Paper AR03

Quality Tolerance Limits: Understanding the added value and statistical need of implementing QTLs to assure subject safety and data quality

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ABSTRACT

Quality Tolerance Limits have been an ICHE6R2 requirement since 2016. The need to have a monitoring tool linked to the statistical design of a trial has been the biggest asset of QTLs. Though the industry is still working on best practices, the new ICH E6 R3 has been drafted, potentially expanding monitoring oversight to acceptable ranges. As there is a statistical benefit in implementing QTLs companies should be putting efforts in establishing processes to set appropriate acceptable ranges that are linked to the key objectives of a trial. This paper will outline the importance of defining and monitoring QTLs and the statistical need to monitor closely and to implement real time mitigation actions as well as understand the evolving of study data throughout a trial.

RBQM OVERSIGHT MECHANISMS IN CLINICAL TRIALS

Quality by Design (QbD) principles should be embedded in all trial aspects. Companies need to have a quality management system in place that supports a risk-based approach. Therefore, central trial oversight should be risk based while assuring patient safety and reliability of trial results. First step is to identify risks to critical data and processes, resulting in critical to quality factors.

From a RBM perspective, central trial oversight consists of 3 main focus areas:

KRIs

- Study KRIs: These can be on portfolio, compound, study, country and site level. And can be generic like: Time to enter data, Adverse events over and underreporting. These will identify overall/ general quality issues. There is a need to add thresholds that will need to be based on historical and industry standards.
- Study specific KRI's: Can be on study, country, site and subject level, to drive day-to-day actions and mitigations. These are operational focused while providing an indication of risk. Examples are compliance reviews for study specific assessments.

Central Statistical Monitoring

- Allow for oversight of any statistical anomalies that cannot be detected by compliance data review.

Quality Tolerance Limits

- On of the tools that has been introduced by the ICH E6 R2 are Quality Tolerance Limits. These need to consider the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial results.

Utilizing these three tools will establish a robust central oversight for trials by focusing on trial compliance, addressing data requirements for the statistical design, and identifying any underlying statistical anomalies.

Importance of Quality Tolerance Limits

- QTLs are linked to critical to quality factors based on primary and key secondary endpoints
- Early discussions with the clinical team and statisticians help understand what data is needed for the statistical design
- Signal detection – which data will be critical to perform the statistical analysis?

By performing a risk assessment on the protocol and identify Critical to Quality factors you will be able to identify the areas of risk. The CTQs with the highest impact on the primary and key secondary endpoint need to be considered for QTLs.
Since QTLs are linked to the medical and statistical characteristics of a study, there is a need to early involve the clinical team as well as the statisticians to understand the data impact to the statistical design. This will allow to understand what data is collected for the primary and secondary endpoint, and how the different roles will use that data.
When defining the parameter there needs to be understanding of the statistical design and analysis as well as the protocol defined assessments.

Statistical benefits of Quality Tolerance Limits

- Ongoing discussions on the data quality impact on statistical analysis
- Reducing bias
- Updates to protocol or SAP to mitigate signals detected

Monitoring Quality Tolerance Limits

What does this look like throughout a study?

First the study team will need to define a parameter and thresholds

The parameter should be linked to the primary or key secondary endpoints of a study, linked to the ones with the highest impact. These could be linked to missed assessments at critical endpoints for analysis. These can also be linked to the statistical design.

An appropriate threshold then needs to be set. We would recommend setting a QTL as well as a secondary threshold. The secondary threshold will help the study team see early on where there is a trend/ signal detected. The primary threshold can be set using historical data, data simulation, protocol assumption. We do recommend using multiple methods, if possible to have the most appropriate threshold.

Throughout the study the study team needs to assess the QTL trends and signals. It is key to have the statisticians involved to make sure that the signals that are seen are true or false, to decide on actions

When a breach is detected or a trend to a breach is seen, there is a need for the study team to perform a root cause analysis. This should be an effort across all roles in the study team, including the clinical team and statistician. A secondary breach may not seem important enough to put mitigation actions in place, but the team needs to realize that gives a good overview throughout the study if there is sufficient data for the statistical analysis. Study teams need to keep in mind the data evolvement. Data can still come in, that would make the breach go away but understanding in real time where potential problems can occur, will help with the success of a trial.

For a statistical point of view it is important to understand the evolution of the data, to assess updates to the protocol or SAP.

Mitigation actions can vary per breach. It needs to be determined what causes the breach. If the breach is based on limited data, if there is a site/country signal that can be followed up by an operations team. The clinical and statistical team can perform preliminary analysis to assess the impact to data quality and subject safety, assess the protocol and if any updates/ amendments are required. Teams need to expand the mitigations across all roles, and not just focus on a site or country level because QTLs are designed to oversee the data quality on trial level.

Study teams should keep in mind to not bias the data while putting in mitigations in place. The statistician's role is key to guide the study team in the correct way of mitigation.

Once the Breach has been identified and mitigated, the CSR needs to reflect this. Leading up to the CSR, clinical team and statisticians should have a good understanding of what happened throughout the trial and the quality of the data.

Quality Tolerance Limits Challenges

Challenges seen in clinical trials relate to:

- Small studies
- Short duration of trials
- Statistical design
- Threshold setting
- Setting correct parameters and thresholds

Study teams need to take study specifics into account and assess the need of the trial when including QTLs.
Although there are challenges, working close with all cross-functional roles will help to identify appropriate QTLs even for these challenging situations.

CONCLUSION

The added value of QTLs has been established within the industry. There is a need to implement QTL parameters and thresholds to support a risk based quality management system. Together with KRI review and Central statistical monitoring, QTLs complement oversight in such a way for study teams to need to work together to oversee a successful trial.

Currently the ICH E6 R2 is being updated to ICH E6 R3, and although there is unclarity if QTLs will remain a key focus in the document, the wider term acceptable ranges does indicate that a risk based approach is key. From our perspective QTLs are bridging the gap between KRIs and the statistical needs of a trial, that we are convinced this is an approach that will be needed to continue.

There are within Phuse working groups that are discussing QTLs and how to implement these for different trials as well as refining what is meant with parameters, thresholds, and the best approach to set these QTLs to continue to improve the QTL process.

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