Assessing the Use of Quality Tolerance Limits in the Pharmaceutical Industry

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Contents

Revision History

Version	Date	Summary
0.1	21 Dec 2023	First stable draft produced by the Working Group ready for PHUSE review
0.2	12 Feb 2024	Incorporated feedback and included authors/significant contributors
1.1	12 Mar 2024	Finalised during QTL meeting
1.1	22 Mar 2024	Updated following feedback from proofreader

1. Abstract

Risk-based quality management (RBQM) has been encouraged since 2013, when the EMA published a reflection paper on RBQM to support effective monitoring and quality of clinical trials.[1] RBQM applies the quality by design (QbD) principles, and, over the past several years, the industry's understanding of a QbD approach to clinical trials has improved. Using QbD encourages designing quality into a trial during the planning phase.[2] The identification of critical to quality factors (CtQs) as part of QbD is key to implementing RBQM.[3]

One method of monitoring risk associated with CtQs is to use quality tolerance limit (QTL) parameters which are linked to the key scientific question(s) of a trial and identify systemic issues that can jeopardise the integrity of trial endpoints.[4,5]

By surveying the industry to gather information on the current use of QTLs, this white paper aims to provide the reader with valuable insights into the depth and breadth of their use. It will also address how QTLs are used in the wider scope of implementing RBQM, and the direction of stakeholders, given that the regulations regarding the conduct of clinical trials continue to evolve.

2. Key Words

Critical to Quality Factors, Key Risk Indicators, Quality Tolerance Limit, Quality by Design, Risk Assessment and Categorization Tool, Risk Based Quality Management

3. Introduction – QTLs in Clinical Trials

Clinical trials should adopt RBQM[6] whereby quality is embedded in design, conduct and reporting activities. RBQM applies QbD principles[2] to ensure that the quality of a study can be driven proactively by designing quality into the study protocol and associated processes. This involves using a prospective, multidisciplinary approach to promote the quality of the protocol and study processes in a manner proportionate to the perceived risks.

Quality is achieved by focusing on key elements, also known as CtQs.[3] When developing protocols, CtQs should be considered important study elements as they are key to participant safety and/or the integrity of data.[7]

During risk assessment activities, it is important there is a focus on CtQs and attributes that will help the study team prioritise risk parameters that can be measured directly (factors), indirectly or not at all (attributes). These parameters are likely to have a meaningful impact on the participant's rights, safety, and well-being as well as the reliability of the results. Risk assessment should be undertaken using methodologies such as TransCelerate RACT,[8] proprietary risk assessment technology or Clinical Trials Transformation Initiative (CTTI) groupings.[7]

CtQs can be monitored by means of key risk indicators (KRIs) and QTLs. KRIs are a useful tool within risk management and are used to enhance the monitoring and mitigation of risks and facilitate risk reporting on an ongoing basis. KRIs are measures that enable risk management stakeholders to identify potential losses from inadequate or failed internal processes, people and systems, or external events before or as they happen.[9,10,11]
ICH E6 (R2)[1] proposes QTLs as a risk control method to proactively identify systematic quality concerns during the conduct of a clinical trial which, following corrective actions, may avoid safety and data quality deviations. However, in the draft of ICH E6 (R3),[12] QTLs appear to have been replaced with the setting of 'Acceptable Ranges'. Further comments on the potential impact of ICH E6 (R3) can be found in the Discussion section.

There has been considerable literature published on implementation, interpretation, and recommendations for QTL use, and there seemed to be an uptake of QTL use during the COVID pandemic.[13,14,15,16] However, there is no literature on the cross-industry perception and execution of QTLs in the RBQM framework.

To better understand the use of QTLs in the pharmaceutical industry, as well as how their use is placed within an organisation's risk management framework, the PHUSE QTL team developed and released a survey to gather information from RBQM stakeholders. This white paper presents the results of that survey.

4. Data Gathering Methods

A survey was developed using Google Forms. This data collection method was selected as it could reach a broad range of stakeholders and facilitate standardisation of the questions and responses, with the flexibility to collect additional details, and provide anonymity to respondents (and their employers) if so desired.

Respondents were directed to answer according to the current state of QTL implementation within their organisation. The survey contained thirty (30) questions, twelve (12) of which contained subparts in table format. The remaining questions were multiple choice, with twenty-two (22) opportunities to add detail or specificity using free text. Respondents had the option to break their anonymity by entering their email address if they were interested in participating in other PHUSE Working Groups related to QTLs.

5. Analyses

Frequency distributions of responses to each question were developed. Proportions of responses were assessed based on the total number of responses to each question, since this could vary.

Where appropriate, additional analyses (e.g. correlation, regression, t-test) were performed to explore potential relationships between QTLs currently in use and their perceived value, as well as between QTL parameters identified by TransCelerate[5] and other potential parameters.

6. Results

6.1. Demographic Information

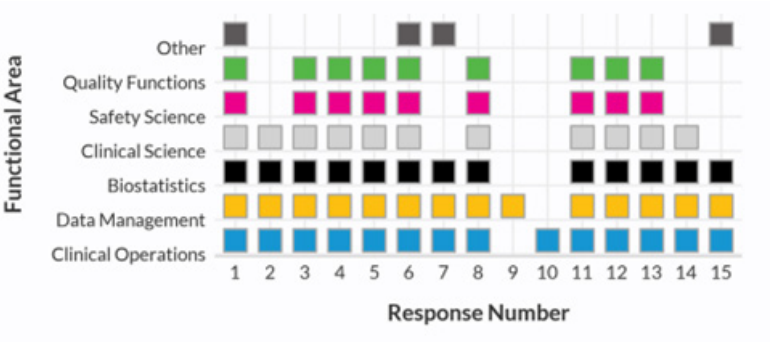
Figure 1 shows the demographics of the survey respondents. There were fifteen (15) respondent organisations, of which thirteen (13) were sponsors and two (2) were service providers. Of these respondents, six (6) were large organisations running >200 ongoing Phase I to III trials, four (4) were medium sized with 100–200 Phase I to III trials and five (5) were small companies running <100 Phase I to III trials.

Figure 1 *– Demographic information for survey respondents*

6.2. Roles Responsible for Risk-Based Approaches to Quality

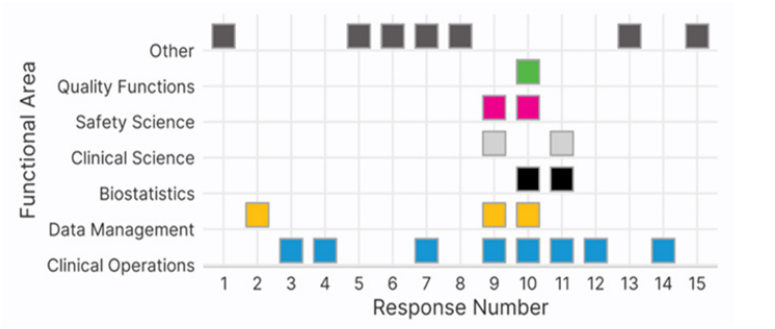
Trial-level risk management appears to be a cross-functional activity (Clinical Operations, Data Management and Biostatistics, Clinical Science and Safety Science) in nature (Figure 2) but often in differing mixes. In detail, two (2) organisations involved Clinical Operations (CO), Data Management (DM), Biostats (B), Clinical Science (CS), Safety Science (SS), Quality Functions (QF) and others. Seven (7) organisations, however, involved CO, DM, B, CS, SS and QF only. A further two (2) organisations involved only CO, DM, B and CS, with another two (2) organisations involving CO, DM, B and others. Finally, one (1) organisation relied only on Data Management and one (1) on Clinical Operations. This suggests most organisations employed some degree of cross-functional approach to risk management.

Figure 2 *– Functional areas involved in trial-level risk-based approaches to quality*



Clinical Operations (53.3%, n=8/15) or Other (46.7%, n=7/15) functions (e.g. Risk Management, Clinical Compliance) appear to take the lead; however, a number of Other responses were at the role level (Dedicated Risk Specialist/Member of RBQM Working Group/Centralised Monitor/Project Manager or Clinical Quality Manager), which makes it difficult to determine which functional organisation they might belong to (Figure 3).

Figure 3 *– Functional area leading trial-level RBQM approaches to quality*



6.3. Application of RBQM

All respondent organisations apply risk-based approaches to quality for Phase II, Phase III and complex study designs, as seen in Figures 4 and 5.

Figure 4 *– Risk-based approaches applied by trial type*

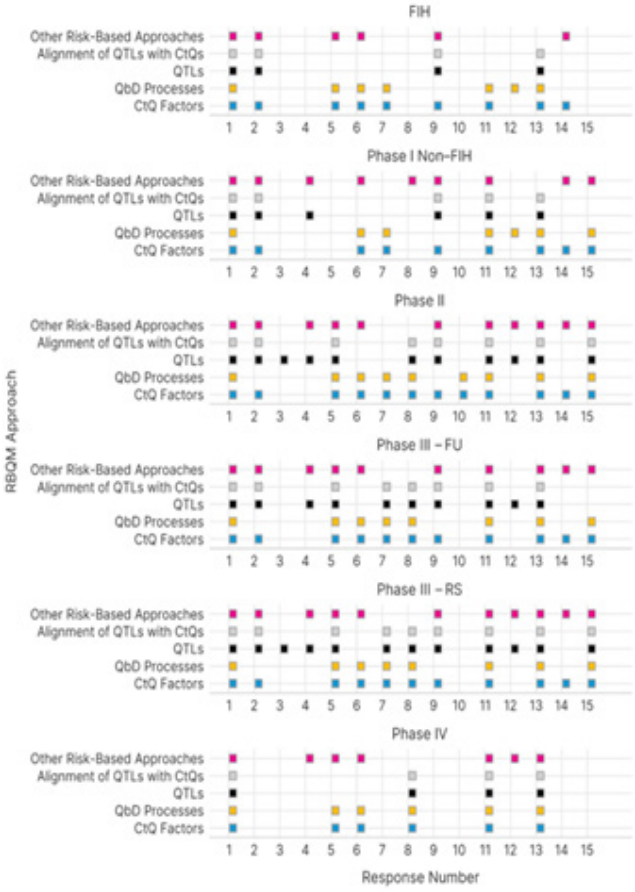
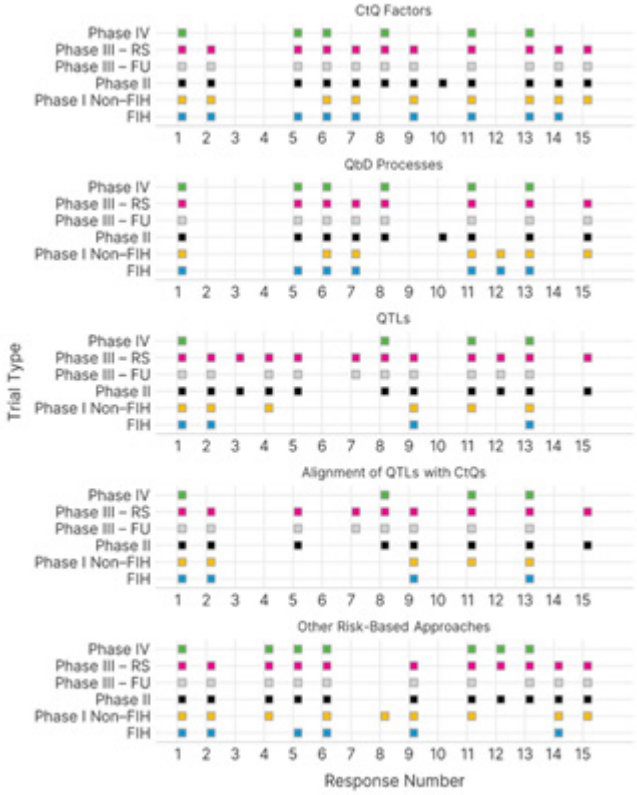


Figure 5 *– Risk-based approaches applied by trial attribute*



There appears to be more consistent use of risk-based efforts for Phase II and Phase III trials than other trial types. It is encouraging to see the widespread adoption of CtQ, QbD and QTL across the spectrum of clinical trials, even for FIH and Phase I Non-FIH. This suggests that the approach is maturing, and organisations are not discounting applicability to early-phase trials. The uptake of QTLs in Phase IV trials is not as expected, given that these often have large volumes of data, but the reason for the difference between Phase IV and Phase III may be that Phase IV trials are more often non-interventional.

There appears to be favourable uptake of CtQ factors across all the phases, with nine to eleven (n=9–11/15 (60–73%)) organisations using them. A similar trend is seen for QbD Processes, QTLs and Other Risk-Based Approaches. However, it is interesting that there is not always total alignment between QTLs and CtQs.

As expected, the trial design, trial phase and trial size are the main elements that impact on the use of QTLs across eight to nine (n=8–9/15 (53–60%)) organisations. This also affects the identification of CtQs, and there seems to be some uncertainty over implementation of QbD in general, with three (n=3/15 (20%)) organisations not using CtQs or implementing QbD. The uptake of QTLs aligning with CtQs is still quite low, with a maximum of five (n=5 (33%)) organisations aligning with the trial design attribute.

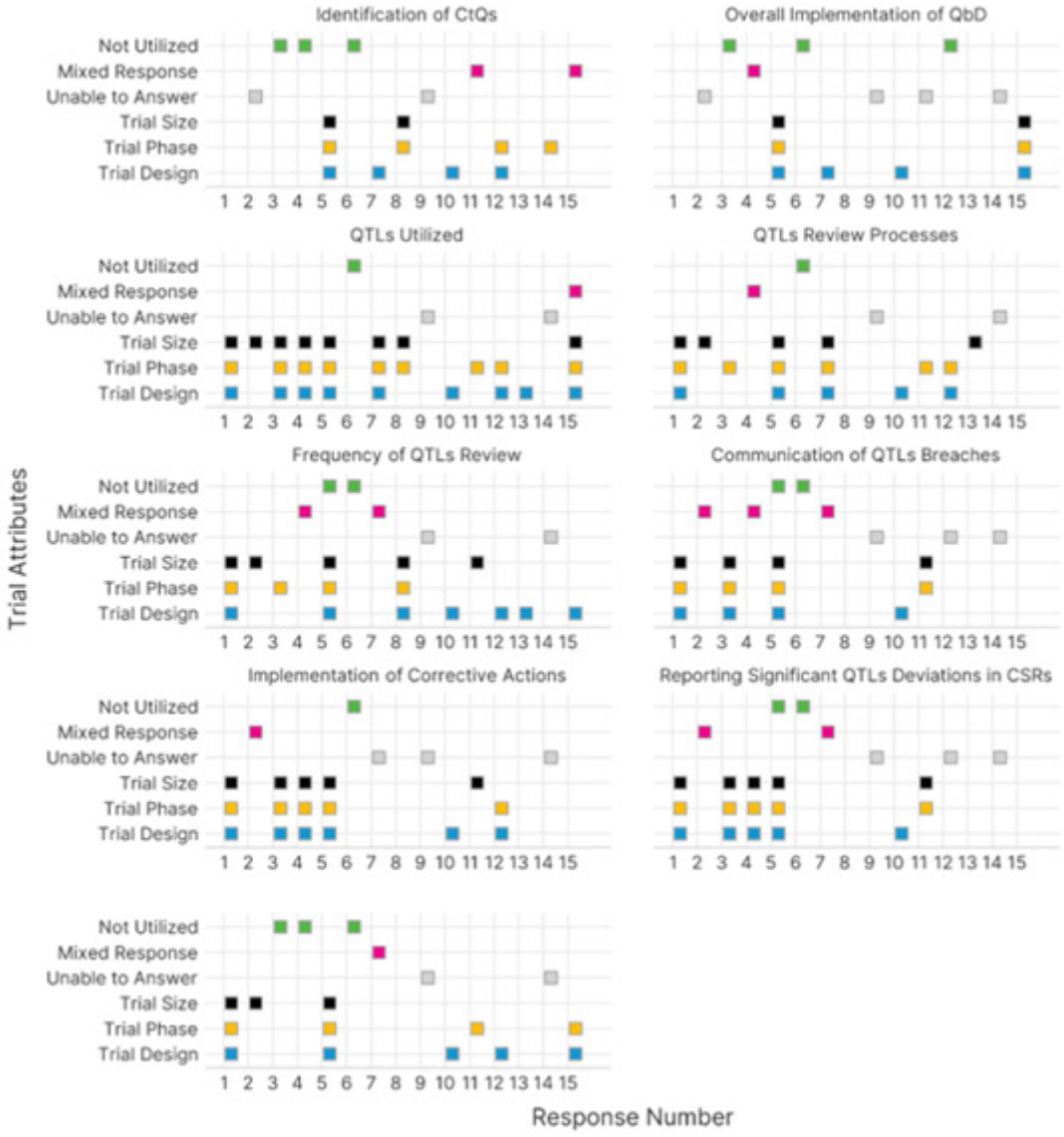
Furthermore, there is consistency in responses for trial design, phase, and size regarding communication of QTL breaches. As this is a process and should be independent of trial attributes, it is to be expected that these attributes influence the frequency of QTL review. There does seem to be a consistent 'Not utilized' flavour across the choices within this question, and that does seem to contradict the

data provided in Figures 4 and 5. There may be a lack of understanding of the connection between QbD and QTLs. There were also a few 'Unable to answer' responses; perhaps some of the questions were difficult for the organisations to answer.

Some reasons why QTLs are not applied were captured in comments, but they seem to revolve around small trials, difficulties in identifying meaningful measures, and non-interventional/observational/epidemiological trials.

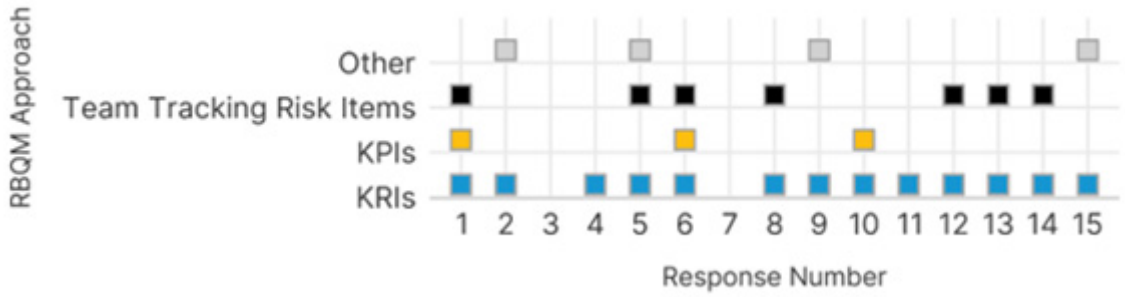
Most organisations (~60% or more) indicated that trial design, trial phase and trial size are the primary attributes that impact on the use of QTLs. Communication of deviations, however, were less impacted by these same attributes (according to ~30% of respondent organisations), as can be seen in Figure 6.

Figure 6 *– RBQM approaches are applied differently depending on trial attribute*



Thirteen (n=13/14 (93%)) respondent organisations employ KRIs, three (n=3/14 (21%)) use KPIs, and seven (n=7/14 (50%)) employ the study team to track items. The four (n=4/14 (29%)) 'Other' approaches were unspecified, as can be seen in Figure 7.

Figure 7 *– Details of other RBQM approaches by organisation response*



6.4. QTL Implementation

Of the organisations surveyed, approximately 87% (n=13/15) indicated that they use QTLs. Of these thirteen (13) respondents who answered 'Yes they are implemented', two (2) did not identify the year of implementation. Also, two (2) organisations did not reply 'yes' to implementation of QTLs and hence also did not reply to the date of implementation. Of those who indicated they use QTLs, the majority responded that they have employed QTLs since 2018 (n=10), with one (1) organisation implementing in 2017.

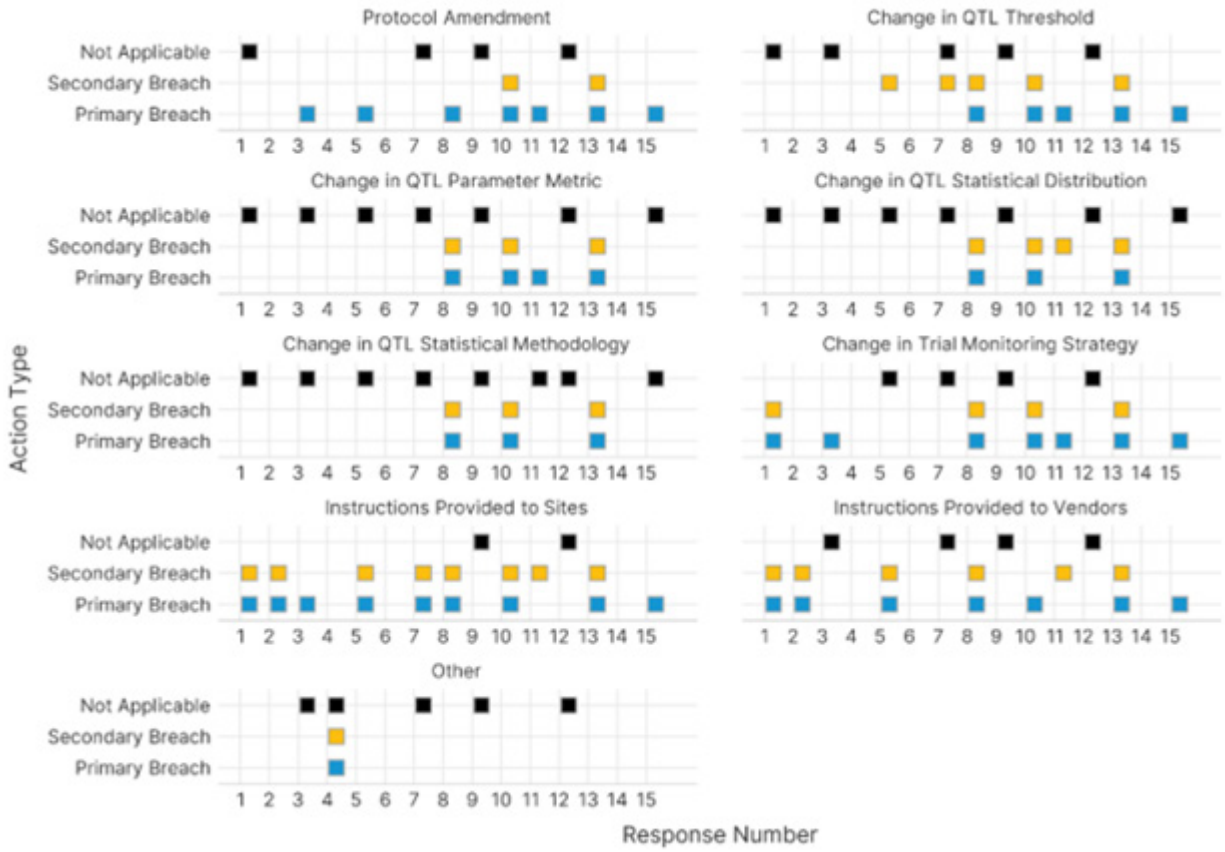
The top three drivers identified by the respondent organisations as to which parameters they would define their QTLs from are Key Safety (80%, n=12/15), Efficacy Objectives (>86%, n=13/15) and Choice, as guided by subject matter experts (60%, n=9/15). Those that are easy to measure, or control, were not widely chosen (13%, n=2/15 of respondent organisations).

Approximately 30–40% of organisations are currently, or plan to, formally integrate QTLs into their quality management system (QMS), inspections, continuous improvements, reviews, and oversight. The majority (47%, n=7/15) are integrating or planning to integrate QTLs into their QbD processes, with a greater number (60%, n=9/15) integrating or planning to integrate them into their CtQ processes (Figure 8).

Figure 8 *– QTL alignment with QbD processes*

Most respondent organisations (64%, n=7/11) implement a protocol amendment in the event of a primary QTL deviation, with one indicating they would use an amendment in the event of a secondary deviation as well. Additionally, 45% (n=5/11) of respondent organisations would reset the thresholds and 64% (n=7/11) would change the trial monitoring strategy or provide instructions to vendors, whilst 82% (n=9/11) would provide instructions to sites (Figure 9).

Figure 9 *– Actions taken in response to a QTL deviation*

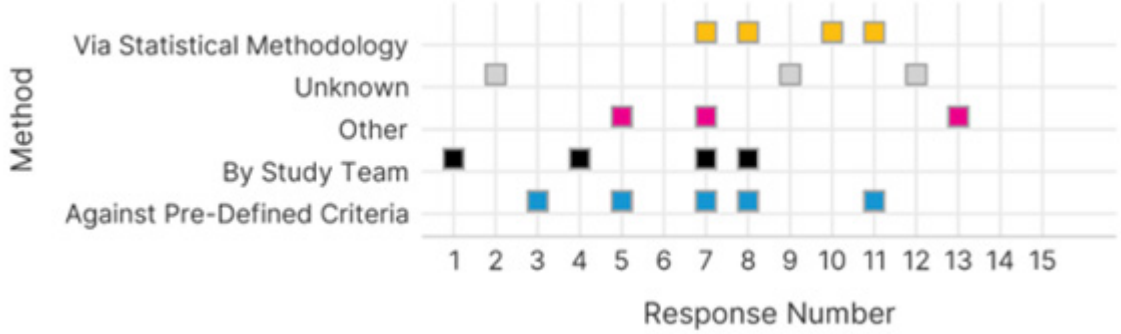


In determining whether a primary deviation of the QTL should be reported in the clinical study report (CSR),[1] 41.7% (n=5/12) of respondent organisations compare the QTL against pre-defined criteria, 33.3% (n=4/12) use statistical methodology and/or study team decisions to define the need to report in the CSR (Figure 9), and 17% (n=2/12) were not sure (Figure 10).

The question of consistent approaches to evaluating primary deviation for importance was posed. An equal number of respondent organisations (41.7%, n=5) indicated that it was both consistent and inconsistent.

The question of whether the process of evaluating primary QTL deviations for importance was like the process for evaluating important protocol deviations was also posed. The outcome was not conclusive, as an equal number (33.3%, n=5/15) of respondent organisations indicated it was/it was not, or they were not sure.

Figure 10 *– Evaluating primary QTL deviations for importance*



6.5. Focus of Health Authority Inspections on QTLs

To better understand if health authorities (HAs) have focused, at least in part, on the use of QTLs, the survey posed a series of questions. Only one (1) of the fifteen (15) respondents (7%) indicated that they had, at least in part, an HA inspection that focused on QTLs. A second question regarding more specifics about the HA focus resulted in data that is not interpretable and is not presented here.

6.6. Parameters Used for the Application of QTLs

The next series of questions focused on the current or planned use of QTLs as identified by TransCelerate, as well as other sources.

Of the parameters recommended by TransCelerate,[5] Primary Endpoint Assessment was the most heavily used, with 87% (n=13/15) of respondent organisations indicating that they used, planned to use or were under consideration to use in connection with QTLs.

Investigational Product – Compliance and Censored Data – Statistical Analysis (80%, n=12/15), Lost to Follow Up and Disposition – Early Termination (73%, n=11/15), Secondary Endpoint Assessment (60%, n=9/15) and Randomization Failure (67%, n=10/15) were the other parameters with a response greater than or equal to 60% that used, planned to use or were under consideration to use that parameter.

Of the remaining parameters, Protocol Deviations – Study Conduct, Protocol Deviations – Other, Investigational Product – Other, Stratification, and Informed Consent were all viewed by most respondent organisations (<60% response rate) as not considered to be a QTL (Figure 11).

Figure 11 *– Use of TransCelerate parameters*

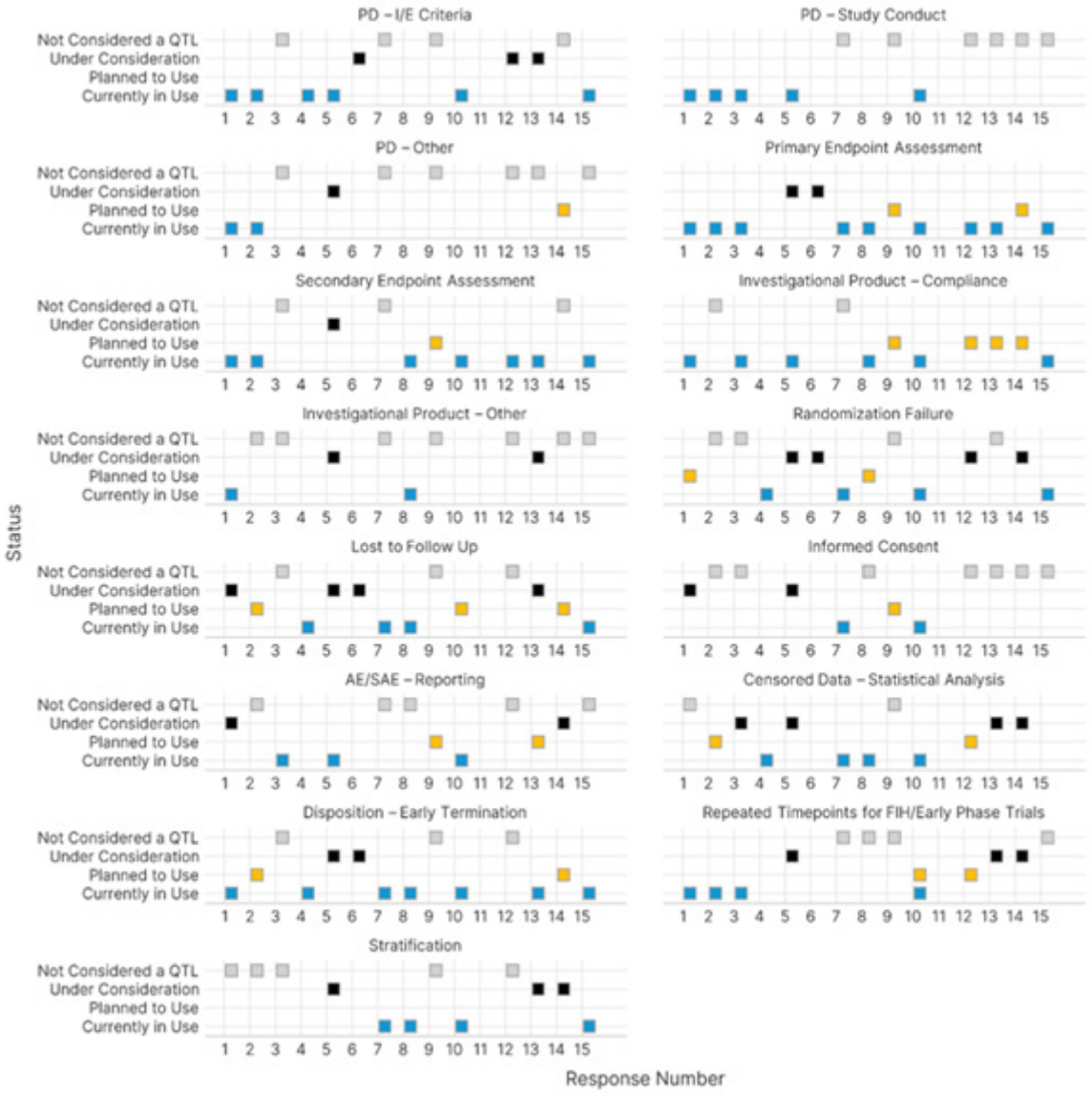
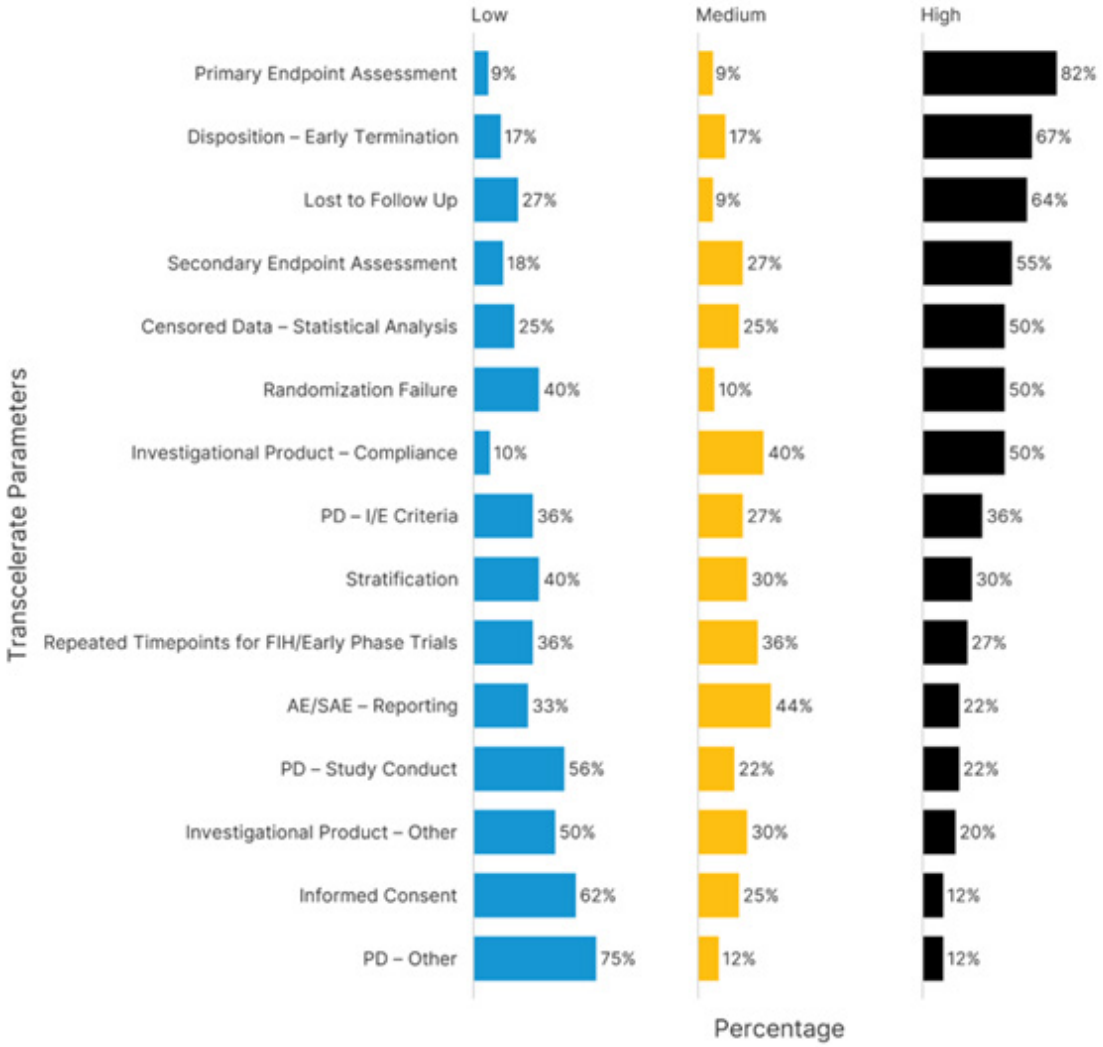


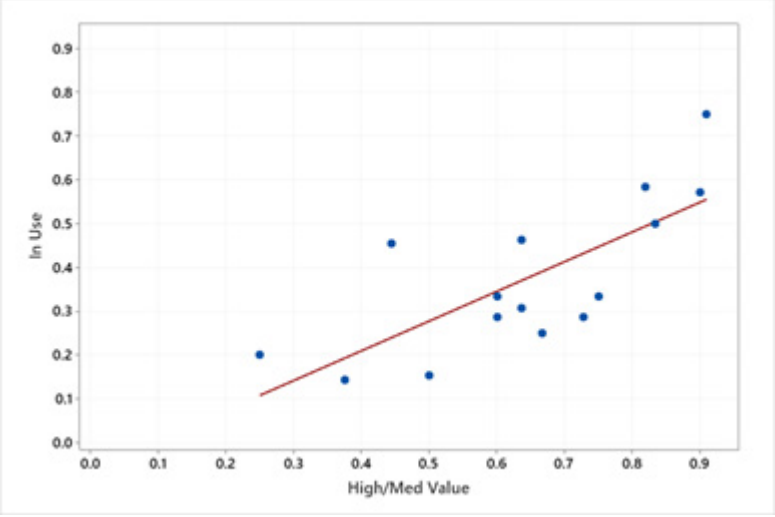
Figure 12 represents the perceived value of the QTLs as recommended by TransCelerate. Primary Endpoint Assessment had a high perceived value (82% of respondent organisations, n=12). An average of 56% of the respondent organisations consider Protocol Deviations in general to be of low perceived value. The majority (90%, n=9) consider IP Compliance to be a parameter with strong perceived value. Informed Consent has a low perceived value (62%, n=8).

Figure 12 *– Rating the parameters defined for QTLs by TransCelerate guidance*



An analysis was conducted to further evaluate the relationship between QTLs currently in use and their perceived value. There was a strong correlation (Pearson R2= 0.745) and a strong linear relationship (p=0.001) between use and perceived value (Figure 13).

Figure 13 *– Relationship between QTLs currently in use and their perceived value*



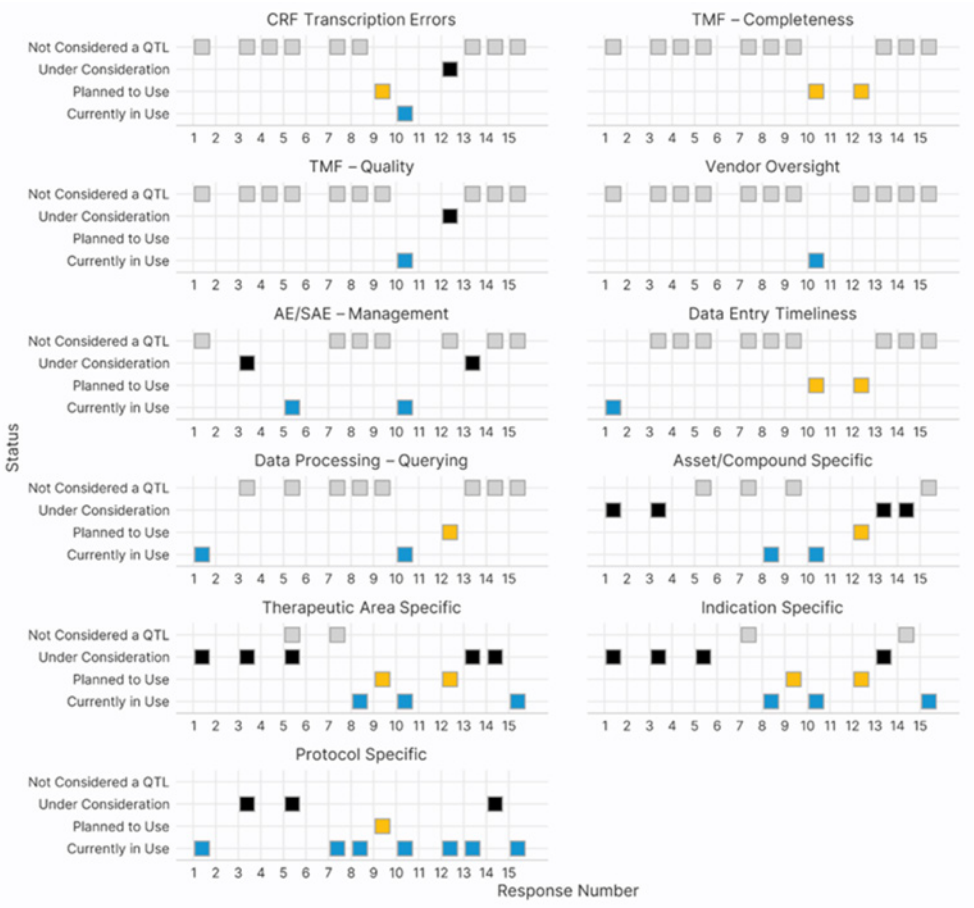
Figures 14 and 15 represent data collected on other parameters that might be considered for use with QTLs.

CRF Transcription Errors, TMF – Completeness, TMF – Quality, Vendor Oversight, AE/SAE – Management, Data Entry Timeliness and Data Processing – Querying were all thought by seven to nine (7–9) organisations to NOT be considered a QTL, with only two to four (2–4) organisations using, planning, or considering using them as QTLs.

Asset/Compound Specific, Therapeutic Area Specific, Indication Specific and Protocol Specific were more likely to be used, planned or under consideration rather than not considered.

It should be noted that the results for the Protocol Specific parameter may have been biased by the TransCelerate Primary and Secondary Endpoint Assessment parameters, as shown in Figure 11. This may also be the case for the Indication Specific parameter, as shown in Figure 12.

Figure 14 *– Additional parameters considered parameters for QTLs*

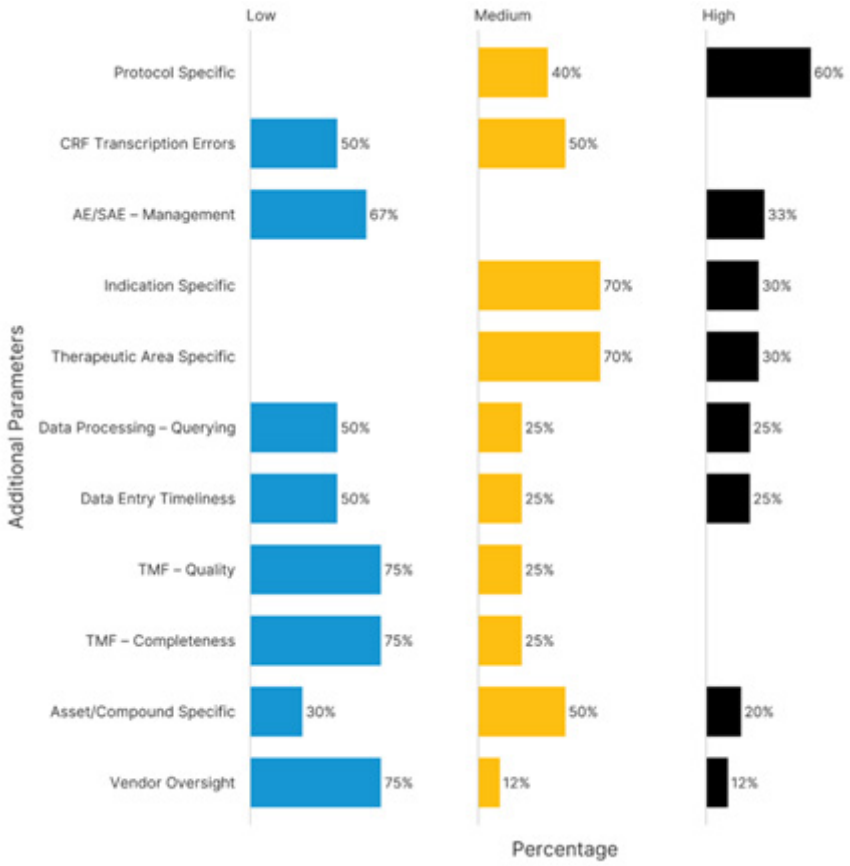


If the Asset/Compound Specific, Therapeutic Area Specific, Indication Specific and Protocol Specific parameters are excluded, AE/SAE – Management and Data Processing – Querying are the two parameters used by the highest proportion of responders but still less than 25% with regard to having a high perceived value. Both were of low perceived value (30 or 50%, respectively, of the respondent organisations).

Only the Asset/Compound Specific, Therapeutic Area Specific, Indication Specific and Protocol Specific parameters had strong perceived value. For these parameters, the perceived value decreases from Protocol to Indication to Therapeutic Area to Asset/Compound (60%, 30%, 30%, 20%, respectively). Again, this may be an artifact based on the Primary and Secondary Endpoint Assessment parameters.

Neither TMF parameter had strong perceived value (25%), and both were identified as not being QTLs by a strong majority of the respondents (>80%), as shown in Figure 15.

Figure 15 *– Perceived value of additional parameters (note rounding errors)*



An analysis was conducted to further evaluate the relationship between those parameters identified by TransCelerate and other parameters that may be considered for use with QTLs (Figure 14), specifically to focus on any differences in use. A two-sample t-test was employed to test this hypothesis; the results were significant ($p < 0.001$), indicating that the parameters identified by TransCelerate were employed more than the other parameters (Figure 16).

Figure 16 *– Relationship between those parameters identified by TransCelerate and other parameters that may be considered for use with QTLs*

Descriptive Statistics: InUse

Group	N	Mean	StDev	SE Mean
NonTC	7	0.0955	0.0666	0.025
TC	15	0.374	0.174	0.045

Test

Null hypothesis $H_0: \mu_1 - \mu_2 = 0$

Alternative hypothesis $H_1: \mu_1 - \mu_2 \neq 0$

T-Value	DF	P-Value
-5.41	19	0.000

A similar analysis was conducted to further evaluate the relationship between those parameters identified by TransCelerate and other potential QTL parameters (Figure 15), specifically to focus on any differences in perceived value. For this analysis, the High and Medium responses were aggregated. A two-sample t-test was employed to test this hypothesis; the results were significant ($p < 0.001$), suggesting that the parameters identified by TransCelerate had higher perceived value than the other parameters. (Figure 17)

Figure 17 *– Perceived value difference between those parameters identified by TransCelerate and other parameters that may be considered for use with QTLs*

Descriptive Statistics: High/Med Val

Group	N	Mean	StDev	SE Mean
NonTC	7	0.369	0.126	0.048
TC	15	0.643	0.191	0.049

Test

Null hypothesis $H_0: \mu_1 - \mu_2 = 0$

Alternative hypothesis $H_1: \mu_1 - \mu_2 \neq 0$

T-Value	DF	P-Value
-3.99	17	0.001

In a final question regarding the potential evolution of QTL language to 'Acceptable Ranges' in ICH E6 (R3), 40% (n=6/15) of the respondent organisations felt they might change their approach as a result, 26.7% (n=4) felt they would not change, and 40% were not sure if any changes would be made (n=6).

7. Discussion

7.1. QTL Implementation

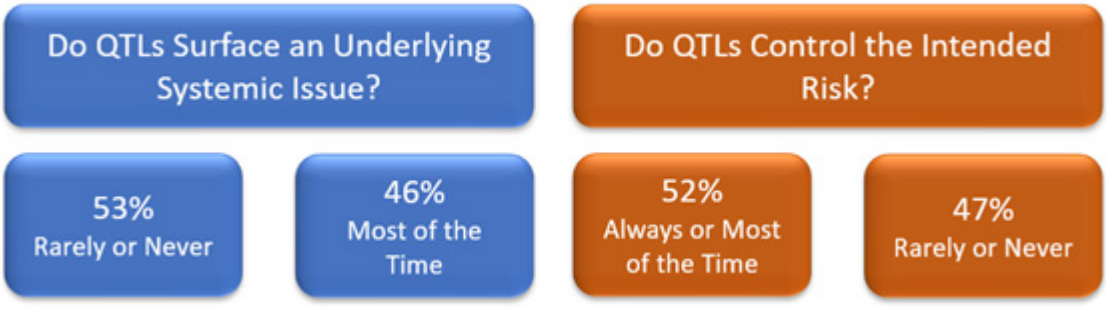
Respondents supplied valuable insights regarding the implementation and impact of QTLs at their respective organisations. QTLs are implemented across organisations of all sizes. Implementation is most prevalent in Phase II and Phase III trials, while Phase I, Phase IV and more complicated designs had mixed implementation. This was not surprising as there are known challenges with setting parameters and thresholds for these types of trials.

7.2. QTLs are Integrated into the RBQM Approach

Organisations are aligning QTLs with CtQs and QbD as part of RBQM, as shown by the trend of implementing and finding the most value in study-specific parameters. This suggests that effort is being directed to where it matters most, i.e. to areas that could impact on patient safety and/or on the reliability of study results.

There appears to be an opportunity to broaden the practice of assessing the importance of primary QTL deviations based on the root cause, to determine appropriate mitigation actions and reportability.

7.3. Are QTLs Effective?



This suggests that by drawing upon CtQs, there are opportunities to evaluate how to choose the most impactful parameters. It also may indicate that QTLs must work in tandem with other mitigation strategies (e.g. robust root cause analysis) as part of an overarching RBQM framework. By considering QTL parameters in the context of the estimand framework,[17] it may make it easier to identify the most meaningful parameters. It may also be that an organisation's choice of parameters does not sufficiently align with trial outcomes and thus lead to the question of appropriate application of QTLs. Additionally, the robustness of the evaluation may be insufficient to detect (or not cause a substantial number of false positives) a deviation.

7.4. Draft Wording of ICH E6 (R3)

Considering that defining a QTL is setting a threshold for a parameter and then identifying deviations to an acceptable range, QTLs can clearly be seen as acceptable ranges. The change in language suggests ranges can be set using a sophisticated statistical model or by a simpler methodology. When thought about in this way, the change in wording in ICH E6 R3 (draft) appears to broaden the ability of organisations to use this important measure in more types of trials.

7.5. Functional Area that Leads RBQM

RBQM appears to be a cross-functional task, drawing upon input from Clinical Operations, Data Management and Biostatistics in the main but often supplemented with input from Clinical Science and Safety Science as well as other subject matter experts. This supports the ICH E6 (R2 + R3) requirement to work cross-functionally across a wide group of stakeholders.

Based on the responses received, the Clinical Operations function (53.3%) typically leads RBQM. However, upon closer review, it appears to be a more dedicated 'risk management' role despite having differing nomenclature. There was also the suggestion that a Working Group Lead could come from any one of the functions mentioned. Another viewpoint is that the relevant function takes the lead when it comes to their area of expertise during RBQM activities, which might be indicative of a more decentralised approach.

In the future it would be interesting to dive into the benefits of having an independent function rather than RBQM activities embedded in a function (a decentralised approach) and vice versa.

Most companies are trying to implement a consistent form of RBQM, but often the known challenges of size, design, duration of study and phase all make it more difficult.

7.6. Application of Risk-Based Approaches to Quality

It is encouraging to see the widespread adoption of CtQs, QbD and QTL, even for FIH and Phase I Non-FIH trials. This suggests that the approach is maturing, and organisations are no longer discounting early-phase trials. The lack of QTL uptake in Phase IV trials is surprising; given that these often have large volumes of data, we could expect results aligned with those of Phase III trials. One reason for the difference between Phase IV and Phase III may be that Phase IV are more often non-interventional. It could also relate to how companies characterise a trial as a Phase IIIB vs. a Phase IV.

There is not always total alignment between CtQs and QTLs; QTLs should evolve out of the CtQ discussion. Our experience suggests there is often difficulty with teams understanding the critical data they need to first identify that alignment with the CtQs. The estimand framework and the key safety criteria identify the key outputs needed for a registrational filing, which, in turn, identify the required critical data and the relevant CtQs. Over time, this can enable organisations to develop a library of CtQs and associated parameters to support the estimand framework and key safety. It may be that organisations are struggling with how to consistently implement these aspects into their trial activities. Furthermore, when asked whether organisations would be interested in an industry-level collaboration with regards to open-source software to support QTL development, 87% (13) replied positively.

While the alignment of CtQs with QTLs was quite high (question 11: How would you characterise the success of the deployment of all risk-based approaches to quality in your company?), technology is not being used for CtQs (question 10: How does your company document your risk-based approaches to quality?). This may show a lack of area in which to document CtQs in RBQM technology platforms, or that CtQs may not be properly understood.

For the identification of CtQs, implementation of QbD and a risk strategy, including whether QTLs are analysed and how frequently they are used, a Protocol-Level Plan or an Integrated Quality Plan can be used to document these activities.

There is evidence that CtQs are not aligned with the risk plan, which suggests that they may not be well understood and/or that RBQM technology platforms are not able to reference/use CtQs.

Risk plans, whether integrated or standalone, are being used to document the risk strategy, the relevant corrective actions, and how to report important deviations into the CSR. Alignment with CtQs is still a work in progress, since our survey results suggest that some organisations are still learning what is required to link CtQs and QbD.

Technology features more in the implementation of risk strategy, the use of QTLs, the implementation of corrective actions and the reporting of important deviations. However, this type of technology and the ability to implement a robust RBQM platform requires adequate budget, resources with specific skill sets, time, and end-to-end planning.

7.7. QTL Application in Practice

As anticipated, the trial design, trial phase, trial size and duration of the trial are the main elements that impact on the use of QTLs. Interestingly, this impacts on the identification of CtQs as well.

Trial design phase and size influence the frequency of QTL review. Experience has shown that it can occur independently of traditional risk review, given the criticality of the parameters selected and the potential need to bring the study back into compliance as a priority. It is encouraging that communication of deviations is consistent regardless of trial design, phase and size. This is to be expected, as this is a process and should be independent of trial attributes.

We did observe a consistent 'Not utilized' flavour across the choices within the QTL application question, which does seem to contradict the data provided elsewhere in the survey. It suggests a disconnect for some companies between QbD and QTLs, e.g. there were several 'Unable to answer' responses. This may also be because some organisations have not yet implemented QTLs.

7.8. Types of Action Taken

An area of consideration for organisations is the development of a library/libraries of mitigating actions that can be taken depending on the reason for any QTL deviation. These actions may include:

- protocol amendment and impact on the statistical analysis plan (SAP)
- the possible allowance of amending the thresholds following feedback from early monitoring
- amending the distribution if the historic data is found to not be a suitable reference model
- the realisation that the parameter may not be a suitable measure or that the methodology is not suitable for that type of data
- sites needing to address certain issues (e.g. confirming the correct measuring of a parameter by investigators)
- revisiting the role of the key risk indicators within the study.

The main point is that whatever action is taken, this action should be documented with clear justifications for any changes. Study teams need to understand the reason for the QTL deviation and the actions that would be helpful in mitigating the deviation to allow the process to return to a state of control or to inform the design and/or conduct of future trials.

It is interesting that approximately two thirds of the respondents said that a QTL deviation led, or could lead to, a protocol amendment and/or resetting the thresholds. This suggests insufficient rigour during protocol development, identification of CtQs and/or root cause analysis post deviation.

7.9. Reporting Important Deviations in CSRs

ICH E6 (R2) states that all important deviations should be discussed in the CSR; the results of the survey suggest that this is not consistently occurring. More clarity may be required in this area for companies, or it may be that the deviation is not thought to be of concern, i.e. deviations are occurring due to lack of data at the beginning or towards the end of the study. The latter would depend on the methodology used.

Some organisations finalised a CSR with a subset of deviations/excursions excluded because the QTL deviation was determined not important. If this happens at the study team level, there is often no feedback on the overall RBQM system. It may be useful to introduce a QTL library to document if there was a QTL deviation during the study and if so, whether the deviation was deemed important.

7.10. TransCelerate Parameters Used and Perceived Value

The importance of employing parameters that are linked to either key efficacy outcomes (or parameters that could impact on the interpretability of these outcomes) or safety came across clearly in the survey. And there was a strong association between the use of those parameters and their perceived value.

In contrast, parameters that were more operational in nature (e.g. stratification, randomisation) were viewed as less informative. This suggests that stakeholders in general are focusing on what is critical in their ability to interpret the data generated, either scientifically or statistically.

7.11. Non-TransCelerate Parameters Used and Perceived Value

Non-TransCelerate parameters, the majority of which are operational in nature, were not used across a broad set of stakeholders, and their perceived value was aligned with their use – the exception being those parameters that were Protocol Specific, Therapeutic Area Specific, or Asset/Compound Specific. This aligns with the use and perceived value of key efficacy/safety parameters, as noted above.

8. Conclusion

Even though there may be changes because of ICH E6 (R3), this work suggests that most organisations are moving ahead with using QTLs and embedding their use in a framework for RBQM. This is a very encouraging sign in that most organisations that responded to the survey see the value of risk-based approaches to quality. There is evidence from this work that most organisations that employ QTLs focus on the data that support primary objectives and key safety. While there may be nuanced differences in how organisations define those two types of data, the importance of measuring them, at a minimum, cannot be understated and is highly recommended.

It is not possible to tell how many organisations may have submitted more than one response (to protect the anonymity of the responders and their organisations, and to avoid discouraging responses). As such, this work may be biased towards organisations implementing QTLs because of the technical nature of some of the questions, the length of the survey and/or because several of the respondents, based on their roles in their respective organisations, were already interested in RBQM.

A consideration for the future, and with the introduction of R3, is the greater influence of principal investigator and patient advocacy organisations, particularly when it comes to developing the protocol; they will play a pivotal role in early QbD activities.[2]

9. Disclaimer

The opinions expressed in this document are those of the authors and should not be construed to represent the opinions of PHUSE members, respective companies/organisations or regulators' views or policies. The content in this document should not be interpreted as a data standard and/or as information required by regulatory authorities.

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11. Abbreviations

CSR	Clinical Study Report
CtQs	Critical to Quality Factors
CTTI	Clinical Trials Transformation Initiative
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
FIH	First in Human
ICH	International Council for Harmonisation
KRI	Key Risk Indicator
RBQM	Risk Based Quality Management
SAP	Statistical Analysis Plan
QbD	Quality by Design
QTL	Quality Tolerance Limit

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