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Concentration-QTc Analysis Implemented by R Shiny

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Abstract

As the International Council for Harmonisation revised the E14 guideline, A well-designed and conducted QTc assessment based on concentration-QTc (C-QTc) modeling is used as the primary analysis for assessing the QTc interval prolongation risk of new drugs, which can be an alternative approach to a thorough QT (TQT) study to reliably exclude clinically relevant QTc effects. In this paper, an APP established by R shiny, which is a brilliant visualization tool, is introduced to provide a way on how to conduct a definitive QTc assessment of a drug using C-QTc modeling in early phase clinical pharmacology and studies, including study design, modeling objectives and approach, exploratory plots and tables, the linear mixed effects model and mixed model for repeated measures and their assumptions and predictions for modeling analysis.

INTRODUCTION

Delays in cardiac re-polarization can lead to life-threatening heart arrhythmia. On May 2005, International Council for Harmonisation (ICH) E14 issued a clinical guidance, and the central piece of it is the thorough QT/QTc study(TQT), which is a dedicated study with the primary objective to quantify the effect of a new molecular entity (NME) on the QT interval. The objective of TQT study is to confidently exclude that a drug prolongs the QTc interval 10 ms or more at the one-sided upper 95% confidence limit.

On December 2015, the ICH E14 Guideline[1] was revised to allow for concentration-QTc (C-QTc) modeling to be used as the primary analysis for assessing the QTc interval prolongation risk of new drugs. Considering the C-QTc modeling approach utilizes data from all doses and time points, a reliable assessment of QTc prolongation can be based on smaller-than-usual TQT trials or be obtained during trials in early development not specifically targeted at QT effects. From now on, sponsors of pharmaceutical products can either perform smaller TQT studies or use C-QTc modeling with high quality electrocardiogram (ECG) measurements in single- and/or multiple- dose escalation (SAD/MAD) studies during early-phase clinical development as an alternative to the TQT analysis.

When utilizing a modeling approach for regulatory purposes, it is particularly important that the quantitative methods used be clearly described to enable reproducibility. It is expected that data sources and modeling details, including the structural model, assumptions, criteria for assessment of model robustness and goodness-of-fit, be adequately described in a pre-specified modeling analysis plan (MAP), and reported in a standardized format. Although the E14 implementation working group did not provide a detailed technical guidance on performing and reporting C-QTc modeling, a scientific white paper on concentration-QTc modeling[2] published in the Journal of Pharmacokinetics and Pharmacodynamics in 2018 solved this problem. The white paper was developed on the best modeling practices from industry, scientific literature, and the experiences from regulatory scientists. This paper will mainly focus on the model implementation and report visualization by R shiny.

STUDY DESIGN AND INPUT DATA

In most early phase clinical studies, commonly used designs are the sequential parallel group design (where the doses are gradually escalated, and after each dose administration and subsequent safety evaluation, a new cohort with new subjects is included and administered the next dose level) and the alternating panel crossover design (where dose escalation is alternated between 2 or more panels and each panel receives every other dose, and during the dosing of one cohort, the other cohorts are in washout). The choice of design is based on the study objectives, only one of which is the assessment of QTc prolongation. A placebo cohort should be used whenever possible to control for potential bias introduced by study procedures and to increase the power to exclude modest QTc effects in small-sized studies.

The input of R shiny would be a standard analysis dataset called ADCQT (Concentration-QTc Analysis Dataset) for C-QT analysis, which follows the FDA guideline[3] released in 2019. This data set is primarily based on the ADEG and ADPC used in Clinical Study Reports (CSR), which is explicitly described in a paper named “Implementation on concentration-QTc modeling”[4]. The majority of the data in ADCQT comes from ADEG, such as PARAMCD, AVAL, CHG, etc., while the time-matched concentrations of the investigational drug and/or its metabolites are from ADPC.

APP interface

This APP is mainly composed by four parts and all of them will be introduced in detail in the following sections in this paper. Figure 1 shows the interface of the APP structure and the first part. In this paper, an analysis data set named *adcqt_dummy* is used as the demo input data. The first part is *data overview*. After reading data, information including study numbers and subject numbers will appear in the main panel. The second part is *data setup*, it help users to control the input variables and values. The third part is *assumptions*, which is to find if all assumptions of the pre-defined model are met. The last part is named *exposure-response analysis*. Users could not only design their model, but evaluate the model and visualize their predictions in this part.

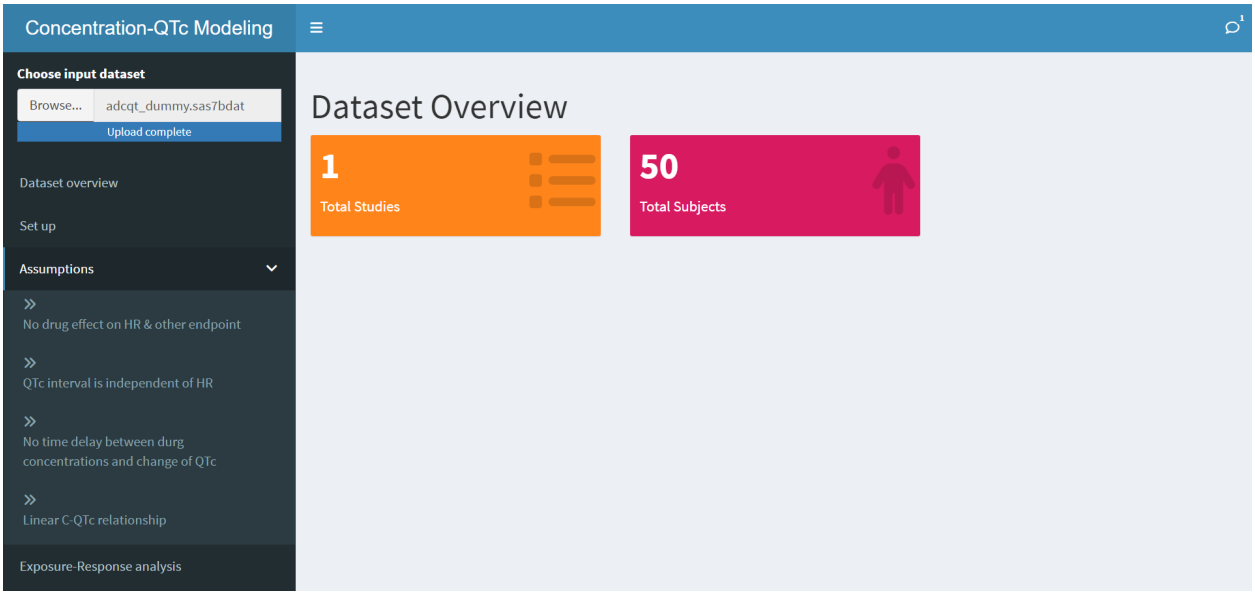

Figure 1: Interface of R shiny APP

MODELING APPROACH

When C-QTc analysis is utilized as the primary basis for decisions to classify the risk of a drug, the upper bound of the two-sided 90% confidence interval for model-derived placebo corrected and baseline corrected QTc interval ($\Delta\Delta$QTc) should be less than 10 ms at the highest clinically relevant exposure to conclude that an expanded ECG safety evaluation during later stages of drug development is not necessary. A pre-specified linear mixed effects model is recommended as the primary analysis to exclude a 10 ms QTc prolongation effect. For drugs that prolong the QTc interval, however, this objective may not be appropriate in this setting.

Model independent check of assumptions

Prior to introducing linear mixed effect C-QTc model, there are four basic assumptions which are supposed to be met. Otherwise, if the following assumptions are not satisfied, the model development for adapted C-QTc model is recommended.

Assumption 1: No drug effect on heart rate

The first consideration is the potential of a drug to significantly increase or decrease heart rate. Although there is no consensus on the specific threshold effect on heart rate that could influence QT/QTc assessment, mean increases or decrease > 10 beats per minute (bpm) have been considered problematic.

In Dizal's studies, we choose mixed model with repeated measures (MMRM) to analyze the first assumption. This model is a kind of linear mixed model and is particularly well-suited for analyzing data with a hierarchical structure, such as modeling continuous variables that are repeatedly measured at discrete time points in longitudinal studies in clinical trials. The advantage of MMRM is that it not only explicitly account for the correlation between repeated measures from the same individual, but can handle missing data more effectively than some other methods.

The general form of the Linear mixed model can be expressed as

$$Y = X\beta + Z\gamma + \epsilon \tag{1}$$

Where *Y* is the response vector; *X* is the design matrix for the fixed effects, which includes the variables of primary interest (e.g., treatment, time); β is the vector of fixed effect coefficients; *Z* is the design matrix for random effects, which account for the variability among subjects; γ is the vector of random effect coefficients; ϵ is the vector of error terms.

The distinguishing feature of MMRM, compared to other implementations of linear mixed models, is that subject-specific random effects (which are not of direct interest for estimation and inference) are considered as residual effects. We assume that the observations are independent between the subjects and the Eq.1 could be rewritten as

$$Y = X\beta + \epsilon \tag{2}$$

Where $\epsilon \sim N(0, \Omega)$ has a multivariate normal distribution and Ω is block-diagonal containing the subject specific covariance matrices on the diagonal and 0 in the remaining entries.

The MMRM model could be implemented by mmrm package[5] in R with the following code,

```
model_mmrm <- mmrm::mmrm(
  formula = CHG ~ TRT + TIME + TIME * TRT + BASE + us(TIME | USUBJID),
  data = df,
  reml = TRUE,
  control = mmrm_control(method = "Kenward-Roger")
)
```

Where CHG is the change from baseline of such parameter; TIME is time point, TRT is treatment and TIME * TRT is time-by-treatment interactions. They are all fixed effects; BASE is baseline HR, which is the covariate; us(TIME | USUBJID) means random effects of subjects on each time point with unstructured variance-covariance estimator for coefficients. In this paper, the restricted maximum likelihood estimation and Kenward-Roger approximation method are used in the model, which can be varied in different studies or designs. Figure 2 shows some types of covariance structures.

Structure	Description	# of Parameters	{i,j}th element
AR(1)	Autoregressive(1)	2	$\sigma_{ij} = \sigma^2 \rho^{\lvert i-j \rvert}$
CS	Compound Symmetry	2	$\sigma_{ij} = \sigma_1 + \sigma^2 1(i = j)$
UN	Unstructured	t(t+1)/2	$\sigma_{ij} = \sigma_{ij}$
TOEP	Toeplitz	t	$\sigma_{ij} = \sigma_{\lvert i-j \rvert+1}$
VC	Variance Components	q	$\sigma_{ij} = \sigma_k^2 1(i = j)$ and i corresponds to the kth effect
ARH(1)	Heterogeneous AR(1)	t+1	$\sigma_{ij} = \sigma_i \sigma_j \rho^{\lvert i-j \rvert}$
CSH	Heterogeneous CS	t+1	$\sigma_{ij} = \sigma_i \sigma_j [\rho 1(i \neq j) + 1(i = j)]$
TOEPH	Heterogeneous TOEP	2t-1	$\sigma_{ij} = \sigma_i \sigma_j \rho_{\lvert i-j \rvert}$

Figure 2: Types of covariance structures

Then the least square mean, standard error and two-sided 90% CI will be calculated for each treatment group, each dose level and at each post-dose time point separately. The result can be visualized in a line chart with error bar.

APP interface In shiny APP, it is needed to set up some key variables and initial values at the beginning.

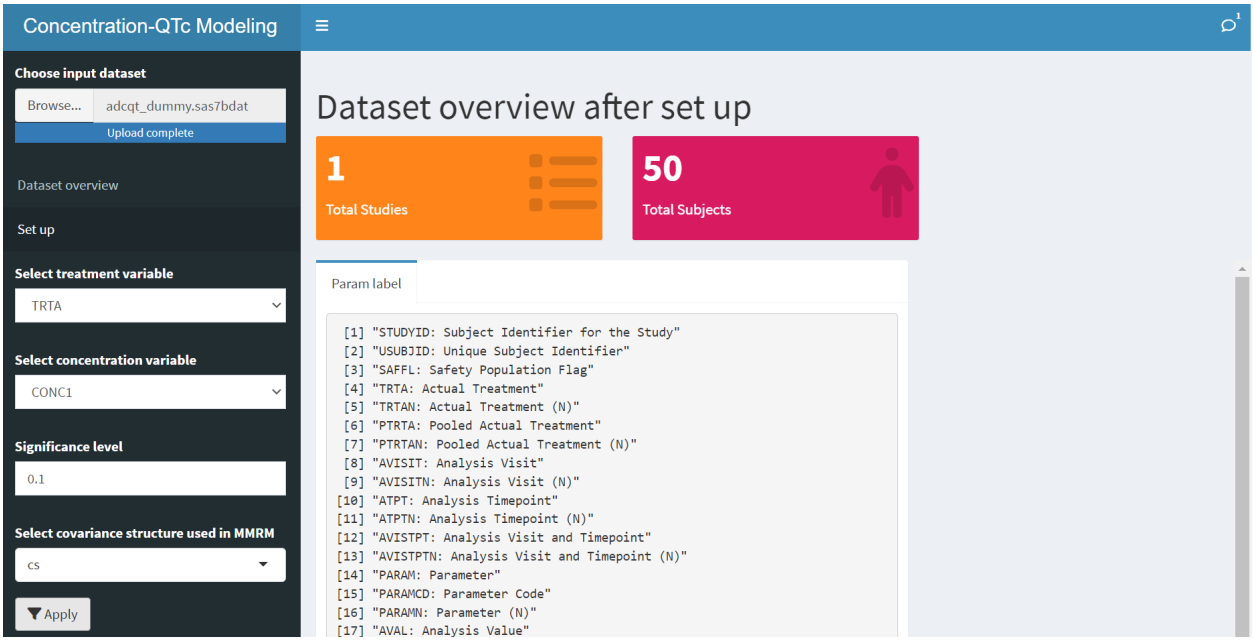

Figure 3: Interface of set up

We need to set up treatment variable, concentration variable, significance level used in the model and covariance structure used in MMRM in this part (Figure 3). After clicking *Apply* button, the right panel would show the updated studies and subjects numbers and param labels. Then users could move to the next step, which is visualizing first assumption by shiny.

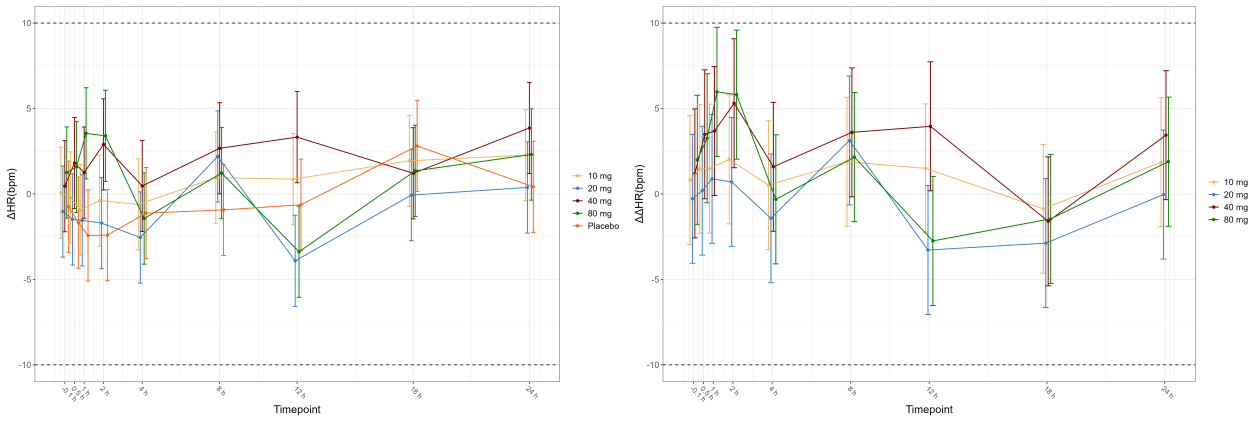

Figure 4: ΔHR(left) and $\Delta\Delta$HR(right) across time points with modeling

Figure 4 shows the plots for the first assumption. In this case, least square mean of $\Delta\Delta$HR is below 10 bpm for all dose levels across all post-baseline time points, indicating that this drug has no clinically relevant effect on heart rate. The p-values for the time-by-treatment interaction, if above 0.05, will suggest that there is no significant difference between the dosed group and placebo group in terms of heart rate change over time.

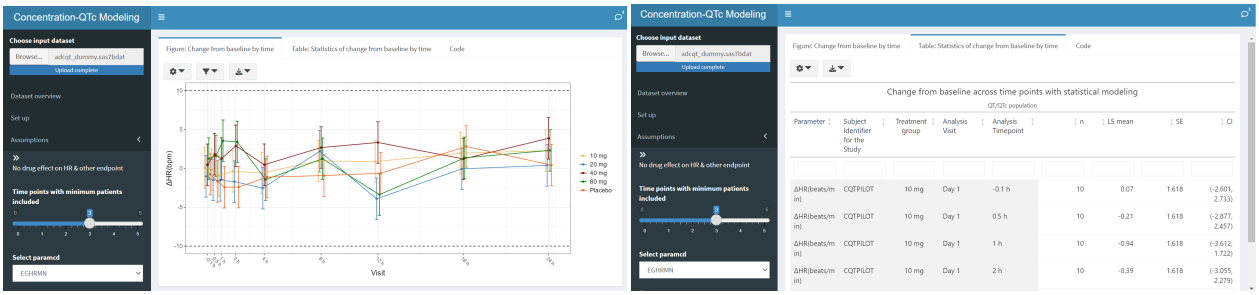

Figure 5: Interface of first assumption

In the APP, the interface of first assumption will include 2 blocks: one for change from baseline versus time points, which is shown as the example here, and another one for placebo corrected change from baseline.

Each block will be separated by 3 panels as well. In the figure panel (left one in Figure 5), on the left siderbar, users can select the minimum number of subjects within each visit to avoid bias leading from limited data. Parameters could also be selected since users might prefer to explore some other electrocardiogram measurement parameters by time points, like QTcF, QRS, RR, PR, etc., in exploratory period, instead of focusing on heart rate only. On the top of the plot, there are 3 buttons. The first gear button is to control if model will be used when plotting. If it is not checked, MMRM model will not be implemented here and a simple line plot with numeric mean and error bar will be drawn instead. The second filter button is to help users to select specific single dose group that are interested in. The last download button allows users to download the plot as a png file.

In the table panel (right side in Figure 5), users are possible to check the data plotted in figure panel and interact with the data, which could be download as a table in docx file as well.

Figure 6: Code tab of first assumption

Reproducibility The third code panel is for users to view the code generating the output (figure 6) since it is important for us to add functionality for reproducibility so that users could use this APP for submissions. Here we relied on the framework provided by *expandChain* function within the *shinymeta* package[6], which was built for purpose of reproducing R Shiny code in real time for distribution.

Since the majority of outputs in this APP is designed in a same way shown above. In the following sections of this paper, similar layout of interface will not be shown again and only outputs will be attached to clarify the model or methodology design.

Assumption 2: QTc interval is independent of heart rate

If drug do not have significant effect on heart rate, Fridericia corrected QT interval (QTcF) is usually a sufficient correction method for drugs with insignificant effects on HR. If an individualized heart rate correction method is used, the appropriateness of the selected method should be assessed to determine if QTc is independent of HR using drug-free data.

A scatter plot of QTcF versus RR interval by treatment could evaluate the heart rate corrected QT interval. In addition, QTcF and RR interval can be fitted to a linear mixed effect model with $QTcF \sim RR$ and evaluated by a quantile plot compared with a mean fitted regression line (90% CI) comes from model, which could show if there exists linear relationship between QTc interval and heart rate.

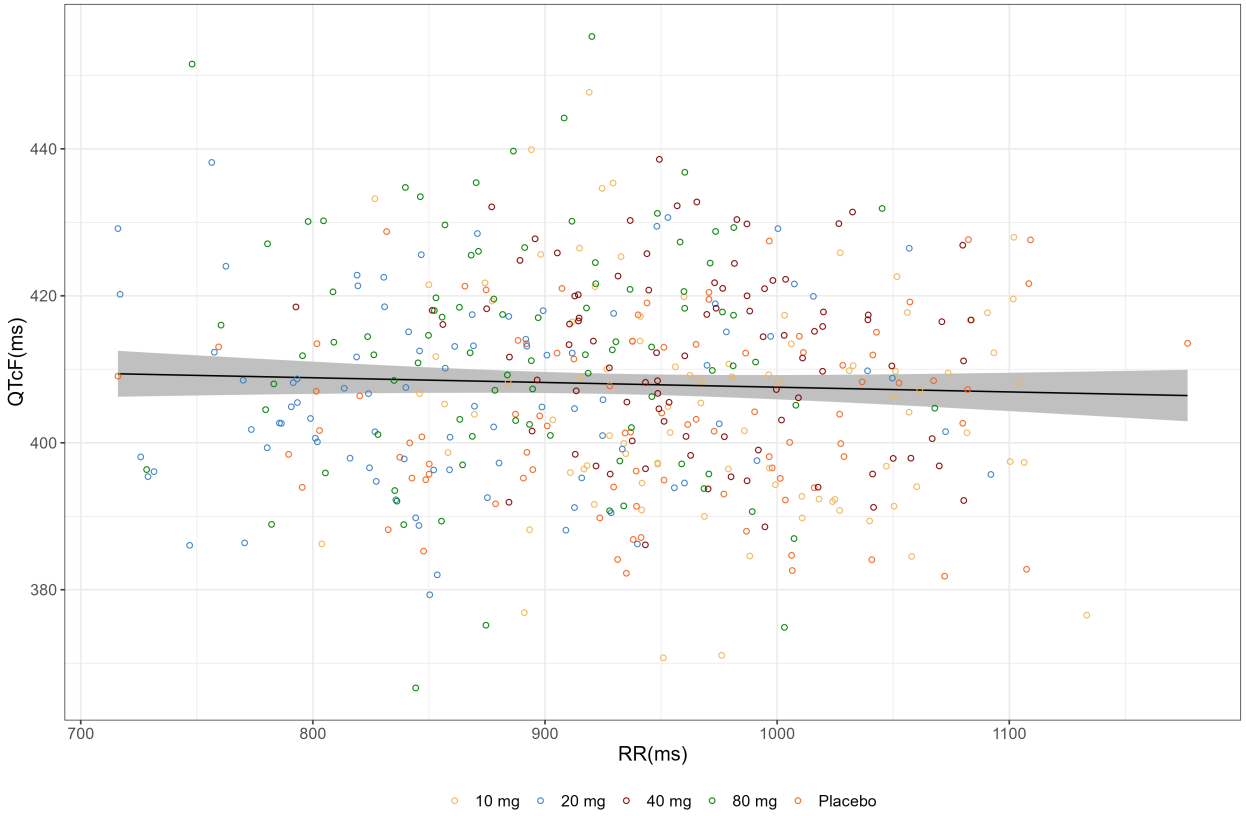

Figure 7: Scatter plot of QTcF and RR intervals

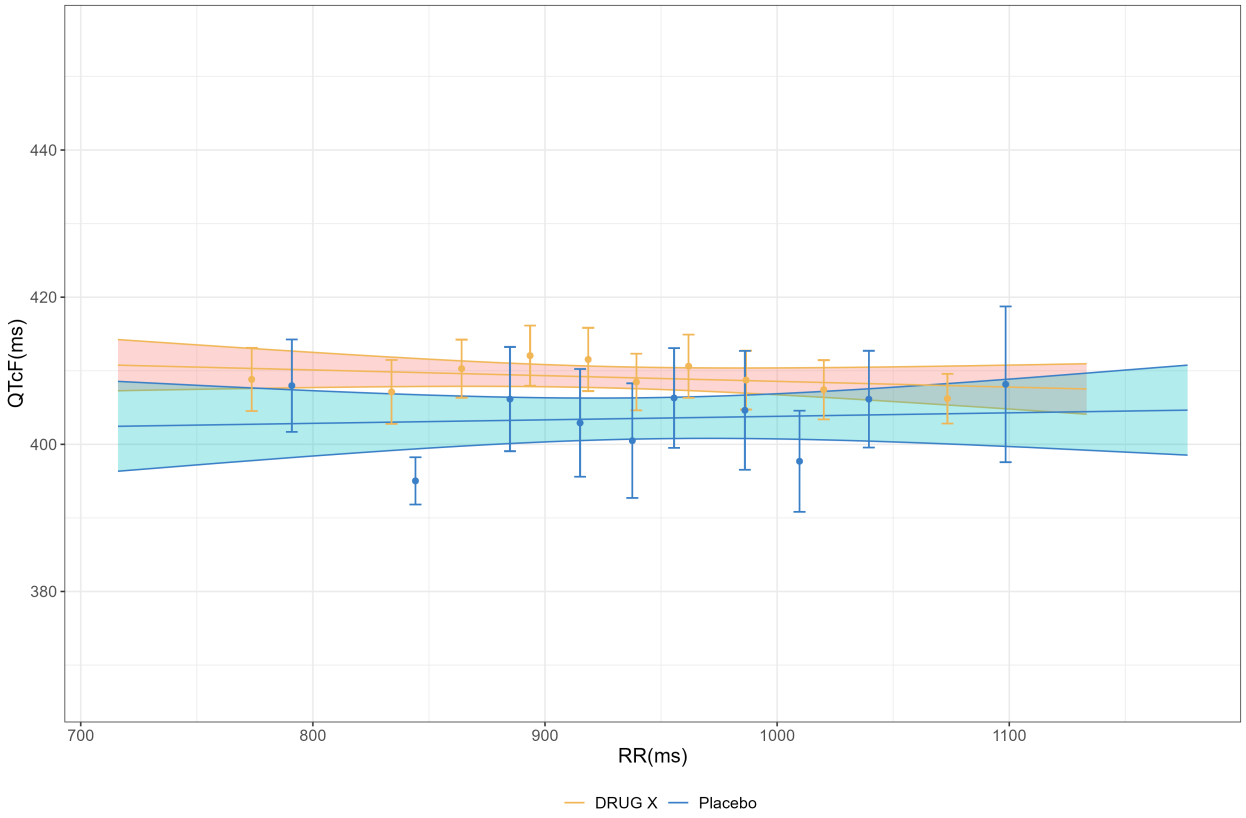

Figure 8: Decile plot of QTcF and RR intervals

It can be seen that, from Figure 7 and Figure 8, there is no obvious linear relationship between QTcF and RR interval.

Assumption 3: No time delay between drug concentration and △QTc

This assumption can be evaluated by examining the mean concentration and QTc profiles by dose level and time. If the time course of QTc is concordant with the PK profile, the default model assumption of a direct temporal relationship between drug concentration and QTcF can be supported. However, if there is a delay between peak concentration and peak QTcF, the analyst must consider the possibility of a delayed temporal effect and the model applied should account for this delay.

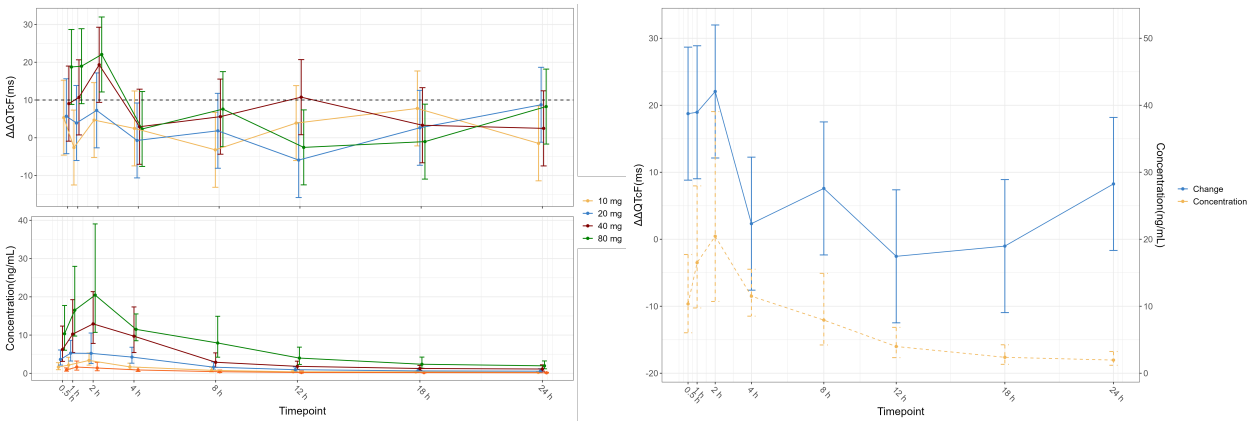

Figure 9: Joint plot of DRUG X plasma concentrations and $\Delta\Delta$QTcF(right) across time point

From Figure 9, it can be seen that the both peak drug concentration and peak $\Delta\Delta$QTcF are reached at round 2 hours after dosed, which indicates that there is no time delay between them. The plot on the right hand takes group 80 mg as an example and we can find that trend more explicit.

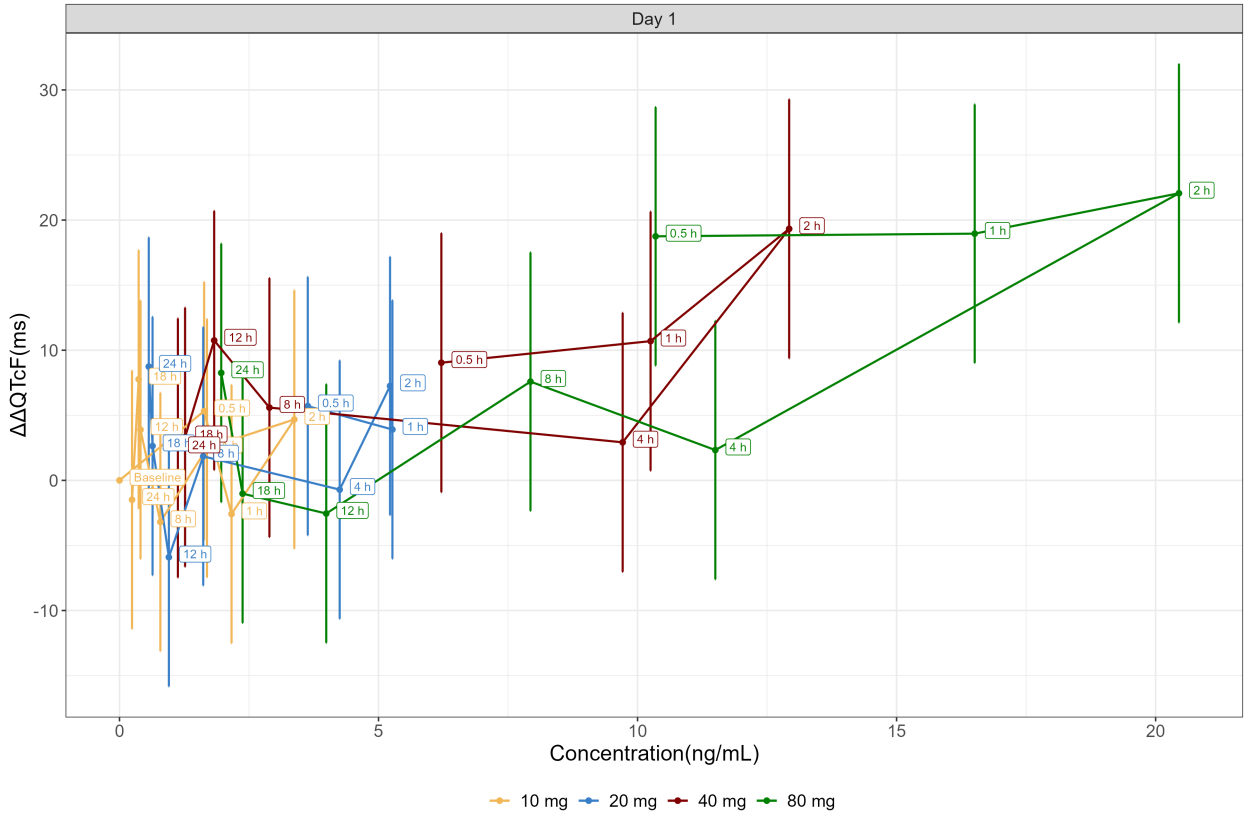

Figure 10: Concentration and mean $\Delta\Delta$QTcF connected in temporal order by dose

Figure 10 also shows that the time course of $\Delta\Delta$QTcF is concordant with the PK profile. Thus the default model assumption of a direct temporal relationship between drug concentration and QTc effect can be supported.

Assumption 4: linear C-QTc relationship

The adequacy of using a linear model can be assessed by the concentration versus ΔQTcF plot incorporating a trend line (e.g., loess smooth or linear regression). The trend line does not reflect a model fit of data, but rather is used to detect drug effect. The loess line is supposed to be close to the linear regression line if the linear assumption is valid. If data are pooled from multiple studies, the regression lines are to be displayed for each study.

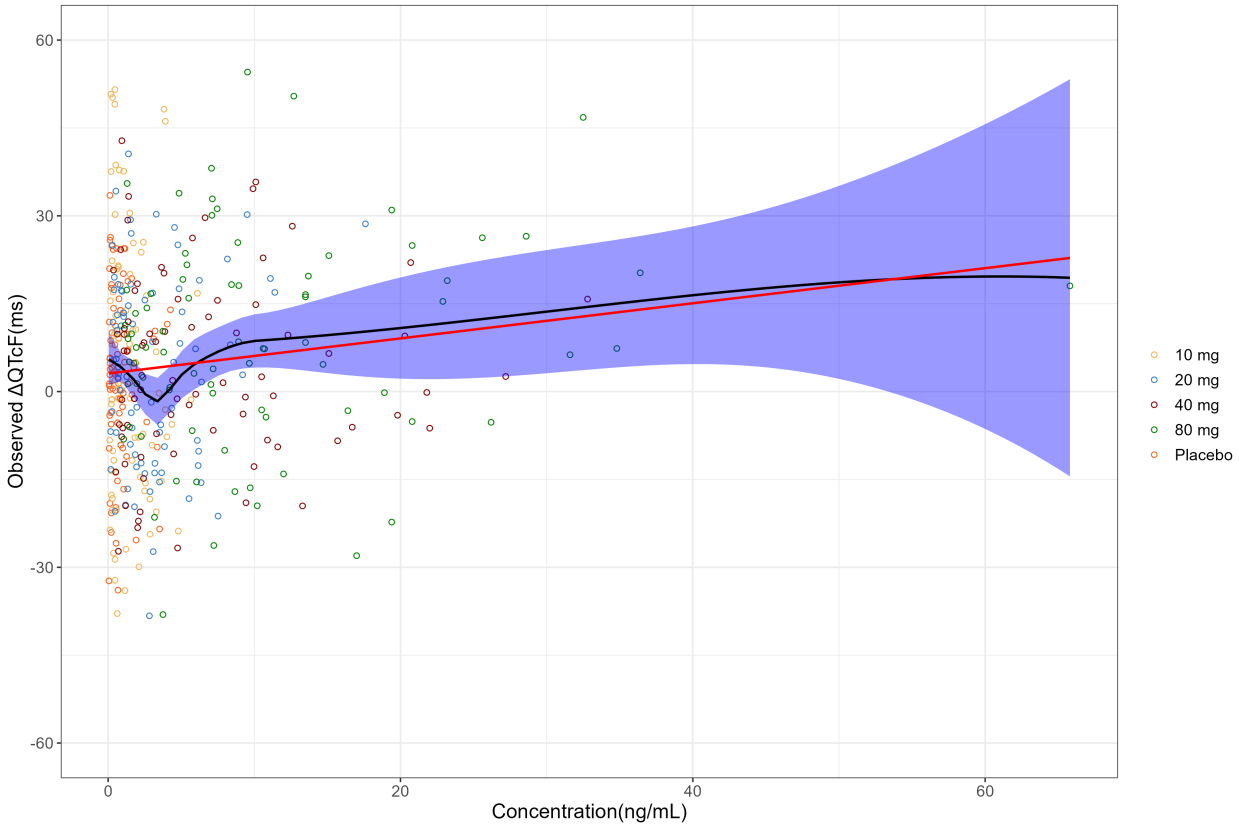

Figure 11: Scatter plot of observed concentrations and ΔQTcF

In Figure 11, the linear regression line is in red and loess smooth line is in black with 90% confidence intervals in blue band. They are close enough to prove that this assumption is valid.

Pre-specified linear mixed effects model

Referring the white paper, a pre-specified linear mixed effect (LME) C-QTc model is used as the primary analysis. The default dependent variable of the model is ΔQTcF, which represents the change from baseline in QTc interval corrected using Fridericia's formula. The fixed effect parameters include intercept, slope, baseline influence on intercept, treatment (active = 1, placebo = 0), and nominal time from the first dose. Subject is included as an additive random effect on both intercept and slope terms.

$$\Delta QTcF_{ijk} = (\theta_0+\eta_{0,i})+\theta_1 TRT_j+(\theta_2+\eta_{2,i})C_{ijk}+\theta_3 TIME_j+\theta_4(QTcF_{i,j,k=0}-\overline{QTcF_0}) \quad (3)$$

In the Eq.3, $\Delta QTcF_{ijk}$ is the change from baseline in QTcF for subject i in treatment j at time k, which is the dependent variable; θ_0 is the population mean intercept in absence of a treatment effect; $\eta_{0,i}$ is the

random effect associated with intercept term θ_0; θ_1 is the fixed effect associated with treatment; θ_2 is the population mean slope of the assumed linear association between concentration C_{ijk} and $\Delta QTcF_{ijk}$; $\eta_{2,i}$ is the random effect associated with the slope θ_2; θ_3 is the fixed effect associated with time; θ_4 is the fixed effect associated with baseline QTcF; $\overline{QTcF_0}$ is the overall mean of all baseline QTcF values.

The equation assumed the random effects are normally distributed with mean [0,0] and an unstructured covariance matrix *G*, whereas the residuals are normally distributed with mean 0 and variance *R*.

Although following ICH E14 guidelines, placebo group is recommended to be included in the model, sometimes studies may not design placebo arm initially. In that case, treatment affected items can be avoid and θ_1, θ_3 terms in Eq.3 could be deleted:

$$\Delta QTcF_{ik} = (\theta_0 + \eta_{0,i}) + (\theta_2 + \eta_{2,i})C_{ik} + \theta_4(QTcF_{i,k=0} - \overline{QTcF_0}) \tag{4}$$

In R, generally we could implement Eq.3 and Eq.4 by *lmer* function from *lme4* package[7] with the following code, where CHG is the change of QTcF from baseline; TRT is treatment variable with factor type; TIME is visit variable with factor type; CONC1 is the plasma concentration variable; CBASE is the centralized baseline QTcF and (1 + CONC1 | USUBJID) means random effects of subjects on each concentration and intercept with unstructured (can not be changed in *lmer*) variance-covariance estimator for coefficients. Here the restricted maximum likelihood estimation and Kenward-Roger approximation method are used again, which can be varied in different studies or designs.

```
CQT_model_with_placebo <- lme4::lmer(
  CHG ~ 0 + TRT + TIME + CONC1 + CBASE + (1 + CONC1 | USUBJID),
  data = df,
  REML = TRUE,
  control = lmerControl(optimizer = "Nelder_Mead")
)

CQT_model_no_placebo <- lme4::lmer(
  CHG ~ CONC1 + CBASE + (1 + CONC1 | USUBJID),
  data = df,
  REML = TRUE,
  control = lmerControl(optimizer = "Nelder_Mead")
)
```

ESTIMATION OF MODEL-DERIVED $\Delta\Delta$QTC AT CONCENTRATION OF INTEREST

The final C-QTc model should be used to compute the $\Delta\Delta$QTc at concentrations of interest. For decision making, the concentration of interest will be derived from the drug development program and can be treated as a prediction variable.

For the pre-specified C-QTc model, the change from baseline QTc adjusted for placebo ($\Delta\Delta$QTcF) is the difference between the model-derived ΔQTcF at concentration of interest and model-derived ΔQTcF for placebo, see Eq.5

$$Mean\Delta\Delta QTcF = Mean\Delta QTcF_{i,j=1,k} - Mean\Delta QTcF_{i,j=0,k} \tag{5}$$

Thus, with the pre-specified linear model, the mean and two-sided 90% condidence interval for $\Delta\Delta$QTcF at concentrations of interest can be derived as

$$Mean = \theta_{1,Est} + \theta_{2,Est} \times C \tag{6}$$

$$SE = \sqrt{var(\theta_{1,Est}) + C^2 var(\theta_{2,Est}) + 2C(cov(\theta_{1,Est}\theta_{2,Est}))} \tag{7}$$

$$90\%CI = Mean \pm t(0.95, DF) \times SE \tag{8}$$

where $\theta_{1,Est}$ is the estimated treatment-specific intercept; $\theta_{2,Est}$ is the estimated slope; $var(\theta_{1,Est})$ is the variance of the treatment specific intercept; $var(\theta_{2,Est})$ is the variance of the slope; $cov(\theta_{1,Est}\theta_{2,Est})$ is the covariance of the intercept and slope; t is the critical value determined from the t-distribution; DF is the degrees of freedom; C is the concentration.

As for adapted C-QTc models with different structures (e.g., nonlinear models or linear models with interaction terms), the mean and 90% CI for $\Delta\Delta$QTcF can be computed by non-parametric bootstrap methods, which should be stratified by dose levels within the active arms and the subjects in placebo arm.

Model evaluation and visualization

APP interface

The interface of fitting linear mixed model is shown in Figure 12. Users are supposed to select fixed effect variables, random effect variables and the parameter to be dependent variables they would like to include in the model in the left siderbar firstly. Then after clicking “Build report” button, all model fitted statistics and estimate results visualized by plots and tables, which are demonstrated in the following sections, will be created. The R code will be displayed in code panel in each tab for outputs reproducibility(shown in Figure 13).

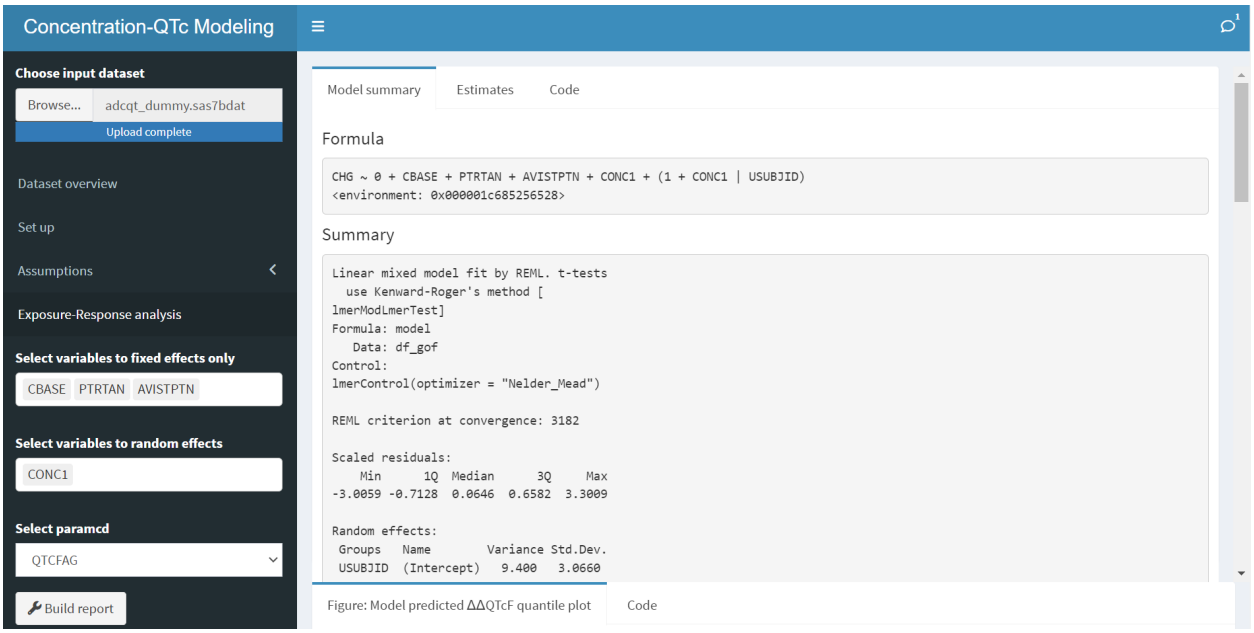

Figure 12: APP interface of model evaluation

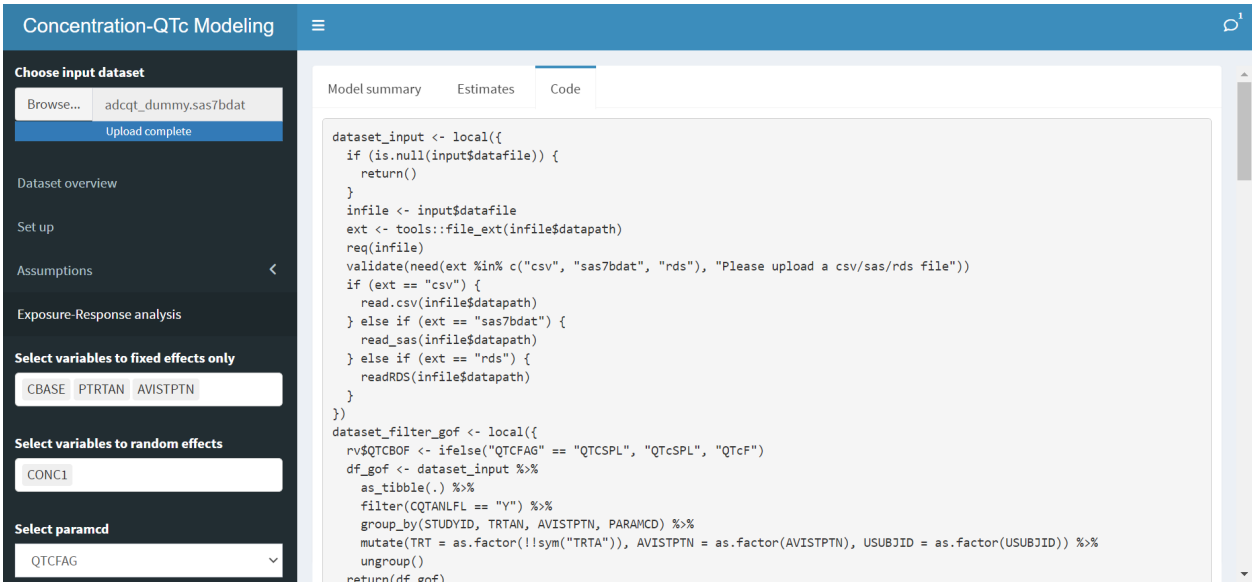

Figure 13: Code panel in APP of model evaluation

Goodness-of-fit evaluation

Goodness-of-fit (GOF) plots should always be presented for the final C-QTc model. A C-QTc quantile plot of observed data overlaid with the model predictions is a visual assessment of how well the model fits the data. Figure 14 shows the observed mean $\Delta\Delta$QTcF (90% CI) within each concentration decile in red point with error bar and the model-predicted mean $\Delta\Delta$QTcF in black line with 90% CI in grey band. Besides that, Figure 15 shows the observed $\Delta\Delta$QTcF(placobo ajusted ΔQTcF) versus concentrations scatter plot and the model-predicted mean $\Delta\Delta$QTcF in black line with 90% CI in grey band.

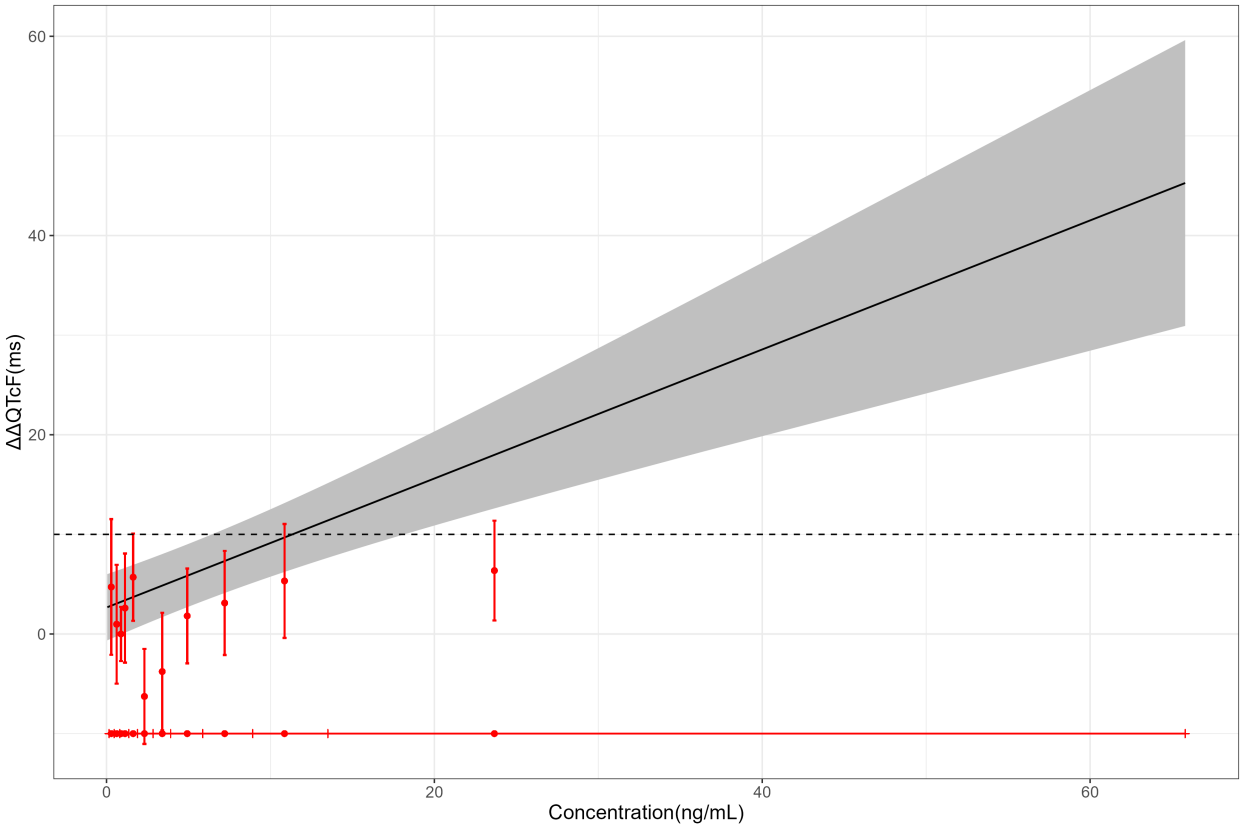

Figure 14: ΔΔQTcF versus drug concentration quantile plot

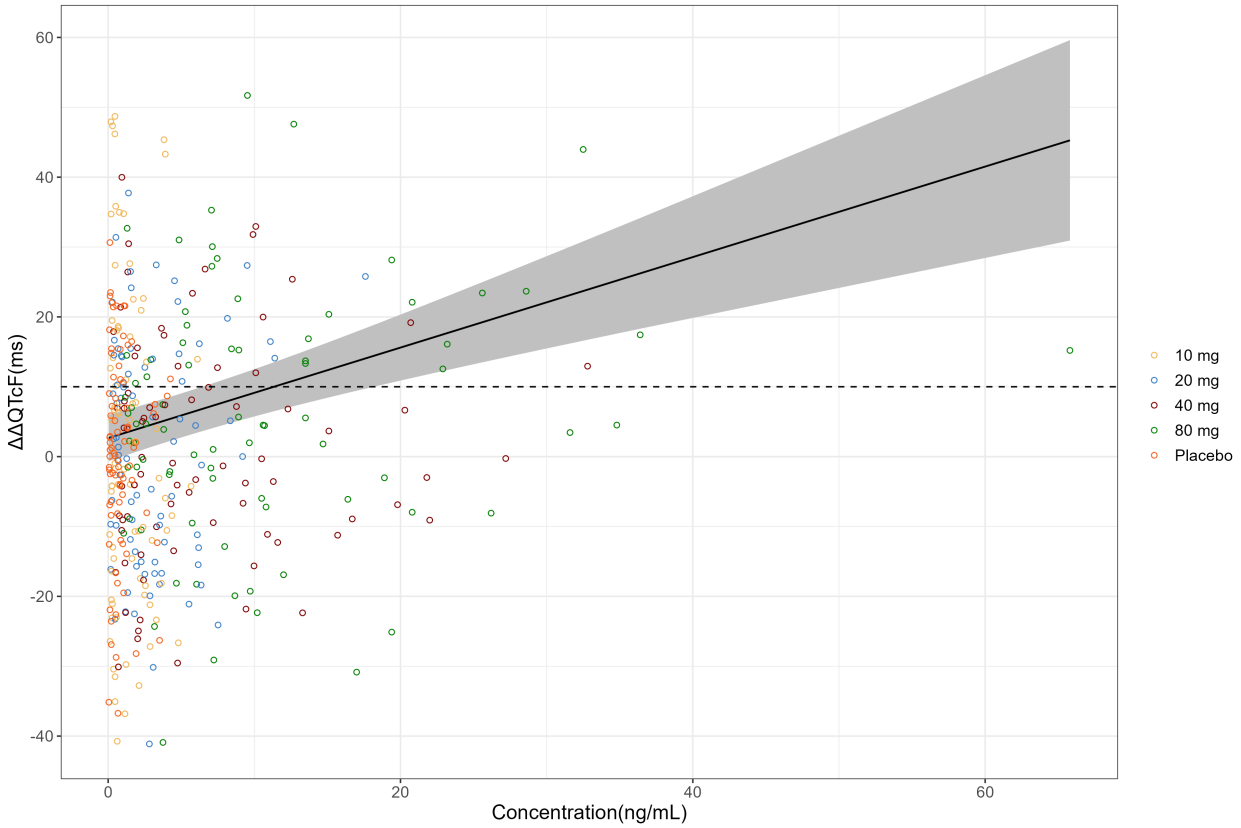

Figure 15: $\Delta\Delta$QTcF versus drug concentration scatter plot

From Figure 14 and 15, the model predicted $\Delta\Delta$QTcF values are close to the observed $\Delta\Delta$QTcF values across entire concentration intervals.

In the other hand, generally, systematic bias indicates model misspecification. For example, model predictions will be negatively biased at high values when PK/PD hysteresis is ignored and model predictions will be positively biased at high values when a linear model is applied to nonlinear data. Thus another way to evaluate the model and show the relationship between observed $\Delta\Delta$QTcF versus model predicted $\Delta\Delta$QTcF is to draw a scatter plot with loess smooth line (Figure 16).

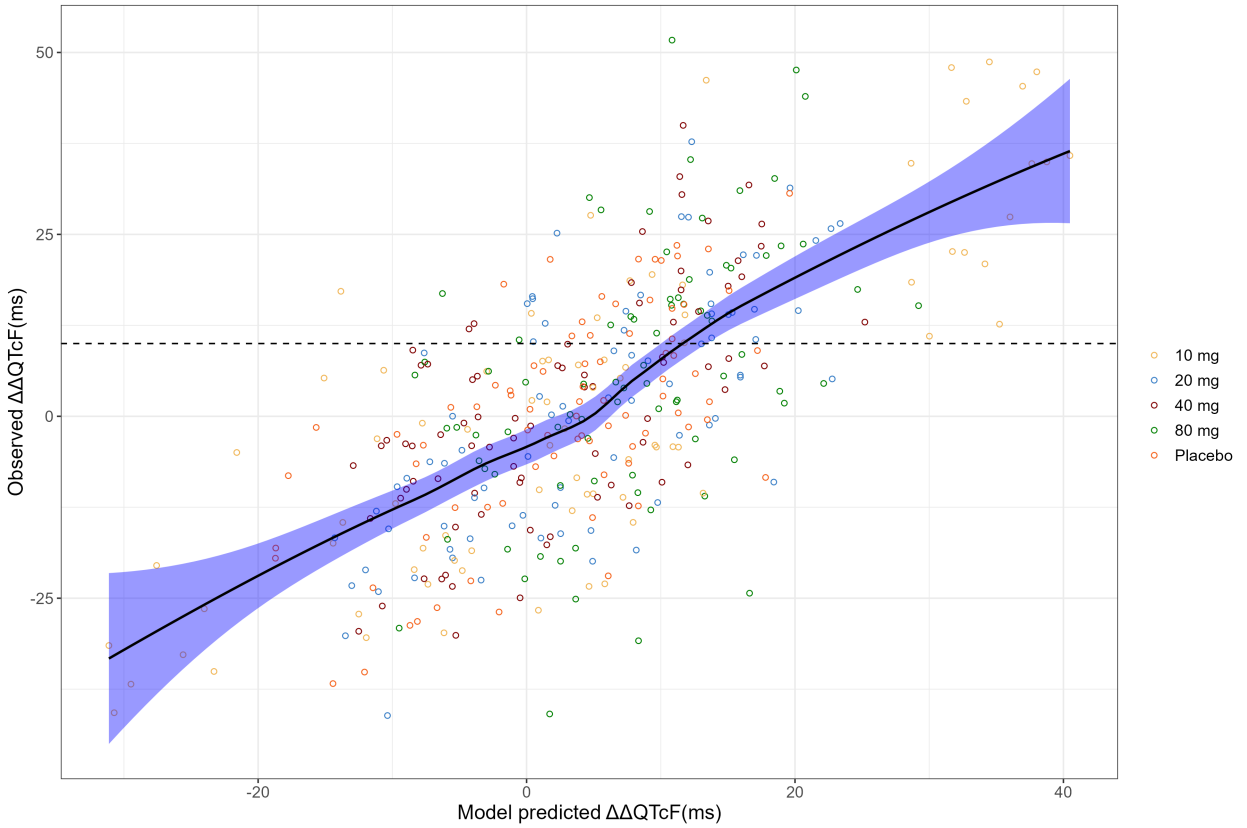

Figure 16: Scatter plot of observed $\Delta\Delta$QTcF versus model predected $\Delta\Delta$QTcF

Estimates of model

PK/QTc population

Parameter	Estimation	SE	DF	t-value	p-value	90% CI
CBASE	-0.9465	0.0648	45.86	-14.5951	0	(-1.0554, -0.8376)
PTRTAN	2.6554	2.0338	35.61	1.3057	0.2	(-0.7791, 6.09)
AVISTPTN0.5	-4.8986	2.4821	120.22	-1.9736	0.0507	(-9.013, -0.7843)
AVISTPTN1	-4.5933	2.5413	132.8	-1.8075	0.073	(-8.8027, -0.3839)
AVISTPTN2	-0.3518	2.6048	139.99	-0.135	0.8928	(-4.6648, 3.9613)
AVISTPTN4	-3.6614	2.5039	122.1	-1.4623	0.1462	(-7.8114, 0.4885)
AVISTPTN8	2.9332	2.4732	116.43	1.186	0.238	(-1.1675, 7.034)
AVISTPTN12	-1.1971	2.4825	117.55	-0.4822	0.6306	(-5.3128, 2.9187)
AVISTPTN18	4.7788	2.4927	117.63	1.9171	0.0577	(0.646, 8.9115)
AVISTPTN24	2.4144	2.496	117.62	0.9673	0.3354	(-1.7237, 6.5526)
CONC1	0.6477	0.1526	15.68	4.2437	6e-04	(0.3809, 0.9144)

Figure 17: Model estimation

From Figure 16, model and observed values are fall around the line of unity without evidence of systematic bias. Combining the model parameter estimates for the intercept, slope, and time effect of the linear mixed-effects model, as well as their standard errors, 90% confidence intervals, and p-values in Figure 17, which could be interactive in the shiny APP, we can conclude that all these reports indicate the model fits the data well.

As for evaluation of residuals, both scatter plots and quantile plots are useful representations of the residuals for continuous model parameters (e.g., concentrations, baseline QTc) and boxplots are useful for categorical parameters (e.g., time, treatment). Figure 18 provides some of residual plots as an example from shiny APP.

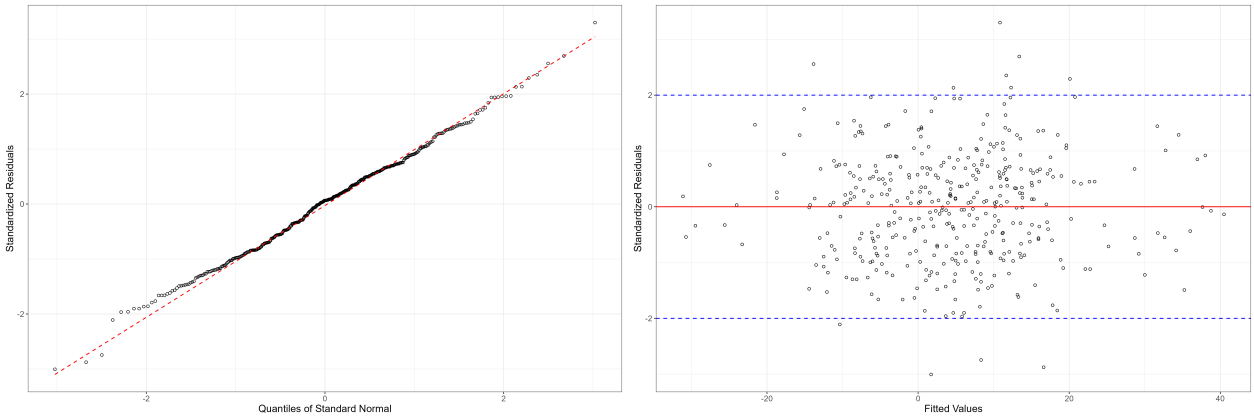

Figure 18: Residual plots

Model predicted value at concentration of interest

With the fitted linear mixed model, we can have some critical values at the concentration of interest. The Figure 19 shows the placebo adjusted QTcF change from baseline at each geometric mean of peak concentration of each subject within each visit of each dose group. In the meanwhile, since The dashed horizontal line indicates the regulatory threshold of 10 ms for $\Delta\Delta$QTcF, we can get the exact concentration that make the upper limit of $\Delta\Delta$QTcF first reach the threshold as well.

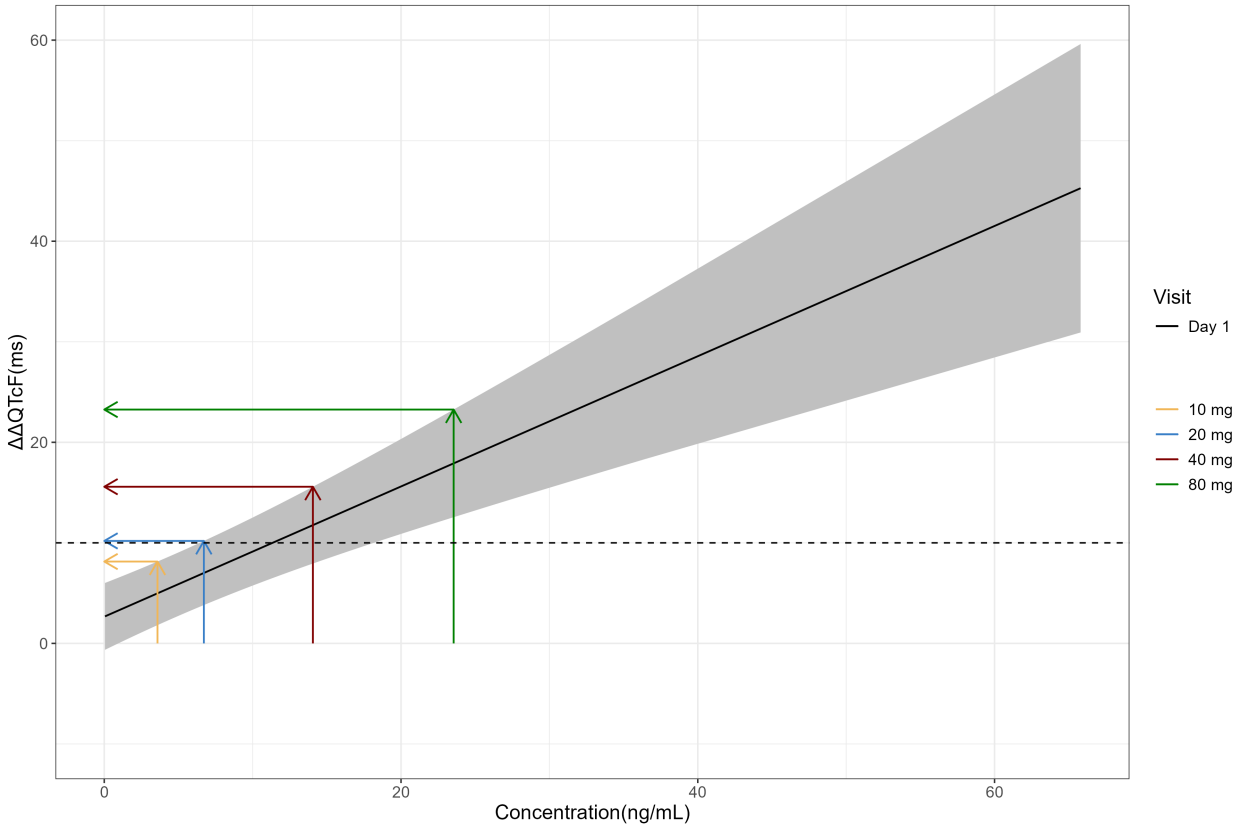

Figure 19: $\Delta\Delta$QTcF versus concentration with associated predictions shown by arrows at mean C_{max} by dose

CONCLUSION

This paper provides the whole process, methodology, model coded by R and reports visualized by R shiny APP on how to plan and conduct definitive QTc assessment of a drug using C-QTc modeling in early phase clinical pharmacology and TQT studies. The process refers to the white paper which is based on current best modeling practices, examples in scientific literature, and industry experiences.

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CONTACT INFORMATION

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