

Application of bias metrics during IRT review

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Disclaimer

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Role of positive controls in TQT studies

- A positive pharmacological control, typically moxifloxacin, is included in thorough QT (TQT) studies to demonstrate that the study is able to detect small mean increases in the QTc interval.
- The inclusion of a positive control therefore provides reassurance that if the investigational drug product is negative that it is truly negative, i.e. the positive control protects against false negative results.

Positive controls in early-phase trials

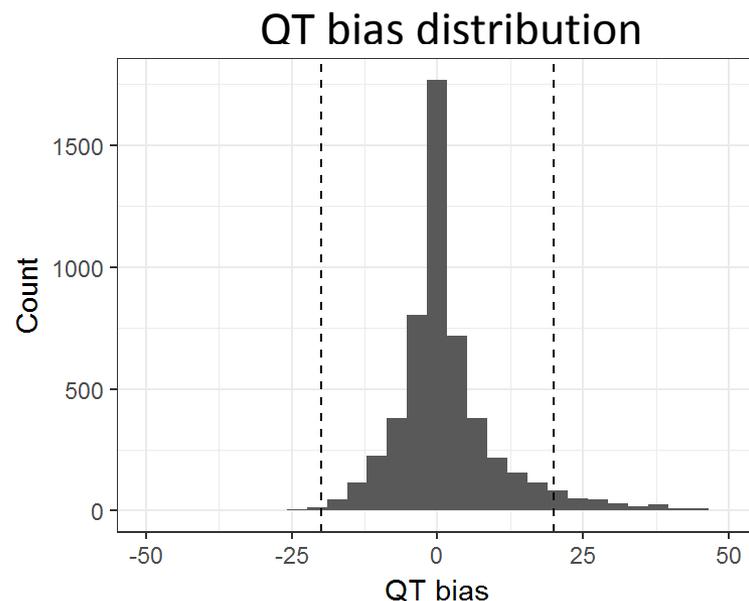
- Inclusion of a traditional positive pharmacological control in early-phase trials is challenging and might not always be possible.
- The requirement for a positive control can be waived if the early-phase trial evaluated doses resulting in a sufficiently high multiple of the clinically relevant exposure.

Alternative methods to show assay sensitivity

- Several alternatives have been proposed for demonstrating the ability to detect small mean increases (assay sensitivity).
- An alternative strategy that has been proposed is an evaluation of measurement bias by comparison of the QT data for the primary analysis and fully-automated QT data
 - This assessment is only useful for drugs with minimal QT prolongation.
 - This is because the assessment relies on accuracy of the fully-automated measurements, which might be compromised in the setting of significant QT prolongation and/or T-wave morphology changes.

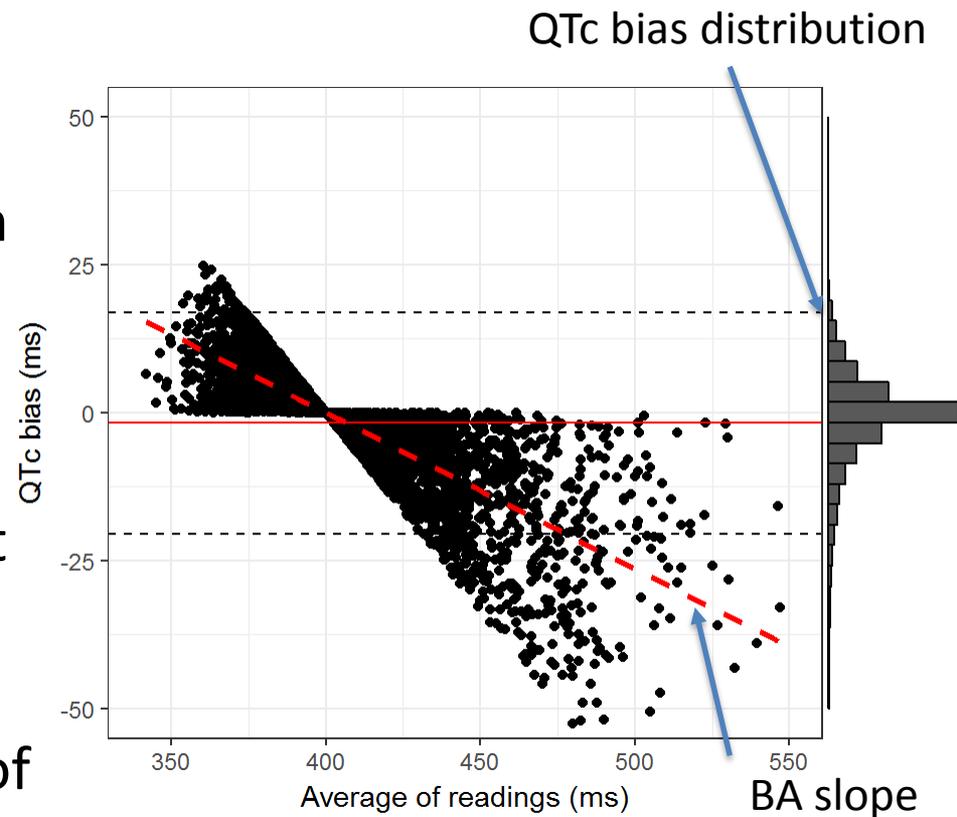
QT Bias in the ECG Warehouse (EWH)

- QT bias is currently assessed by evaluating the proportion of ECGs with significant QT bias, relative to other studies in the EWH
 - For studies with significant QT bias, the distribution of ECGs with significant QT bias is evaluated further by treatment
- However, this evaluation does not differentiate between constant QT bias and QT bias that is a function of the underlying QT measurement.



QT Bias: Bland-Altman slope

- The Bland-Altman slope evaluates the relationship between QT bias and the mean QT, i.e. the Bland-Altman slope (“BA-slope”).
- A simulation study by Ferber et al.¹ using IQ-CSRC study data suggests that a negative “BA-slope” impacts the prediction of the C-QT analysis.



Application of QT bias within the IRT

- At present the IRT are not regularly evaluating QT bias (BA-slope), but rather on a case-by-case basis.
- For example, QT bias (BA-slope) might be considered for a study only marginally meeting or failing to meet the requirement for waiving inclusion of a positive control.

Example: Exposure margin close to threshold

- Concentration-QTc analysis suggested an absence of a concentration-QTc relationship, however, the highest dose did not meet the requirement to waive the requirement for inclusion of a positive control.
- QT bias analysis did not reveal significant negative QT bias (BA-slope) overall or by treatment.
- Altogether, the information provided allowed for excluding the presence of small mean increases in the QTc interval.

Conclusion

- We are still working on gaining experience with QT bias metrics using the ECG warehouse.
- One of the key questions of our work is to compare the Bland-Altman slope for QT and QTcF.
- For studies with an exposure margin close to the threshold, sponsors could consider supplementing their analysis with a QT bias analysis.

