Model Qualification in Industrial Applications
Case Study 4

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QTc Evaluation

- Background
  - Drug is in development for treatment of depression
    - Expected dose is 20 mg QD
  - Other compounds in the class have exhibited QTc prolongation
    - Effect appeared to be greater in women in other compounds
- Data
  - Single ascending dose study
    - Doses from 0.5 to 60 mg QD evaluated
      - 0.5, 1, 5, 10, 20, 40, and 60 mg
    - 6 subjects/dose group
      - 4 active and 2 placebo
    - 28 subjects with active treatment and 14 subjects on placebo
    - PK sampling
      - Dense pk sampling
    - QTc data
      - Triplicate evaluations
      - Time matched with PK data at baseline and peak concentrations

QTc Evaluation

- Aim
  - To evaluate the potential effect of concentration on QT interval
  - To evaluate whether the effect of concentration on QT is greater in women than in men

Concentration - QTc Evaluation

- QTc data described first by an intercept model
  - QTC=Int
    - Int=TVint + exp(η_{Int})
- The effect of drug on QTc is then tested by linear function
  - QTc=Int + Slope*Cp
    - Int=TVInt + exp(η_{Int})
    - Slope=TVslope + exp(η_{Slope})
- Covariate effect (Gender) is tested using the following function
  - QTc=Int + Slope*(1+GEND*Factor)*Cp

Concentration – QTc Evaluation No Concentration Effect

- Attempt to describe concentration versus QTc described by linear function
  - Intercept model converges successfully
  - Slope estimated to be near zero and is estimated with poor standard error (or model terminates)
    - Concentration does not appear to influence QTc when evaluated graphically
- How does one prove lack of effect with model based evaluation? What sort of qualification and testing needs to be done for this model?
  - Parameters
  - Associated Variance Term

Concentration – QTc Evaluation No Covariate Effect

- QTc shown to be linearly related to concentration
  - Slope is non-zero and model parameters are estimated with good standard error
- Evaluation of covariate (1+GEND*Factor) on slope.
  - Factor is estimated to be near zero but estimated with poor precision
- How does one prove lack of effect with model based evaluation? What sort of qualification and testing needs to be done for this model?
  - Parameters
  - Associated Variance Term

Case Study Questions

1. Which method(s) of model selection and/or evaluation would you select? Why?
2. Describe the implementation of the method(s).
3. How would you make decisions based upon the results of the model evaluation method(s)? Which statistics or metrics would you use to guide decision making?

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Potential Method #1

- **Generate at least 500 bootstrap data sets from the original data set.**
  - Sample with replacement from the original dataset.
- **Fit final model to each bootstrap dataset.**
  - **To covariate or concentration based model**
    - **Evaluate distribution of bootstrapped parameters**
  - **To model without covariate or concentration based effect**
    - **Evaluate distribution of bootstrapped parameters**
- **Simulate replicates of original data base under each set of bootstrapped parameter estimates**
  - **Evaluate the prediction intervals across simulated data bases**
  - **Evaluate the 95% CI values**

Potential Method #2

- Estimate the Inter-individual Variance for slope effect of drug on QTc
- Determine number of subjects who have run-in or pre-treatment QTc data as well as treatment QTc data
- Using variance estimate and number of subjects, estimate "power" to detect an effect if it were present
  - Treat as if this is a cross-over design

Potential Method #3

- Assuming a minimally clinically significant drug effect over range of concentrations available (or a minimally significant covariate effect), simulate data based on original data set
- Compare distributions of QTc data between simulated and observed data