Duke | MARGOLIS INSTITUTE for Health Policy

Building Quality into the Design and Conduct of Clinical Studies: Integrating Quality by Design (QbD) and Risk-Based Monitoring (RBM) Approaches

Hybrid Public Meeting • National Press Club • Washington, DC

January 31, 2024 | 9:00 am – 4:20 pm ET

Meeting Summary

Executive Summary

Drug development is a lengthy and expensive process and clinical trials are vital to drug development. Clinical trials are necessary to generate the high-quality data needed to demonstrate the safety and efficacy of a medical product for its intended use; therefore, clinical trials are the backbone of the regulatory approval process for drugs and biologics. Ensuring the reliability of clinical trial data and the safety of study participants are clear priorities for industry sponsors, regulators, and all other contributors to clinical trials.

To address the increasing time and costs associated with clinical trials while ensuring participant safety and data reliability, regulators and other interested parties continue to collaborate on comprehensive strategies to modernize trial design and conduct. Regulators and other interested parties support the adoption of an Risk-Based Quality Management (RBQM) framework to maintain standards for safety and efficacy while increasing efficiency. Within an RBQM framework, Quality by Design (QbD) principles can be applied to clinical study design, including protocol development, and Risk-Based Monitoring (RBM) approaches can enable study oversight focused on the risks most critical for maintaining data quality and participant safety.

Underpinning QbD approaches to quality management is the premise that clinical trials can be constructed with a clear, feasible protocol at the design phase to facilitate implementation of RBM approaches during the trial conduct phase. A complicated protocol can interfere with timely trial implementation by site staff — creating additional burden that may impact trial recruitment, enrollment, and retention of trial participants.[1,2] Integration of QbD and RBM approaches into clinical trials requires accounting for clinical trial complexity, overcoming organizational risk aversion, competing against internal organizational interests, and complying with regulatory expectations related to generation of fit-for-purpose evidence.

Despite long standing efforts of the U.S. Food and Drug Administration (FDA or Agency) and other interested parties to encourage their use, widespread adoption of QbD and RBM approaches for clinical investigations has not been fully realized. To promote the implementation of these approaches, the Duke-Margolis Institute for Health Policy (Duke-Margolis) under a cooperative agreement with FDA convened a public workshop on January 31, 2024 to facilitate discussion among the clinical trials community and

[1] Getz, K.A., Campo, R.A. & Kaitin, K.I. Variability in Protocol Design Complexity by Phase and Therapeutic Area. Ther Innov Regul Sci 45, 413–420 (2011). https://doi.org/10.1177/009286151104500403

[2] Getz, K., Campo, R. Trends in clinical trial design complexity. Nat Rev Drug Discov 16, 307 (2017). https://doi.org/10.1038/nrd.2017.65

interested parties about the successes and challenges of integrating QbD and RBM into the design and conduct of clinical studies. The following themes emerged from presentations and participant discussion:

1. **Clearly demonstrating the value** of integrating QbD and RBM into the clinical trial enterprise may assist with adoption
2. **Including participant and caretaker community** input can meaningfully inform certain trial design and conduct elements, and implementation of QbD and RBM approaches
3. **Culture change and change management strategies** are required to transform organizational culture and foster sustainable QbD and RBM adoption
4. **Benefits of RBM** are increasingly evident to existing adopters but broad implementation is still needed
5. **Alignment on terminology and concepts** within and across organizations is needed

Throughout the workshop, participants noted that adoption and implementation of QbD and RBM approaches can benefit industry sponsors, clinical research organizations (CROs), additional third-party vendors, investigative site staff, and all other participants in the clinical trial enterprise, but that it has only been fully utilized in select instances. Furthermore, thoughtful, invested engagement with study participants and the patient community can provide extensive, specific examples of quality-based trial design and protocol improvements aligned with an RBQM framework. Although more work is needed to ensure wholesale adoption and implementation of QbD principles and RBM approaches in clinical research study design and conduct, there are many opportunities to build on conversations from the workshop.

This project was supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award U01FD006807 totaling $3,493,089 with 100 percent funded by FDA/HHS. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS, or the U.S. Government.

Background

Clinical trials are integral to the drug development process, vital for the generation of high-quality data needed to demonstrate the safety and efficacy of a medical product for its intended use and must be conducted in a way that ensures participant safety. However, clinical trials have increased in cost and duration. To address the rising cost of clinical trials and need to shorten the drug development process, sponsors and regulators have worked to modernize clinical trials. Modernization of clinical trials is intended to increase availability of safe and effective drugs for patients, while maintaining participant safety and data quality in the design and conduct of studies.

The adoption of an Risk-Based Quality Management (RBQM) framework, through Quality by Design (QbD) principles and Risk Based Monitoring (RBM) approaches, is foundational to ensuring participant safety and data reliability. Integral to the adoption of QbD principles is attention to prevention of errors that matter through thoughtful protocol design and planning of trial conduct.[3] The idea of centering quality in clinical trial design is not new; the 2012 Report to the President's Council of Advisors on Science and Technology (PCAST) included several references to incorporating quality into clinical trial design and conduct. [4]

To promote improved quality management in clinical studies, leadership within FDA's Center for Drug Evaluation and Research (CDER) encouraged utilizing concepts on design and conduct from manufacturing. Advocates for adoption of QbD approaches, within CDER and other organizations, understand the need to identify critical to quality factors (CTQ) that prioritize participant safety and to generate reliable results at the onset of study design, prior to protocol drafting. Once CTQ factors are identified, study protocol drafting follows, along with additional risk-based management planning. In order to inform regulatory decision-making, an RBM plan is developed for study oversight to ensure maintenance of participant safety and attainment of data quality.

Foundational milestones to advance the use of QbD and RBM approaches include initial QbD program development by the Clinical Trials Transformation Initiative (CTTI)[5] in 2009 and FDA's 2013 guidance, Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring.[6] In 2019, Duke-Margolis and FDA co-convened a meeting titled *Improving the Implementation of Risk-Based Monitoring Approaches of Clinical Investigations*[7], where FDA and international regulators, sponsors, CROs, trade associations, academics, and others discussed how to advance adoption of risk-based monitoring. In 2023, FDA expanded on the 2013 guidance with a supplemental guidance[8] that is structured in a question-and-answer format. This expanded guidance on risk-based monitoring provides additional information for sponsors' implementation of RBM, as well as additional recommendations for planning a monitoring

[3] Meeker-O'Connell, A., Glessner, C., & Landray, M. Enhancing Clinical Evidence by Proactively Building Quality into Clinical Trials. Society for Clinical Trials, Vol 13, Iss 4 (2016). https://doi.org/10.1177/1740774516643491
[4] Woodcock J. The PCAST report on pharmaceutical innovation: implications for the FDA. Clin Pharmacol Ther. 2013 Sep;94(3):297-300. doi: 10.1038/clpt.2013.88. PMID: 23963215.
[5] https://ctti-clinicaltrials.org/our-work/quality/quality-by-design/
[6] https://www.fda.gov/media/116754/download
[7] https://healthpolicy.duke.edu/events/improving-implementation-risk-based-monitoring-approaches-clinical-investigations
[8] https://www.fda.gov/media/121479/download

approach, developing the content of monitoring plans, and addressing and communicating monitoring results.

Additionally, FDA leads and contributes to the development and promotion of clinical trial modernization as a founding member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Recent revisions to ICH guidance on General Considerations for Clinical Studies—E8(R1)[9]—and Good Clinical Practice—draft E6(R3)[10]— have incorporated principles underlaying QbD.

Despite the efforts of FDA and other interested parties, QbD and RBM approaches to plan and conduct clinical investigations have not been fully utilized. To better understand this lack of adoption, Duke-Margolis and FDA co-convened a public workshop on January 31, 2024 titled *Building Quality into the Design and Conduct of Clinical Studies: Integrating Quality by Design and Risk-Based Monitoring Approaches*. The purpose of this workshop was to encourage the incorporation of QbD principles into the design and conduct of clinical studies, including the development of study protocols and workflow processes; to identify barriers to QbD and RBM adoption by sponsors, CROs, and clinical trial sites; and to inform best practices for incorporating QbD and RBM approaches into the design and conduct of clinical studies.

The public workshop provided numerous examples from presenters and panelists highlighting the effective incorporation of QbD and RBM approaches. Examples were shared by sponsors, CROs, patient organizations, academics, and additional third-party vendors, who identified the elements and internal organizational processes needed to influence decision-making. Interested parties across the clinical trials community also commented on the significant implementation gaps, remaining real and perceived challenges to adoption, and suggestions for overcoming obstacles for sustainable gains.

This document synthesizes presentations and panel discussions to distill key themes identified by meeting participants.

Demonstrating the Value of Integrating QbD and RBM into the Clinical Trial Enterprise May Assist with Increasing Adoption

Participants noted that implementing QbD practices in the study design phase can lead to more effective and efficient trial conduct and assist with the application of an RBQM framework. An RBQM framework centers quality through the clinical development lifecycle, connecting RBM approaches to CTQ factors identified at the study design phase, helping to provide confidence in the reliability of the results, and ensuring the protection of trial participants. Several meeting participants noted that improved trial efficiencies and results have been demonstrated by identifying CTQ factors, developing the monitoring plan, and promoting centralized/statistical monitoring to establish quality tolerance limits (QTLs) that are proportionate to the risks of trial participants. Adoption of QbD approaches was also suggested by meeting participants to potentially help increase recruitment, enrollment, and retention, in part through identifying opportunities to reduce participant burden. Meeting participants reiterated that prioritizing

[9] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e8r1-general-considerations-clinical-studies

[10] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e6r3-good-clinical-practice-gcp

efficiency, flexibility, and innovation over complicated protocols is essential to realizing the benefits of QbD and RBM approaches.

An industry sponsor presented a case study on the impact of identifying two study specific CTQ factors for a Phase 3 idiopathic pulmonary fibrosis trial. Participant blood pressure (BP) criteria were identified as CTQ factors related to participant safety and abnormal blood pressure was reported as an adverse event (AE) of special interest. This resulted from learning that dosage titration could lead to significant BP changes. The protocol was also adjusted to account for accurate BP data capture. Participants visited sites with validated equipment provided by the trial sponsor for BP measurement, instead of using BP monitors at home. This ensured close monitoring of potential low BP events observed after first drug dose. Identical validated equipment was also used to obtain data on the primary outcome, automatically transferring data from sites.

The second CTQ factor identified was the impact of overall study data collection on patient burden related to protocol design. The QbD-guided draft protocol review process found that frequent clinical site visits by participants had limited benefit and overly generic questionnaires did not collect data relevant to CTQ factors. As a result, the sponsor updated the protocol to decrease the number of visits and the questionnaire was revised to garner more pertinent data while ensuring participant safety and data reliability. The same industry case study also described how centrally-based clinical scientists reviewed the automated BP data remotely on a regular basis. If concerns around data quality or trends emerged, the sponsor communicated with sites directly to discuss test results.

Quality Gain Measurement in Terms of ROI

Workshop participants suggested that better quantification of quality gain measurements in terms of return on investment (ROI) can help with improving adoption by demonstrating the value of incorporating QbD principles and RBM approaches. One example is through a cost-savings lens (e.g., targeted site monitoring, fewer protocol amendments, and increased study completion) that may require QbD and RBM specific metrics to be defined in more strictly financial terms. One presenter remarked that sponsors are ready to pour endless resources into preventing loss and ensuring data is still reliable, reproducible, and complete when a significant error is detected during study conduct. However, implementation of effective QbD and RBM approaches has the potential to reduce costs otherwise spent on remediation efforts. This view justified the presenter's advocation of additional time spent in the study design phase through use of QbD principles.

Inclusion of Participant and Caretaker Input Can Meaningfully Inform the Trial Design and Conduct

Drug development programs intend to generate evidence that a product is safe and effective for a specified population. At the meeting, regulators and clinical trial sponsors discussed the importance of building trust with patient communities, with sponsors sharing examples of when participant input meaningfully informed protocol design.

Meeting participants suggested that study participant and patient community involvement in the development and evaluation of protocols can improve feasibility, and that engagement with patient advocacy groups can be helpful for identifying CTQ factors. Participating advocacy groups also mentioned the benefits of leveraging their established trial networks. Established trial networks have long-standing

experience with how to limit risks to achieve appropriate participant recruitment, enrollment, and retention even with complicated trial designs. Meeting participants advised integrating patient and caretaker perspectives into drug development beyond the study design and protocol drafting phase. Patient advocacy group representatives indicated that their communities express wanting to receive updates on trial progress and results. A bidirectional partnership between sponsors and study participants was highlighted by meeting participants as complementary to implementation of an RBQM framework.

Case Studies Demonstrate Benefits of Partnerships with Participants

Case studies from an industry sponsor and patient advocacy organization provided specific examples of how early study participant input led to protocol changes. Protocol adjustments based on study participant feedback made trials more feasible to execute and less burdensome on participants. Both presenters viewed these revised protocols as resulting in fewer deviations, eliminating unnecessary visits, and resulting in less extraneous study conduct criteria. The patient advocacy organization discussed initiating dual enrollment standard operating procedures (SOPs) with some interventional trials that include invasive procedures, such as a lumbar puncture (LP). Leveraging examples from other studies informed eligibility considerations, while also lowering participant burden. This participant-centric approach proved valuable, as a new biomarker to understand the pathology of the disease was discovered but identification of the biomarker required use of a LP. Broadening support to include a greater representation of participants in studies has helped grow data banks that contribute to eligibility considerations for future studies.

Another strategy used by a patient advocacy organization to increase the number of lower-income participants was providing financial support for caregivers and pet boarding. Financial support for caregivers demonstrated quality gains, including improved enrollment and retention. This suggestion was made based on feedback from study participants.

Participant and Patient Community Input on the Value of Incorporating Decentralized Elements

Several of the presented case studies highlighted that study participant feedback led to the incorporation of decentralized trial elements during the study design phase. In one example, a smartphone app was developed to collect real-world data on study participants. User testing with participants revealed that data collection was too burdensome, which led to updating the schedule of activities to condense the frequency of active visits required from participants. Another example was the development of an online portal to collect questionnaire data that was more convenient for participants and clinical trial site staff. The online portal also allowed for data to be obtained more than once a year, allowing for the collection of more relevant data.

Cultural Change and Effective Change Management Strategies Are Generally Required to Achieve Increased QbD and RBM Adoption

Throughout the meeting, participants discussed that change management efforts within sponsor organizations and other trial contributors are needed, but they are challenging to implement and sustain. Adopting QbD principles and RBM approaches requires shifting organizational culture to one that values spending more time on clinical trial design, including the thoughtful development and execution of a RBQM framework. Through consistent efforts, clinical trial sponsors can incorporate QbD principles and

RBM approaches with informed training, knowledge management and transfer, cross-organizational input, and continued persistence.

Senior Leadership Investment and Working Across Organizational Silos

Workshop participants with experience implementing QbD principles and RBM approaches emphasized that support from senior leadership and management was critical for adoption. Ingrained implementation partly hinges on collaboration between quality management, operational, statistical, and other divisions. Clinical trial sponsor participants also suggested building staff feedback loops that encourage consistent interactions throughout all parts of an organization to facilitate the adoption of QbD principles and RBM approaches.

Processes Used When First Incorporating QbD Principles

Case studies presented by both sponsor and patient advocacy organizations referenced CTTI's QbD Principles Document[11] to help initiate QbD-guided protocols. Applying this document and associated CTTI tools, staff at these organizations met with cross-functional teams to review and solicit feedback on the draft protocol. Both organizations also solicited external input from site staff on protocols.

The patient advocacy organization shared that they also serve in a consultant role for clinical trial sponsors, providing feedback on implementing QbD principles focused on study feasibility and protocol design. Feedback on consulted study QbD principles also includes considerations for participant safety, study conduct, and study reporting quality efforts.

Sponsor Engagement with Additional Partners

As sponsors continue to foster a multi-disciplinary team focus, several meeting participants suggested that direct input from CROs and site staff can be beneficial for implementation of an RBQM framework. Other participants also suggested early collaboration with third-party vendors to develop RBM approaches to be beneficial, as they often have a role in analyzing trends from clinical trial monitoring. Shared investment in the adoption of RBM approaches can position site staff to highlight where protocol design may inhibit study conduct feasibility.

Continuous Investment in Training Needed

Training on implementation of QbD principles and RBM approaches across an organization is time intensive and an evolving endeavor. Throughout case study presentations and meeting participant panel dialogue, speakers encouraged adopters to view training as continuous and informed by cross-organizational feedback loops.

Incorporating Lessons from the COVID-19 Public Health Emergency and Managing Other Disruptions

Numerous workshop presenters shared that during the COVID-19 Public Health Emergency (PHE), clinical trial sponsors worked rapidly to collaborate across different clinical development divisions in a less siloed manner. While this collaboration was a significant cultural shift from standard operations and described as highly beneficial by several participants, many processes reverted to the status quo following the end

[11] CTTI Quality by Design Project – Critical to Quality (CTQ) Factors Principle Document (2015). https://ctti-clinicaltrials.org/our-work/quality/qbd-quality-by-design-toolkit/teach-others-about-qbd/qbd-principles-document/

of the PHE. Organizations could review those changed behaviors achieved during the PHE and update SOPs, job descriptions, and workflows to embed cross-division study design and protocol drafting collaborations. This is also true for the use of decentralized trial elements and digital health technologies, which saw increased use in the PHE and a subsequent decline following the end of the declared emergency.

A workshop presenter described managing unanticipated disruptions, using recent natural disasters and military conflicts as examples. In addition, the presenter suggested that strongly embedding QbD principles connected to RBM approaches can improve process resiliency and develop a proactive readiness to anticipate and manage disruptions upon occurrence. The examples the presenter provided can serve as a good starting point for anticipating disruptions when developing RBM approaches.

Additional Development and Public Sharing of Case Studies

A workshop presenter emphasized that storytelling—inclusive of the growing numbers of publicly available case studies—can broadcast implementation of QbD principles and RBM approaches to overcome adoption challenges. Further efforts to consistently and continually share QbD and RBM implementation examples were recommended by many presenters. This included the suggestion of using tailored examples to demonstrate how specific sponsor staff roles outside of the quality and clinical operations departments contribute to the adoption and implementation of RBQM frameworks. Multiple presenters also expressed that additional public forums discussing these implementation experiences and remaining challenges can contribute to increased adoption. Supportive CTTI QbD case studies and additional resources are available in the Appendix.

Benefits of RBM Are Known by Existing Adopters, but Broad Implementation Remains Low

Meeting presenters from a trade association, industry collaboration, and academia each presented organizational surveys and independent research showing that sponsors and CROs are developing initial risk assessments, but few have publicly presented examples applying comprehensive RBM activities throughout trial conduct. While these initial risk assessments are part of overall risk management planning, the follow-up activities and implementation have generally lacked identification and implementation of QTLs specific to data quality, participant safety, and central/remote monitoring. Overall efforts at RBM implementation have also contained limited source data review (SDR) and source data verification (SDV) reductions. Additionally, after an increase in RBM activities during the COVID-19 PHE, adoption has trended downward.

Ability to Reduce Source Data Verification and Source Data Review

CRO meeting presenters noted that effective implementation of centralized monitoring can significantly improve study participant-level monitoring, while reducing the burden of full SDR and SDV. Beyond the efficiency gains of centralized monitoring, 100% SDR and SDV can miss critical components and quality management study trends, in part due to focusing on minor discrepancies (e.g., transcription errors). Reduction of SDV and SDR aligns with the broader goal to implement QbD principles and RBM approaches by limiting consequential errors, with one CRO presenter suggesting increased central monitoring and a focus on appropriately reducing SDV and SDR should be the initial focus when expanding use of RBM plans.

Effective Use of QbD to Identify CTQ Factors and Establish QTLs

Meeting presenters discussed the iterative nature of implementing QbD principles and shared how the process informs the development of RBM approaches. Identification of study-specific CTQ factors directs the acceptable ranges of QTLs. Establishing these acceptable ranges identifies when an intervention is needed and provides direction for managing deviations. Statistical monitoring then tracks how well the QTLs are being followed, with faster detection of parameters trending outside acceptable ranges creating the opportunity for faster remediation. Multiple participants highlighted resources to develop QTLs and manage their implementation, including work done by TransCelerate BioPharma and PHUSE listed in the Appendix.

Understanding and Application of QTLs Remain in Need of Improvement

A meeting presentation on QTLs also suggested the need for clarification of terminology and definitions within QTL frameworks. QTL parameters were noted to be primarily defined by proportions or rates, and the presenter recommended data-driven, acceptable statistical ranges for derivation of QTL monitoring. The presenter also noted that since thresholds are primarily defined by experts with support of statistical methodology, smaller companies may benefit from outside expertise when applying these concepts.

Centralized Monitoring: Effectiveness in Early and Late-Stage Trials

Meeting presenters promoted the effectiveness of centralized monitoring across all stages of clinical development— not just late-stage trials with a large sample size. Early phase, first-in-human studies may collect over 100,000 data points for a single study participant. Central monitoring tools and advanced data analytics can enable real-time access to rapidly detect deviations. Building a statistical and centralized monitoring plan that focuses on mitigation of risks most critical to maintain data quality and participant safety during earlier clinical study phases, can facilitate the development of monitoring plans in later study phases. One presenter noted the additional motivation for risk-based monitoring, estimating that 3.5 million data points are collected in an average Phase 3 study, and potentially, 6 million data points per oncology study.

RBM and Inspections

Although guidance documents reflect current FDA thinking for sponsors and industry regarding QbD principles and RBM approaches, one participant expressed concerns that investigators may view RBM approaches negatively during regulatory inspections. One example mentioned was uncertainty surrounding how data elements that were not considered relevant to CTQ factors would be regarded during an inspection. Another workshop presenter emphasized the importance of a well-written RBM plan detailing RBQM principles and associated decision-making. Their experience was that thoughtful documentation facilitated understanding during inspections. The same presenter also questioned how much of the sponsor and CRO concerns about potential inspection findings are based on perceptions or FDA Form 483 report observations.

Artificial Intelligence in Risk Mitigation

Meeting participants briefly discussed the use of artificial intelligence (AI) and machine learning (ML) in risk mitigation strategies to develop predictive measures to monitor participant safety and drug adverse events. AI and ML tools may help to mitigate risk when identifying CTQ factors and acceptable tolerance ranges for QTLs. Participants suggested that AI may fundamentally change how clinical trials are monitored in the future and that implementation is still in early exploratory phases.

Alignment on Terminology and Concepts Within and Across Organizations is Needed

Participants discussed how the broader adoption of QbD may be limited by different views on key terminology and core concepts, leading to different understandings of what to prioritize in risk management strategies. One presenter remarked that risk may be viewed through budgets and timelines, in addition to CTQ factors, participant safety, data quality, and reliability of trial results – terms more associated with an RBQM framework.

Open discussion within an organization may help with greater understanding of divergent views impacting implementation of QbD principles and RBM approaches. Divergent views can include identifying CTQ factors, determining core versus non-core study procedures, and characterizing what information collected is most relevant to ensure participant safety and data reliability. Each risk determination is trial specific, which makes alignment on risk management challenging to achieve sustainable adoption. Rather than a one-size fits all approach, study-specific RBQM may focus on prevention, monitoring, and mitigation of the most-critical risks for participant safety and data reliability.

A sponsor presenter referenced a Risk Assessment Categorization Tool (RACT)[12] that helped harmonize language, principles, and processes in their company. Regardless of the tools used, early engagement can facilitate alignment on core terminology to understand and identify study-specific risks. Interested parties within and across organizations (i.e., sponsors, regulators, third-party vendors, sites, and study participants) still have significant room for improved agreement.

Conclusion

Increasingly, incorporation of QbD principles and RBM approaches are shown to enhance the efficiency of clinical trials. Despite regulatory agencies' longstanding support for the use of QbD principles and RBM approaches to modernize the design and conduct of clinical studies, incorporating these strategies to improve trial efficiency is still lagging. Workshop participants from industry, patient advocacy groups, and academia—representing early adopters and implementers of QbD principles and RBM approaches—identified opportunities to promote adoption as part of a larger RBQM framework. Clear demonstration of the value and benefits of integrating QbD principles and RBM approaches were identified as areas for further work. Specifically, workshop presenters noted that uptake may benefit from identifying and measuring additional metrics to translate quality management gains to company ROI.

Inclusion of study participants and patient community input was recognized for providing meaningful contributions to trial design and conduct. Study participant feedback can contribute to the design of simpler, more feasible trials as well as improvements in recruitment, enrollment, and retention. A major point of discussion was how change management strategies and genuine culture change is required to foster adoption of QbD principles and RBM approaches. Persistence is also needed to maintain the uptake of these operational shifts. Additional public dissemination of case studies and discussions at public forums that highlight examples of successes can increase adoption. Many workshop presenters emphasized continued dialogue to help realize the potential benefits. Although more work is needed to ensure wholesale adoption of QbD principles and RBM approaches to bolster quality management frameworks in clinical studies, there are starting points for continued scaling up of successful

[12] https://www.transceleratebiopharmainc.com/assets/risk-based-monitoring-solutions/

implementation. FDA is committed to working with its global regulatory partners to modernize clinical trial design and conduct, including expanding the implementation of QbD principles and RBM approaches to improve clinical trial efficiency, protection of study participants, and reliability of clinical trial data.

This project was supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award U01FD006807 totaling $3,493,089 with 100 percent funded by FDA/HHS. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS, or the U.S. Government.

Duke | MARGOLIS INSTITUTE for Health Policy

Appendix I - Resources

This appendix contains the QbD and RBM/RBQM resources discussed or referenced during public workshop. Please follow the hyperlinks for more information. *Inclusion of a resource on this list does not constitute endorsement by the U.S. Government, the Department of Health and Human Services, or the Food and Drug Administration.*

CTTI QbD Resources

- Quality by Design Project - Critical to Quality (CTQ) Factors Principles Document
- Quality by Design Maturity Model
- Quality by Design Toolkit
- CTTI Implementation Case Studies

PHUSE Research on Centralized Monitoring, QTL Selection/Threshold Setting, and Risk-Based Monitoring

- Can the Value of Centralized Monitoring Be Quantified?
- Centralized Monitoring: Exploring the Considerations and Challenges of Implementation
- Quality Tolerance Limits: A General Guidance for Parameter Selection and Threshold Setting
- Risk-Based Monitoring in Clinical Trials: 2021 Update

TransCelerate BioPharma, Inc.

- Interpretation of Clinical Guidances & Regulations Solutions. Quality Tolerance Limits: ICH E6(R1)
- Risk Assessment Categorization Tool (RACT)

Tufts CSDD Manuscripts on Protocol Complexity

- Assessing the Impact of Protocol Design Changes on Clinical Trial Performance
- Measuring the Incidence, Causes, and Repercussions of Protocol Amendments
- New Governance Mechanisms to Optimize Protocol Design
- Protocol Design and Performance Benchmarks by Phase and by Oncology and Rare Disease Subgroups
- Protocol Design Variables Highly Correlated with, and Predictive of, Clinical Trial Performance
- Quantifying the Magnitude and Cost of Collecting Extraneous Protocol Data
- The Impact of Protocol Amendments on Clinical Trial Performance and Cost
- Therapeutic Area Variability in the Collection of Data Supporting Protocol End Points and Objectives
- Trends in Clinical Trial Design Complexity
- Variability in Protocol Design Complexity by Phase and Therapeutic Area

This project was supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award U01FD006807 totaling $3,493,089 with 100 percent funded by FDA/HHS. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS, or the U.S. Government.