# Effect of Model Overparameterization in QT Analyses

***Background:*** The purpose of this simulation was the test the impact of using the prespecified linear mixed effect model compared to a reduced model containing only statistically significant terms on Type I error rate, confidence interval, and declaring QT prolongation greater than 10 msec.

***Simulation:*** Concentration-QT data were simulated from a hypothetical SAD study using 6 subjects per dose level and 6 dose levels: 0, 100, 500, 1000, 1500, and 1750 mg. True concentration data measured without error were simulated from a 1-compartment model with first order absorption having the following mean parameters: Ka=0.7 per h, CL=12 L/h, and V=400 L with 33% between subject variability for each parameter. Observed concentrations were calculated by adding 10% log-normally distributed random error to each true concentration. Under this model, drug concentrations ranged from 0 to ~ 5000 ng/mL.

Individual predose QTcF data were simulated as follows:



where 400 msec was the population mean, ηintercept was normally distributed random error with a standard deviation of 12 msec, *Slope* was the slope of drug concentration-QT relationship which was systematically varied from 0 to 0.1 msec/ng/mL, ηslope was normally distributed random error with a standard deviation of 0.002 msec/ng/mL, *Concentration* was the true drug concentration at the time of the ECG, and ε was normally distributed random error with a standard deviation of 4 msec. A total of 3 predose ECGs were simulated and the baseline was taken as the mean of the three replicates. dQTcF intervals were then computed as:

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Paired post-dose concentration-QTcF intervals were collected at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing.

The data were first analyzed using the prespecified linear mixed effects model defined in the white paper using Proc Mixed using Treatment (0=placebo, 1=active), nominal time, deviation of baseline from the population mean of 400 msec, and observed drug concentration as fixed effects. Nominal time was treated as factor level data. Intercept and drug concentration were treated as unstructured random effects. Denominator degrees of freedom (DDFM) for the F-test testing statistical significance of the model parameters was calculated using either the Kenward-Rogers (KR) method or Satterthwaite’s approximation (SAT). Parameters were estimated using either maximum likelihood (ML) or restricted maximum likelihood (REML). Placebo-corrected dQTcF intervals (ΔΔQTcF) were then estimated at 5 different concentration levels: 250, 750, 1500, 2500, and 4000 ng/mL, assuming a change from baseline equal to the mean predose baseline (400 msec). Because the data generating mechanism consisted of only the intercept and drug concentration, the prespecified linear mixed effects model was specifically overparameterized.

Fixed effects that were not statistically significant (p < 0.05) in the overparameterized model were then removed. Further, variance components that were < 1E-6 were removed from the model. The reduced model was then fit using ML or REML. DDFM were estimated with KR or SAT using the Mixed procedure in SAS. ΔΔQTcF intervals were then estimated at the same concentrations as in the overparameterized model: 250, 750, 1500, and 4000 ng/mL, assuming a change from baseline equal to the mean predose baseline (400 msec). These were the results from the reduced model.

The ratio of the predicted mean dQTcF interval at each concentration level tested (250, 750, 1500, 2500, and 4000 ng/mL), standard error of the prediction, and upper 1-sided 95% confidence interval (u1sCI) of the predictions from the overparameterized model to the reduced model were calculated. Whether the 2-sided 90% confidence interval contained the true dQTcF value was determined and set equal to 1 for ‘yes’ and 0 for ‘no’. Whether the u1sCI was greater than 10 msec was determined and set equal to 1 for ‘yes’ and 0 for ‘no’. Lastly, when the true slope was 0, whether the 2-sided 90% confidence interval contained zero was determined and set equal to 1 for ‘yes’ and 0 for ‘no’. A total of 250 simulations were done for each level of slope, estimation method, and DDFM method tested.

The mean ratio of the overparameterized to the reduced model was calculated for the point estimates, standard error of the estimate, and u1sCI. The percent coverage was calculated as the percent of simulations that contained the true drug effect. The percent of simulations where the u1sCI was greater than 10 msec was calculated. These estimates were calculated for each level of drug concentration tested and slope examined. Further, the Type I error rate was determined.

**Results:**  Figure 1 shows the median ratio of the overparameterized model to the reduced model for the parameter estimates, standard errors, and u1sCI for each level of concentration examined when all models were fit using maximum likelihood. Figure *2* shows the same data with a scale of 0.8 to 1.4. Neither the estimation method nor method used to estimate the denominator degrees of freedom (DDFM) had any effect on the results. Therefore, the results will focus on maximum likelihood estimation and Kenward-Roger approximation to DDFM (Figure *3*).

In general, the predictions made by the models and the differences between the overparameterized and reduced model were sensitive to the choice of concentration used in the estimation and did not depend on the number of samples collected for the analysis, the estimation method, or method used to estimate DDFM. When the concentration value was 250 ng/mL, there were very large differences between the standard errors and u1sCIs, regardless of the slope. But as the slope increased, i.e., as the signal increased, the standard errors and u1sCIs decreased and became closer and closer to 1. At 2500 ng/mL the differences between the overparameterized and reduced models were < 20%. Interestingly, although the width of the confidence intervals increased as the concentration value increased, the width of the confidence intervals relative to the point estimate remained a constant. For example, Table 1 shows the results from 1 iteration of the simulations using the prespecified linear mixed effects model when the slope was 0.0050.

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| **Table 1: Results from 1 iteration of the simulation when the slope was 0.0050.** | | | | |
| ***Concentration Value*** | ***Point Estimate*** | ***Lower 90% CI*** | ***Upper 90% CI*** | ***Width/Estimate*** |
| 250 | 1.24 | 1.00 | 1.47 | 0.39 |
| 750 | 3.71 | 2.99 | 4.42 | 0.39 |
| 1500 | 7.41 | 5.99 | 8.84 | 0.39 |
| 2500 | 12.36 | 9.98 | 14.7 | 0.39 |
| 4000 | 19.77 | 15.96 | 23.7 | 0.39 |
| Model estimation done using maximum likelihood. DDFM estimated using Kenward-Rogers Approximation. | | | | |

Figure 4 shows a panel plot of the coverage of the 2-sided 90% confidence interval for containing the true drug effect. There were some differences between models but not large ones. By and large, coverage remained between 85% and 90% for both the overparameterized and reduced models under all conditions.

Table 2 presents the Type I error rates for the models. Number of samples, estimation method, and DDFM had no impact on the Type I error rate. The Type I error rate was near its nominal value of 0.10 for both the overparameterized model and reduced model. There was no evidence of Type I error inflation with the overparameterized model.

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| **Table 2: Type 1 Error Rate For the Slope** | | | |
| ***DDFM*** | ***# of Samples*** | ***Overparameterized Model*** | ***Reduced Model*** |
| Kenward-Rogers | 6 | 10.3 | 10.3 |
|  | 9 | 7.91 | 10.7 |
|  | 13 | 13.0 | 13.0 |
| Sattterthwaite | 6 | 12.6 | 11.1 |
|  | 9 | 9.88 | 11.1 |
|  | 13 | 14.6 | 13.4 |
| Model estimation done using maximum likelihood. | | | |

Figure *5* presents a series plot of the percent of simulations where the u1sCI exceeded 10 msec. Despite some of differences in standard errors and u1sCI, under most conditions there was no difference in the percent of simulations where the u1sCI exceeded 10 msec. That is not to say there were no differences. Under certain conditions, e.g., 6 samples at 750 ng/mL when the slope was 0.01 msec/ng/mL, there did appear to be a difference between the overparameterized and reduced model with the overparameterized model being more likely to exceed the 10 msec threshold.

**Discussion:** These results show that using an overparameterized model can result in situations where the u1sCI can exceed 10 msec because of the increased standard error of the estimate. There was, however, no evidence that the overparameterized model biased the slope or point estimate. It is important that phase 1 studies to be used to replace the TQT study have adequate number of subjects to avoid either false positive results or inconclusive results when applying the pre-specified model. The results of this simulation were based on assuming a linear relationship between concentration and effect give that the true data generating mechanism was in fact linear. How these results would hold in a nonlinear concentration-effect relationship is not known, but it is likely the recommendation with regards to model reduction will still hold.

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| The SGPanel Procedure |
| Figure 1: Panel plot of the median ratio comparing the overparameterized model to the reduced model for the prediction estimates, their standard errors, and 1-sided upper 95% confidence interval for each level of estimate (Cmax) examined. All models were fit using maximum likelihood (ML). |
| The SGPanel Procedure |
| Figure 2: Same figure as Figure 1 with Y-axis scaled from 0.8 to 1.5. |

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| The SGPanel Procedure |
| Figure 3: Panel plot of the median ratio comparing the overparameterized model to the reduced model for the prediction estimates, their standard errors, and 1-sided upper 95% confidence interval for each level of estimate (Cmax) examined. All models were fit using maximum likelihood (ML) with Kenward-Rogers approximation to the DDFM. |

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| The SGPanel Procedure |
| Figure 4: Panel plot of the coverage (whether the 2-sided 90% confidence interval contained the true drug effect). For a 90% confidence interval, the coverage should be near 90%. Black line is the reference line of 90%. Models were estimated using maximum likelihood with KR DDFM. |

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| The SGPanel Procedure |
| Figure 5: Panel plot of percent of simulations where the 1-sided upper 90% confidence interval exceeded 10 msec. Models were estimated using maximum likelihood with KR DDFM. |

Appendix: SAS Code

Overparameterized Model Using Proc MIXED with Maximum Likelihood and Kenward-Rogers Approximation to the DDFM:

proc mixed data=concqt method=ml maxiter=**2000** scoring=**5** convg=**1E-6** convf=**1E-6**;

class sid nomtime;

model dqtcf = trt nomtime chgbase conc / ddfm=kr solution;

random intercept conc / subject=sid type=un;

estimate '250' trt **1** conc **250** / cl alpha=**0.10**;

estimate '750' trt **1** conc **750** / cl alpha=**0.10**;

estimate '1500' trt **1** conc **1500** / cl alpha=**0.10**;

estimate '2500' trt **1** conc **2500** / cl alpha=**0.10**;

estimate '4000' trt **1** conc **4000** / cl alpha=**0.10**;

run; quit;