Not-In-Trial Simulation: Predicting Cardiovascular Risk from Clinical Trial Data

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Introduction

Many efforts have been made towards improving the technical requirements for thorough QT studies. Despite these initiatives, thorough QT studies continue to lack the predictive power to translate cardiovascular risks from clinical settings to real life situations. In a previous work*, it has been demonstrated in addition to drug effect, concomitant medications and co-morbidity conditions can significantly alter QTc values. Based on clinical trial simulation scenarios, here we demonstrate how to assess risk of not-in-trial patients, i.e., those ineligible due to inclusion/exclusion criteria, but who also receive drug treatment.

As part of risk management, create a not-in-trial simulation model to foresee different scenarios when drug is given to patients with various comorbidity conditions.

***Figure 1.** Diagram proposing when not-in-trial simulation would be beneficial in the drug development process.*

Objectives and Method

Objective: To resolve the discrepancies between predicted drug-induced QTc values and actual observed values in real-life population.

Hypothesis: In contrast to the long-established assumptions for the evaluation of QTc interval prolongation, we assume that QTc(real life population) = current clinical drug-effect model + effects other causal factors.

Approach: Using *d,l*-sotalol as a paradigm compound, the effects of additional factors are estimated using the Rotterdam Study cohort as reference population while the actual added-effect size is evaluated by linear regression. Then the distribution of QTc values associated with drug effects, baseline values and comorbidities are characterised assuming a full compliance scenario. Finally, the simulated QTc distribution is compared non-parametrically with the observed real life distribution.

Data

Real Life Population: Rotterdam Study Cohort

- Observational data of subjects >= 55 years of age
- Residents of Ommond (Rotterdam, The Netherlands)
- Longitudinal data of maximum 4 visits
- Selection criteria: subjects with no left ventricular hypertrophy, left or right bundle branch block

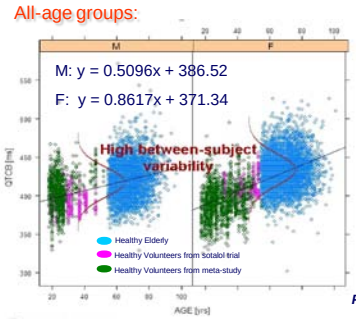
Dates of baseline and follow-up measurements

Clinical Trial Population: Phase I Healthy Volunteers

- Standard inclusion/exclusion criteria
- "Healthy subjects are defined as individuals who are free from clinically significant illness or disease as determined by their medical history (including family history, physical examination, laboratory studies, and other tests"
- Male or female between 18-55 years of age, inclusive
- Body mass index between 19-30 kg/m2, with a weight of 50-95 kg, inclusive
- Non smokers

Baseline Correction

All-age groups:



Data on placebo treatment arms in healthy young and elderly subjects were combined to find a cross-sectional baseline relationship, which can be used in the not-in-trial simulation model. The combined dataset reveals a high between subject variability. The resulting baseline equations are sex and age dependent. Genetic factors, such as the long-QT sydrome, can also be included.

***Figure 2.** Age and sex dependent baseline equations.*

Not-In-Trial Simulation

QTc = fnc(drug effects ← Clinical model with WT as covar on CL
+ baseline ← Baseline eq derived from wide-age range
+ ß(HF) ← 5.8 (3.49) for F, 7.7 (±4.02) for M
+ ß(MI) ← 3.2 (2.11) for F, 3.0 (±2.31) for M
+ ß(Arr/C01BD) ← 3.0 (2.0) for F, 5.4 (±2.28) for M
+ ß(Diab)) ← 20.4(9.51) for F, 18.5 (±9.21) for M

The contribution of comorbidities to QTc interval prolongation was analysed in R v.2.8.0 (http://www.r-project.org/). Using linear regression concepts, and taking intra-individual variability into consideration, slopes are calculated with and without each comorbidity. Subjects are also split into sotalol users and non-users to determine if a drug-disease interaction is present. Since users and nonusers showed similar findings, final results quoted here are from non-sotalol users.

Results from Simulation Model

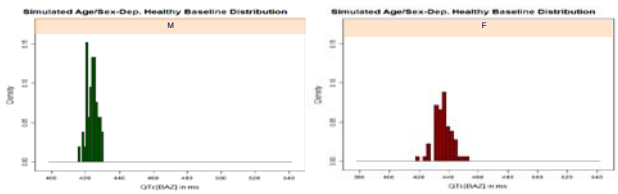


***Figure 3.** Simulation of age/sex dependent baseline values of Rotterdam Cohort*

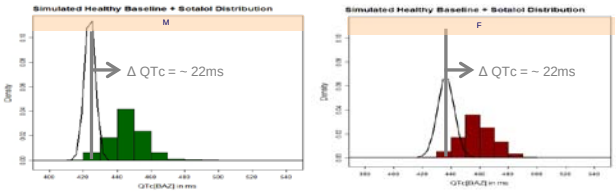


***Figure 4.** Comparing QTc effects between baseline-only results and simulated baseline and sotalol effects*

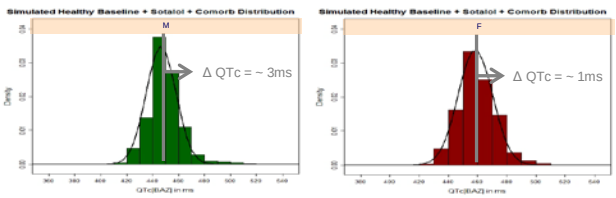


***Figure 5.** Comparing QTc effects between baseline + sotalol and simulated baseline + sotalol + comorbidities effects*

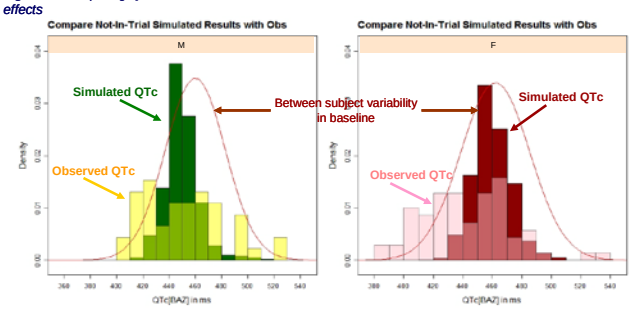


***Figure 6.** Simulation outcomes using the all-age group population baseline equations.*

QTc outcomes due to drug exposure are simulated using NONMEM v. 6.0. When between-subject variability is included in the model, all observed values are described well by the model and its boundaries.

Discussions

Baseline QTc values are age and gender dependent. This correlation plays an important role in that observed QTc values will increase over time irrespective of drug treatment. Drug effect and comorbidity conditions also contribute to further increase in QTc values. Overall, drug-induced QTc interval prolongation alone cannot adequately explain the QTc distribution observed in real life.

*Ref: Chain et al., PAGE 17 (2008) Abstr 1317 [www.page-meeting.org/?abstract=1317]

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