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QTc Analysis in Decision Making - Programming perspective to meet NMPA guidance on E14

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ABSTRACT

NMPA have published the guidance that Initiated drug clinical research must be applicable the guidelines E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. To evaluate the risk of QT/QTc Interval Prolongation in current project and if need carry out the Thorough QT/QTc (TQT), it is necessary to perform a QTc analysis, which also laid the foundation for the subsequent clinical research.

This paper will present from programmer's perspective of how to investigate QT/QTc risk based on existing projects, how to support study team to explore and understand the relationships between QT/QTc interval prolongation and drug compliance, other safety endpoints, so that sufficient evidence can be presents to drive team to make decision.

INTRODUCTION

Because E14 is officially released in China and QT/QTc analysis is not avoidable, many sponsors will summarize the existing data in the ongoing project to assess whether the product/drug is causally related to causing QT/QTc prolongation and potential arrhythmias. The main point of this article is how, as statistical programmers, to quickly and accurately complete the medical needs to help them make decisions about whether to perform thorough QT/QTc study.

BACKGROUND OF QT/QTC ANALYSIS

The NMPA announced in 2022 that it will be officially launched on 31 July 2023, and that newly submitted drug studies need to match the guidelines of applicable E14. The purpose of the guideline is to investigate the relationship between the study drug and QT/QTc prolongation or resulting arrhythmia as one of the supporting evidence for the safety of the drug.

Figure 1 Announcement of NMPA.

国家药监局关于适用《E8（R1）：临床研究的一般考虑》和《E14：非抗心律失常药物致QT/QTc间期延长及潜在致心律失常作用的临床评价》国际人用药品注册技术协调会指导原则的公告（2022年第61号）

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为推动药品注册技术标准与国际接轨，经研究，国家药品监督管理局决定适用《E8（R1）：临床研究的一般考虑》和《E14：非抗心律失常药物致QT/QTc间期延长及潜在致心律失常作用的临床评价》国际人用药品注册技术协调会（ICH）指导原则。现就有关事项公告如下：

一、自2023年7月31日起，启动的药物临床研究的相关要求适用《E8（R1）：临床研究的一般考虑》和《E14：非抗心律失常药物致QT/QTc间期延长及潜在致心律失常作用的临床评价》。E8（R1）实施之日起，E8停止实施。

二、相关技术指导原则可在国家药品监督管理局药品审评中心网站查询。国家药品监督管理局药品审评中心负责做好本公告实施过程中的相关技术指导工作。

特此公告。

PURPOSE OF QT/QTC ANALYSIS

In existing studies of new drugs not submitted, studies of compound need to be integrated for combined analysis. In many previous drug studies, the design of ECG is not perfect, and ECG is not detected according to the time point for detecting plasma concentrations, so it can only be analyzed based on the existing data at present, and the existing data results can be provided to the decision-making department to facilitate the decision-making department to decide whether to carry out a new study like thorough QT/QTc study; or in the initial trial, c-QT program can be carried out.

Drugs are expected to receive a clinical electrocardiographic evaluation in early phase of clinical development, typically including a single trial dedicated to evaluating their effect on cardiac repolarization ('thorough QT/QTc study').

SOCPE OF QT/QTC ANALYSIS

According to the guidance, the analysis of ECG data from clinical trials includes an analysis of QT/QTc to investigate the relationship between exposure and QT interval and whether relevant AEs have occurred. In this paper, based on the scope of analysis provided by the regulations, statistical programmers need to provide what results are needed to help medical departments better understand the QT/QTc profile in existing tumor/non-tumor studies.

Before performing the analysis, it is important to understand that ECG data were collected in different ways in the experiments performed. Mainly include: one visit for multiple consecutive measurements; multiple measurements during screening period, one measurement during treatment period or multiple measurements for averaging; only one measurement at any visit. Different collection methods require different data processing, and taking the mean or the latest record of the visit is considered reasonable.

In the statistical analysis, the correction formula of QT is mainly calculated by Fridericia 's correction formula.

Fridericia's correction: $QTc = QT/RR^{0.33}$

Based on the regulatory requirements, we need to analyze from different perspectives.

ANALYSIS OF ECG DATA FROM CLINICAL TRIALS

Analyses of central tendency and categorical analyses should be presented according to the guidelines, they both can provide relevant information on clinical risk assessment.

ANALYSES OF CENTRAL TENDENCY

Analyses of central tendency generally takes mean, standard deviation, maximum and minimum range, as well as 25% quantile and 75% quantile by visit. What needs to be provided is as table 1.

Table 1 Mock shell of central tendency analysis

Baseline	**ΔQTcF**	**Visit 1 (N=xx)**	**Visit 2 (N=xx)**	**…**	**Visit X (N=xx)**
Mean	Mean	xx.x			xx
	95% CI	CLM, UCLM			
	SD	xx.xx			

ANALYSIS OF CATEGORICAL DATA

Categorical analyses of QT/QTc interval data are based on the number and percentage of patients meeting or exceeding some predefined upper limit value. Clinically noteworthy QT/QTc interval changes might be defined in terms of absolute QT/QTc intervals or changes from baseline.

The general classification criteria were analyzed in terms of both measured values and baseline change values. In order to facilitate comparative analysis, it is usually placed in the same table for analysis. Prolongation of QTc > 500 ms during treatment has been identified as a threshold of special interest in clinical trials. QT/QTc to > 500 ms or of > 60 ms over baseline is sometimes used as one of the criteria for withdrawal from the trial.

Table 2 Mock shell of categorical analysis

Criteria	**Dose 1 (N=xx)**	**…**	**Total (N=xx)**
QTcF value > 450 ms to <= 480 ms	xx (xx.xx)		xx (xx.xx)
QTcF value > 480 ms to <= 500 ms			
QTcF value > 500 ms			
QTcF value change from baseline > 30 ms to <= 60 ms			
QTcF value change of from baseline > 60 ms *			
QTcF >500ms and QTcF value change of from baseline > 60 ms			

*Sometimes list QTcF value change from baseline >60 ms to <=90 ms and QTcF value change of from baseline >90 ms are also needed.

In these subjects meeting abnormal conditions, the results of ECG examination during the trial for these subjects, the line list of the medical history and concomitant medications should be provided to facilitate the decision-making department to investigate the influencing factors and better judge the relationship between the investigational drug and QT/QTc interval.

A scatter plot of patient test results of ECG examination is also necessary, plotted by test result-visit, more intuitive presentation of the relationship between visits and ECG results for the decision-making department.

ANALYSIS OF ADERVESE EVENTS

According to guidelines, QT/QTc may not be symptomatic, and some adverse events may have a potential link to proarrhythmic effects, which require special attention, and the listed adverse events are: torsades de pointes (TdP); sudden death; ventricular tachycardia; ventricular fibrillation and ventricular flutter; syncope; and seizures.

In the projects I came into contact with, the general medical department will provide Meddra SMQ to search for adverse events.Torsade de pointes/QT prolongation (SMQ) (SMQ Code: 20000001) will be provided from medical department. Meanwhile, the AE line list of patients with these adverse events should be provided with CTCAE grade, action taken with study treatment and serious AE or not, these parameters may be more intuitive and clear if listed. Action taken with study treatment need to be listed because drug withdrawn or dose reduction are the aspects of concern in the guideline.

Table 3 Mock shell of adverse events

Description	**Dose 1 (N=xx)**	**…**	**Total (N=xx)**
Subjects with TdP QT Prolongation	xx (xx.xx)		xx (xx.xx)
Leading to Drug Reduction			
Leading to Interruption			
Leading to Discontinuation			
Meeting SAE Criteria			
Leading to Death			
Grade ≥3			
PT1			
PT2			

CONCLUSION

This paper elaborates only in the current situation that the new guidelines need to be implemented, based on how the guidelines to analyze the existing completed or ongoing trials, the best operation is when open the new trial, it is necessary to do a QTQ trial to explore the relationship between the drug and QT/QTc, so as to better ensure the safety of the drug in the subsequent studies. Although programmers can only do some tables, listings, and graphs to assist decision-making departments, but visualization of raw data is one of the implications of statistical programmers. In the future, QT/QTc analysis will appear in our work as a routine analysis, and storing relevant knowledge can also bring more convenience to our work.

REFERENCES

THE CLINICAL EVALUATION OF QT/QTC INTERVAL PROLONGATION AND PROARRHYTHMIC POTENTIAL FOR NON-ANTIARRHYTHMIC DRUGS
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