

## **Multiple Testing Issues of Thorough QTc Trials**

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### **Abstract**

The ICH E14, 2005 defined that drug-induced prolongation of QT interval as evidenced by an upper bound of the 95% confidence interval around the mean effect on QTc of 10 ms. Further more it defined that a negative thorough QT/QTc study is one in which the upper bound of the 95% one-sided confidence interval for the largest time-matched mean effect of the drug on the QTc interval excludes 10 ms. It leads to the requirement of showing non-inferiority of the test treatment to placebo at multiple time points. Conventionally, it is carried out by testing multiple hypothesis at 5% type I error rate each. On the other hand, when the study result is negative, ICH E14 recommended to validate the negative result by showing that the study population is sensitive enough to show at least 5 ms prolongation of QTc interval of a carefully selected positive control. The validation test is often carried out by demonstrating that the mean difference between positive control and placebo is greater than 5 ms at at least one of the selected few time points. The multiple comparison nature of the validation test led to the concerns of type I error rate adjustment for multiple comparisons. Boos et al (2007) showed that when the repeated measured responses follow a multivariate normal distribution with equal variance, the conventional test is conservatively biased. Based on the objective for bias correction, Boos et al (2007) proposed three confidence intervals of maximum of multiple sample mean differences with no type I error rate adjustment requirement for multiple comparisons. It has been shown that the proposed approaches can improve the power of the QTc studies with crossover design. However, Boos et al (2007) didn't show that the proposed approaches control type I error rate. We evaluated the type I error rate of the three proposed procedures under various configurations of the null hypothesis using a simulation study. The results are compared with the conventionally used approaches by regulatory reviewers. Our simulation study shows that the all three unbiased confidence interval approaches proposed by Boos et al (2007) inflate type I error rate in the setting of demonstrating rejecting null hypothesis at all time points.