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ORIGINAL ARTICLE

Cardiovascular Safety Assessment in Early-Phase Clinical Studies: A Meta-Analytical Comparison of Exposure-Response Models

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Exposure-response analysis of QT interval in clinical studies has been proposed as a thorough QT study alternative. Many exposure-response model structures have been proposed for cardiovascular (CV) safety markers, but few studies have compared models across multiple drugs. To recommend preferred drug-effect exposure-response models on vital signs and electrocardiogram (ECG) intervals, an individual-level model-based meta-analysis (39 studies and 1,291 subjects) compared 90 model structures. Models were selected to describe the data and cross-validate studies on the same drug. The most commonly selected baseline model was an unstructured model (estimation of a value at each study nominal time) for all measures but blood pressure. The unstructured model estimated a better cross-validated drug-effect when considering all markers. A linear model was the most commonly selected to characterize drug-effect on all markers. We propose these models as a starting point assisting with CV safety exposure-response assessment in nondedicated small studies with healthy subjects.
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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Different exposure-response models have been proposed for CV safety markers, but few studies compared models predictions across multiple drugs.
WHAT QUESTION DID THIS STUDY ADDRESS?
☑ What are the preferred models assessing exposure-response on vital signs and ECG intervals in phase I studies?
WHAT THIS STUDY ADDS TO OUR KNOWLEDGE
☑ The preferred baseline model was an unstructured model (estimation of a placebo-value at each study nominal time) for all CV markers but BP. The unstructured model provided a better cross-validated drug-effect when aggregating CV markers. A linear model was the most commonly selected to characterize drug-effect on all CV markers.
HOW THIS MIGHT CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS
☑ The model structure comparison supports and extends ongoing efforts to update the International Conference on Harmonisation E14 guidance with a model-based assessment of exposure-response. By prespecifying preferred and alternative models in the phase I analysis plans and criteria for model selection, we hope to reduce the need for dedicated studies on CV safety marker assessment (for example, the thorough-QT study).

Cardiac safety concerns are a leading cause for the withdrawal of marketed drugs and discontinuation of drug development programs regardless of their indication.[1] QT interval, heart rate (HR), and blood pressure (BP) are well-established markers of cardiovascular (CV) events. Abnormal BP and HR are risk factors for stroke, heart failure, and myocardial infarction.[2–7] QT interval prolongation is a risk factor for torsade de pointes.[8,9]

Given the potential for unwanted CV effects, early characterization of the drug-exposure relationship on QT interval, HR, and BP in phase I studies can be influential in: (a) decision-making for continuing development; (b) establishing electrocardiogram (ECG) monitoring requirements for late-phase clinical studies; and (c) defining label recommendations.[10,11] Recently, a prospective study by the International Consortium for Innovation and Quality in Pharmaceutical Development-Cardiac Safety Research Consortium provided evidence that intense ECG assessment with simultaneous pharmacokinetic (PK) sampling in single ascending dose (SAD) and/or multiple ascending dose (MAD) studies can serve as an alternative to the thorough-QT study.[12]

Despite SAD and MAD studies being well-suited for CV safety assessment, there are limited published studies on the topic. Moreover, modeling of CV effects for non-CV drugs often focuses on QT interval prolongation,[13–20] and reported exposure-response or PK-pharmacodynamic analysis of drug-effects on BP, HR, or QT interval mostly involves drugs for which these CV markers are a target pharmacological action (e.g., antihypertensive and antiarrhythmic agents).[21–37] Nevertheless, a wide range of non-CV drugs have evidence of off-target CV effects and, hence, risk.[3,13]

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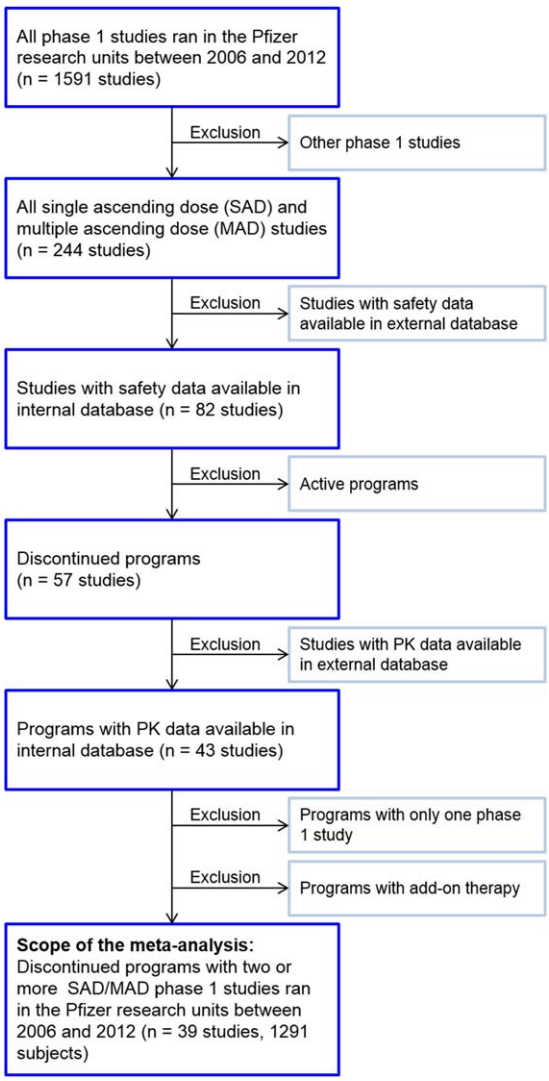

Figure 1 Study selection metrics. PK, pharmacokinetic.

To recommend a suite of exposure-response models assessing drug-effect on QT interval, HR, and BP in SAD and MAD studies and determine if one structure was most often selected, we conducted an individual-level model-based meta-analysis evaluating a variety of mixed-effects models. Models were compared for ability to describe the observed data and cross-validate drug-effects across different studies on the same drug. To our knowledge, this is the largest and most comprehensive meta-analysis on exposure-response modeling for assessment of CV safety.

METHODS

Studies data

We selected drug-development programs with two or more SAD and/or MAD phase I studies that ran in the Pfizer clinical research units between 2006 and 2012, following the steps outlined in **Figure 1**. All studies followed Good Clinical Practice, adhered to the Declaration of Helsinki, received institutional review board or ethics committee approval, and all subjects had documented informed consent before initiation of study procedures. An initial pool of 1,591 phase I studies resulted in 43 SAD/MAD studies meeting the study inclusion criteria. An additional three studies were excluded as they were the only study available for the respective investigational drugs, and one study was excluded because of the presence of add-on therapy. Therefore, 39 SAD or MAD phase I studies remained for analysis, encompassing 18 parent drugs, 2 active metabolites, and a total of 1,291 subjects (**Table 1**). PK data was obtained from the Pfizer electronic Non-Compartmental Analysis database. Vital signs, ECG, demographics, and dosing information were downloaded from the Pfizer phase I management system database using the Pfizer Automated Monitoring of Phase I tool.

SAD studies typically were dosed in the fasted state with water restrictions immediately before and 1–2 hours postdosing, and in SAD studies, the subjects were typically supine for ~4 hours postdosing. SAD studies typically have many assessments on day 1 with sparse measurements on subsequent days, and the subjects were typically inpatients for 3–4 days after dosing. MAD studies typically were dosed in the fed state with water restrictions immediately before and 1–2 hours postdosing, and the subjects were typically not restricted to be supine postdosing. MAD studies were typically 14 days in duration with many assessments on days 1 and 14 and sparse measurements on intermediate days. Subjects in MAD studies were typically inpatients through day 16 after the first dose. General procedures for ECG, vital signs (BP and pulse rate (PR)) and PK assessments were similar across studies. Intense ECG/vital signs assessment along with PK sampling were performed in each study with a median of 17 (range, 5–77) simultaneous PK and vitals or ECG interval measurements per subject in a given treatment. When simultaneous, the order of assessments was ECG, then vital signs, and then PK.

Electrocardiogram assessments

Scheduled 12-lead ECG assessments were performed after the subject rested quietly ≥10 minutes in a supine position. Triplicate 12-lead ECGs were obtained ~2–4 minutes apart.

Blood pressure and pulse rate assessments

BP and PRs were recorded after resting supine for 5 minutes. BP was measured with the subject's arm supported at the level of the heart and recorded to the nearest mm Hg. The same arm (preferably the dominant arm) was used throughout the study. Recordings were typically obtained in single or triple measurements pre-dose and as single assessments at other protocol-specified times. Each BP measurement used the same size cuff, properly sized and calibrated. Automated devices for measuring BP and PR were typically used; when manual, PR was measured in the brachial/radial artery for ≥30 seconds.

Pharmacokinetic assessments

PK assessments and sampling methods varied by protocol and compound. Typically, blood samples (4–5 mL) to provide 1.5–2 mL of plasma or serum for PK analysis were collected into appropriately labeled tubes with or without anticoagulant at specified times. Sample collection within 10% of the nominal time from dosing was not a protocol deviation, as long as the exact time of collection was

Table 1 Single ascending dose and multiple ascending dose phase I studies included in the analysis ($n = 39$).

Study ID	Parent drug	Metabolite	Pro-drug	Indication	Exclude metabolite? Reason	Total no. of subjects	No. of subjects who received placebo
A8121001	PF-00868554	–	–	Hepatitis C virus	–	16	16
A8121003	PF-00868554	–	–	Hepatitis C virus	–	33	8
A8341001	PF-02400013	–	–	Schizophrenia	–	25	25
A8341002	PF-02400013	–	–	Schizophrenia	–	32	8
A8641001	PF-03084014	–	–	Alzheimer disease	–	26	26
A8641002	PF-03084014	–	–	Alzheimer disease	–	51	14
A8811003	CP-70.429	–	PF-03709270	Antibacterial	–	35	15
A8811008	CP-70.429	–	PF-03709270	Antibacterial	–	24	0
A9131001	PF-03463275	–	–	Schizophrenia	–	28	28
A9131002	PF-03463275	–	–	Schizophrenia	–	24	6
A9541001	PF-03049423	–	–	Stroke	–	24	24
A9541002	PF-03049423	–	–	Stroke	–	48	14
B0011001	CP-70.429	–	PF-04064900	Antibacterial	–	9	9
B0151001	PF-04236921	–	–	Rheumatoid arthritis	–	33	12
B0151004	PF-04236921	–	–	Rheumatoid arthritis	–	10	0
B0171001	PF-03882845	–	–	Diabetic nephropathy	–	33	18
B0171002	PF-03882845	–	–	Diabetic nephropathy	–	10	2
B0581001	PF-04287881	–	–	Antibacterial	–	79	19
B0581002	PF-04287881	–	–	Antibacterial	–	39	7
B0861001	PF-04308515	–	–	Rheumatoid arthritis	–	27	25
B0861002	PF-04308515	–	–	Rheumatoid arthritis	–	58	10
B0911001	PF-04802540	PF-04831035	–	Schizophrenia	–	28	25
B0911002	PF-04802540	PF-04831035	–	Schizophrenia	–	40	8
B0961001	PF-04620110	–	–	Type 2 diabetes mellitus	–	27	26
B0961002	PF-04620110	–	–	Type 2 diabetes mellitus	–	73	18
B0961010	PF-04620110	–	–	Type 2 diabetes mellitus	–	60	35
B1071001	PF-04455242	–	–	Bipolar depression	–	18	18
B1071002	PF-04455242	PF-04831035	–	Bipolar depression	Yes. Metabolite is not analyzed across other studies on the parent drug.	36	9
B1171001	PF-02341272	PNU-101603 PNU-101244	–	Tuberculosis	–	19	19
B1171002	PF-02341272	PNU-101603 PNU-101244	–	Tuberculosis	–	59	10
B1521001	PF-04971729	–	–	Type 2 diabetes mellitus	–	24	24
B1521002	PF-04971729	PF-05217539	–	Type 2 diabetes mellitus	Yes. Metabolite is not analyzed across other studies on the parent drug.	40	8
B1701001	PF-04958242	–	–	Schizophrenia	–	24	24
B1701002	PF-04958242	–	–	Schizophrenia	–	20	4
B1701007	PF-04958242	–	–	Schizophrenia	–	39	8
B2911001	PF-05161704	PF-05200145	–	Type 2 diabetes mellitus	–	18	18
B2911002	PF-05161704	PF-05200145	–	Type 2 diabetes mellitus	–	32	8
B3301001	PF-05190457	–	–	Type 2 diabetes mellitus	–	35	32
B3301002	PF-05190457	–	–	Type 2 diabetes mellitus	–	35	11

Excluded compounds are highlighted in gray.

recorded. Samples were analyzed using validated analytical methods.

Meal schedule

Typically, breakfast was consumed $\leq$30 minutes before dosing (if dosed in the fed state), a standard lunch was provided at $\sim$4 hours after the first drug dosing, and a standard dinner was provided at $\sim$9–10 hours after morning dosing. A post-dinner evening snack may have been permitted. Meal schedules may have been altered from the typical schedule. The first drug dosing typically occurred at approximately 8:00 AM.

Model building

In total, 90 models were tested for each study and each endpoint. The baseline models (5 structures), drug effect models (3 structures).

Independent and dependent variables

The independent variable of the exposure-response analysis was the plasma/serum concentration of the parent drug. When present, the plasma/serum concentration of the active metabolite was also used (separately) as the independent variable. The dependent variables were RR interval, QT interval, Fridericia corrected QT interval (QTcF), systolic blood pressure (SBP), diastolic blood pressure (DBP), and PR. RR interval is the time between beats (time between QRS complexes) and is related to HR, as shown in Eq. 1. QT interval is related to QTcF, as shown in Eq. 2.

$$HR\ (beats\ per\ minute) = \frac{60}{RR\ interval\ (seconds)} \tag{1}$$

$$QTcF\ (milliseconds) = \frac{QT\ (milliseconds)}{\sqrt[3]{RR\ interval\ (seconds)}} \tag{2}$$

Investigated fixed-effects model structures

PubMed, OVID MEDLINE, and Embase were surveyed for model structures investigated to describe changes in SBP, DBP, PR, RR, QT, and QTcF intervals in the absence (baseline model) and presence of drug (baseline plus drug-effect model). For each study, we separately tested each baseline and drug-effect model pair. The selection of baseline and drug-effect model structures was based on exposure-response or PK-pharmacodynamic analyses of BP, PR/HR, or QT interval published in the scientific literature before August 2013 (**Supplementary Table S1**); models in $\geq$2 references were investigated. One additional baseline model estimating a mean value at each nominal time after the first dosing (unstructured model) was also included, as initially described by the authors of ref. 38 and a modified version is used by Darpo *et al.*[12] The investigated baseline and drug-effect model structures were as follows.

Baseline models

Time-invariant baseline: estimated pre-dose baseline value

$$Baseline = E_0 \tag{3}$$

Time-varying baseline: unstructured model, estimated baseline value at each nominal time after the first dosing:

$$Baseline\ (t) = \begin{cases} E_{0,t}, NTAFD == t \\ 0,\ NTAFD \neq t \end{cases} \tag{4}$$

Time-varying baseline: cosine (12-hour period) function:

$$Baseline\ (T) = Mean + Amplitude \cdot Cosine\left[\frac{2 \cdot \pi \cdot T}{12} - Shift\right] \tag{5}$$

Time-varying baseline: cosine (24-hour period) function:

$$Baseline\ (T) = Mean + Amplitude \cdot Cosine\left[\frac{2 \cdot \pi \cdot T}{24} - Shift\right] \tag{6}$$

Time-varying baseline: double cosine (12- and 24-hour period) function:

$$\begin{aligned} Baseline\ (T) = {} & Mean + Amplitude_1 \\ & \cdot Cosine\left[\frac{2 \cdot \pi \cdot T}{12} - Shift_1\right] + Amplitude_2 \\ & \cdot Cosine\left[\frac{2 \cdot \pi \cdot T}{24} - Shift_2\right] \end{aligned} \tag{7}$$

Drug-effect models

Linear:

$$Effect = Baseline + Slope \cdot Concentration \tag{8}$$

Maximum effect (E_{max}):

$$Effect = Baseline + \frac{E_{max} \cdot Concentration}{EC_{50} + Concentration} \tag{9}$$

Sigmoidal E_{max}:

$$Effect = Baseline + \frac{E_{max} \cdot Concentration^{\gamma}}{EC_{50}{}^{\gamma} + Concentration^{\gamma}} \tag{10}$$

In the above equations, t is nominal time after the first dosing, T is 24-hour clock time, amplitude is the amplitude of the cosine term, shift is the phase shift of the cosine term, mean is the average over the cosine period, EC_{50} is the concentration yielding 50% of the E_{max}, and γ is the Hill coefficient.

Data analysis was conducted in R version 2.15.2 using the nlme library version 3.1-111. Precision of estimated parameters was assessed based on standard errors calculated from the variance-covariance matrix of the estimates.

Introducing three levels of random effects

Models were fit by study, and three levels of random variability were tested: between- and within-subject variability and between-occasion variability. Between- and within-subject variability were separable given that multiple measures of the CV marker and drug concentration over time were available for each subject. Between-occasion variability was tested in studies with more than one period (i.e., occasion) per subject. Ninety mixed-effects model structures, including different baseline (5 structures) and drug-effect models (3 structures) with or without between-subject and between-occasion variability (2 to 4 structures depending on drug model), were tested. Random effects were considered to be normally distributed given the homeostatic control mechanisms involved in the regulation of the CV markers. EC_{50} and its between-subject variability were estimated on the log scale to constrain the estimates to positive numbers.

Between-subject variability was tested in virtually all fixed effect parameters and their combinations. For the cosine baseline models, between-subject variability was tested for the mean parameter and dropped for the other parameters

because of excessive computational time; for the drug-effect models, between-subject variability was tested for all parameters, except in the sigmoidal E_{max} model, in which between-subject variability was not tested for γ.

Between-occasion variability was only tested for baseline parameters; for the cosine models, it was only tested for the mean parameter. Between-occasion variability was dropped when the baseline model was paired with a sigmoidal E_{max} drug-effect model with between-subject variability for the EC_{50} or E_{max} parameter because of excessive computational time without convergence.

Model selection and meta-analysis

For each CV marker and study, the relative best overall model structure (baseline plus drug-effect model) was selected based on a modified version of the Akaike's information criterion (AIC_{mod})[39] with a per parameter penalty of 6.635 ($AIC_{mod} = 6.635 \cdot k - 2 \cdot \ln(L)$, where k is the number of estimated parameters and L is the maximized likelihood). The AIC_{mod} was used to select the preferred model as the AIC does not require nested models; the per-parameter penalty of 6.635 was selected to be equivalent to a one-parameter, nested-model χ^2 test with a P value of 0.01.[40] Including $k = 6.635$ rather than the classical AIC with $k = 2$ is more likely to select models with fewer parameters, and this is included to alleviate concerns about the potentially large number of parameters in the unstructured baseline model. The selected model was the one with the lowest AIC_{mod} value. For studies with more than one period, the model selection was conducted separately in the absence and presence of between-occasion variability; this helped to evaluate whether the introduction of between-occasion variability influenced the selection of the baseline and drug-effect model structures (i.e., fixed-effects component; Eqs. 3–10).

The baseline models were also evaluated by the predicted effects' agreement between studies on the same compound. Here, we assumed that two studies on the same compound should yield similar predictions of the effect on CV markers at a given concentration. For each baseline model structure (Eqs. 3–7), considered with and without between-occasion variability, the AIC_{mod} was used to select the model for the drug effect. For a given compound, the concentration was selected similarly to Darpo *et al.*[12] by computing the geometric mean peak plasma concentration (C_{max}) for each dosage regimen in each study, selecting the highest geometric mean C_{max} in each study, and then selecting the lowest of these between studies to prevent model extrapolation; this concentration was denoted $C_{max,common}$. As the methods tested are attempting to define concentration- and not dose-response, unlike Darpo *et al.*,[12] uncertainty in $C_{max,common}$ was not incorporated. Using the selected models, 1,000 simulations of drug effect at $C_{max,common}$ were performed with the multivariate normal distribution with the mean and variance-covariance matrix of the parameter estimates from the selected models. For each combination of CV marker, baseline model, and absence/presence of between-occasion variability, a graph of predicted median effect along with the 90% confidence interval (CI) of the simulated effects was generated for all pairs of studies by compound. For each pair, the earlier study was denoted as study 1. We then calculated the distance of each intersection (median estimate) from the unit line and summed them across all compounds using the following (derived from Euclidean geometry):

$$\sum_{i=1}^{n}\left[\left(\frac{median\ effect_{study\ 1,i} - median\ effect_{study\ 2,i}}{2}\right)^2 + \left(\frac{median\ effect_{study\ 2,i} - median\ effect_{study\ 1,i}}{2}\right)^2\right]^{1/2} \quad (11)$$

where n is the number of compounds and i represents the compound. There were three compounds with three studies each, and for each of these compounds, a pair of studies was randomly selected.

The cumulative distance divided by the number of compounds was calculated to yield the average between-study disagreement for each CV marker. We also calculated the CI-normalized distance from each coordinate from the unit line and summed them across all compounds using the following:

$$\sum_{i=1}^{n}\left[\left(\frac{median\ effect_{study\ 1,i} - median\ effect_{study\ 2,i}}{2\times CI_{study\ 2,i}}\right)^2 + \left(\frac{median\ effect_{study\ 2,i} - median\ effect_{study\ 1,i}}{2\times CI_{study\ 1,i}}\right)^2\right]^{1/2} \quad (12)$$

where CI is the 5th to 95th percentile of simulated effects divided by two. The preferred baseline model structure was the one minimizing CI-normalized distance (i.e., better between-study agreement). Although the CI-normalized distance may favor a model with high imprecision, its comparison to the aforementioned (non-normalized) distance minimizes that bias.

Diagnosis of drug-effect delay

Diagnosis for anticlockwise hysteresis (drug-effect delay) was performed in order to evaluate the appropriateness of the direct-link exposure-response analysis. For the model with the lowest CI-normalized distance for each marker in each study, the first derivative of the drug concentration with respect to time was numerically calculated. The concentration derivative (horizontal-axis) was plotted vs. standardized (Pearson) residuals from the nlme model (vertical-axis). A linear regression analysis was performed and the 99% lower confidence bound for the slope was calculated. If the lower confidence bound for the slope was greater than zero, then the presence of a drug-effect delay was inferred while acknowledging the sensitivity of this method to increasing amount of data.

Analysis of meal effect on baseline

As CV changes have been reported after a meal,[41–44] a post-hoc analysis was conducted to evaluate whether meal intake is able to explain some of the temporal changes in the baseline CV markers. The model structure (Eq. 13) was selected based on the visual inspection of the standardized residuals (when a time-invariant model structure was fitted) vs. the time after the last meal (i.e., breakfast, lunch, or dinner). For example, for PR and RR, a postprandial "peak" and "trough," respectively, was observed with a return to the preprandial value consistent with published studies on

Table 2 Counts of AIC_{mod}-selected baseline models to describe the different CV markers (in the absence of drug effect) for two different phase I studies on the same compound (total number of compounds for vital signs = 20; total number of compounds for ECG-intervals = 16).

Study 1 \ Study 2	Estimated pre-dose one time point baseline (E_0)	Unstructured[a]	Cosine (12-h period)	Cosine (24-h period)	Double cosine (12- and 24-h periods)	Sum
SBP						
E_0	1 (2)	2 (2)	1 (0)	2 (1)	0 (0)	6 (5)
Unstructured[a]	1 (0)	1 (1)	1 (1)	3 (4)	0 (0)	6 (6)
Cosine (12-h period)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cosine (24-h period)	3 (4)	0 (0)	1 (2)	4 (3)	0 (0)	8 (9)
Double cosine (12- and 24-h periods)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Sum	5 (6)	3 (3)	3 (3)	9 (8)	0 (0)	20 (20)
DBP						
E_0	0 (0)	0 (0)	0 (0)	2 (3)	0 (0)	2 (3)
Unstructured[a]	1 (1)	0 (0)	1 (1)	2 (2)	0 (0)	4 (4)
Cosine (12-h period)	0 (0)	0 (0)	1 (1)	2 (1)	0 (0)	3 (2)
Cosine (24-h period)	3 (3)	0 (0)	3 (3)	5 (5)	0 (0)	11 (11)
Double cosine (12- and 24-h periods)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Sum	4 (4)	0 (0)	5 (5)	11 (11)	0 (0)	20 (20)
PR						
E_0	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)
Unstructured[a]	2 (2)	7 (7)	1 (1)	6 (6)	0 (0)	16 (16)
Cosine (12-h period)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cosine (24-h period)	0 (0)	2 (2)	0 (0)	1 (1)	0 (0)	3 (3)
Double cosine (12- and 24-h periods)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Sum	2 (2)	10 (10)	1 (1)	7 (7)	0 (0)	20 (20)
RR interval						
E_0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Unstructured[a]	0 (0)	12 (13)	2 (2)	0 (0)	0 (0)	14 (15)
Cosine (12-h period)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cosine (24-h period)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)	2 (1)
Double cosine (12- and 24-h periods)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Sum	0 (0)	14 (14)	2 (2)	0 (0)	0 (0)	16 (16)
QT interval						
E_0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Unstructured[a]	1 (1)	14 (13)	1 (0)	0 (2)	0 (0)	16 (16)
Cosine (12-h period)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cosine (24-h period)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Double cosine (12- and 24-h periods)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Sum	1 (1)	14 (13)	1 (0)	0 (2)	0 (0)	16 (16)
QTcF						
E_0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Unstructured[a]	2 (1)	5 (4)	3 (4)	1 (1)	0 (0)	11 (10)
Cosine (12-h period)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cosine (24-h period)	0 (0)	2 (2)	0 (0)	3 (4)	0 (0)	5 (6)
Double cosine (12- and 24-h periods)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Sum	2 (1)	7 (6)	3 (4)	4 (5)	0 (0)	16 (16)

AIC_{mod}, modified Akaike's information criterion; CV, cardiovascular; DBP, diastolic blood pressure; ECG, electrocardiogram; PR, pulse rate; QTcF, Fridericia corrected QT interval; SBP, systolic blood pressure.

The results outside of the parentheses are for models without between-occasion variability. The results inside the parentheses are for models that allow between-occasion variability when the study has more than one period.

[a]Unstructured model corresponds to the estimation of a baseline value at each study nominal time after the first drug dosing. Values between parentheses represent the counts when between-occasion variability was incorporated in the respective baseline model for studies with more than one period. Cells highlighted in gray represent the same baseline model across both studies.

Table 3 Counts of AIC_{mod}-selected drug-effect models to describe drug effect on the different CV markers for two different phase I studies on the same compound (total number of compounds for vital signs = 20; total number of compounds for ECG-intervals = 16).

	Study 2			
Study 1	**Linear model**	**E_{max} model**	**Sigmoidal E_{max} model**	**Sum**
SBP				
Linear model	14 (14)	3 (4)	0 (0)	17 (18)
E_{max} model	2 (2)	1 (0)	0 (0)	3 (2)
Sigmoidal E_{max} model	0 (0)	0 (0)	0 (0)	0 (0)
Sum	16 (16)	4 (4)	0 (0)	20 (20)
DBP				
Linear model	16 (16)	1 (1)	0 (0)	17 (17)
E_{max} model	2 (2)	1 (1)	0 (0)	3 (3)
Sigmoidal E_{max} model	0 (0)	0 (0)	0 (0)	0 (0)
Sum	18 (18)	2 (2)	0 (0)	20 (20)
PR				
Linear model	10 (12)	3 (3)	0 (0)	13 (15)
E_{max} model	5 (2)	2 (3)	0 (0)	7 (5)
Sigmoidal E_{max} model	0 (0)	0 (0)	0 (0)	0 (0)
Sum	15 (14)	5 (6)	0 (0)	20 (20)
RR interval				
Linear model	7 (9)	3 (2)	0 (0)	10 (11)
E_{max} model	4 (4)	2 (1)	0 (0)	6 (5)
Sigmoidal E_{max} model	0 (0)	0 (0)	0 (0)	0 (0)
Sum	11 (13)	5 (3)	0 (0)	16 (16)
QT interval				
Linear model	3 (7)	5 (3)	0 (0)	8 (10)
E_{max} model	7 (3)	1 (2)	0 (0)	8 (5)
Sigmoidal E_{max} model	0 (0)	0 (1)	0 (0)	0 (1)
Sum	10 (10)	6 (6)	0 (0)	16 (16)
QTcF				
Linear model	9 (9)	2 (1)	0 (0)	11 (10)
E_{max} model	2 (4)	2 (2)	0 (0)	4 (6)
Sigmoidal E_{max} model	1 (0)	0 (0)	0 (0)	1 (0)
Sum	12 (13)	4 (3)	0 (0)	16 (16)

AIC_{mod}, modified Akaike's information criterion; CV, cardiovascular; DBP, diastolic blood pressure; ECG, electrocardiogram; E_{max}, maximum effect; PR, pulse rate; QTcF, Fridericia corrected QT interval; SBP, systolic blood pressure.
Cells highlighted in grey represent the same drug-effect model across both studies.

the topic.[41,43] The analysis was conducted in R version 3.1.2 using linear and nonlinear mixed-effects modeling (with the nlme library), and previous model structures were rerun with this R version only for comparison of the aforementioned model selection criteria.

$$Baseline\ (Tm) = \frac{Intercept \cdot 4}{(1+e^{kd \cdot Tm}) \cdot (1+e^{ki \cdot Tm})} \quad (13)$$

where Tm is time after the last meal, intercept is the baseline value when Tm equals zero, the constant 4 normalizes the numerator to the denominator when Tm = 0, and kd and ki are constants describing the rate with which the CV marker separates from and returns to the intercept.

RESULTS

The analysis dataset consisted of 39 SAD or MAD phase I studies, including 18 parent drugs, 2 active metabolites, and a total of 1,291 subjects. Of the 39 studies, 34 studies enrolled healthy adult subjects, and 5 studies enrolled otherwise healthy overweight and obese subjects. Of the 18 parent drugs under investigation, 15 (38%) were to treat neurologic/psychiatric diseases, 11 (28%) were to treat CV/metabolic diseases, 9 (23%) were to treat infections, and 4 (10%) were to treat chronic inflammation (**Table 1**). For the ECG intervals (i.e., RR, QT, and QTcF intervals), observations from 1,078 subjects (33 studies, 18 compounds) were retrieved; 2 of 18 compounds had data available for only one phase I study and ECG results comparing two studies were only presented for the 16 remaining compounds. There were ~44,590 observations for each of the vital signs (i.e., SBP, DBP, and PR) and ~54,069 observations for each of the ECG intervals in the analysis dataset; 23.5% and 27% of the observations, respectively, were from placebo. Approximately half of the studies in the vitals and ECG datasets had more than one period.

The selected baseline and drug-effect model structures based on AIC_{mod} are summarized in **Tables 2 and 3**,

Table 4 Between-study prediction of change from baseline at the maximum drug concentration ($C_{max,common}$).

Surrogate marker	Estimated pre-dose one timepoint baseline (E_0)	Unstructured[a]	Cosine (12-h period)	Cosine (24-h period)	Double cosine (12- and 24-h periods)
Distance					
SBP	19 (21)	24 (21)	21 (22)	20 (19)	DNC
DBP	17 (17)	24 (22)	14 (15)	15 (15)	DNC
PR	25 (23)	20 (23)	17 (18)	20 (19)	DNC
RR interval	360 (356)	196 (256)	377 (504)	386 (397)	DNC
QT interval	82 (71)	39 (38)	79 (77)	82 (82)	DNC
QTcF interval	45 (45)	19 (17)	29 (34)	37 (39)	DNC
Distance divided by number of compounds					
SBP	0.95 (1.05)	1.20 (1.05)	1.05 (1.10)	1.00 (0.95)	DNC
DBP	0.85 (0.85)	1.20 (1.10)	0.70 (0.75)	0.75 (0.75)	DNC
PR	1.25 (1.15)	1.00 (1.15)	0.85 (0.90)	1.00 (0.95)	DNC
RR interval	22.5 (22.3)	12.3 (16.0)	23.6 (31.5)	24.1 (24.8)	DNC
QT interval	5.13 (4.44)	2.44 (2.38)	4.94 (4.81)	5.13 (5.13)	DNC
QTcF interval	2.81 (2.81)	1.19 (1.06)	1.81 (2.13)	2.31 (2.44)	DNC
Normalized distance					
SBP	38 (80)	37 (76)	43 (49)	35 (76)	DNC
DBP	100 (99)	122 (58)	40 (66)	85 (79)	DNC
PR	65 (43)	35 (55)	36 (37)	43 (57)	DNC
RR interval	28 (37)	34 (42)	53 (66)	47 (56)	DNC
QT interval	35 (32)	20 (29)	72 (74)	50 (72)	DNC
QTcF interval	43 (96)	22 (26)	28 (81)	34 (76)	DNC
Sum	309 (387)	270 (286)	272 (373)	294 (416)	–

CV, cardiovascular; DBP, diastolic blood pressure; DNC, did not converge; PR, pulse rate; QTcF, Fridericia corrected QT interval; SBP, systolic blood pressure. Values represent the summation of the (CI-normalized) distance of each compound coordinate from the unit line (divided by the number of compounds) for the different baseline models to describe the CV markers. A lower value represents a better between-study agreement, and the lowest (CI-normalized) distance value for each CV marker is underlined in the cells shaded in grey.

[a]Unstructured model corresponds to the estimation of a baseline value at each study nominal time after the first drug dosing. Values between parentheses represent the summation of the normalized distance when between-occasion variability was incorporated in the respective baseline model for studies with more than one period. Maximum drug concentration was calculated as the geometric mean C_{max} for each dosage regimen in each study, selecting the highest geometric mean C_{max} in each study, and then selecting the lowest of these between each two studies on the same compound ($C_{max,common}$).

respectively, for each CV marker. The overall model selection was similar between the two sets with and without between-occasion variability. All baseline models included between-subject variability; ~26% and 23% of the selected models with linear drug-effect models had between-subject variability incorporated in the slope parameter for models without and with between-occasion variability; ~67% and 68% of the selected E_{max} drug-effect models had between-subject variability incorporated in the E_{max} parameter for models without and with between-occasion variability. Very few selected E_{max} models had a between-subject variability component for the EC_{50} parameter. The most commonly selected baseline model for SBP and DBP was the cosine function with a 24-hour period. For PR, RR, QT, and QTcF intervals, the most commonly selected was the unstructured baseline model (i.e., estimation of a baseline value at each study nominal time after the first dosing). A linear drug-effect model was most commonly selected to characterize drug effect on CV markers. The results were the same regardless of analyzing all studies, studies 1 and 2 separately, or only pairs of studies with the same selected model.

The unstructured baseline model yielded the lowest overall (i.e., sum of all CV markers) CI-normalized distance in the meta-analysis (**Table 4**). This was observed within both sets of models (i.e., with and without between-occasion variability), and a comparison between the two sets revealed that the overall CI-normalized distance was lower for that without between-occasion variability. Using the CI-normalized distance metric for the individual CV markers, the unstructured baseline model yielded a better between-study agreement for PR, QT, and QTcF intervals; PR had a similar normalized distance value between the unstructured baseline model and the 12-hour cosine model. For SBP, DBP, and RR interval, respectively, the 24-hour cosine, 12-hour cosine, and E_0 model yield a better agreement; in particular, for SBP and RR interval, the normalized distance values from the respective 24-hour cosine and E_0 models were similar to the ones of the unstructured baseline model. Using the baseline models with the lowest CI-normalized distance metric for each CV marker, **Figure 2** shows the predicted median change from baseline effect at $C_{max,common}$ for the different compounds. The conclusion was virtually the same for non-normalized distance, where the unstructured baseline model yielded the best between-study agreement for RR, QT, and QTcF intervals. For SBP and DBP, respectively, the 24-hour cosine and 12-hour cosine model yielded a better agreement (**Table 4**). For the PR interval, a 12-hour cosine model yielded a better agreement, but the distance was similar to that of the unstructured baseline model. For the RR interval, the

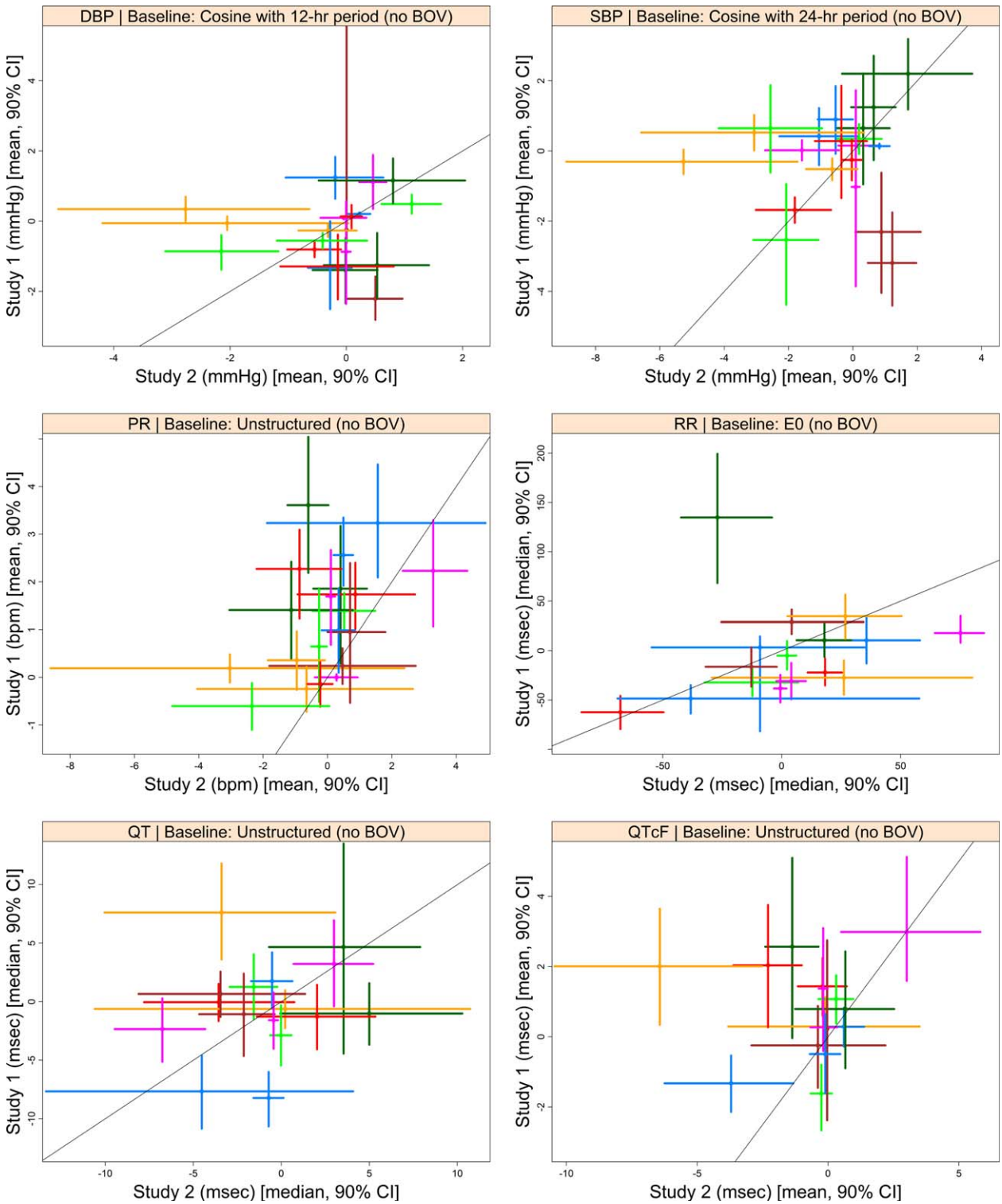

Figure 2 Change from baseline of cardiovascular markers at maximum drug concentration ($C_{max,common}$) for different compounds (1,000 simulations). BOV, between-occasion variability; CI, confidence interval; DBP, diastolic blood pressure; PR, pulse rate; QTcF, Fridericia corrected QT interval; SBP, systolic blood pressure.

comparison between non-normalized and CI-normalized distance reveals a relatively high imprecision for the E_0 model, which reduces the CI-normalized distance value. The relative range of average disagreement (i.e., ratio of higher and lower value) across baseline model structures was higher for ECG intervals (i.e., RR, QT, and QTcF intervals) than for vital signs

Table 5 Diagnosis of drug-effect delay for two different phase I studies on the same compound (total number of compounds for vital signs = 20; total number of compounds for ECG-intervals = 16).

Study 1 \ Study 2	No drug effect delay	Drug effect delay	Sum
SBP			
No drug effect delay	17	2	19
Drug effect delay	1	0	1
Sum	18	2	20
DBP			
No drug effect delay	17	3	20
Drug effect delay	0	0	0
Sum	17	3	20
PR			
No drug effect delay	20	0	20
Drug effect delay	0	0	0
Sum	20	0	20
RR interval			
No drug effect delay	7	0	7
Drug effect delay	6	3	9
Sum	13	3	16
QT interval			
No drug effect delay	16	0	16
Drug effect delay	0	0	0
Sum	16	0	16
QTcF interval			
No drug effect delay	16	0	16
Drug effect delay	0	0	0
Sum	16	0	16

DBP, diastolic blood pressure; ECG, electrocardiogram; PR, pulse rate; QTcF, Fridericia corrected QT interval; SBP, systolic blood pressure.
Cells highlighted in gray represent the same diagnosis across both studies.

(i.e., SBP, DBP, and PR), which emphasizes the importance of the model choice for the former.

The drug-effect delay diagnosis (anticlockwise hysteresis) is summarized in **Table 5**. For PR, QT, and QTcF intervals, none of the studies showed evidence of drug-effect delay. For SBP and DBP, three studies on different compounds suggested the presence of drug-effect delay, however, the second study for each of the compounds did not support the findings. For RR interval, three compounds had evidence of drug-effect delay in both studies, six compounds had evidence in one study but not the other, and seven compounds had no evidence in either study.

The time after the last meal (i.e., breakfast, lunch, or dinner) explained a portion of the temporal changes in the baseline CV markers. Based on the AIC_{mod} criteria, the baseline model structure accounting for the time after the last meal was selected to describe QTcF in four studies, PR in one study, DBP in seven studies, and SBP in three studies. All cases were without between-occasion variability. Interestingly, this baseline model structure yielded a better between-study agreement for RR, PR, and DBP based on a CI-normalized distance (22, 15, and 15, respectively; please refer to **Table 4** for comparison with other models). With regard to the non-normalized distance, this baseline model structure yielded the lowest distance not only for RR, PR, and DBP, but also for QT and SBP.

DISCUSSION

The objective of this study was to recommend preferred exposure-response models—from a pool of previously published studies and a new suggested baseline model—to assess drug effect on ECG intervals and vital signs in SAD and MAD phase I studies. To this end, we compared a total of 90 mixed-effects models across several studies and CV markers (19,440 attempted models in total) for their ability to: (a) describe the observed data and (b) produce similar prediction of drug effects at $C_{max,common}$ across studies with the same compound. The most commonly selected baseline model was the unstructured baseline model for PR, RR, QT, and QTcF intervals and the cosine function (24-hour period) for BP. A linear model was the most commonly selected to characterize drug effect on all markers. Overall, the unstructured baseline model yielded a better between-study agreement of predicted drug effect at $C_{max,common}$. We propose that these preferred models can be a starting point, and along with the other compiled models, assist with CV safety assessment using exposure-response analysis in nondedicated small studies with healthy subjects. The presented modeling work aligns with ongoing efforts to update the International Conference on Harmonisation E14[10] (in which current methods suggest statistical comparison of the $\Delta\Delta$QTc by time point—similarly to the unstructured model—without regard to concentration) with a model-based assessment of changes in response over a range of plasma concentration (i.e., exposure-response analysis) as an alternative to a "by timepoint" approach, as required for the thorough-QT study.[12] Additionally, by prespecifying preferred models in the analysis plan for SAD and MAD along with alternative models and criteria for model selection, we hope to reduce the need for dedicated studies on CV safety assessment.

Additional model structures could be tested in practice during early clinical development, and we believe that the thorough examination of the model for both hysteresis (**Table 5**) and meal effects is warranted to ensure a robust inference. Within the models tested, the AIC_{mod}-selected baseline models were the same with the best between-study agreement of drug effects at $C_{max,common}$ as measured by the Euclidean or CI-normalized distance. This consistency gives us confidence in the reproducibility of our results, and the feasibility of decision-making using exposure-response for CV safety markers in phase I studies. The exception was DBP, in which the AIC_{mod} selected a cosine 24-hour period and the CI-normalized distance selected a 12-hour period. One surprising result was the fact that a drug-effect delay was estimated as potentially significant for RR interval in three studies but not PR; because the RR delay did not replicate in the second study for the RR interval, the measurement modalities are different (with different error structures and precision), and the measurement datasets were different, we believe that this

is likely related to the method of the test for delay rather than the underlying modeling methods.

The cross-validation between studies and a large dataset of unique compounds—some with positive and some with neutral effects—allowed a relatively unbiased assessment of concentration effects for each endpoint. Potential limitations of the analysis include that: (a) the effect may be related to a drug concentration site of action other than plasma; (b) the drug could have tolerance with multiple dosing; (c) unmeasured metabolites may affect the result; (d) the patient population response could differ from the healthy subject population; (e) the model structures limit potential for response shapes in a way that may not be biologically relevant; (f) correlation between replicate response measurements at the same nominal time for a particular individual could be taken into account in the model structure; (g) the variability in the measurements may be heteroskedastic, and (h) additional model diagnostic tools could be used to help with model selection. In this analysis, evidence of anticlockwise hysteresis (drug-effect delay) was not present for the majority of the CV markers across the different studies, and perhaps a similar assessment could be performed for the diagnosis of clockwise hysteresis (tolerance). Although a dose-response could alleviate the potential for alternate compartments or unmeasured metabolites, dose-response typically is not able to establish the time-course postdose, and when a measured drug or metabolite causes the change to the response, it will be significantly less precise. Whereas this analysis was conducted in healthy subjects, if there are differences between healthy subjects and the patient population, identical analyses are possible in the patient population. Last, the model structures were selected to test those commonly used in the literature; most drugs are linear in response to these markers because doses that saturate the effect are not typically tested because of safety concerns.

We believe that the methods presented for exposure-response modeling of drug and metabolite effects on vital signs and ECG intervals aligns well with the recent suggestions from Darpo *et al.*[12] and partially addresses the concerns of Bloomfield[45] on the power and potential limitations of exposure-response analysis from early development through regulatory decisions on labeling. Further work is warranted to ensure that both biases are minimized and that the limitations of prespecified models neither minimize nor exacerbate the clinical relevance of a signal during drug development.

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