A Glance at QTLs

Pre-defined Quality Tolerance Limits

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Overview of QTLs

Fact is …

Certain events in a study will occur that may impact interpretation of key efficacy or safety endpoints.

Traditional methods of ensuring patient safety and data integrity can be time-consuming, expensive, and inefficient

- Traditional mechanisms used to assess overall data quality are less frequent and/or performed close to database lock and study completion.
- Traditionally, focus of reviews is usually geared toward correction of identified data issues, and does not evaluate these issues in the context of risk and proactive mitigation and monitoring of that risk.

Overview of QTLs

Background

ICH E6 (R2) recommends QTLs to help “identify systematic issues that can impact subject safety or reliability of trial results”.

5.0.4 Risk Control

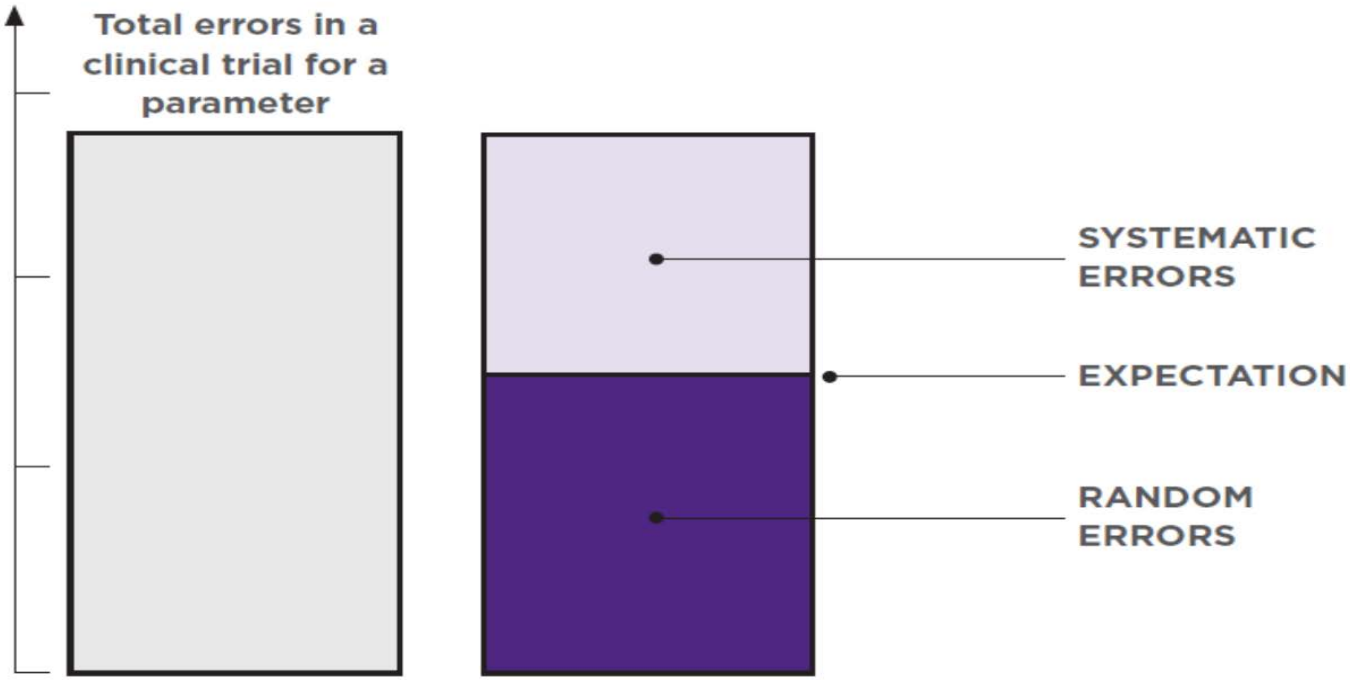
Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial results. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

5.0.7 Risk Reporting

The sponsor should describe the quality management approach implemented in the trial and summarize important deviations from the predefined quality tolerance limits and remedial actions taken in the clinical study report (ICH E3, Section 9.6 Data Quality Assurance).

Overview of QTLs

Systematic Error vs Random Error



Overview of QTLs

Systematic Error vs Random Error

- A systematic error is a source of variability that can be linked to a certain reason
  - Common root cause – events or errors share the same underlying cause
  - Imbalance in error distribution – imbalance across geographic regions or treatment arms in open-label studies are examples
  - Skewing of results – systematic component in an apparently random collection of errors

- Systematic error in historical data shall be evaluated when such data is used in defining QTLs in new trials (ex protocol violation % QTL)

Implementation of QTLs

Establishing QTLs

- QTLs should be established based on expert (medical and statistical) knowledge of similar trials, historical data of similar trials, and/or statistical methods and modeling.

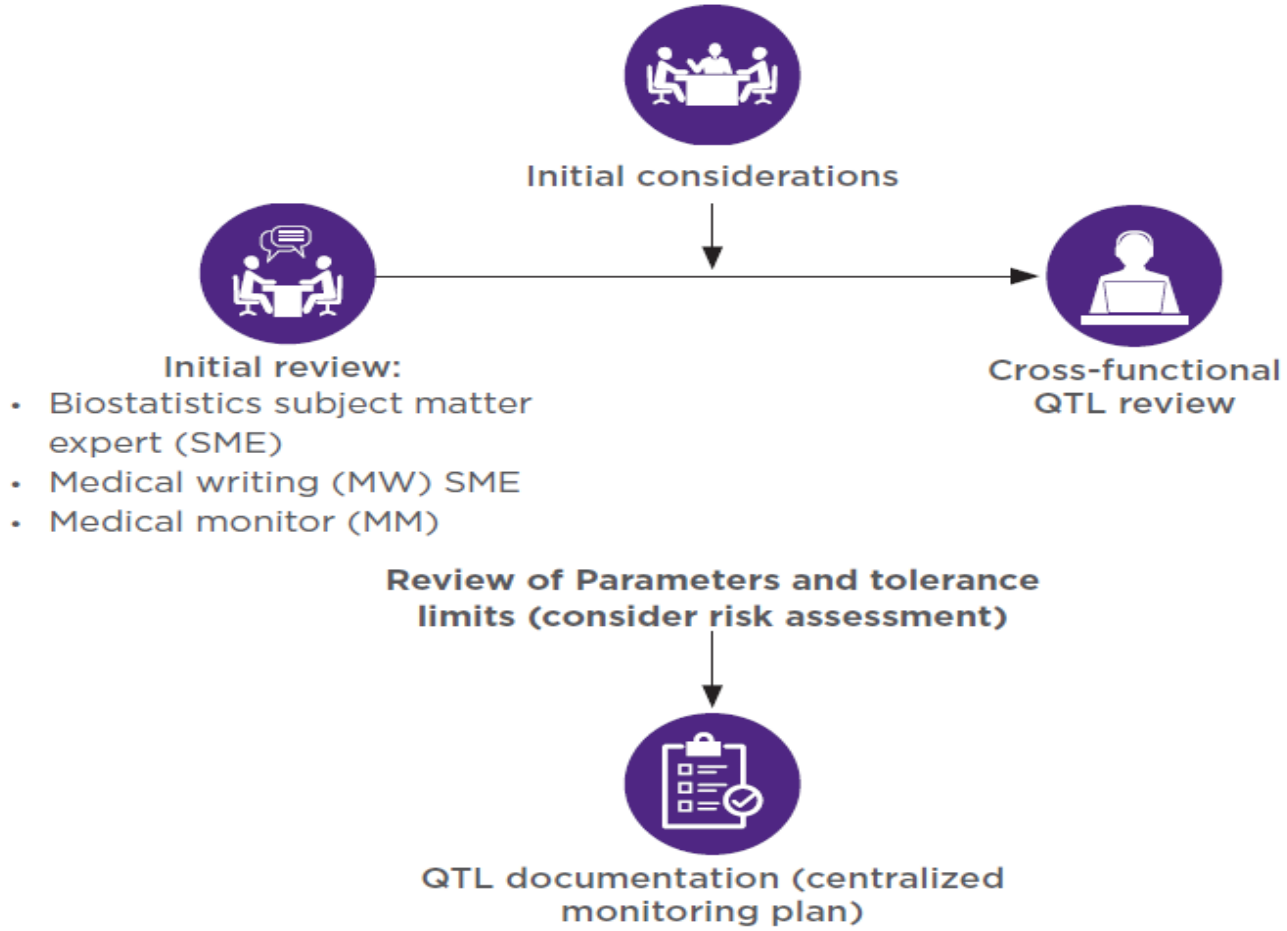
- QTLs should be established for a limited number of parameters (for example, 3 to 5) that can impact subject safety and reliability of trial results.

- Before initiation of the trial, sponsors should develop written, prospectively defined plans for monitoring parameters and addressing deviations from the QTLs.

- The following elements should be considered when defining QTLs: parameter, definition, unit, expectation, tolerance limit (upper, lower, or both), and justifications.

Implementation of QTLs

Establishing QTLs



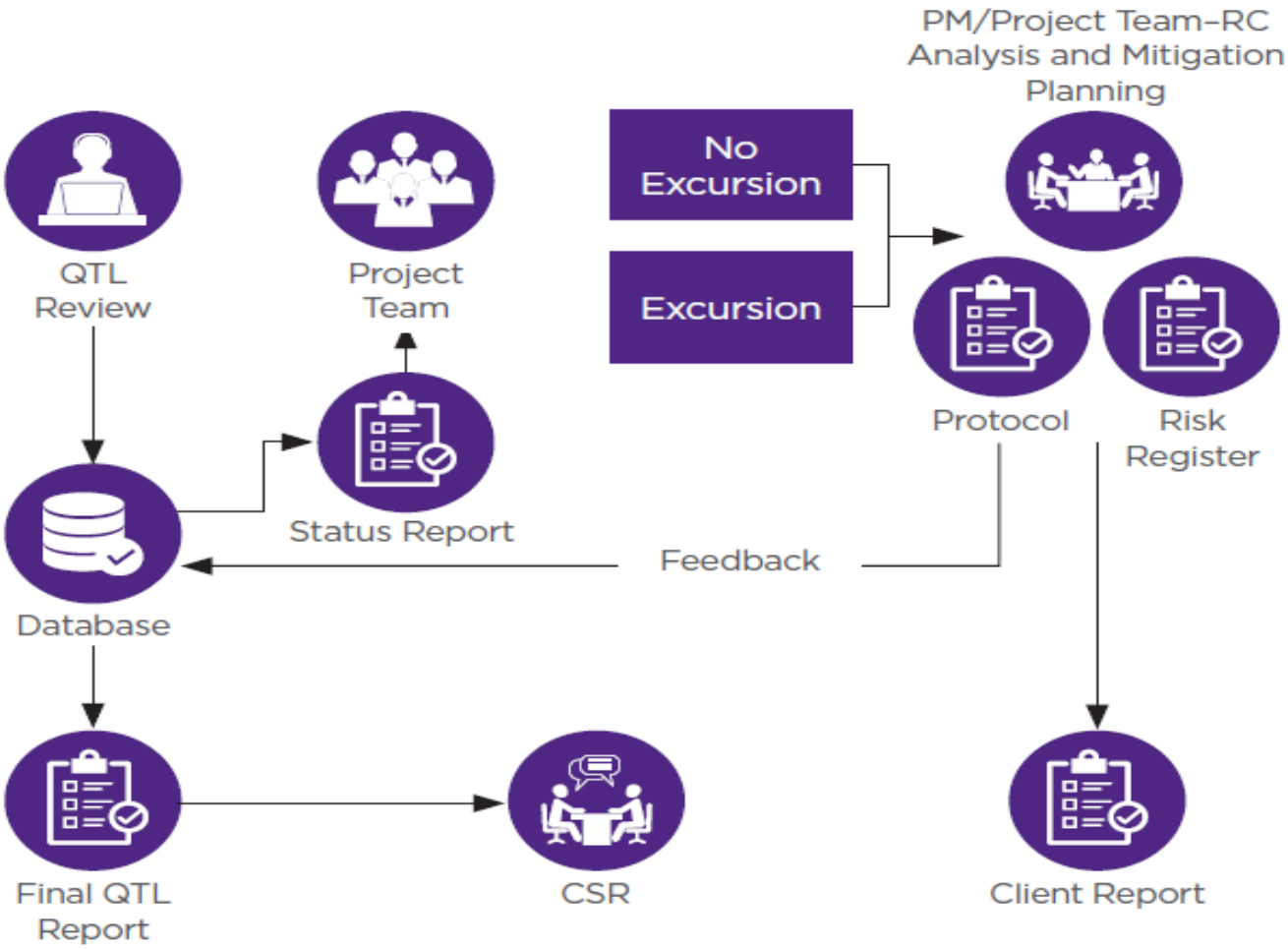
Implementation of QTLs

Monitoring QTLs

- Frequency
  - ✓ Data robustness while balancing data availability.
  - ✓ Sufficient time allocated.
- A comprehensive root cause analysis would be performed by the study team。
- Follow-up actions would be recommended subsequent to the excursion.

Implementation of QTLs

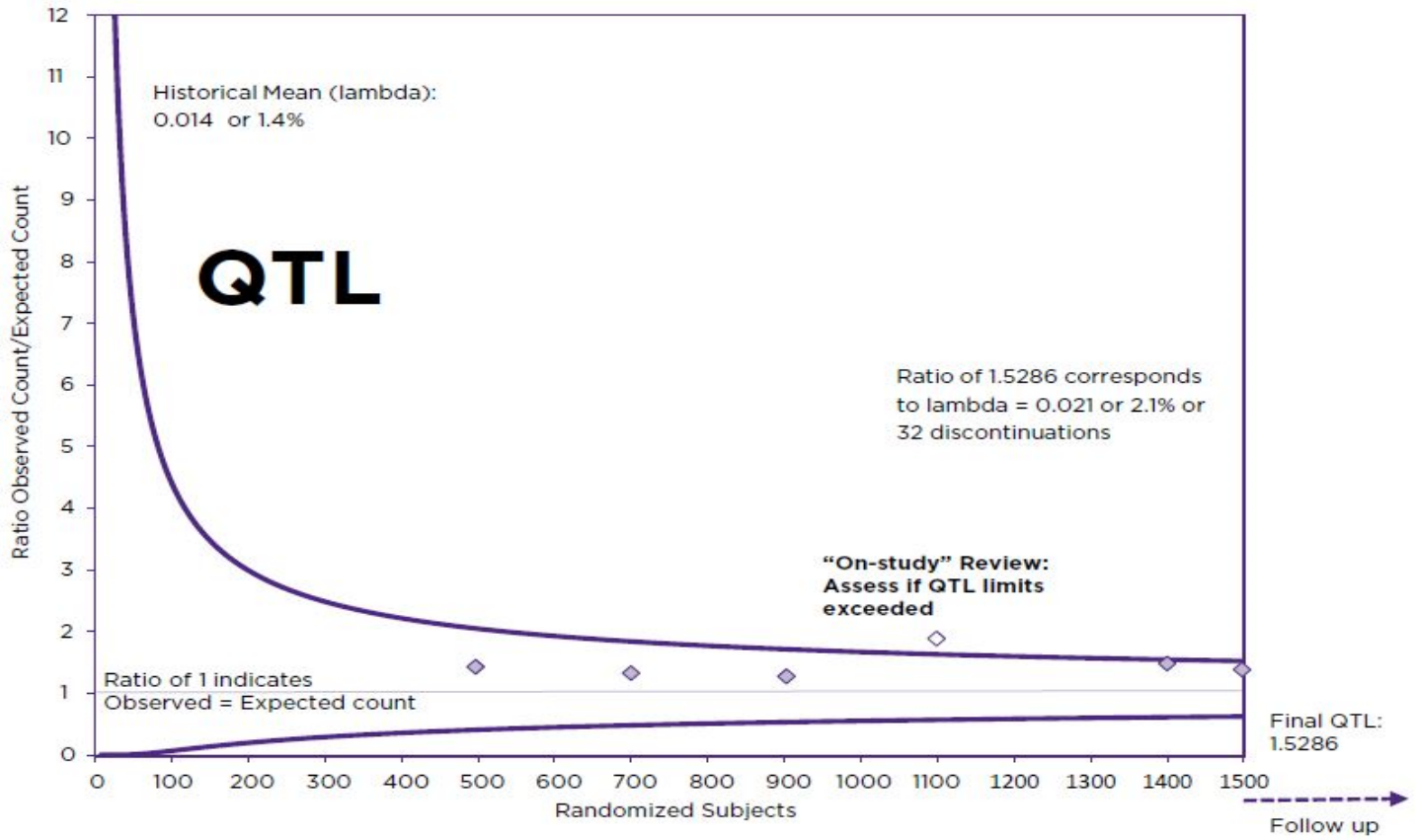
Monitoring QTLs



Implementation of QTLs

Monitoring QTLs

Parameter: subjects randomized who discontinued the study treatment prematurely (before protocol defined time point)



Implementation of QTLs

QTLs Tracking and Reporting

- Tracking of QTLs should be streamlined to allow visibility into the status of each parameter throughout the trial.
- Collection and documentation should be detailed enough to allow sufficient information to be collected so the medical writing team is able to construct the story around excursions and actions taken after the study closed.
- These QTL components shall be included in CSR:
  - Frequency of monitoring for each parameter
  - Number of times the QTLs were exceeded
  - Summary on when excursions occur, for which parameter and the extent of excursion
  - Summary of root cause analyses when on-study excursions occur
  - Provide a narrative of certain parameters exceeding tolerance limits at the end of the trial as it pertains to the impact on patient safety and trial objectives
  - Information summarized in the clinical study report will include justification on any QTL adjustments during root cause analysis

Case Study

Background:

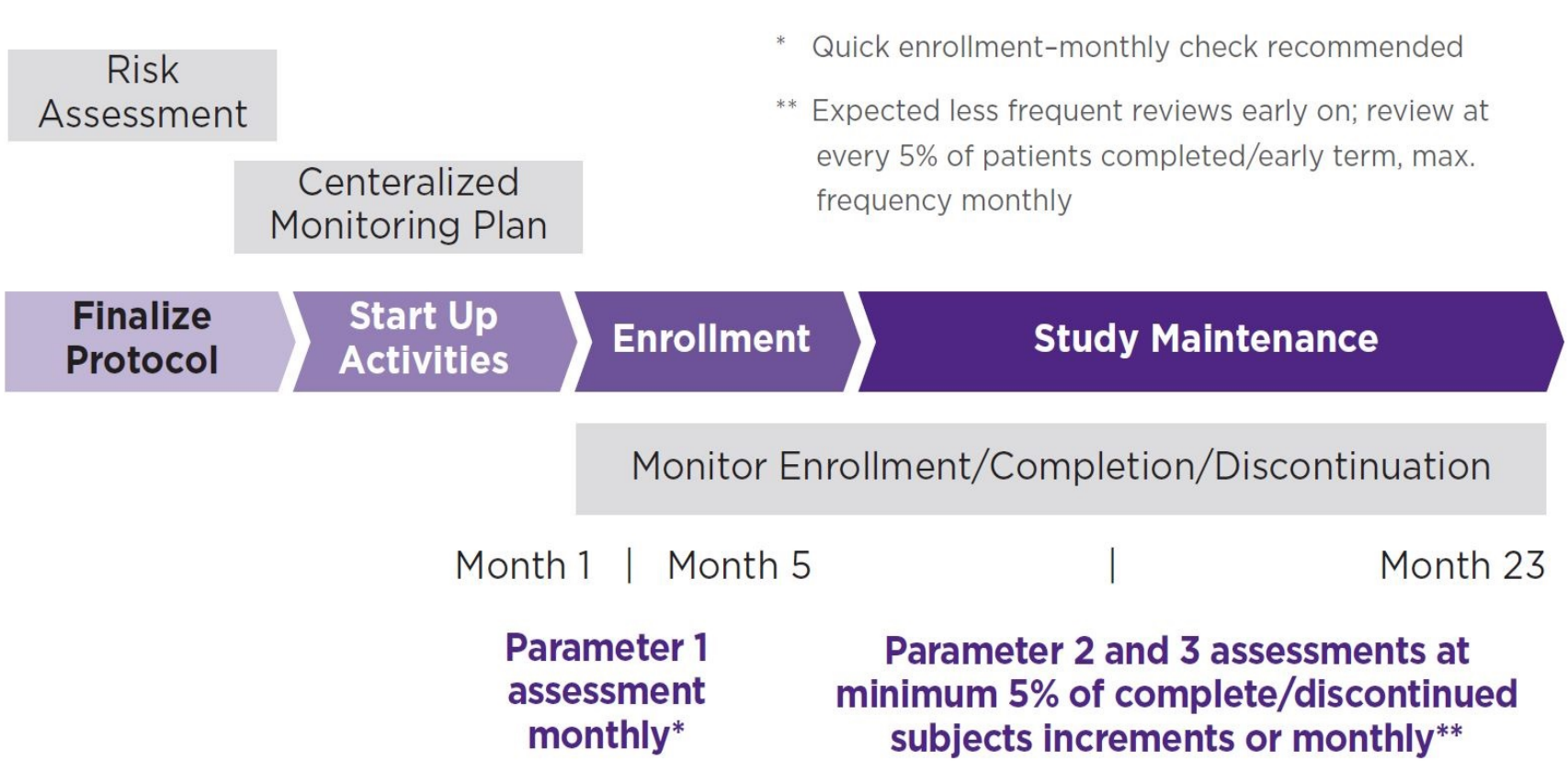
QTL monitoring service was offered on a Phase III cardiovascular program for three studies involving a cholesterol lowering drug where 1,500 subjects were to be enrolled into the first study within a five-month period. The total duration of the study was 24 months, from the first subject enrolled until the last subject completed.

QTLs were recommended for the following parameters:

- Percentage of subjects randomized with predefined, important inc./exc. criteria violations that led to the exclusion of the subject from the primary analysis.
- Percentage of subjects randomized who discontinued the study treatment prematurely.
- Percentage of subjects who have no status documented by the site in the close out period.

Case Study

QTL review timeline



Q&A