Paper AR03

Quality Tolerance Limits – More Critical Aspects of Clinical Trials with Much Less Visibility

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ABSTRACT

We will be covering about Quality Tolerance Limits (QTLs) in this session to bring in awareness along with implementation of standards with its importance, focus areas, considerations, significance, framework, the primary differences between KRIs and QTLs along with an automation methodology to implement these QTLs in faster turnaround to be compliance with ICH-GCP guidelines.

INTRODUCTION

Let's dive into to understand Quality Tolerance Limits (QTLs) and learn more about implementation of these in faster turnaround to be following regulatory requirements that helps to bring life-changing treatments faster!

QUALITY TOLERANCE LIMITS DEFINITION

A QTL is a value associated with a trial parameter which can potentially indicate a systematic issue that could impact participants safety or the reliability of trial results. If exceeded, should trigger an evaluation and an action to be taken.
A QTL is a value associated with a trial variable that, QTLs are part of Risk Based Quality Management and are specifically mentioned in ICH-GCP E6(R2). QTLs define acceptable values for trial parameters that, when breached, may impact subject safety or the reliability and/or integrity of trial results. If the parameter value is within the acceptable values (tolerance limits), then quality is being maintained. Once the parameter value exceeds the tolerance limits, then quality is no longer being maintained and mitigation efforts should be undertaken.

WHAT/WHY/HOW

There are lot of questions about QTLs from study teams, and from sponsors when discussing about QTLs. The questions usually boil down to three simple ones: WHAT? WHY? HOW? So, let's cover those questions in the next.

WHAT are QTLs?

QTLs are part of Risk Based Quality Management and are mentioned in ICH-GCP E6 (R2).

QTLs define acceptable values for trial parameters that when breached, may impact subject safety or the reliability and/or integrity of trial results. If the parameter value is within the acceptable values (tolerance limits) then quality is being maintained, once the parameter value exceeds the tolerance limits then quality is no longer being maintained and mitigation efforts should be undertaken. QTLs should be defined focusing on those parameters that are critical to quality factors. These are factoring that impact trial quality for: primary objectives, safety objectives, patient eligibility, or Investigational Product exposure.

WHY QTLS?

Subject Variability: Clinical trials involve diverse patient populations, making it challenging to define universal QTLs. Tailoring QTLs to study-specific factors is necessary.

Early Phase Trials: In early phase trials, QTLs may need to be adjusted based on the exploratory nature of the study and the evolving understanding of the treatment's safety and efficacy.

Data Integration: When combining data from multiple sources or studies, harmonizing QTLs becomes important to maintain consistency and comparability.

Regulatory Updates: Stay updated with changing regulatory requirements to ensure QTLs align with the latest standards and guidelines.

Ensuring Data Integrity: QTLs play a crucial role in detecting and addressing data errors, inconsistencies, or outliers that may compromise the integrity of clinical trial results.

Protecting Patient Safety: By maintaining data quality, QTLs help ensure that any conclusions drawn from the trial are based on reliable information, minimizing potential risks to patient safety.

Regulatory Compliance: Regulatory authorities require adherence to predefined QTLs to ensure data quality and validity during the drug approval process.

Enhancing Confidence in Results: Applying QTLs increases confidence in the trial results and supports decision-making regarding the safety and efficacy of investigational treatments.

Ensure corrective and preventive actions are implemented in a timely manner to prevent impact on **QUALITY** of study objectives, QTLs are required per the **ICH GCP E6** sections on Risk Control and Risk Reporting

HOW TO IMPLEMENT QTLS

Define: Based on Clinical Development Plan & Draft Protocol, perform risk assessment analyzing quality by design, critical to quality factors, critical data & processes, and risks; Define critical parameters and Thresholds; Design QTL monitoring plan by listing timeframe, frequency, data sources and programming

Monitor: Program & validate the QTLs; execute to perform trend analysis; If any deviations identified, assess the root cause, determine the criticality, revise QTLs if needed

Report: Generate the summary report for deviations with actions taken and report in CSR

QTL AND KRI

QTL- Quality Tolerance Limit, a higher-level indication of overall quality in a trial, driven by process, report important QTL deviations in CSR (Study level).

KRI- Key Risk Indicator, typically measured at the site level to inform site monitoring activities; driven by risk, monitor quality performance during study progression (Site & Country level).

QTLs should be established for a limited number of parameters (for example, 3 to 5) that can impact subject safety and reliability of trial results. Too many QTLs will dilute the importance of each QTL. KRIs can be 15 to 20 per study based on the risk factors.

STANDARD QTLS AND AUTOMATION

Based on earlier studies QTL implementation we have setup a pool of standard QTLs, which can be used as a starting point for QTL definition. QTLs selected from a library may need to be adapted to trial-specific characteristics.

Scripts that can work on Standard QTLs with passing minimum inputs – study specific attributes and threshold values. These are easy to implement with less efforts and quick turnaround. Easy to deploy on a scheduling tool to execute on required frequency and share the outputs over mail or at a specific path automatically.

CONCLUSION

Here we summarize that this helped to understand what the QTLs are, why these are important and how do we define these along with few methodologies on standardization/automation of these QTLs which will help to follow regulatory authorities and how we were able to achieve this.

CONTACT INFORMATION

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