Simulation Study for Exposure-Response(ER) Model in QT study

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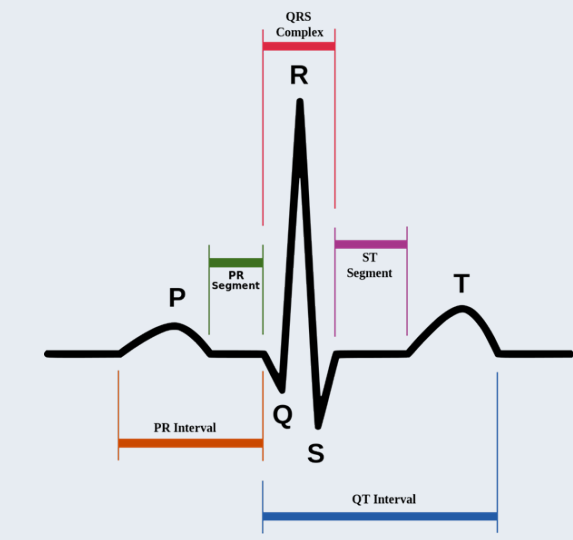[2]Center for Drug Evaluation and Research, US FDA

DISCLAIMER

Objectives

To see if **ER model** can be used to determine whether a drug has a threshold pharmacologic effect on cardiac repolarization, as detected by **QTc prolongation**.

Background

- **The QT interval** can reflect the duration of ventricular depolarization and subsequent repolarization.

- As least 1 thorough QT/QTc(TQT) study when submitting a new drug application.
- **QTc = QT Interval corrected for heart rate**

TQT study

- **TQT study** is used to determine whether the drug has a threshold pharmacologic effect on cardiac repolarization, as detected by QTc prolongation.
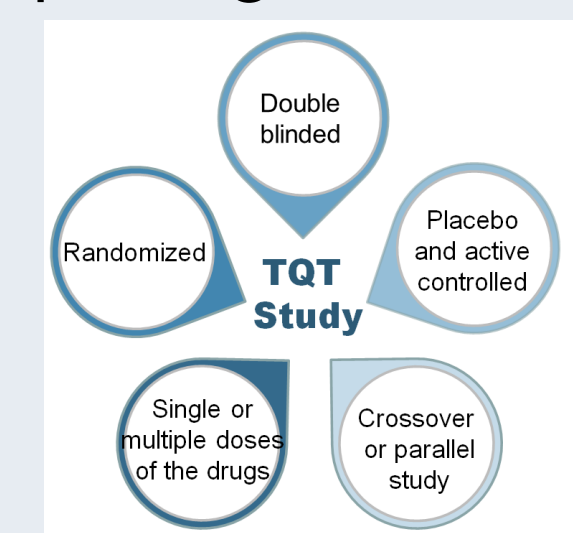
- In order to rule out a difference between the drug and placebo of greater than $10ms$, the largest two-sided 90% upper bound for baseline adjusted difference of the drug and placebo across all time points is used. The test result is negative or non-inferior if H_0 is rejected at **all** K **points**.

$$H_{0k} : (\mu_{TR_k} - \mu_{PL_k}) \geq 10ms, H_{1k} : (\mu_{TR_k} - \mu_{PL_k}) < 10ms \quad (1)$$

- A linear mixed effect model with random intercept is used here.

$$\Delta QT_{ijk} = \mu + \tau_i + t_k + \tau_i * t_k + b_j + \epsilon_{ijk} \quad (2)$$

Where ΔQT_{ijk} represents the baseline adjusted QT_c value of jth subject of the ith treatment at the kth time point; τ is the treatment effect; t is the time-point effect; b is the random intercept.

ER Model

- The primary analysis is based on the relationship between each **drug plasma concentrations** (Pharmacokinetic) and the effect on change from baseline QTc (Pharmacodynamic), which has **a different hypothesis from IUT hypothesis as in TQT study**.
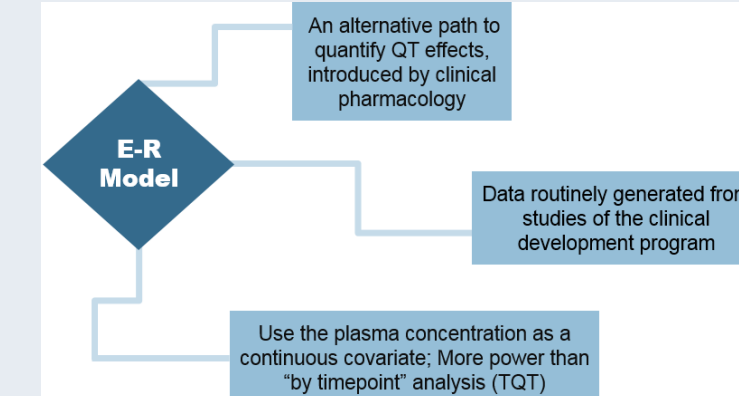
- According to the protocol, if the upper bound of the two-sided 90% confidence interval (CI) of the predicted placebo-corrected $\Delta QT_c(\Delta\Delta QT_c)$ at the **geometric mean** $Cmax$ of concentration is above $10ms$, a positive QT-effect is demonstrated. Then the test may be stated as:

$$H_0 : \Delta\Delta QT_{cmax} \geq 10ms, H_1 : \Delta\Delta QT_{cmax} < 10ms \quad (3)$$

- Even though the truth is that $Cmax$ is a random variable, Type I and II error rate is based on the assumption that $Cmax$ **is either fixed or estimated with little error** in this test.
- Still a linear mixed effect model with random intercept is used here.

$$\Delta QT_{c_{ij}}(t) = \mu + \tau_i + \beta * C_{ij}(t) + b_j + \epsilon_{ijt} \quad (4)$$

Where $\Delta QT_{c_{ij}}(t)$ represents the baseline adjusted QT_c value of jth subject of the ith treatment at the kth time point; τ is the treatment effect; $C_{ij}(t)$ is the drug plasma concentration value of the jth subject of the ith treatment at time t ($C_{ij}(t)$ is always 0 for placebo); b is the random intercept.

- The interval prediction is gotten by both normal assumption and bootstrapping.

Hypothesis Testing

- **Endpoint**: placebo-adjusted change from baseline QT Interval corrected for heart rate at the geometric mean $Cmax$ of plasma concentration values, denoted as $\Delta\Delta QT_{cC_{max}}$.

- It's a **safety study**, thus we put no prolongation effect in the alternative hypothesis.

$$H_0 : \mu_{cmax} \geq 10ms, H_1 : \mu_{cmax} < 10ms, \quad (5)$$

- Test statistics: $T = \dfrac{\widehat{\Delta\Delta QT_{cC_{max}}} - \mu_{C_{max}}}{se(\widehat{\Delta\Delta QT_{cC_{max}}})}$
- Type-I error: $P(\text{test no prolongation}|\text{real prolongation})$
  Type-II error: $P(\text{test prolongation}|\text{real no prolongation})$
- Control **Type-I error** and see what **Type-II error** we can get.

Data Generation

- Usually in ER model, each drug should be tested on **different doses** and each dose should have values for **multiple time-points**.
- The data can be generated from the following model:

$$\Delta QT_{ijt} = \alpha + \beta * x_{ijt} + b_i + e_{ijt} = \alpha + \beta * x_{ijt} + err_{ijt} \quad (6)$$

Where $b_i's$ and $e_{ijt}'s$ are both from iid normal distribution with mean 0 and they are independent of each other.

- x_{ijt} represents the plasma concentration value of subject i in treatment j at tth time-point. The values of x between subjects are independent. The values of x within subject can be generated from **truncated multivariate normal distribution** for plasma concentration value should be positive.

- All the parameter and covariates values are from the real study data.

- We set mean $\Delta\Delta QTc$ at Cmax as **10ms** when there is prolongation effect (for Type-I error), and to be **3ms** when there is none (for Type-II error).

- Choose certain proportion of subjects to have **placebo** in one of the treatment and some observations may be **missing** randomly.

Simulation Study

I have **three cases** in the simulation study.

- **Case I**: Generate data from (6), put 0 to concentration values for Placebo data; then take the generated data into (4) and get prediction interval.

- **Case II**: Generate data from (6), but generate **independently** for Placebo data from $y_{i0t} = \alpha + err_{i0t}$; then take the generated data into model (4) and get prediction interval.

- **Case III**: Generate data the same as in Case II; then take the generated data into model $\Delta QT_{c_{ij}}(t) = \mu + \beta * C_{ij}(t) + b_j + \epsilon_{ijt}$ and get prediction interval.

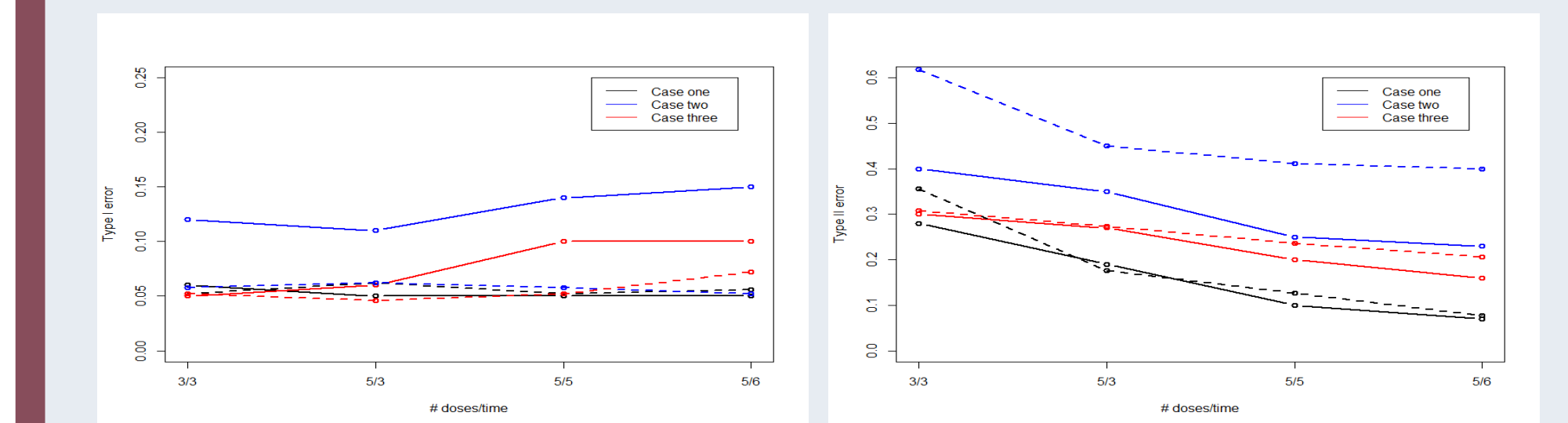## Literature review

Some similar simulation study in [2]

- When a true ΔQT_c prolongation effect at the supratherapeutic concentration is 10 msec, they have a Type-I error **0.065**.

- When a true ΔQT_c prolongation effect at the supratherapeutic concentration is 3 msec, they have a Type-II error **0.191**.

Results

I fixed correlation structure in error terms and let number of doses and number of time-points change. The results are on both therapeutic and supratherapeutic doses:
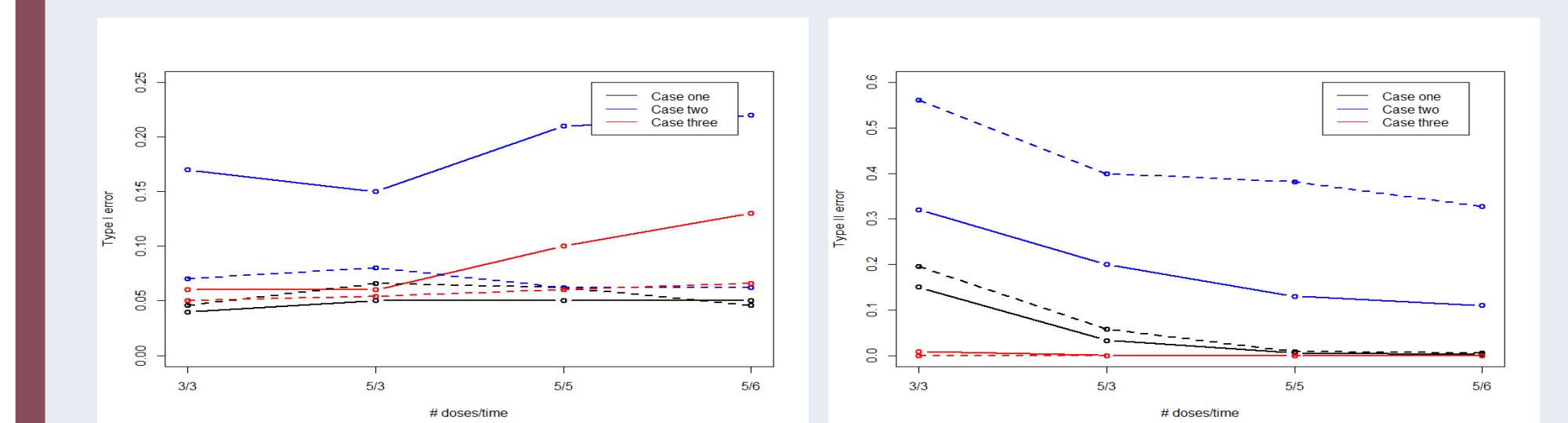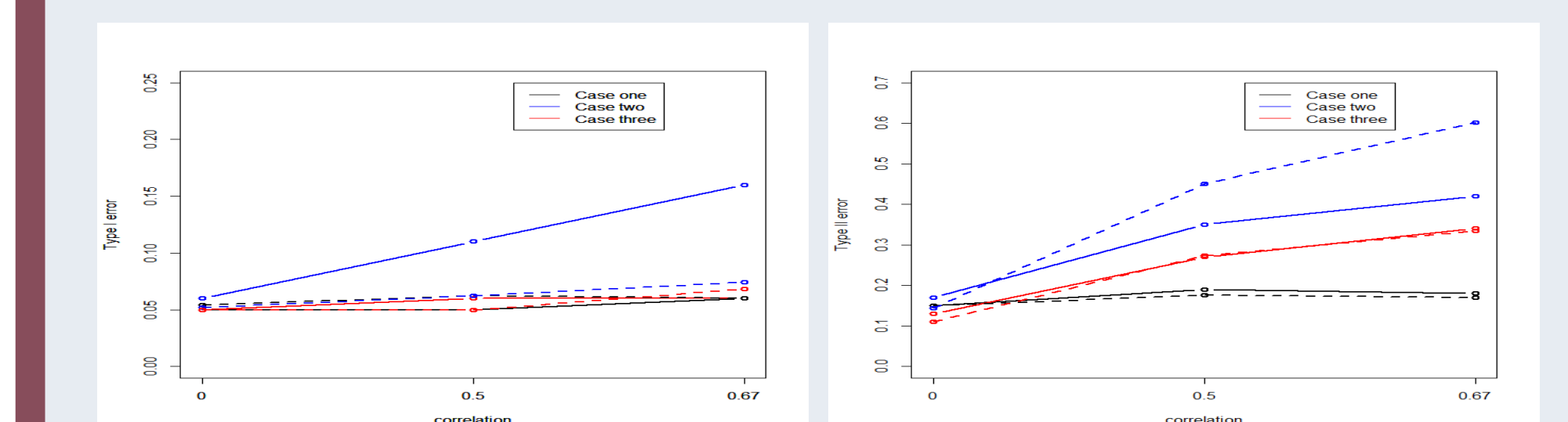

(a) Type I error Therapeutic dose
(b) Type II error Therapeutic dose
(c) Type I error Supratherapeutic
(d) Type II error Supratherapeutic

If I set the number of doses to be 5 and number of time-points to be 3 and let the correlation among errors change:

(e) Type I error
(f) Type II error

Solid: normal assumption, dashed: bootstrapping

Discussion and Future Work

- Many elements such as **covariance structure, number of time-points, number of doses, test on therapeutic/supratherapeutic dose** may affect the Type I and Type II error in Exposure-response Model.

- The model works slightly better without adding treatment factor in the model.

- More research should be done on estimating $Cmax$.

References(Highlighted)

[1] Yi Tsong(2006). On the Designs of Thorough QT/QTC Clinical Trials. *Journal of Biopharmaceutical Statistics*, 23: 43-56.

[2] Cara H. Nelson et al.. GS-4997 Concentration-QT Analysis in First-in-Human Study to Evaluate the Proarrhythmic Risk to Support a Waiver of a Thorough QT Study.