Example: Estimating the sample size needed in a trial for chronic pulmonary diseases

- Chronic pulmonary diseases (such as Chronic Obstructive Pulmonary Disease – COPD) concern the development of emphysema. It is a slow progression over many years and the assessment of drug efficacy requires the observation of ***large numbers of patients for a long period of time***.
- Recently, lung densitometry (measuring the lung density through CT scan) considered for assessing the lung tissue loss over time in patients with emphysema.
- A clinical trial with lung densitometry as an endpoint is typically designed as a **longitudinal study with repeated measurements at fixed time intervals**.
- Since lung density measurements are closely correlated with lung volume (inspiration level), it is important to include lung volume measurements in statistical analyses as a longitudinal covariate. Lung volume is normally measured at the same time as the lung density is measured.

- The clinical efficacy can be assessed by comparing the progression of lung density loss between two treatment groups using a random coefficient model – a longitudinal linear mixed model with a random intercept and slope.
- *In planning the clinical trial with such complex statistical analyses, the calculation of the sample size required to achieve a given power to detect a specified treatment difference is a complex issue.*
- In this example, an empirical approach is used to calculate the sample size by simulating trajectories of lung density and lung volume using SAS. We present step-by-step details for sample size calculation through simulation, and discuss the pros and cons of this approach.

$$Y_{ij} = (\beta_0 + b_0) + \beta_1 * TRT + (\beta_2 + b_2) * TIME + \beta_3 * COV_{ij} + \beta_4 * TRT * TIME + \varepsilon_{ij} \quad (1)$$

- Here Y_{ij} is the efficacy endpoint (i.e. lung density) measurement for subject *i = 1, 2,…, n, at fixed time point j = 1, 2, …, K.*
- *TRT is an indicator of subject i's treatment group (i.e. TRT=1 for active drug; TRT=0 for placebo).*
- *COV_{ij} is a longitudinal covariate (i.e. logarithm of lung volume) for subject i = 1, 2,…, n, at fixed time point j = 1, 2, …, K.*
- *Here b_0 and b_2 are subject-specific random effects for the intercept and slope, respectively, which are from a normal distribution with mean 0 and variance σ_0^2 and σ_0^2, respectively.*
- *ε_{ij} is the random error from a normal distribution with mean 0 and variance σ^2 .*
- *The regression parameters β_0, β_1, β_2, β_3, and β_4 are the fixed effects for intercept, treatment, time, covariate and interaction of treatment and time respectively.*
- Here we assume that the benefits can be assessed quantitatively by comparing the slopes of lung density trajectories for the two treatment groups. This quantity is captured by β_4.

Sample Size Estimation Using Simulations

- In the model, β_4 is typically of interest. There is no direct mathematical formula to calculate the sample size for a given statistical power (i.e. 80%) to test the null hypothesis: $\beta_4=0$ with a specified type I error (i.e. $\alpha=0.05$).
- One approach to calculate the sample size for a given power is through the simulation.

Simulating the response

- Assume we know the parameters (β_0, β_1, β_2, β_3, *and* β_4 , and σ_0^2 *and* σ_0^2) from either history data, previous clinical trials or meaningful clinical differences we want to test, the study design in terms of number of time points (*K) and fixed time intervals (TIME), and the longitudinal covariate* COV_{ij}.
- *For a fixed equal sample size* n *for each treatment, the trajectories of efficacy measurement* Y_{ij} *(i.e. lung density) for the* n *subjects can be simulated through the model for each treatment group.*
- *Then, perform a statistical test on* $\beta_4 = 0$ *by using the SAS Proc MIXED on the simulated data set, and record whether the p-value < 0.05.*

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- In order to simulate the trajectories of Y_{ij}, it is necessary to simulate the trajectories of longitudinal covariate COV_{ij}. Assume COV_{ij} is from a linear model regressing against time with a random intercept

$$\mathrm{COV}_{ij} = (\gamma_0 + r_0) + \gamma_1 \mathrm{TIME} + \varepsilon_{ij} \qquad (2)$$

- Where γ_0 and γ_1 are the fixed intercept and slope respectively; r_0 and ε_{ij} are from a normal distribution with mean 0 and variance δ_1^2 and δ_2^2, respectively. If we know the parameters (γ_0, γ_1 , δ_1^2 and δ_2^2) from history data or previous clinical trials for the study population, it will be simple to simulate the trajectories of the longitudinal covariate COV_{ij} by using SAS random generating functions.

- A sample size can be determined for the models above through the following steps:

1. **Obtain the pre-specified parameters** through either history data, previous clinical trials or meaningful clinical difference to be tested from clinicians
2. **Specify a desired statistical power** (i.e. 80%) **and** a **type-1 error rate** (i.e. 5%)
3. **Simulate trajectories of efficacy measurement** (i.e. lung density) **and longitudinal covariate** (i.e. logarithm of lung volume) for a fixed sample size (*n) of subjects within each treatment arm*
    - A. Trajectories of longitudinal covariate (i.e. logarithm of lung volume) are simulated through model (2)
    - B. Trajectories of efficacy measurement (i.e. lung density) are simulated through model (1)

4. **Perform the statistical test** on $\beta_4=0$ *using the SAS Proc MIXED* based on the simulated data set. Record whether a p-value < 0.05 was obtained
5. **Repeat** steps 3 and 4 M (i.e. M=1000) **times and calculate the statistical power** for the fixed sample size
6. Repeat steps 3 - 5 for various values of *n. Stop when desired statistical power is obtained*

- The sample code to perform the test is as follow:

```
proc mixed data = data;
class id trt;
model y = trt time trt*time cov / solution;
random intercept time/ subject = id type = un;
run;
```

- For the fixed sample size *n per treatment group, simulate M (i.e. M=1000) times and the proportion of significant tests of* $\beta_4 = 0$ *among the total M simulations is the statistical power for the sample size n per treatment group. Then, adjust the sample size n to achieve desirable statistical power.*

Example of a Simulation

- Assume there are two treatment groups (active vs. placebo) in a study design. The efficacy endpoint along with the longitudinal covariate will be measured at *K=4 time points at baseline, 1 year, 2 years and 3 years.*
- All corresponding parameters specified in model (1) and (2) could be obtained either through historical data, previous clinical trials or meaningful clinical difference to be tested from clinicians. For purpose of simulation, they are randomly selected and specified as below:

$$\beta_0 = 150, \beta_1 = 5, \beta_2 = -1.8, \beta_3 = -57, \beta_4 = 0.7, \text{ and } \sigma_0^2 = 280, \sigma_2^2 = 0.4, \sigma^2 = 5;$$

$$\gamma_0 = 2, \gamma_1 = 0.0007, \delta_0^2 = 0.05, \delta_1^2 = 0.0016.$$

- The summary of statistical power for a given sample size per treatment based on M = 1000 simulated data sets is listed below:

N per treatment	Statistical Power (%)
30	62.4
40	76.9
45	**79.9**
50	84.4
60	91.3

- Therefore, a sample size 45 per treatment arm has an estimated statistical 80% power to detect the treatment slope difference of 0.7 in a random coefficient model for the study design above.

Conclusions and Discussion

- As described above, it is possible to perform sample size calculations for a random coefficient model using simulation techniques and SAS.
- It is also straightforward to **extend** the simulation frame to other linear mixed models (LMM) or generalized linear mixed models (**GLMM**).
- Other extensions: **multiple treatment groups** (i.e. treatment groups greater than 2), **unequal sample size** among treatment groups (i.e. 2:1 for active vs. placebo) etc.
- For an **active-controlled** trial, it is usually of interest to test **non-inferiority** of test drug compared to active-control.

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