Chapter 372

Mixed Models Tests for Two Means at the End of Follow-Up in a 2-Level Hierarchical Design

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 group means at the final time point. This procedure assumes that the group means are identical at the beginning of the study (which they often are in a randomized trial).

All subjects in a group are assumed to have a common (fixed) slope. Each subject is assigned to receive one of two possible interventions.

Technical Details

Our formulation comes from Ahn, Heo, and Zhang (2015), chapter 5, section 5.4.4, pages 165-167. The longitudinal mixed model that is adopted is a re-parameterized version of fixed-slope model

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

in which the time variable is rescaled using $S_{ij} = T_{ij} - T_{end}$. Therefore, the S_{ij} become $-T_{end}, \ldots, 0$.

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

$$Y_{ij} = \beta_0' + \delta_e X_{ij} + \tau S_{ij} + \delta_f X_{ij} S_{ij} + u_i + e_{ij}$$

where

Y_{ij}	is the continuous response of the *j*th measurement in the *i*th subject.
β_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*.
S_{ij}	is the rescaled time value. It is assumed that $S_{ij} = j - (M - 1)$ for all *i* and *j*.
ξ	is the intervention effect at baseline and is assumed to be zero.
δ_f	is the treatment-by-time interaction effect.

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.

u_i is a random effect (subject-specific intercept) term for the *i*th subject that is distributed as $N(0, \sigma_u^2)$.

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

σ_u^2 is variance of the subject random effects.

σ_e^2 is variance of the measurement random effects.

σ^2 is the variance of *Y*.

ρ 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.

λ is K_1/K_2.

M is the number of measurements per subject.

$V(T)$ is $\sum_{j=1}^{M}\left(T_j - \bar{T}\right)^2/M$. Note that $V(T) = V(S)$ and $\bar{S} = -\bar{T}$.

$CV(S)$ is $\sqrt{V(S)}/\bar{S}$.

$C_{(2)}$ is $1 + \frac{(1-\rho)}{CV(S)^2 f}$.

The test of significance of δ_e in the mixed model analysis is the test statistic of interest. It tests the difference of the two means at the final time point. The power calculations assume that the estimated value of δ, called $\hat{\delta}$, has an approximate normal distribution with mean δ and known variance.

The power is calculated using

$$Power = \Phi\left\{\frac{|\delta_e|}{\sigma}\sqrt{\frac{K_2 M}{(1+\lambda^{-1})C_{(2)} f}} - \Phi^{-1}(1-\alpha/2)\right\}$$

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 compare the end of follow-up heart rate of 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 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.

Similar studies have found a standard deviation of 9.2. These studies also showed a correlation among measurements on the same individual of 0.5. The two-sided test 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* =10 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 .... **Power**
Alpha.. **0.05**
K1 (Group 1 Subjects) **10 15 20 25**
K2 (Group 2 Subjects) **K1**
M (Measurements Per Subject) **4**
μ1 - μ2 (Mean Difference).............................. **9 10 11**
σ (Standard Deviation).................................. **9.2**
ρ (Within Subject Correlation)........................ **0.5**

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

	Number of Subjects							
Power	Group 1 K1	Group 2 K2	Total K	Measurements per Subject M	Mean Difference μ1 - μ2	Standard Deviation σ	Within-Subject Correlation ρ	Alpha
0.6601	10	10	20	4	9	9.2	0.5	0.05
0.8279	15	15	30	4	9	9.2	0.5	0.05
0.9186	20	20	40	4	9	9.2	0.5	0.05
0.9634	25	25	50	4	9	9.2	0.5	0.05
0.7506	10	10	20	4	10	9.2	0.5	0.05
0.8977	15	15	30	4	10	9.2	0.5	0.05
0.9615	20	20	40	4	10	9.2	0.5	0.05
0.9864	25	25	50	4	10	9.2	0.5	0.05
0.8264	10	10	20	4	11	9.2	0.5	0.05
0.9443	15	15	30	4	11	9.2	0.5	0.05
0.9839	20	20	40	4	11	9.2	0.5	0.05
0.9957	25	25	50	4	11	9.2	0.5	0.05

Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
K1 and K2 The number of subjects in groups 1 and 2, respectively.
K The total number of subjects.
M The number of equally spaced measurement times.
μ1 - μ2 The difference in the two group means at the final measurement time: M - 1.
σ The standard deviation of the response.
ρ 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 subjects (level-2 units) randomly assigned to each of the 2 groups (level-2 randomization), 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 (μ1 - μ2) 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 Yij, assuming a fixed-slope model, is assumed to be 9.2 (this standard deviation is the square-root of the variance of Yij, where the variance of Yij is the sum of the error term variance and the level-2 random intercept variance). The correlation of level-1 units within a level-2 unit (repeated measurements on a subject) is assumed to be 0.5. To detect a mean difference at the final time point (μ1 - μ2) of 9, with 10 level-2 units (subjects) in Group 1 and 10 level-2 units (subjects) in Group 2, and with 4 level-1 units (repeated measurements) obtained from each level-2 unit, the power is 0.6601.

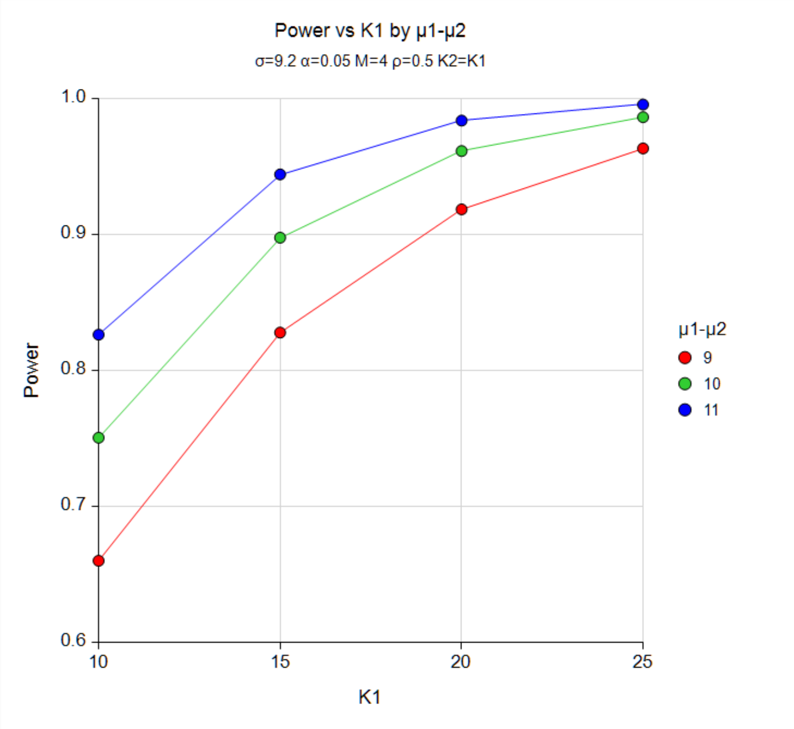
References

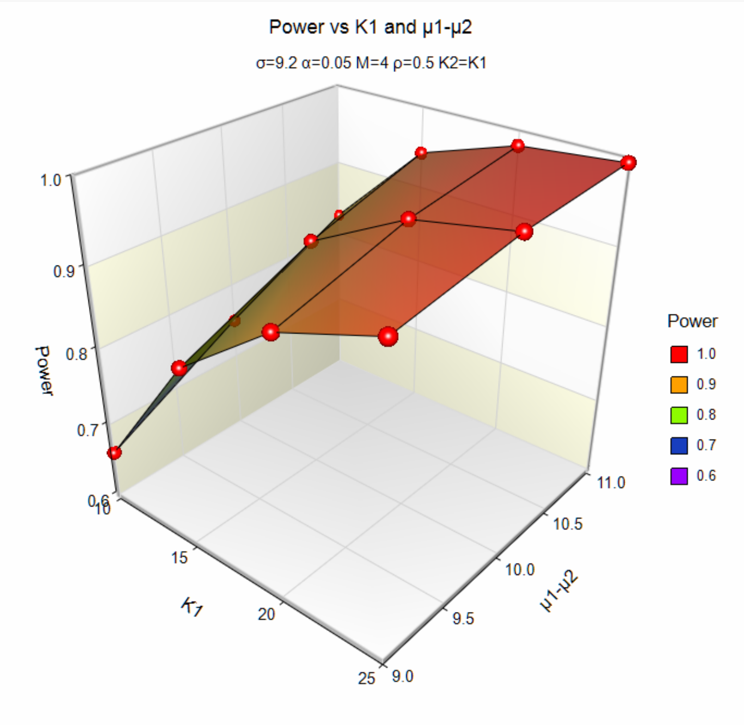
Ahn, C., Heo, M., and Zhang, S. 2015. Sample Size Calculations for Clustered and Longitudinal Outcomes in Clinical Research. CRC Press. New York.

This report shows the power for each of the scenarios.

Plots Section

Plots





These plots show the power versus K1 for the various 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**
μ1 - μ2 (Mean Difference)............................. **9 10 11**
σ (Standard Deviation).................................. **9.2**
ρ (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

	Number of Subjects							
Power	Group 1 K1	Group 2 K2	Total K	Measurements per Subject M	Mean Difference μ1 - μ2	Standard Deviation σ	Within-Subject Correlation ρ	Alpha
0.9050	19	19	38	4	9	9.2	0.5	0.05
0.9154	16	16	32	4	10	9.2	0.5	0.05
0.9109	13	13	26	4	11	9.2	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 167 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; $\mu 1 - \mu 2 = 0.4$; $\sigma = 1$; $\rho = 0.1$; $M = 5$; and $\alpha = 0.05$. The reported value of $K1$ is 63. 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... **0.80**
Alpha.. **0.05**
K2 (Group 2 Subjects) **K1**
M (Measurements Per Subject) **5**
μ1 - μ2 (Mean Difference)............................. **0.4**
σ (Standard Deviation).................................. **1**
ρ (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

	Number of Subjects							
Power	Group 1 K1	Group 2 K2	Total K	Measurements per Subject M	Mean Difference μ1 - μ2	Standard Deviation σ	Within-Subject Correlation ρ	Alpha
0.8013	63	63	126	5	0.4	1	0.1	0.05

PASS also calculates the value of K1 to be 63. The calculated power is also 0.801.