 Units Assigned to Group 2).....	C1
K (Level 2 Units Per Level 3 Unit).....	5
M (Level 1 Units Per Level 2 Unit)	5
$\mu_1 - \mu_2$ (Mean Difference).....	9 10 11
σ (Standard Deviation).....	9.2
ρ_1 (Correlation Among Level 1 Units).....	0.1
ρ_2 (Correlation Among Level 2 Units).....	0.05

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	Total Sample Size N	Number of Level 3 Units			Number of Level 2 Units per Level 3 Unit K	Number of Level 1 Units per Level 2 Unit M	Mean Difference $\mu_1 - \mu_2$	Standard Deviation σ	Correlation		Alpha
		Group 1 C1	Group 2 C2	Total C					Level 1 Units ρ_1	Level 2 Units ρ_2	
0.6652	100	2	2	4	5	5	9	9.2	0.1	0.05	0.05
0.9215	200	4	4	8	5	5	9	9.2	0.1	0.05	0.05
0.9851	300	6	6	12	5	5	9	9.2	0.1	0.05	0.05
0.7555	100	2	2	4	5	5	10	9.2	0.1	0.05	0.05
0.9633	200	4	4	8	5	5	10	9.2	0.1	0.05	0.05
0.9958	300	6	6	12	5	5	10	9.2	0.1	0.05	0.05
0.8307	100	2	2	4	5	5	11	9.2	0.1	0.05	0.05
0.9848	200	4	4	8	5	5	11	9.2	0.1	0.05	0.05
0.9990	300	6	6	12	5	5	11	9.2	0.1	0.05	0.05

- Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
- N The total number of Level-1 units.
- C1, C2, and C The number of Level-3 units assigned to groups 1, 2, and both, respectively.
- K The average number of Level-2 units per Level-3 unit.
- M The average number of Level-1 units per Level-2 unit.
- $\mu_1 - \mu_2$ The difference in the two group means at the final measurement time: $M - 1$.
- σ The standard deviation of the Level-1 responses.
- ρ_1 The correlation among Level-1 units in a particular Level-2 unit.
- ρ_2 The correlation among Level-2 units in a particular Level-3 unit.
- Alpha The probability of rejecting a true null hypothesis.

Summary Statements

A 2-group 3-level hierarchical design will have subjects (level-2 units) in clusters (level-3 units, e.g., classes, clinics, or hospitals), with random assignment of clusters to each of the 2 groups (level-3 randomization), and with repeated measurements (level-1 units) on each subject (over time). This design will be used to test 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 fixed slopes, with a Type I error rate (α) of 0.05. The standard deviation of Y_{ijk} , assuming a fixed-slope model, is assumed to be 9.2 (this standard deviation is the square-root of the variance of Y_{ijk} , where the variance of Y_{ijk} is the sum of the error term variance, the level-2 random intercept variance, and the level-3 random intercept variance). The correlation of level-1 units within a level-2 unit (repeated measurements on a subject) is assumed to be 0.1, and the correlation of level-2 units within a level-3 unit (subjects within clusters) is assumed to be 0.05. To detect a mean difference at the final time point ($\mu_1 - \mu_2$) of 9, with 2 level-3 units (clusters) in Group 1 and 2 level-3 units (clusters) in Group 2, with 5 level-2 units (subjects) in each level-3 unit, and with 5 level-1 units (repeated measurements) obtained from each level-2 unit (for a grand total of 100 level-1 measurements), the power is 0.6652.

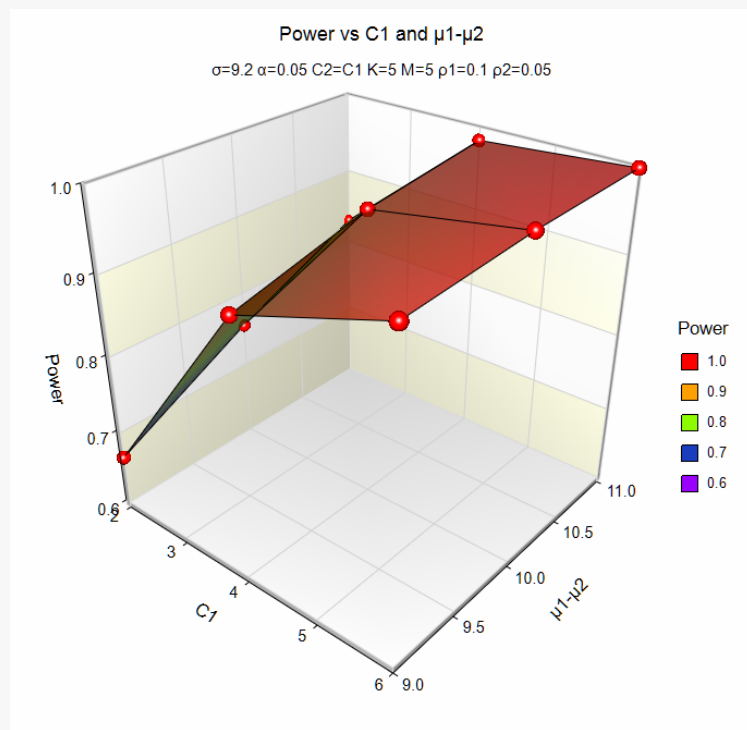
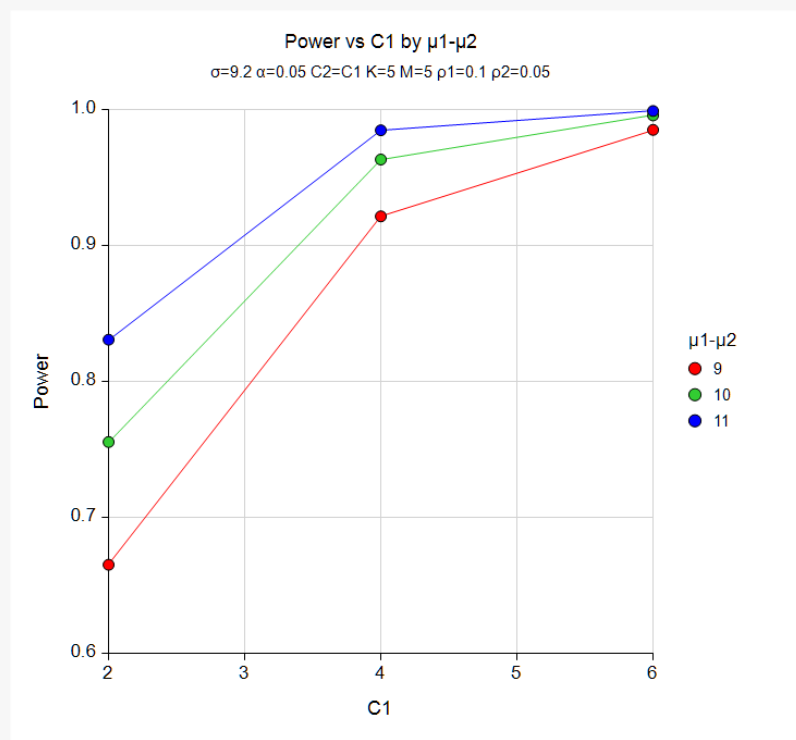
References

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.

Plots Section

Plots



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

Example 2 – Calculating Sample Size (Number of Clinics)

Continuing with the last example, suppose the researchers want to determine the number of clinics (level-3 units) needed to achieve 90% power for the values of the mean difference.

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	C1 (Number Level 3 Units)
Power.....	0.90
Alpha.....	0.05
C2 (Level 3 Units Assigned to Group 2).....	C1
K (Level 2 Units Per Level 3 Unit).....	5
M (Level 1 Units Per Level 2 Unit)	5
$\mu_1 - \mu_2$ (Mean Difference).....	9 10 11
σ (Standard Deviation).....	9.2
ρ_1 (Correlation Among Level 1 Units).....	0.1
ρ_2 (Correlation Among Level 2 Units).....	0.05

Output

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

Numeric Results												
Solve For: C1 (Number Level 3 Units)												
Groups: 1 = Treatment, 2 = Control												
Power	Total Sample Size N	Number of Level 3 Units			Number of Level 2 Units per Level 3 Unit K	Number of Level 1 Units per Level 2 Unit M	Mean Difference $\mu_1 - \mu_2$	Standard Deviation σ	Correlation			Alpha
		Group 1 C1	Group 2 C2	Total C					Level 1 Units ρ_1	Level 2 Units ρ_2		
0.9215	200	4	4	8	5	5	9	9.2	0.1	0.05	0.05	
0.9011	150	3	3	6	5	5	10	9.2	0.1	0.05	0.05	
0.9466	150	3	3	6	5	5	11	9.2	0.1	0.05	0.05	

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 211 provide a table in which several scenarios are reported. We will validate this procedure by the first row of the table. The following parameter settings were for the analysis: power = 0.80; $\mu_1 - \mu_2 = 0.3$; $\sigma = 1$; $\rho_1 = 0.1$; $\rho_2 = 0.05$; $K = 4$; $M = 5$; and $\alpha = 0.05$. These settings resulted in a value of C1 and C2 (their $N_3^{(0)}$) of 35 and an attained power of 0.806.

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 **C1 (Number Level 3 Units)**
 Power..... **0.80**
 Alpha..... **0.05**
 C2 (Level 3 Units Assigned to Group 2)..... **C1**
 K (Level 2 Units Per Level 3 Unit)..... **4**
 M (Level 1 Units Per Level 2 Unit) **5**
 $\mu_1 - \mu_2$ (Mean Difference)..... **0.3**
 σ (Standard Deviation)..... **1**
 ρ_1 (Correlation Among Level 1 Units)..... **0.1**
 ρ_2 (Correlation Among Level 2 Units)..... **0.05**

Output

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

Numeric Results

Solve For: **C1 (Number Level 3 Units)**
 Groups: 1 = Treatment, 2 = Control

Power	Total Sample Size N	Number of Level 3 Units			Number of Level 2 Units per Level 3 Unit K	Number of Level 1 Units per Level 2 Unit M	Mean Difference $\mu_1 - \mu_2$	Standard Deviation σ	Correlation		Alpha
		Group 1 C1	Group 2 C2	Total C					Level 1 Units ρ_1	Level 2 Units ρ_2	
0.8062	1400	35	35	70	4	5	0.3	1	0.1	0.05	0.05

PASS calculates the same values of C1 and power: 35 and 0.806.