

A Simulation Study for Power Analysis in a Longitudinal Study Using SAS®

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ABSTRACT

Background: In many longitudinal studies, a subject's measurement is not available for each time period. To study the incomplete data across time and the influence of subjects on their repeated observations, mixed-effect regression models (MRMs) can be used. The purpose of this research is to study the power characteristics of the likelihood ratio test for hierarchical correlated data using MRMs.

Methods: We conducted simulation study based upon 10,000 replicates of data. We fitted a random intercept model employing a longitudinal design. We studied the effect of varying sample size and the number of measurements (time points) on power. Data was generated assuming a mixed random model with normally distributed error with mean of 0 and a pre-specified variance. We assumed a 20% drop out rate.

Results: Fixing factors constant (other than the parameter of interest) in the scenarios above, we observed that the power increases: (1) as the variance decreases, (2) as the sample size increases, and (3) as the number of time points increases. SAS software can be used to explore a wide variety of power characteristics in mixed effect models.

BACKGROUND

Frequently, research involves studying a sample from the target population over a period of time and assessing the subjects at different time points. In such cases, research outcomes associated with various time points may be considered¹. Longitudinal analysis can be used for tracking changes occurring within a subject and making population inferences².

Sample size calculations for clinical trials are typically calculated using a primary endpoint. It is important for an investigator to estimate the minimum subjects required to maintain the statistical power and obtain a significant conclusion. The more subjects enrolled, the higher the expenses will be for a study. Therefore, using appropriate sample size can reduce the costs of the study and conserve resources. In a longitudinal study, fewer subjects can be recruited to achieve a similar level of statistical power compared to a cross-sectional study³.

When designing a longitudinal clinical trial, there are several fundamental questions that must be answered, such as (a) what is the minimum number of subjects given different situations such as number of visits or different variances?, and (b) how should the sample size be adjusted if dropouts are expected?^{4,5} In this paper, we will provide examples to answer the two questions asked above and study the power characteristics of the likelihood ratio test for hierarchical correlated data using SAS®.

METHODS

MODELING

In a longitudinal study, information is collected for each subject across time. Since the repeated measurements are nested within an individual, the data are correlated. This violates the usual independence assumption. Moreover, it is unlikely that every subject's information can be obtained at each time point.

To study the incomplete data across time and the influence of subjects on their repeated measurements as a random effect, mixed-effect regression models (MRMs) can be used. The likelihood ratio test is then performed to test the hypothesis associated with MRM models.

The random-intercept MRM model is

$$y_{ij} = \beta_0 + \beta_1 T_{ij} + v_{0i} + E_{ij}$$

where y_{ij} = outcome at the j^{th} time point for the i^{th} subject

β_0 = intercept

β_1 = trend; linear change across time

T_{ij} = time points

v_{0i} = random effect for the i^{th} subject

E_{ij} = error term $E_{ij} \sim N(0, \sigma^2)$

In this study, we used parameter estimates from Hedeker and Gibbons³ and set the coefficients of intercept and time as 23.55 and -0.38 respectively. In the following sections, we demonstrate a step-by-step procedure in utilizing SAS® for generating sample sizes for a longitudinal study.

MODEL ILLUSTRATION

The main goal is to study the effect of the time point on the response process over time. We assumed that fifty subjects were enrolled. The data were randomly generated based on a mean of 23.55, five fixed time points with the error and intercept variance with mean zero and variance 19.04 and 16.15 respectively.

The main interest was in testing

$$H_0: \beta_1 = 0 \quad H_1: \beta_1 \neq 0$$

To obtain the type 1 error rate we created data by setting the coefficient of time as zero

```
SCORE=(23.55+(SQRT(16.15)*NORMAL(RANDOMSEED)))+0*TIMEPT+ SQRT(19.04)*NORMAL(RANDOMSEED);
```

To observe how the error and intercept variances impact power, we used three scenarios:

Scenario 1	Scenario 2	Scenario 3
Error Variance=19.04	Error Variance=12.22	Error Variance=10.52
Intercept Variance=16.15	Intercept Variance=12.63	Intercept Variance=10.11

In SAS®, the data were generated by the following steps:

```
SCORE1= (23.55+SQRT(16.15)*NORMAL(RANDOMSEED))-.38*TIMEPT+(SQRT(19.04)*NORMAL(RANDOMSEED));
SCORE2= (23.55+SQRT(12.63)*NORMAL(RANDOMSEED))-.38*TIMEPT+(SQRT(12.22)*NORMAL(RANDOMSEED));
SCORE3= (23.55+SQRT(10.11)*NORMAL(RANDOMSEED))-.38*TIMEPT+(SQRT(10.52)*NORMAL(RANDOMSEED));
```

To get the type I error rates and powers for testing the parameter of interest, we used the mixed linear model procedure (PROC MIXED) with random intercept.

```
PROC MIXED DATA=DS METHOD=REML COVTEST;
  CLASS SUBJID;
  MODEL SCORE=TIMEPT/SOLUTION;
  RANDOM INTERCEPT/ SUB=SUBJID TYPE=UN G;
RUN;
```

To simulate dropouts, we assume a 20% early termination rate in this study. We used simple random selection procedure (PROC SURVEYSELECT), and dropped 4% at each time point of our sample size before performing the power calculation.

```
PROC SURVEYSELECT DATA=DS METHOD=SRS N=8 SEED=0 OUT=DS; RUN;
```

The mixed model was run 10,000 times to approximate the statistical power. We also repeated the same procedure to study the effects when using a different number of time points (3, 4, and 5) on the power with fixed errors and intercept variances of 19.04 and 16.15 respectively. We tested the above conditions on sample sizes of 50, 100 and 200 for each combination.

RESULTS

The result from the analyses (Table 1) using different variances and sample sizes showed that power increased as the error variances decreased and sample size increased. For small variance, a similar percentage of power was achieved with a much smaller sample size when compared to higher variances. We achieved minimum 80% power with a sample of size 200 for all the variance values under consideration.

Table1: Error and intercept effect on Power

Sample Size	Error Variance=19.04	Error Variance=12.22	Error Variance=10.52
	Intercept Variance=16.15	Intercept Variance=12.63	Intercept Variance=10.11
50	23.89%	34.20%	39.59%
75	35.24%	46.16%	53.48%
100	43.87%	57.55%	63.03%
200	82.08%	85.49%	92.34%
225	84.40%	90.80%	93.90%

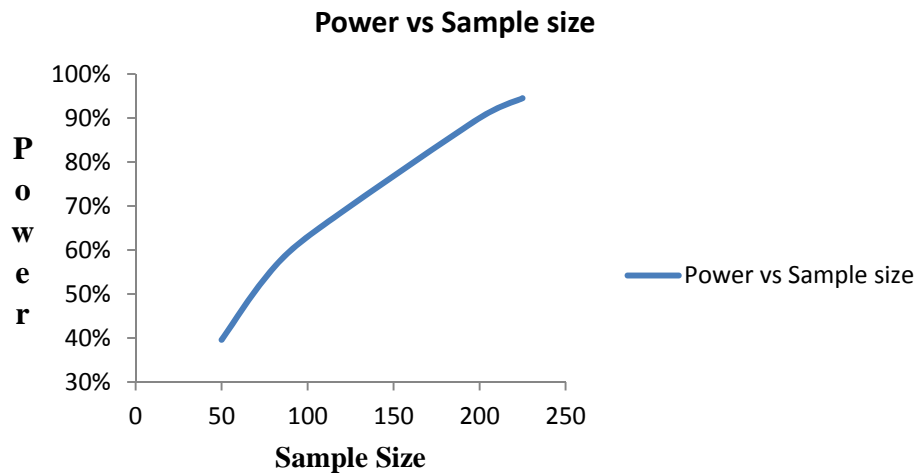
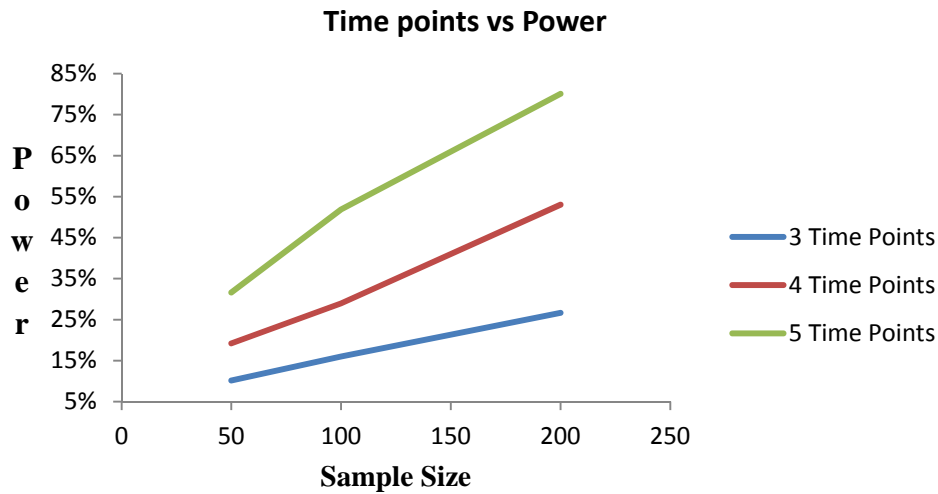


Table 2 shows that the power increased as the number of time points increased. Many more subjects were needed for a study with fewer time points.

Table 2: Effect of number of measurements (time points) on Power

Sample Size	3 Time Points	4 Time Points	5 Time Points
50	10.16%	19.20%	31.63%
100	16.03%	28.95%	51.88%
200	26.65%	53.06%	80.11%



CONCLUSION AND DISCUSSION

Longitudinal studies in general are more costly and require more time and resources. Studies involving large number of human subjects may unnecessarily expose subjects to potentially harmful effects. However, use of too few subjects in a study may result in an under-powered study.

Simulation studies can be helpful for calculating sample size and power in a study when a software is not available to compute. These studies may include non-linear mixed effects model, repeated observations over time, or missing observations. Compared to other softwares, the SAS® software is more flexible in calculating the sample sizes and powers for models involving hierarchically correlated data. Furthermore, one can also explore a wide variety of power characteristics in the mixed effect models using the SAS® software.

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