Concentration-QTc Assessment in Early Phase Trials

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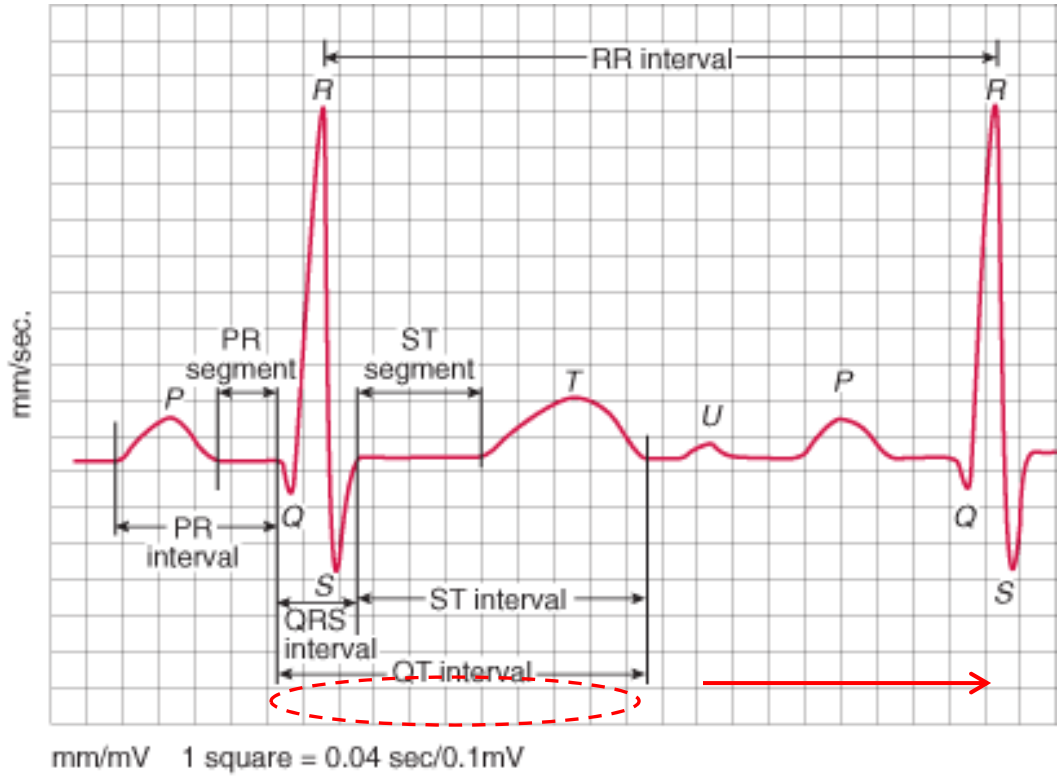
MERCK
Be well

QT and QTc Interval



RR=60/HR
(HR= heart rate)

QT prolongation increases the risk of sudden death

- QT and HR (hence RR) are correlated, so a HR "corrected" QTc is used for analysis: $QTc=QT/RR^b$
- Ideal "b" is such that corr(QTc, RR)=0.
  - b=1/3 (Fridericia's correction) is most common, but population and subject-specific b's are also popular

Background and Key Message

- In December 2015, ICH released 'E14 Q&A (R3)' supporting concentration-QTc (C-QTc) modeling to assess QT prolongation.
  - The C-QTc data could come from first-in-human single-ascending dose (SAD) trials, multiple-ascending dose (MAD) trials, or other trials.
  - If there is an intention to pool data from multiple trials, it is important to test for heterogeneity.
- We show that the power of C-QTc model to claim no QT prolongation using data combining SAD and MAD trials is only slightly higher than using SAD trial alone when the C-QTc association across SAD and MAD trials are consistent.
- We show that our proposed C-QTc model‡ (Method M2) has better power than the C-QTc model in the white paper† (Method M1) and is adequate to reliably quantify the C-QTc association using SAD trial data, making a TQT study unnecessary in most cases.

† Garnett C et al, Scientific white paper on concentration-QTc modeling, J Pharmacokinet Pharmacodyn. 2018; 45 (3): 383-397.

‡ Mehrotra DV, Fan L, Liu F, Tsai K. Enabling Robust Assessment of QTc Prolongation in Early Phase Clinical Trials. Pharm Stat. 2017;16 (3):218-227.

Objectives of C-QTc Assessment in Early Phase Trials

- **Objective #1: guide early phase clinical development**

  Determine the highest "safe" concentration (C_safe) and/or dose level in terms of QTc prolongation.

  Definition of "safe": 90% CI for true mean ΔΔQTc is < 10 msec. (ΔΔQTc means placebo-subtracted QTc change from baseline)

  C_safe is used for go/no-go, dose selection for next trial, etc.

- **Objective #2: enable a TQT waiver in late phase development**

  Later in development, use the C-QTc model to forecast the outcome of a TQT study based on predictions at expected Cmax levels for the clinical and supra-therapeutic doses.

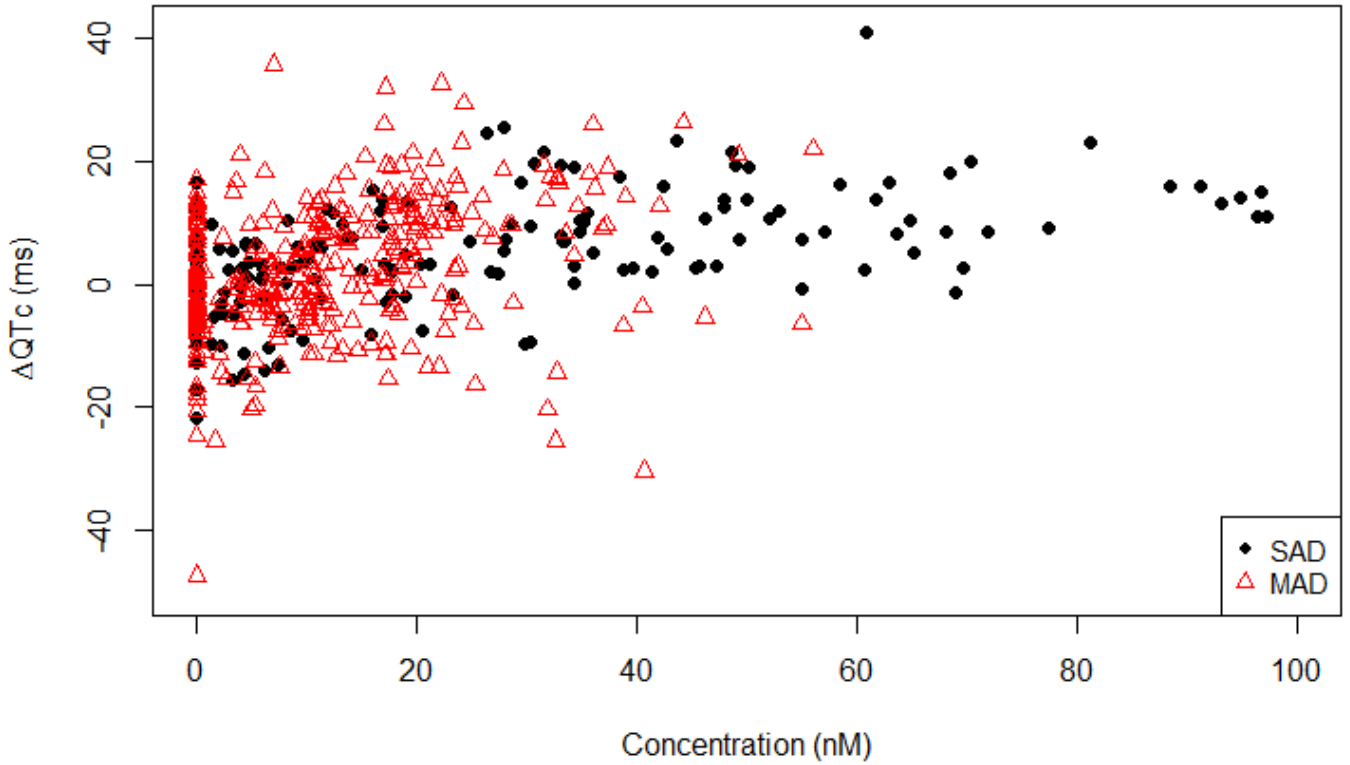
Typical SAD/MAD Trial Design at Merck

SAD: Alternating panel crossover, 4 periods, 8 dose levels, total N = 16

MAD: Parallel design with 3 dose levels

Study	Panel	Number of subjects	Period 1	Period 2	Period 3	Period 4
SAD (Holter ECG)	A	N=2	Placebo	DOSE 3	DOSE 5	DOSE 7
		N=2	DOSE 1	Placebo	DOSE 5	DOSE 7
		N=2	DOSE 1	DOSE 3	Placebo	DOSE 7
		N=2	DOSE 1	DOSE 3	DOSE 5	Placebo
	B	N=2	Placebo	DOSE 4	DOSE 6	DOSE 8
		N=2	DOSE 2	Placebo	DOSE 6	DOSE 8
		N=2	DOSE 2	DOSE 4	Placebo	DOSE 8
		N=2	DOSE 2	DOSE 4	DOSE 6	Placebo
MAD (Non-Holter ECG)	A	N=6	DOSE 3	***NOTE*: DOSE 1 = 10 mg** ***DOSE 2 = 50 mg*** ***DOSE 3 = 100 mg*** ***DOSE 4 = 150 mg*** ***DOSE 5 = 200 mg*** ***DOSE 6 = 300 mg*** ***DOSE 7 = 400 mg*** ***DOSE 8 = 600 mg***		
		N=2	Placebo			
	B	N=6	DOSE 5			
		N=2	Placebo			
	C	N=6	DOSE 7			
		N=2	Placebo			

Motivating Example: Real SAD/MAD Trial



Modeling Objective

Estimate highest concentration for which true mean ΔΔQTc < 10 msec (C_safe)

Analysis Steps

1. Fit C-QTc model (How?)
2. From model fit, find highest concentration for which upper bound of 90% CI for true mean ΔΔQTc < 10 msec

Two C-QTc Modeling Approaches

- Base model for both methods:

  ΔQTc ~ intercept + predose_QTc + (slope x conc) + time* + TRT §+ residual

  *: categorical time level to adjust for diurnal variation in ΔQTc

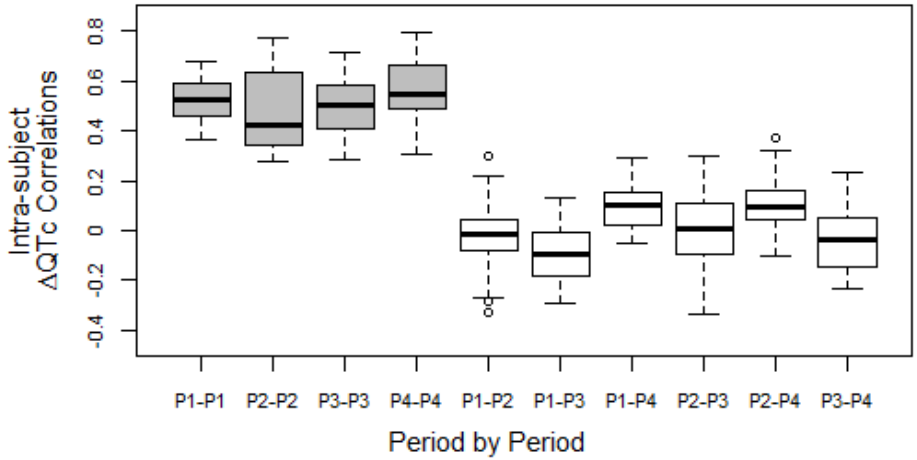
  §: treatment indicator, TRT=0 if receiving placebo, TRT=1 if receiving active drug

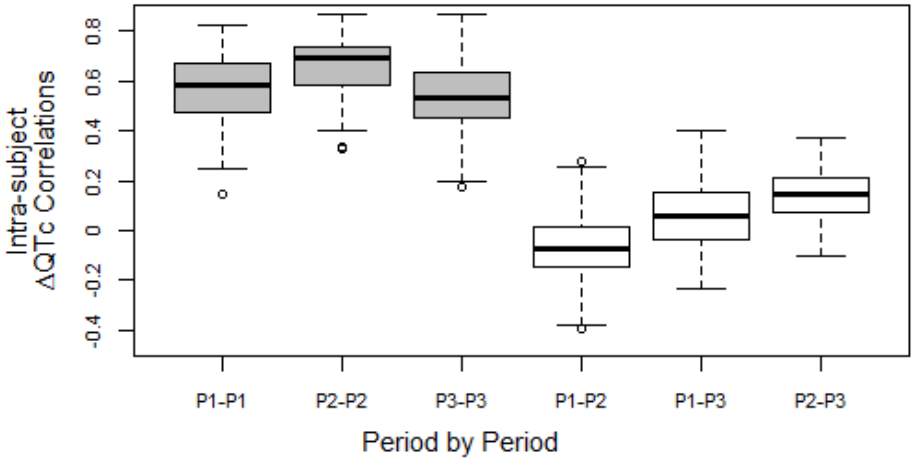
- **Method M1: random intercept and random slope model**
  - Different, potentially correlated subject-level random Gaussian components are added to both intercept and slope by studies;
  - Does not leverage within/between-period feature of SAD study design

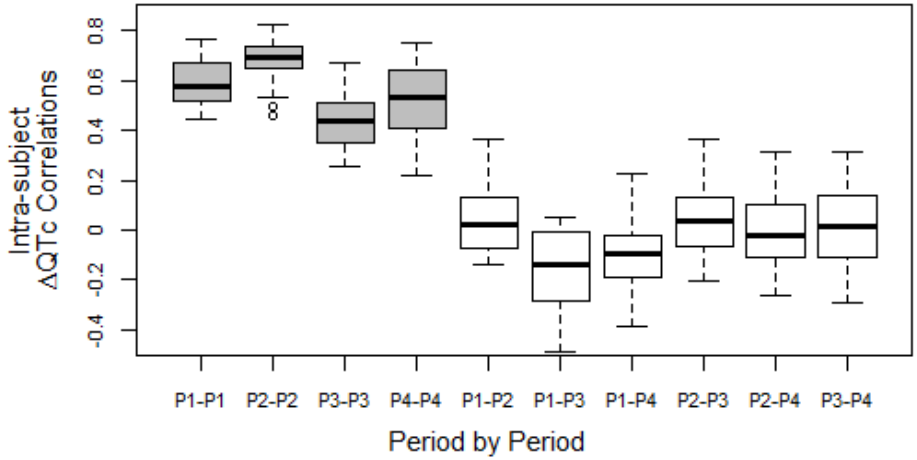
- **Method M2: dual compound symmetry (CS) model (details in paper)**
  - Different intra-subject QTc correlations are assumed for between and within dosing periods by studies (supported by real TQT and SAD study with Holter ECG)

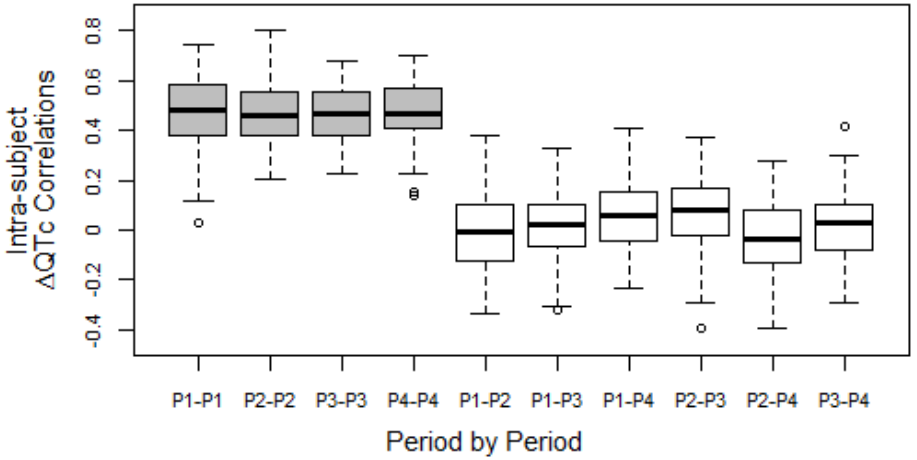
Four Crossover TQT Trials: Correlation Box-Plots

Within-period correlations are larger than between-period correlations



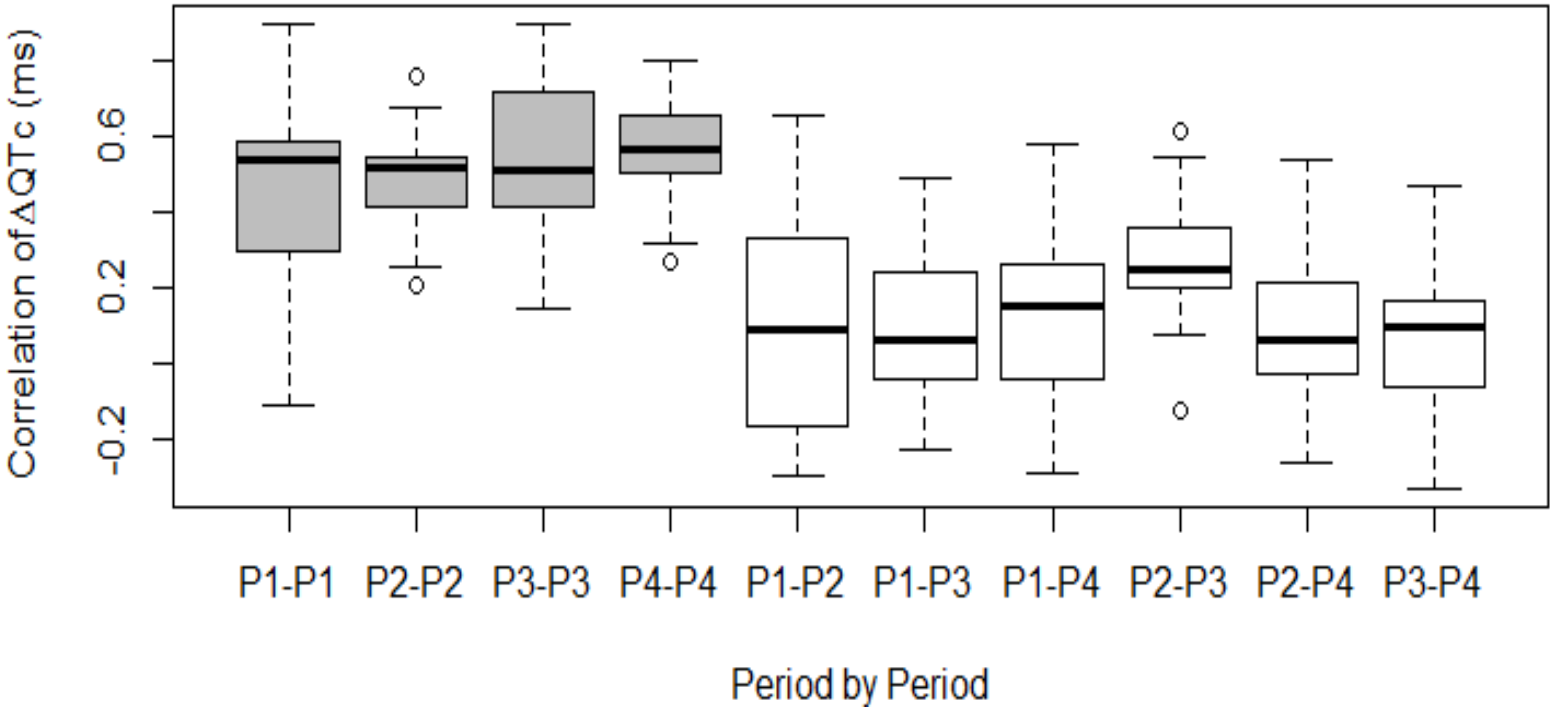






Motivating Example: Correlation Box-plots

Within-period correlations are larger than between-period correlations



SAS Codes for the Two Methods

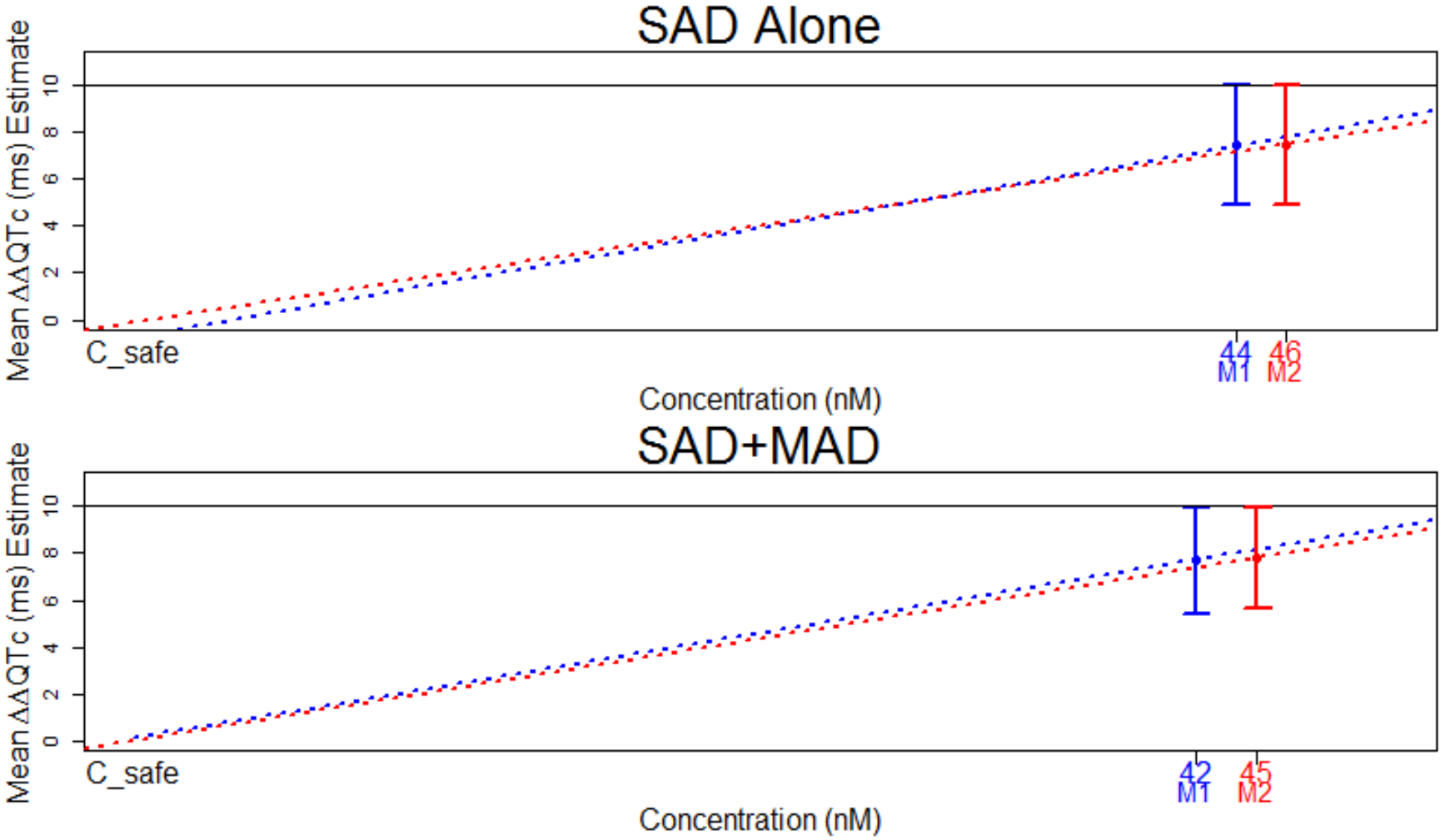
Method M1

```
PROC MIXED DATA=dataset;
  CLASS time subjid study trt;
  MODEL dQTc = predoseQTc  time  conc trt/DDFM=KR;
  RANDOM  intercept conc/SUBJECT=subjid type=UN group=study;
RUN;
```

Method M2

```
PROC MIXED DATA=dataset;
  CLASS time period subjid study trt;
  MODEL dQTc = predoseQTc  time  conc trt/DDFM=KR;
  RANDOM subjid/ group=study;
  REPEATED/SUB=subjid*period   TYPE=CS   group=study;
RUN;
```

Two Methods Applied to the Motivating Example



Two Methods Applied to the Motivating Example (continued)

Data	Parameters	M1 Random Int & Slope	M2 Dual CS
SAD Alone	Slope Estimate	0.185	0.165
	(Std. Error)	(0.033)	(0.029)
	C_safe	44.0	46.0
	AICC	1306	1300
SAD+MAD	Slope Estimate	0.179	0.174
	(Std. Error)	(0.031)	(0.026)
	C_safe	42.4	44.9
	AICC	4021	4009

M2 consistently delivers 'best' fit in crossover SAD datasets and SAD+MAD datasets

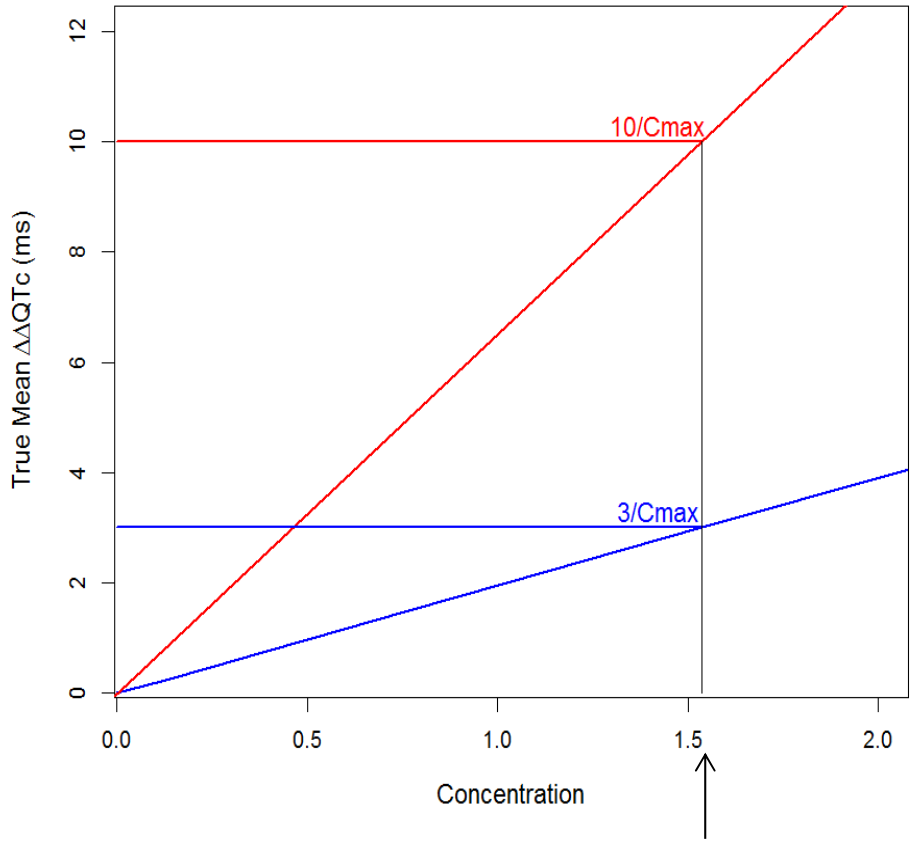
Datasets	Example	M1 Random Int & Slope	M2 Double CS
SAD	Example 1	2989	2953
	Example 2	3165	3159
	Example 3	2028	2027
	Example 4	1799	1797
	Example 5	2201	2186
SAD+MAD	Example 6	7350	7193
	Example 7	5039	5031

$$AICC = 2k - 2\ln(L) + 2k(k+1)(n-k-1)^{-1}$$

In all 7 examples, the observed AICC ordering was:
M1 > M2 (lower is better)

What Dataset should be Used in the C-QTc Model? Which Method is More Reliable?

We **simulated** a typical Merck SAD and MAD trials under two scenarios



600 mg is not safe

600 mg is safe

True mean Cmax for highest simulated dose (Single dose 600 mg)

Assumption: C-QTc relationship are the same across SAD and MAD trials.

Simulation Result - % Bias and 90% CI Coverage

Scenario	Method	% Bias of Slope Estimate		% Coverage* (% Simulation where 90% CI contained true mean ΔΔQTc at 600 mg)	
		SAD Alone	SAD+ MAD	SAD Alone	SAD+ MAD
3/Cmax	M1	1.9	3.7	90.5	88.6
(600mg is safe)	M2	-1.6	1.9	88.9	89.2
10/Cmax	M1	0.6	1.1	90.5	88.6
(600mg is not safe)	M2	-0.5	0.6	88.9	89.2

Simulation Result - % of simulations where 600 mg was declared safe

Scenario	Method	% of simulations where 600 mg was declared safe	
		SAD Alone	SAD+MAD
3/Cmax	M1	80.0	87.7
(600mg is safe)	M2	**88.3**	**92.0**
10/Cmax	M1	3.6	4.4
(600mg is not safe)	M2	4.3	4.4

Conclusions

- Our proposed methodology (Method M2) outperforms Method M1 and is adequate to reliably quantify the C-QTc association using SAD trial data, making a TQT study unnecessary in most cases.

- Assuming the concentration-QTc association is the same across SAD and MAD trials, the power to claim no QT prolongation using SAD+MAD is only slightly higher than SAD alone.

- If the assumption of same concentration-QTc association across SAD and MAD trials is wrong, power of SAD+MAD could be lower than SAD alone.

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