Design and Analysis of QT/QTc Studies - Conceptional and Methodical Considerations Based on Experience

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This talk will address issues of planning and analysis of QTc studies with particular reference to the ICH E-14 guideline. At first the role of the QTc interval as biomarker for life-threatening proarrhythmic risk will be emphasised which actually implies a high degree of uncertainty for the biostatistician with regard to the (clinically) relevant QTc prolongation either intended to be detected in a clinical study or aimed to be ruled out. On the one hand, the clinician’s reply to the question about a clinically relevant QTc prolongation is often “above 500 ms” or “above 50 or 60 ms”. On the other hand, the guideline considers QTc prolongations of 5 ms in the very first instance which however are explicitly denoted as „regulatory threshold pharmacological effect on cardiac repolarisation“. Sample size calculations based on the latter requirement inevitably lead to very large sample sizes for parallel group studies with \( N > 140 \) per treatment group (cf. Marek et al., 2004). This of course appears impracticable since a „thorough QT/QTc“ study would require at least 560 subjects when including the therapeutic dose, placebo, a positive control, and a supra-therapeutic dose. In fact, the FDA appears to accept studies with markedly smaller total sample sizes. Therefore, the following aspects will be discussed in more detail:

1. Choice of an appropriate target criterion (“endpoint”) depending on the study objective either with regard to „no effect“, or to quantification of treatment effects on QTc.
2. Choice of „delta“ for sample size considerations taking regulatory procedures into account.
3. Statistical issues regarding the „largest time-matched mean difference between active drug and placebo“.
4. Design for a „thorough QT/QTc“ study with a non-cardiac drug inducing QTc prolongations (in particular the need of a positive control will be questioned).
5. Simple prediction model for pathological QTc prolongations in order to estimate the risk after intake of a specific dose strength. This exploratory approach tries to provide support for assessing clinical relevance of the results obtained from a QTc study.


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