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Industry recommendations for Risk Based Quality Management in First in Human and Small Clinical Trials

Revision History

Version	Date	Summary
V1	01/12/25	- Final draft for PHUSE committee & Company review

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1: Introduction

Clinical research has traditionally relied on historically proven methods for monitoring trial data, which can be resource-intensive and may overlook critical issues in the new age of intensive regulatory scrutiny, safety issues and data deluge. With the increasing complexity and costs of clinical trials, industry standards are evolving to enhance efficiency and quality. This evolution is essential for compliance with regulatory requirements for Clinical Study Report (CSR) submissions.

One significant advancement in this field is the adoption of risk-based approaches, which is expected by International Council for Harmonisation (ICH) and regulators (1,2). This approach has transformed the management of clinical trials by improving efficiency and effectiveness. Risk-Based Quality Management (RBQM) is a strategic framework that emphasizes the identification, assessment, and mitigation of risks to uphold data quality and ensure patient safety. By systematically focusing on the highest risk areas,

RBQM helps manage quality in clinical trials, ensuring that vital aspects are closely monitored and effectively managed.

Small clinical trials involve a limited number of participants often due to early phase of development, the specific nature of the condition being studied, or the rarity of the disease. Because even small deviations can significantly impact data quality and participant safety, these trials face unique challenges relative to larger trials, such as trial complexity and smaller sample size. Due to these factors, RBQM methodologies such as centralized monitoring are often not used; instead, conservative or traditional quality management methods are employed (e.g. 100% data review by the Clinical Research Associate (CRA)). With the smaller data volume, it can be challenging to find the appropriate balance of risk-based monitoring strategies and timing of implementation to ensure value-added oversight.

An independent survey conducted by PHUSE involving industry experts has corroborated the perceived challenges associated with implementing RBQM in small trials (Appendix 1). This anonymous survey found "limitation of time" and "operational complexity" as the major challenges in implementing RBQM in small trials. The survey respondents, however, also appreciated the benefits of RBQM in small trials by highlighting 'risk proportionate approach' as the major benefit. Details of resistance in implementing RBQM in small trials and the results of the survey are described below in this guidance document.

This document provides targeted recommendations for sponsors to shift from traditional, conservative methodologies to RBQM approaches in First-in-Human (FIH) and small clinical trials while still ensuring participant safety and quality oversight.

For the purposes of these recommendations, a small clinical trial is considered if it meets one or more of the below categories:

- a FIH study
- number of s participants 80 or less
- duration of at least 6 months

The methodology of RBQM in larger studies is already well defined (1) and therefore falls outside the scope of this guidance.

2: Quality by Design (QbD) in small clinical trials

Quality by Design (QbD) is a systematic, proactive approach in the RBQM framework that embeds quality into the clinical trial from its inception. It emphasizes the identification of Critical-to-Quality (CtQ) factors early in the trial design process to prevent issues rather than detect them retrospectively. The ICH guidance, particularly E6(R3) and E8(R1), expects embedding QbD principles in clinical trial planning (2, 3). These recommendations underscore the importance of risk-proportional strategies and stakeholder engagement, with an emphasis on quality as an integral element of scientific and operational trial design.

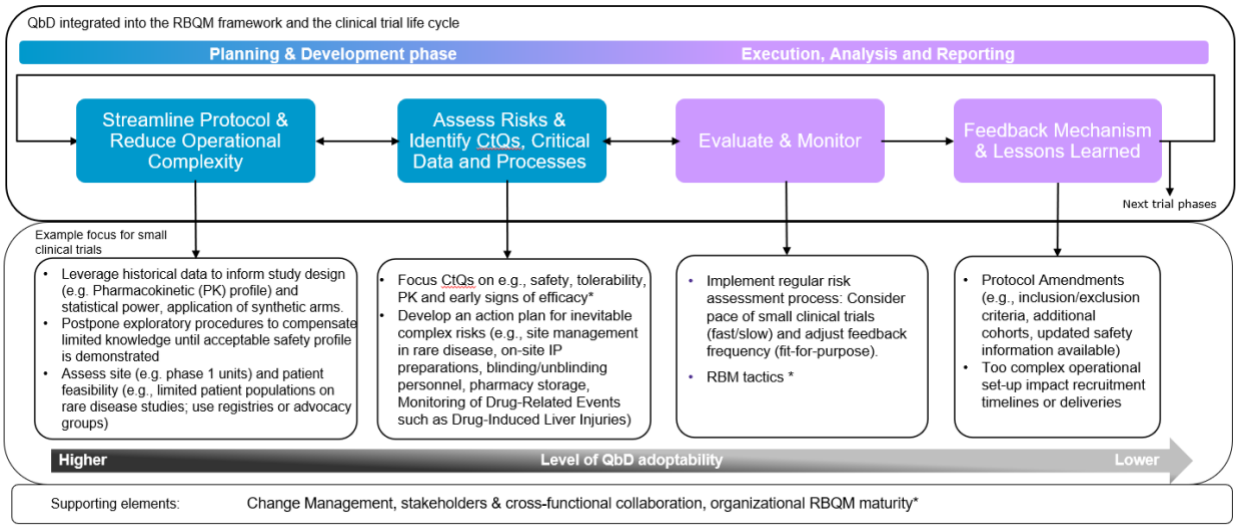
Historically, Risk-Based Monitoring (RBM), the precursor to RBQM, was often perceived narrowly as a set of monitoring techniques, primarily focused on reducing source data verification (SDV) and in some cases implementing centralized monitoring strategies. As a result, RBM was not consistently applied in small clinical trials, where traditional monitoring methods were often favored due to perceived simplicity or concerns about patient safety.

Over time, the concept of RBM has evolved into a broader and more strategic RBQM framework where RBM is just one of several components. Another key pillar is QbD, a proactive approach that integrates quality into the design and planning of a study from the outset. While RBQM outlines the overarching risk management strategy, QbD ensures that quality is considered from the beginning and throughout the trial life cycle (4).

In the context of small clinical trials, incorporating QbD principles is especially important. These studies are often complex and highly sensitive to deviations, making it critical to identify and mitigate risks early in the planning process. Embedding QbD as a formal component of the RBQM framework ensures that quality is built into every phase of the study, not just monitored after the fact. An example of QbD in small clinical trials is developing an adaptive study protocol that allows flexibility in trial execution and supports data-driven decision-making as new evidence emerges. Another example can be utilization of historical controls in rare disease trials to supplement or even replace traditional control arms, improving both the feasibility and cost-effectiveness of the study while maintaining scientific validity.

Figure 1 Illustrates the elements of the RBQM framework and provides examples of how QbD can be integrated into these elements in the context of small clinical trials.

Figure 1: QbD within the RBQM Framework



* Refer to respective sections of the paper for further recommendations and examples

3: Risk assessment in small clinical trials: Integrating Critical to Quality (CTQ) factors for robust risk assessment

A core component of RBQM is a robust risk assessment that systematically identifies CtQ factors, the essential elements that influence the reliability and success of a clinical trial (5), along with the associated critical data and processes. Risks related to these elements are then evaluated for likelihood, potential impact, and detectability and fit-for-purpose mitigation strategies and monitoring plans are defined to enable effective and proactive risk management (2).

By understanding CtQ factors, researchers can ensure the protocol and trial are designed to consistently meet quality standards, implement targeted strategies to mitigate risks, enhance data quality, and ensure that the trial meets its scientific and regulatory objectives. In the context of small clinical trials, CtQs may be challenging in unique ways, for example (figures 2-4):

- Limited target population in rare disease studies (small sample sizes)
- Need for real-time collection and review of safety data during dose escalation in FIH trials
- Completeness and accuracy of pharmacokinetic (PK) primary data with multiple collection timepoints

By integrating risk assessments into the trial design and conduct, sponsors can ensure the trial remains focused on the most important aspects, thereby enhancing the overall quality and reliability of the trial outcomes. In all clinical trials, risk assessments should follow the principle of proportionality, with resources and operational efforts allocated based on the risk and its likelihood and impact (2).

In the context of small clinical trials, based on this risk assessment, greater monitoring efforts may be warranted to ensure participants safety if the safety profile is still being established or to ensure compliance with complex processes such as PK sampling with many timepoints or adherence to complicated dose escalation criteria. On the other hand, other components that are critical but unlikely to be an issue typically should not garner as many resources, e.g., extensive oversight of exploratory endpoints and non-critical data points may need to be minimized.

Performing a robust risk assessment for smaller trials can be more challenging due to limited resources and/or higher trial uncertainties (e.g. unknown safety profile). For example, teams executing smaller clinical trials might have less defined or overlapping roles and responsibilities, limited resources and compressed timelines. Therefore, it is essential to identify the appropriate cross functional stakeholders and to clearly define decision-making roles within the study team as early as possible ensuring the risk assessment leverages collaborative knowledge and views of relevant internal and external stakeholders.

A small clinical trial may also have fewer dedicated functional roles responsible to adequately oversee the risk assessment process and evaluate CtQ factors. To address this challenge, it is essential to provide targeted training for all study team members on how to conduct effective risk assessments and/or to

consider leveraging external expertise to enhance the team's capabilities in risk management and CtQ evaluation e.g., risk advisors. In fact, where resources permit, it is strongly recommended to appoint a dedicated role to oversee the processes and ensure effective RBQM management. Alternatively, organizations may consider developing and leveraging automated tools (e.g., CtQ or risk libraries). Figures 2–4 show CtQ examples for small clinical trials that support RBQM process efficiency and accuracy.

Figure 2. Example of Critical to Quality factor for small clinical trial with dose escalation: real-time safety data collection and review

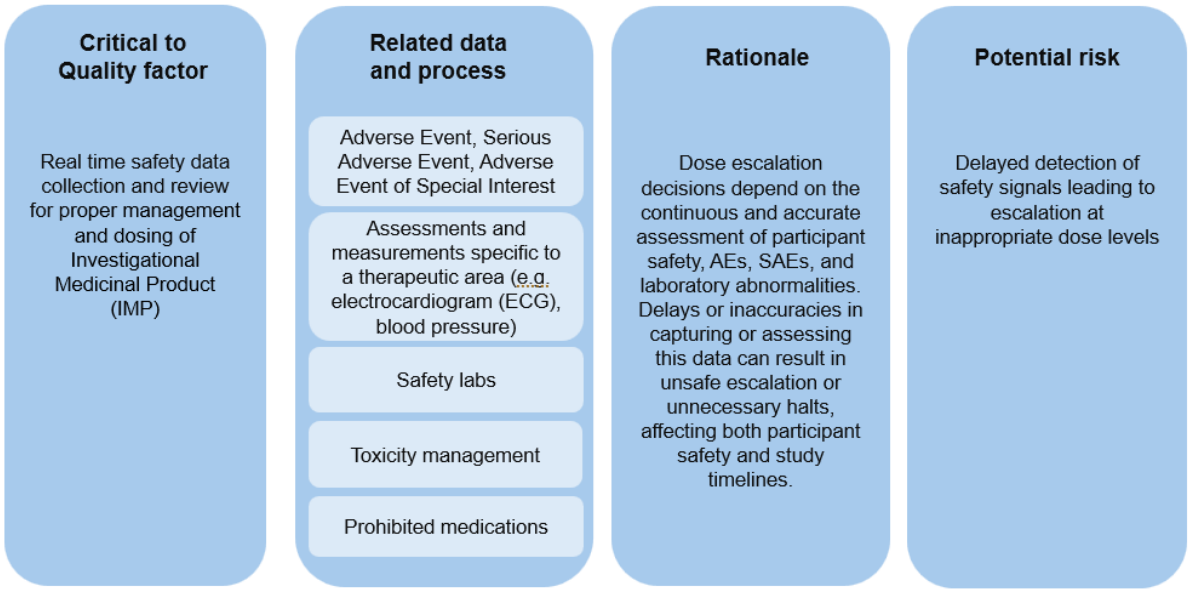


Figure 3. Example of Critical to Quality factor for small clinical trial in rare disease: patient retention

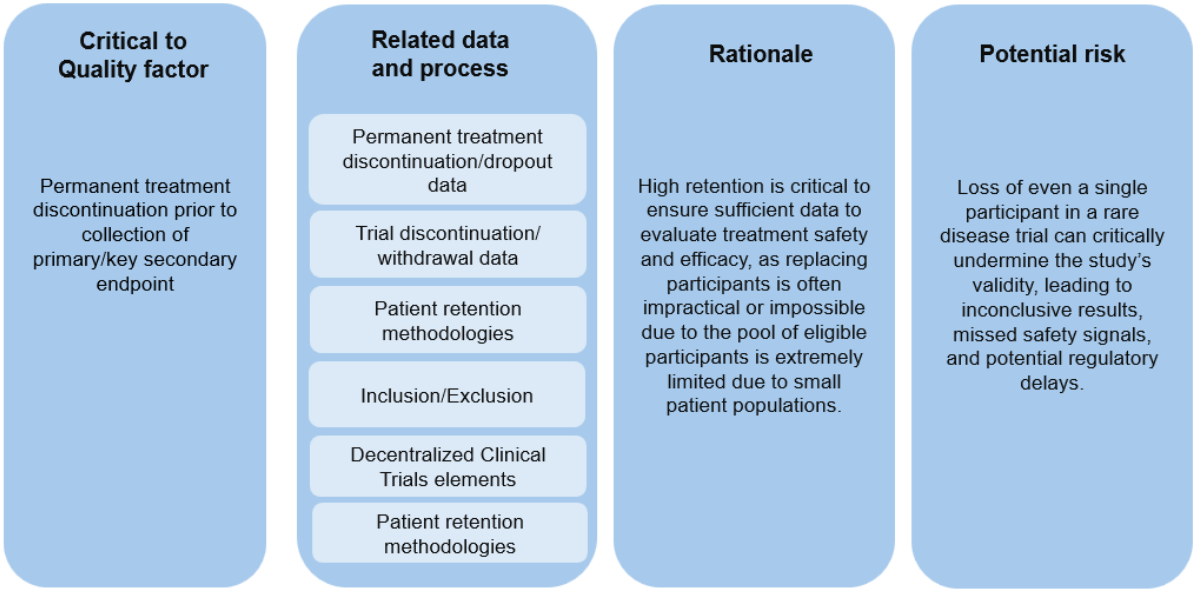
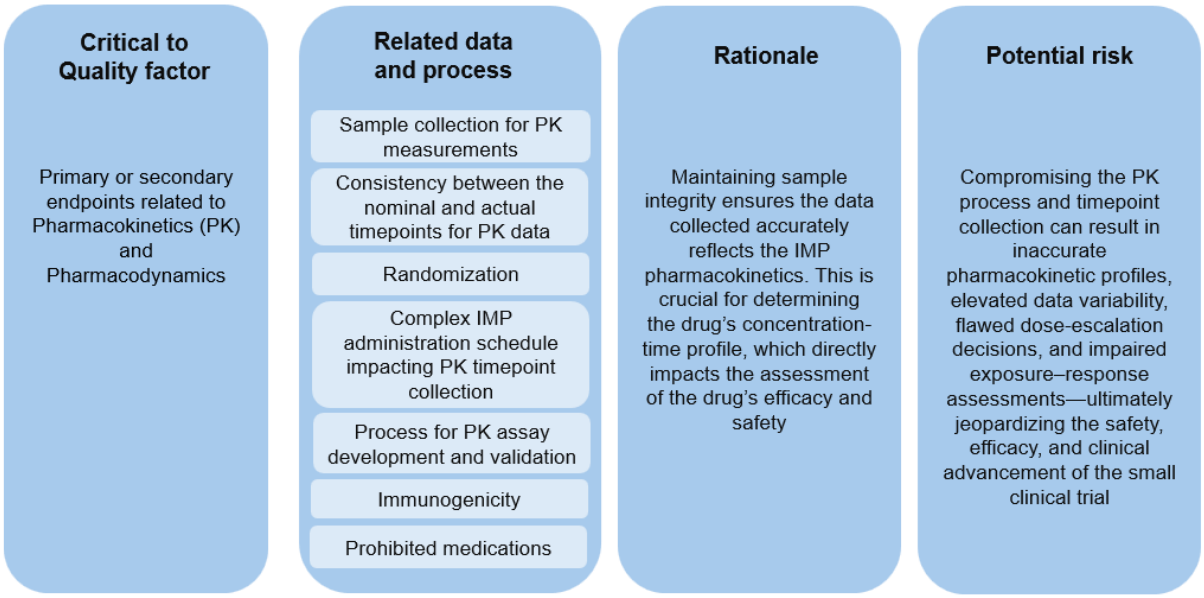


Figure 4. Example of Critical to Quality factor for small clinical trial in FIH: primary or secondary endpoints



4: Targeted monitoring tactics in small clinical trials – Prioritizing critical data and balancing monitoring strategies

Small clinical trials require heightened vigilance due to limited knowledge of the investigational product, focusing on PK, safety events, and careful dose-escalation. In these trials, small sample sizes amplify the significance of every data point, highlighting the importance of participant retention through flexible and adaptive monitoring strategies. Historically, small clinical trials involved highly detailed data reviews that treated all data with equal priority. However, with the updates ICH E6 (R3) guidelines (2), sponsors are required to implement a proportionate review and monitoring of clinical trial data, including small clinical trials, focusing on CtQ factors (6). This shift is enabled by a risk-based monitoring strategy, ensuring that cross-functional monitoring activities are balanced and targeted to the areas of highest importance, as described in the following section.

Targeted Source Data Review (SDR) and Source Data Verification (SDV)

SDR is the review of source documents to verify protocol and GCP compliance, assess process adequacy, investigator involvement, and ensure data are ALCOA - attributable, legible, contemporaneous, original, and accurate. SDV is a process by which data within an electronic case report form are compared to the original source of information (and vice versa) to confirm accurate data transcription.

The scope of data selected in small clinical trials, for targeted SDR and SDV is often broader than in later-phase studies or those investigating products with well-established safety profiles. This is primarily because the safety profile of the investigational compound remains unknown and requires close monitoring. Additionally, centralized monitoring strategies, which rely on a larger volume of aggregated data across multiple sites, are typically less effective in small clinical trials for this reason. Together, these factors may contribute to the hesitance of clinical teams to apply targeted SDV.

However, applying targeted SDR and SDV is becoming increasingly recognized as best practice, since these methodologies enable focused oversight of the most critical data and processes.

Targeted SDR and SDV can be applied at a variety of levels - patient-level, visit, data point, specific study phase or combination of these factors. For example, source data monitoring may focus on certain patients at each site (1st, 3rd, 6th) and/or target specific types of data (e.g. adverse events and safety assessments, rather than supportive information like exploratory biomarkers). Another approach may involve thorough review early in the study (e.g. during dose escalation) with less review in later stages of the trial or targeted to none for screen failure participants where critical data is minimal and the risk is low.

In the context of small clinical trials, applying a patient-level approach can be problematic as the small number of patients per site limits the potential efficiency gains, and the elevated safety risks make it

necessary to verify critical data for all patients to ensure adequate safety oversight. Targeting SDV and SDR efforts on high-priority safety data could therefore be a more preferred strategy.

The implementation of targeted review may follow either a fixed or adaptive model. In a fixed approach, data verification is planned based on predefined categories such as visit type, screening outcomes, or study phase. An adaptive approach, in contrast, allows the level of review to change based on real-time triggers like the number of data entry modifications or frequency of queries. While adaptive methods provide flexibility, they require more effort to monitor and increase operational complexity, which may not be cost-effective in the context of small clinical trials, particularly considering the limited added value of SDV alone.

Targeted Medical Monitoring

Medical monitoring in clinical trials focuses on participant safety and the validity of clinical endpoints. Also, this type of monitoring can be targeted to concentrate on data elements most critical to trial objectives. For example, specific laboratory values for a specific indication or serious adverse events of special interest, investigational product administration, PK/PD and specific diagnostic markers. To increase efficiency and maintain proportionate medical monitoring, targeting medical review on these predefined critical data points enables earlier detection of emerging medical signals, or data issues. Additionally, incorporating targeted clinical alert flags, e.g., for prohibited medications or abnormal dosing, may also assist in highlighting deviations that could compromise patient safety. Such proactive, risk-informed approach supports timely interventions while reducing review of non-critical data.

Centralized monitoring – signal detection and trend analyses

Elements of centralized monitoring such as Key Risk Indicators (KRIs), Quality Tolerance Limits (QTLs) and Central Statistical Monitoring (CSM) enable centralized data reviewers to identify potential trends and outliers and help to ensure timely intervention when risks exceed acceptable thresholds.

Key Risk Indicators

The purpose of Key Risk Indicators is to enable early detection of risks and support proactive action. This is especially critical in small clinical trials, where limited sample sizes and shorter study durations leave little margin for error. Under such conditions, challenges such as few participants or sites may result in weaker or less reliable signals.

To address these challenges, cross-functional collaboration is essential for the identification and validation of KRIs, guided by risk assessments and CtQ factors. Examples of KRIs particularly relevant in small clinical trials include: % of participants with prohibited medications, % of participants with dosing errors, pre-dosing compliance, % of visits with missing safety laboratory results and missing electrocardiograms (ECGs) etc.

Equally important is the establishment of thresholds and escalation plans. A key differentiator in small trials is that, due to the smaller sample size, relative thresholds typically used on larger trials, are often unreliable. For small studies, absolute thresholds can help address this issue, though defining thresholds can still be challenging in the absence of historical data, and may introduce subjectivity. These thresholds may need adjustment during the course of the study, particularly during trial adaptations such as dose escalation, expansion, or other study design modifications. Any changes should be clearly documented with justification, and significant modifications should be approved by key stakeholders.

Quality Tolerance Limits (QTLs)

Recent years have seen significant improvement in the industry's understanding of the implementation of QTLs as described by the ICH E6 Guidance (2,4). QTLs are defined based on critical to quality data (e.g. primary or key secondary endpoint data), are linked to the statistical design of the trial and serve to ensure the reliability of trial results and participant safety. When it comes to small clinical trials, neither the ICH E6 R3 guideline nor other industry standards provide specific guidance for the implementation of QTLs. Small clinical trials pose specific challenges when implementing QTLs compared to large studies.

Due to the small sample size, especially during dose escalation (Figure 6), QTL monitoring may not be very meaningful, potentially leading to false signals despite the use of normalization techniques, thereby reducing the potential benefits of implementing QTLs. This can be re-assessed for later stages of a trial e.g., during dose expansion when the sample size is larger.

For most of small clinical trials (e.g. FIH) it may be challenging to obtain historical data from prior, similar studies with which to set appropriate tolerance limits. This limited prior data makes benchmarking simulated trial data difficult for pre-defining QTL thresholds and may result in multiple adjustments throughout the trial duration, if QTL excursions occur and root cause analysis fails to identify systematic error (indicating the initial threshold was not truly appropriate).

The decision to implement QTLs or not for small clinical trials, as well as the timing of their application (e.g., only during dose expansion), should be determined by the cross-functional study team and consider the statistical design and meaningfulness of the QTLs. For example, in small trials setting a threshold for a QTL parameter monitoring proportion of participants that prematurely discontinue study may amount to only a handful of participants, which would not provide real insight into systematic error, the intent of QTLs. However, when appropriate for the trial, Bayesian predictive probability (9) can provide a robust approach to establishing QTLs by incorporating prior knowledge and thereby improving the reliability of signal detection. Key in this process is the statisticians' input on the parameter and threshold setting with regards to the statistical design and data oversight.

Central statistical monitoring

Central Statistical Monitoring (CSM) is an unsupervised or semi-supervised approach used to oversee

data quality, compliance, and trial integrity by detecting atypical data patterns through statistical techniques. However, applying CSM in small clinical trials can be challenging. Limited data volume reduces the sensitivity of statistical methods, making it harder to reliably detect anomalies or irregularities.

The decision to implement CSM should therefore be carefully assessed to ensure it is fit-for-purpose. Key considerations include expected data volume, which is influenced by enrollment projections and the number of activated sites, as well as overall trial design. For example, in FIH or dose-finding studies, CSM may have limited value due to the small data sets typically generated. In contrast, in later-stage trials with larger sample sizes, CSM can strengthen data integrity and support timely decision-making, provided its use is tailored to the trial's specific needs (Figure 6).

Statistical techniques such as histograms, interquartile ranges, and scatter plots can be used to reveal inconsistencies or anomalies. In small clinical trials, however, their effectiveness depends on whether sufficient data are available to establish meaningful trends. In settings where data are extremely limited, site-level or patient-level KRI monitoring may be more practical and meaningful.

Targeted Data Management Review

By implementing a risk-based and proportionate approach to data management review, Contract Research Organizations (CROs) and Sponsors can optimize data quality. These efforts may include targeted data validation rules (e.g., edit checks), smart query management automation to minimize unnecessary queries (for e.g. queries that may compete with each other) for supportive or exploratory data, risk-based audit trail checks emphasizing critical data modifications rather than exhaustive audit trail log review for all. As these approaches are not distinct for small clinical trials, they will not be further detailed in these recommendations.

Adaptive monitoring - balancing on-site, remote, and Centralized Monitoring

Choosing a blend of on-site and remote visits may depend on risk indicators. Sites deemed high-risk typically warrant more frequent on-site reviews, while remote monitoring may suffice for lower-risk sites.

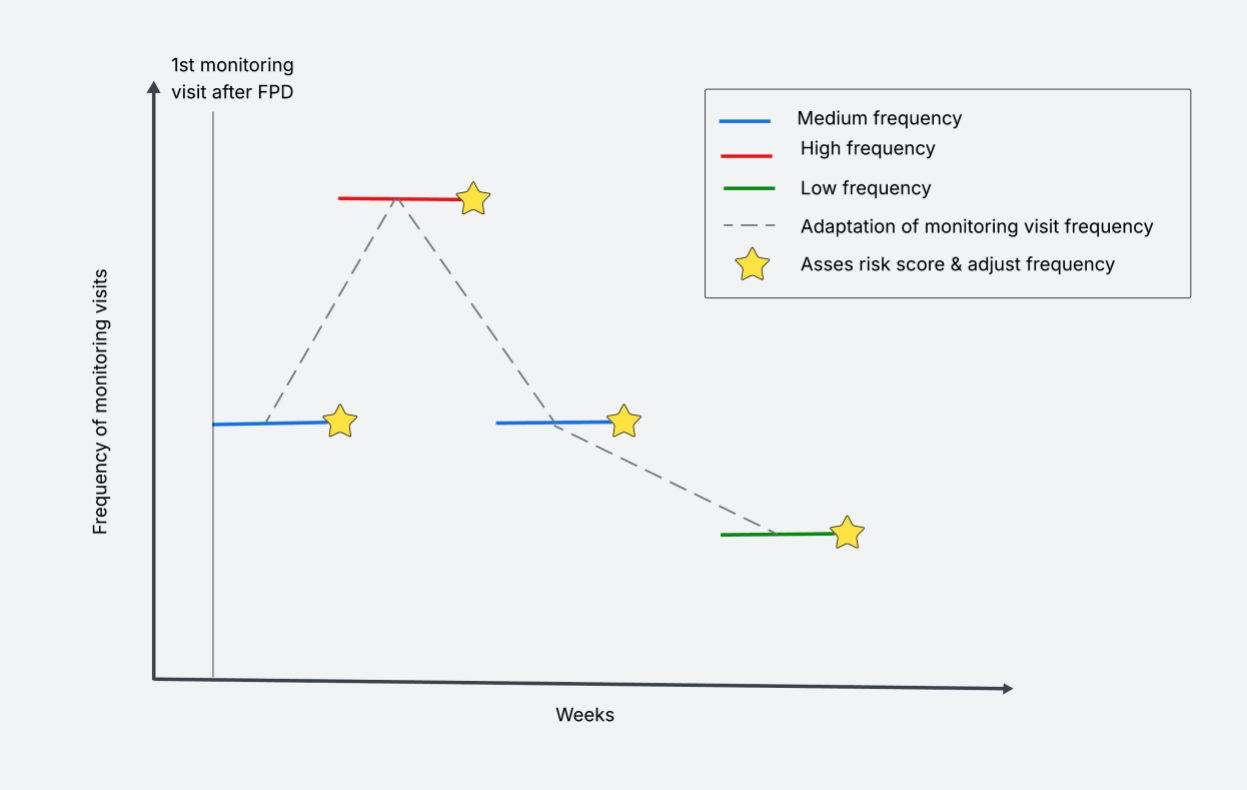
Site prioritization is an effective tool for targeted monitoring in large clinical trials with many sites, helping identify which locations need closer oversight. It supports efficient resource allocation and risk-based decision-making.

However, in smaller studies with few sites, this technique offers less value. With manageable site numbers, direct and consistent oversight is typically more practical. In such cases, site prioritization may introduce unnecessary complexity and is not recommended by this guidance.

When planning monitoring strategies for small clinical trials, it is important to balance on-site and remote

visits even more so than in later-stage studies. For example, during dose-escalation phases, more frequent on-site visits may be necessary to closely monitor safety and protocol adherence. In rare disease trials, maintaining participant engagement is critical, and on-site visits can support site staff in retaining participants. Early in the trial, having the CRA on-site can be particularly valuable to oversee and verify the quality of the Principal Investigator's execution of the study. Sponsors may choose to set a fixed, higher frequency of on-site monitoring visits at the beginning (e.g. first monitoring visit within 2-4 weeks from First Patient Dose (FPD) in FIH trials), which can later be adapted based on risk assessment and site performance as the trial progresses (Figure 5).

Figure 5. Monitoring visit frequency adaptations following the risk score based on the KRIs and signals from cross-functional teams' review.



In general, analytical tools and methods can be effectively employed in small clinical trials; however, it is crucial to remain cognizant of the limited data volume. Such constraints necessitate careful interpretation of the results.

5: Overcoming resistance to RBQM adoption

Resistance to change is common in any organisation, especially with methodologies such as RBQM. Furthermore, the maturity of RBQM implementation within an organisation influences change management approaches, with aversion varying between smaller studies and those with known safety profiles. To identify the most effective strategies for managing change and overcoming these challenges, a survey was conducted among experienced industry professionals to better understand them and the anticipated benefits of implementing RBQM as unique to small studies (see appendix 1).

One of the most significant concerns showed that resistance in small studies, which are often limited in resources, can stem from fears of increased workload and operational complexity, in addition to limited number of data points for analysis, leading to inconsistent adoption. Emphasising that RBQM focuses on the most impactful risks and provides adequate support and resources is therefore required to address these concerns.

Early phase studies often face uncertainty in regulatory expectations, leading teams to default to traditional monitoring methods. While RBQM is broadly accepted in late-phase trials, smaller studies frequently lack clear regulatory guidance. The latest revision of ICH E6 effective July 2025 reinforces RBQM's applicability across all types of clinical trials, including small studies, and encourages sponsors to adapt proportionate and fit-for-purpose RBQM strategies. To support adoption, companies may develop internal decision tree to guide the selection of appropriate RBQM framework elements, tailored for small studies and complemented with clear expectations from senior leadership (Figure 6).

In addition, sponsors may consider implementing RBQM components in stages to adjust processes incrementally, reducing concerns and ensuring a smooth transition. This allows time to supplement processes with training and tools that are essential for supporting decision-making and adoption of risk-based monitoring tactics.

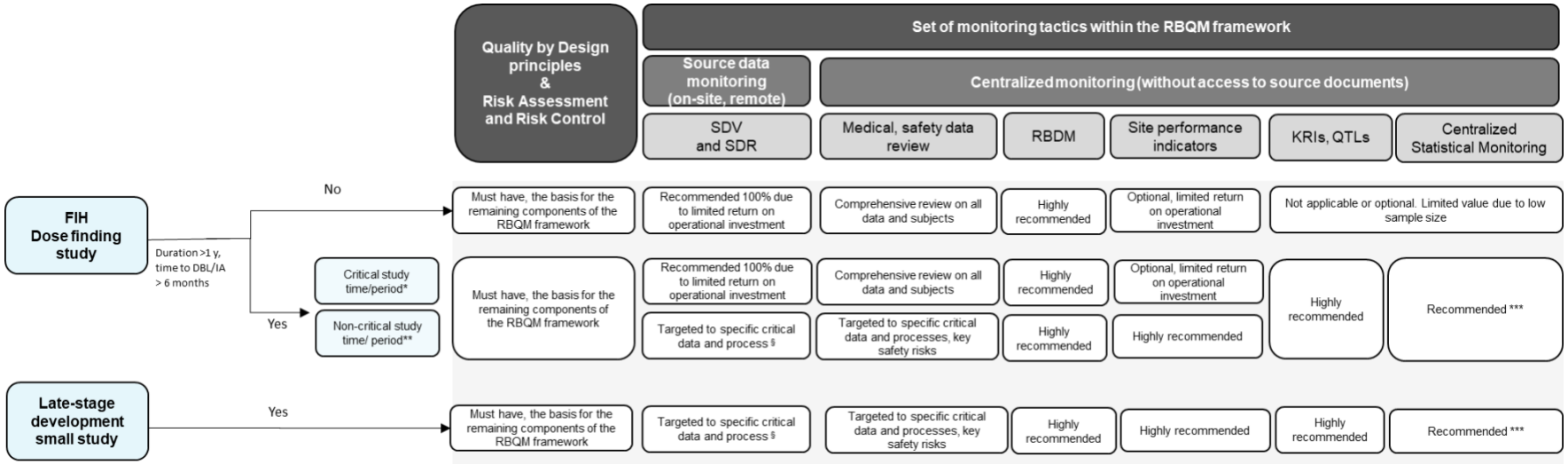
Resistance to change in small studies can be effectively managed using proven change management techniques (7,8), which provide structured approaches to help improve overall adoption and leveraging RBQM's benefits. Complementing these approaches with informal touchpoints with key stakeholders can uncover underlying concerns, enhance engagement and help gradually dismantle perceived barriers.
Empowering cross-functional "change agents" can significantly enhance RBQM adoption in small studies by addressing concerns and fostering a culture of acceptance. Leveraging their participant matter expertise, the change agents can guide their study team, provide practical guidance, use cases and help identify and hone the most impactful and study-appropriate RBQM elements, ensuring an overall smoother and more effective implementation in the setting of small clinical trials.

Demonstrating RBQM's effectiveness through evidence-based information and pilot programs can alleviate senior leadership scepticism of the benefits for smaller studies. Highlighting long-term cost savings from early study de-risking (e.g., fewer protocol revisions, proactively prioritizing and mitigating risks to prevent operational rework) and fewer on-site visits, even in these small studies can show financial efficiency resulting in efficient resource allocation, and improved trial oversight efficiency. Senior leadership should also set company-wide expectations to embed a RBQM culture.

Both sponsors and CROs play a crucial role in the adoption of RBQM in small studies. CROs should consider the opportunities of implementing RBQM in smaller studies as part of their portfolio of services. For companies with fully outsourced RBQM where CROs might not have established RBQM methodologies for small studies, the sponsor should therefore have a clear strategy regarding the RBQM approach required, which should be addressed during RFP discussions. The CRO's staff must be adequately trained in RBQM methodologies, which may differ from their standard operating procedures.

Figure 6: Decision tree for adoption of the RBQM framework in small clinical trials

The below guidance is intended as a recommendation to support study teams in their decision-making processes. While it offers a structured approach, it is not mandatory, and teams should adapt it to their specific study needs. We encourage study teams to follow the 80:20 rule of change management, focus 80% of your efforts on managing and implementing changes that will have the greatest impact, while allowing flexibility for the remaining 20% to address smaller, less critical adjustments.



* For example, time needed to establish dose limiting toxicity, safety run-in, screening period

** For example, time-period after safety run-in

*** Application of statistical techniques to identify unusual data patterns, anomalies, or trends in clinical trial data from a centralized location recommended in

studies with > 25 participants enrolled/randomised and > 3-5 participants per site or at least 3 participants enrolled/randomized with >3 visits. Application of centralized statistical monitoring on participant level can also be utilized

§ Different operating models, from 0% SDV to 100% SDV, dependent on the maturity and risk appetite of the company can be applied.

6: Conclusion

This paper presents industry-led recommendations for implementing RBQM in small clinical trials which is challenging due to limited sample sizes and often complex study designs. This guidance emphasizes applying QbD principles and risk-proportionate strategies to embed quality from the outset, strengthen oversight, and ensure patient safety in alignment with ICH GCP and regulatory expectations. It highlights practical considerations, survey insights, and tailored approaches to help sponsors transition from conservative methods to effective RBQM practices in these challenging settings.

7: References

1. ACRO RBQM Landscape Summary Report June 2025
2. International Council for Harmonisation of Technical, Guideline for Good Clinical Practice, E6(R3), Final version, Adopted on 06 January 2025
3. International Council for Harmonisation of technical Requirements for Pharmaceuticals for Human Use, General Considerations for Clinical Studies, E8(R1), Adopted on 6 October 2021
4. Quality Tolerance Limits: A General Guidance for Parameter Selection and Threshold Setting, https://pubmed.ncbi.nlm.nih.gov/38321191/
5. Meeker-OConnell et al (2016) Enhancing clinical evidence by proactively building quality into clinical trials. Clinical Trials Vol 13(4) 439-444
6. Clinical Trials Transformation Initiative, Exploring the Critical to Quality (CTQ) Factors
7. Rock, D. (2008). SCARF: A Brain-Based Model for Collaborating with and Influencing Others. Neuro Leadership Journal, 1(1), 44–52.5.
8. Hiatt, J. (2006) ADKAR: A Model for Change in Business, Government and Our Community. Prosci Learning Center Publications
9. Lee JJ, Liu DD. A predictive probability design for phase II cancer clinical trials. Clinical Trials. 2008;5(2):93-106. doi:10.1177/1740774508089279

8: Disclaimer

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9: Appendices

APPENDIX 1 SURVEY INVESTIGATING KEY BENEFITS AND RESISTANCE IN RBQM IMPLEMENTATION IN SMALL AND ED STUDIES.

Survey methodology:

The survey was designed to gather insights and perspectives on the main benefits and resistance for RBQM implementation in small and early development studies from the members of PHUSE RBQM networks. These networks comprise a diverse group of RBQM experts, including professionals working across biotechnology, small, mid-sized, and large pharmaceutical companies, as well as RBQM vendors. Conducted anonymously via Microsoft Forms from, the survey was distributed to N individuals, yielding 27 responses from professionals with varied expertise and organizational backgrounds. It comprised two multiple-choice questions with predefined answers and an open-text option for additional insights.

1. What benefits do you see/expect with RBQM in small studies and early development?
    a. Reduced trial complexity
    b. Increased quality of critical data
    c. More efficiency in data monitoring activities
    d. Mitigations during the planning phase
    e. Risk-proportionate approach
    f. Other

2. What are the main reasons for resistance to implement RBQM in small studies and early development?
    a. Time consuming
    b. Challenging vendor collaboration
    c. Increased operational complexity
    d. Data control
    e. Decreased data quality
    f. Other

The respondents could select multiple answers to reflect the diverse perspectives on both benefits and challenges of RBQM implementation. Each question included an 'Other' option, allowing participants to provide free-text input and share additional insights beyond the predefined choices.

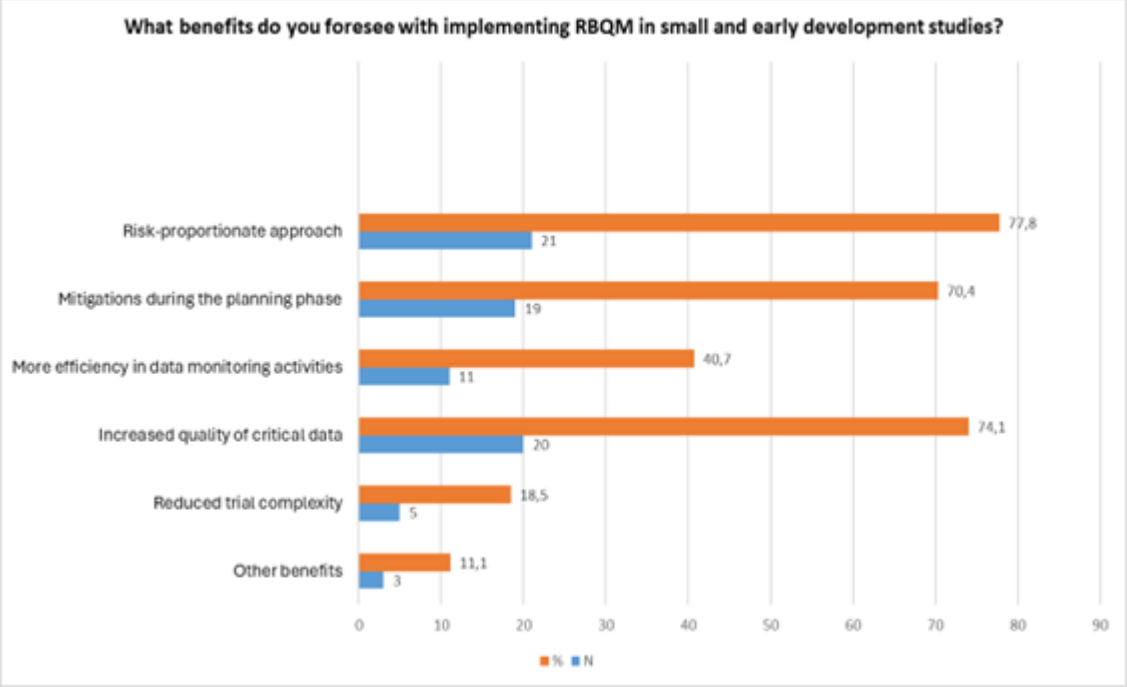
Results:

The survey illustrates the main reasons for resistance and anticipated benefits of implementing RBQM in small and early development studies, highlighting both the percentage of respondents for each category and the number of responses.

Benefits:

- The most significant anticipated benefit of implementing RBQM is the risk-proportionate approach, with a substantial majority (78%) of respondents recognizing its value
- Other notable benefits include increased quality of critical data and mitigations during the planning phase, both of which are also highly regarded (74% and 70%, respectively)
- More efficiency in data monitoring activities is acknowledged but with fewer respondents compared to the top benefits (41%)
- The perceived benefits of reduced trial complexity were the least cited (11%)
- Other benefits were: Define the CtQs will inform other processes to focus on the most critical things of a study; Information to better inform the next phase of studies; The methodology

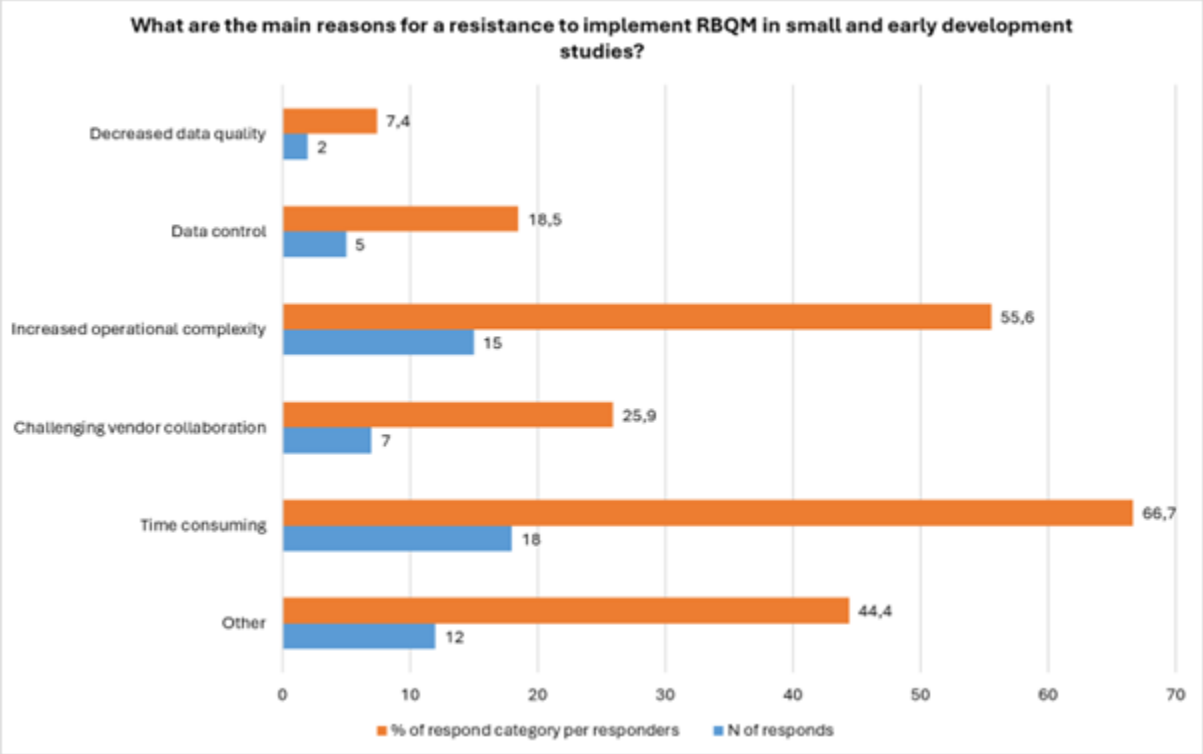
developed for big pharma, e.g., QTL positioning. A small biotech does not have relevant historical data



Resistance:

- The most significant concerns are that implementing RBQM is perceived as time-consuming and lead to increased operational complexity (67% and 56%, respectively)
- Factors like challenging vendor collaboration and data control also contribute to residence but to a lesser extent (26% and 19%, respectively)
- Decrease data quality is least cited reason for resistance (7%)
- Other reasons for resistance stated by the responders were: KRI and other data assessments are less meaningful; Not enough volume of data to facilitate the process e.g QTL, KRI, statistical monitoring. For most of the early phase studies, due to limited number of sites, it is not valuable

to implement RBQM to compare the KRI between sites; Change management; Short timelines between First Participant First Visit to Database Lock; Budget for an additional role / technology; Teams feel their length of exposure is generally too short; Less room for (data) error, therefore clinical teams want all data reviewed; Push back regarding the value add as a lot of the data is considered critical; Number of participants is so small, study duration is short, and speed with which data comes in could be slow - together it makes it difficult to justify implementation of RBQM; Cost on setting up the RBQM database and incorporating them with vendor data; Cost, this is the driver for a risk proportionate approach.



Discussion:

The survey results highlight the strong potential benefits of RBQM in small and early development studies. The most recognized advantage is the risk-proportionate approach (78%), followed by improved quality of critical data (74%) and better mitigation strategies during planning (70%). These findings emphasize how RBQM can improve quality and efficiency of trial execution and optimize monitoring efforts by

focusing on the most critical study aspects while reducing unnecessary oversight for low-risk areas.

However, the primary resistance factors were high time consumption (67%) and increased operational complexity (56%), indicating that widespread adoption of RBQM in small studies remains hindered by concerns over return on investment and the suitability of existing RBQM methodologies. Respondents also highlighted challenges specific to small studies, such as limited data volume, short timelines, and budget constraints, further complicating seamless RBQM implementation in those kinds of studies.

Interestingly, despite these concerns, data quality was not seen as a major risk (7%), indicating that RBQM is not perceived as compromising data integrity. This is a positive finding, as change management can more easily overcome operational resistance compared to challenges associated with concerns about data quality.

In summary, implementing RBQM in small studies requires a tailored approach that considers study-specific factors while addressing operational and financial challenges through strategic RBQM adaptation and effective change management.

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