Risk-based Clinical Data Management

Authors: Patrick Nadolny (Sanofi), Catherine Celingant (Pfizer), Leonie Christianson (Syneos Health Consulting), Pameljit Kalra (ZS), Stacey King (AperioClinical), Nicole Pollard (eClinicalSOL), Jeffrey Rieske (ZS), Jonathan Rowe (ZS), Demi You (Sanofi), Debojyoti Das (Sanofi), Eugene Hayden (Muraloncology), Karen Klein (Veeva), Lynne Cesario (Pfizer), Manny Vasquez (Veeva)

Acknowledgments: We would like to acknowledge the valuable contributions of Cheryl Grandinetti (FDA) and Steve Young (CluePoints) whose input and support greatly assisted the development of this chapter.

Abstract:

Starting over a decade ago, regulators have issued guidance documents advocating for the adoption of risk-based and fit for purpose approaches. The good clinical practice (GCP) guideline from the International Conference of Harmonization (ICH), commonly referred as ICH E6[1] was updated in 2016 and 2025 to reenforce this direction.

Additionally, the ICH guideline on General Considerations for Clinical Studies (ICH E8)[2] emphasized quality by design (QbD), which is grounded in two foundational risk-based principles: Prospectively identifying factors critical to quality and applying risk-based approaches to study design, conduct, monitoring, and reporting. This includes the use of risk-based approaches to quality management throughout the clinical study lifecycle to support the reliability of study results and the protection of participants

Having already implemented risk-based approaches in the site monitoring and system validation spaces for many years, our traditionally risk-averse industry has become more familiar with strategies that align efforts with the risks to study participants rights, safety, and well-being and data quality. As of 2021, 88% of clinical studies had implemented at least one component of risk-based quality management (RBQM) compared to 53% in 2019[3]. Considering the regulatory evolution and the need to accelerate the development of medicines, it is imperative for organizations managing clinical data and related systems to adopt QbD, RBQM, and fit for purpose principles, focusing on what matters most.

Keywords: Critical to Quality Factors, Quality by Design, Risk Based Quality Management

1) Learning Objectives

After reading this chapter, the reader will understand:

- the benefits of applying risk-based approaches to Clinical Data Management (CDM) activities
- the difference between data integrity and data quality

- the key framework associated with risk-based approaches (i.e., QbD, RBQM, and fit for purpose clinical study quality)
- the relevant regulations
- how CDM organizations can drive data quality in a more efficient and effective manner

2) Introduction

This chapter covers how CDM can evolve from traditional, reactive QC-based strategies to proactive, end-to-end Quality Management within an RBQM Framework. This risk-based CDM (i.e., rb-CDM) evolution should begin with the adoption of foundational principles of QbD, and progressively expand to apply RBQM cross-functionally, meaning:

1. Actively participating in study team discussions and decision on CtQ factors, QbD decisions, definitions for Quality Tolerance Limits (QTLs) and Key Risk Indicators (KRIs)
2. Performing a data-specific risk assessment during the planning phase of the study and throughout its entire life cycle
3. De-risking the protocol i.e., updating the protocol prior to study start to prevent avoidable risks (e.g., removing collection of unnecessary data) and implementing a mitigation strategy for each identified risk.

Only then can CDM implement safe and effective risk-based study execution strategies paired with robust continuous process improvements to deliver quality data sufficient to support reliable and timely decision making.

This means moving from reactively catching mistakes to proactively identifying problems that may jeopardize the study. Overall, the end-to-end management of the operational and scientific risks should be embedded throughout the entire CDM Framework, with connection to other functions and disciplines involved in the process when necessary.

2.1) Notes to readers

In the absence of a deep body of knowledge and a comprehensive literature base regarding rb-CDM in clinical trial study execution, this content was gathered from regulations considered as minimum standards as well as feedback and insights from early adopters, regulators and industry leaders to recommend best practices through a consensus-based methodology. As rb-CDM matures, new/revised regulations and guidances emerge, and technology evolves, we anticipate that the body of knowledge on this topic will blossom and lead to further evolution of this Good Clinical Data Management Practice (GCDMP) chapter and the overall SCDM Competency framework[4].

This GCDMP chapter applies to all types of studies—whether interventional or non-interventional—and to all categories of medicinal products, including drugs, devices, and biological products.

The authors have made efforts to standardize terminology throughout the document while preserving the original language of cited regulations.

- The terms “**study**” and “**trial**” are used interchangeably, with no intent to distinguish between them. However, preference has been given to the term “study”, as it broadly encompasses all types of research, whereas “trial” is more commonly associated with interventional studies.
- For similar reasons, the term “**participant**” has been favored over “**patient**”.
- To avoid repetition, the term participant “**protection**” has been used to encompass participant “**rights, safety, and well-being**”.
- To align with ICH E6 (R3)[1], the term “**Service Provider**” has been favored over “**Vendor**”

3) Chapter Scope

This GCDMP chapter provides guidance on the principles, standards, and practical applications of (rb-CDM across the lifecycle of clinical studies. It is intended for sponsors, CROs, service providers, regulators, and other stakeholders involved in the design, conduct, oversight, and reporting of clinical research. The chapter applies to all types of clinical studies, including interventional and non-interventional research as well as all categories of medicinal products such as drugs, devices, and biological products. The scope encompasses both organizational and study-level practices, emphasizing the integration of QbD, RBQM, and fit for purpose strategies to safeguard participant protection and ensure reliable, high-quality data.

This guidance defines the minimum expectations for applying risk-based principles to CDM, while recognizing that implementation should be flexible, context-dependent, and proportionate to study-specific risks. It is not intended to prescribe rigid operational procedures but rather encourages adoption of a pragmatic, critical-thinking mindset that prioritizes what matters most to participant rights, safety, and well-being, and to the credibility of study results. As such, this document provides a framework that organizations can adapt and evolve as regulations mature, technology advances, and industry experience with rb-CDM expands.

4) Minimum Standards

In its GCDMP Chapters, regulations are considered as minimum standards to be met and followed. For this Chapter on rb-CDM, important applicable passages from the following six regulatory guidance's listed chronologically.

- August 2013, FDA guidance on “A Risk-Based Approach to Monitoring[5]
- March 2018, MHRA ‘GXP’ Data Integrity Guidance and Definition[6]
- October 2021, ICH E8 (R1), General Considerations for Clinical Trials[2]
- January 2022, MHRA Oversight and monitoring activities[7]
- April 2023, FDA, A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers[8]
- January 2025, ICH E6 (R3), Guideline for Good Clinical Practice[1]

To ease the reading of this GDMP chapter, those passages have been included in **Appendix A** and organized around **six core concepts** introduced in this section.

4.1) Risk-based approaches

Risk-based approaches are practices that proportionally align focus and efforts on what matters most to prevent and manage risks to participant's rights, safety, and well-being, critical data, processes, and systems and the reliability of study results considering the likelihood of risk occurrence, their potential severity and detectability.

4.2) Fit for purpose considerations

Fit for purpose clinical studies quality means that studies should be of sufficient quality to meet their objectives, provide confidence in the study's results, and support sound decision-making, all while adequately protecting the participants involved. As such, regulations and especially ICH E6 (R3)[1], are emphasizing risk-proportionate strategies that support quality throughout the study

4.3) Data Integrity and Quality

Understanding the difference between data integrity and data quality is critical for CDM professionals, as it is at the core of the evolution of CDM into Clinical Data Science (CDS).

The introduction to MHRA's guidance on GxP Data Integrity[6], states that data integrity is not data quality since "*the controls required for integrity do not necessarily guarantee the quality of the data generated*" [6].

First, "*Data integrity is the degree to which data are complete, consistent, accurate, trustworthy, reliable and that these characteristics of the data are maintained throughout the data life cycle. The data should be collected and maintained in a secure manner, so that they are attributable, legible, contemporaneously recorded, original (or a true copy) and accurate*."[6]. This MHRA definition is consistent with the ALCOA (**A**ttributable, **L**egible, **C**ontemporaneous, **O**riginal and **A**ccurate) principles.

Note: The term "certified copy" in ICH E6 (R3)[1] aligns with the MHRA's use of "true copy," since both are defined as an accurate, verified reproduction of the original record.

Data quality is "*the assurance that data produced is exactly what was intended to be produced and fit for its intended purpose. This incorporates ALCOA*." [6]

Data quality is a broader and more comprehensive goal—it is "fit for purpose." In the context of clinical studies, fit for purpose quality means that study data should be of sufficient quality to achieve the study's objectives, instill confidence in the results, and support sound decision-making, all while adequately protecting the rights, safety, and well-being of participants.

At its core, "fit for purpose" data quality recognizes that no study is conducted perfectly. Striving for perfection may not be realistic or necessary; what truly matters is avoiding errors

that could meaningfully affect participant protection or compromise the reliability of study results. Achieving fit for purpose quality therefore requires a pragmatic, risk-proportionate approach, ensuring that efforts are focused on study attributes that are critical to the protection of participants and the reliability of study results

It is helpful to consider that the initial quality of clinical data during study execution is dependent on two distinct steps:

- The **first** step is the actual generation of the data, which depends on all of the people, processes, materials and/or equipment involved in conducting the relevant participant assessments or measurements.

- The **second** stage involves the reliable management of the source data after its generation, including its proper recording (using ALCOA principles), transmission, storage, review and reporting.

Data integrity – which has traditionally been the primary focus of data management activities - covers this second stage but generally not the first. Monitoring the reliability of the first stage was traditionally considered outside of the scope of clinical data management and instead considered the primary responsibility of site monitoring.

As stated in SCDM's 2022 'The evolution of Clinical Data Management into Clinical Data Science', "*Clinical data management is primarily focused on data flows and data integrity (i.e., data is managed the right way). Clinical Data Science broadens this focus by adding the data risk, data meaning and value dimensions for achieving data quality (i.e., data is credible and reliable)*" [9].

In conclusion, we could conceptually differentiate Data Quality vs. Data Integrity as follows:

Data Integrity means that the Data is **managed the right way**

Data Quality means that the Data is **reliable and fit for purpose for decision making**

4.4) Quality by Design (QbD)

ICH E8 (R1)2, states that "*QbD in clinical research sets out to ensure that the quality of a study is driven proactively by designing quality into the **study protocol and processes***"[2]. This involves the use of a prospective, cross-functional (e.g., clinical operations, quality, data management) and multidisciplinary (i.e., across different areas of expertise such sponsor, CROs, technology providers, clinical investigators, patients, patient advocates, and health care providers) approach to promote the quality of protocol and process design in a manner proportionate to the risks involved, and clear communication of how this will be achieved.

4.5) Critical to Quality Factors (incl. Critical Data and Processes)

The ICH E8 guidance states that "*The quality by design approach to clinical research involves focusing on CtQ factors*" [2] and defines them as "*attributes of a study whose integrity is fundamental to the protection of study participants, the reliability and interpretability of the study results, and the decisions made based on the study results*"[2].

In addition, *CtQ factors* should be considered holistically, so that dependencies among them can be identified and managed appropriately. Understanding these interdependencies is essential for designing robust, efficient quality oversight strategies.

Refer to Figure 1 for example of CtQ Factors representing Critical Data and Processes to consider.

4.6) Risk Management

Risk Management is a systematic approach to managing risks. It includes the identification, assessment, monitoring, mitigations, controls, communications, and evaluation of risks throughout the lifecycle of a clinical study.

5) Best Practices

With these guidelines in mind, we recommend the following best practices for applying a risk-based approach within CDM.

5.1) overall rb-CDM Framework considerations

It is essential to recognize that quality in clinical studies is multi-dimensional, bringing together **QbD** and **RBQM** which complement each other to ensure fit for purpose study quality. Within this broader, cross-functional and multidisciplinary quality framework, rb-CDM serves as a key component contributing to both QbD and RBQM.

Quality should be embedded from the study design stage through ***critical thinking***. This requires anticipating issues *before they occur* by evaluating trial activities from multiple perspectives — scientific, operational, and regulatory.

Critical thinking enables proactive, risk-based quality management by:

- **Identifying vulnerabilities** — determining which data or processes are most susceptible to errors or deviations and understanding the potential consequences.
- **Anticipating proactively** — evaluating study activities holistically to foresee and address risks early in the trial lifecycle.
- **Prioritizing risks** — assessing which risks could most significantly impact trial outcomes or participant safety.
- **Targeting mitigation** — deciding where enhanced procedures, monitoring, or validation are needed to prevent or control high-priority risks.

- **Adapting in real time** — continuously monitoring trial data, systems, and processes, and being flexible when new risks emerge.

To support this mindset, flexible and targeted quality oversight approaches should be implemented through predefined, risk-based strategies and continuously refined throughout the study. This ensures that quality is not an afterthought, but a fundamental design principle driving the success and integrity of clinical trials.

A critical concept underpinning this quality framework is "**fit for purpose clinical study quality**". Fit for purpose clinical study quality means that the study should be of sufficient quality to meet the study's objectives, provide confidence in the study's results, and support sound decision-making, all while adequately protecting the participants involved. At its core, "fit for purpose" clinical study quality acknowledges that studies are rarely conducted perfectly. Striving for data perfection may not be realistic and necessary; what matters is avoiding errors that could meaningfully impact participants' protection or the reliability of study results. Achieving fit for purpose quality therefore requires a pragmatic and risk-proportionate approach to design and conduct, ensuring that efforts are focused on study attributes that are critical to the protection of participants and the reliability of study results.

In essence, QbD establishes the foundation for clinical study quality by proactively identifying and embedding quality into the study from the outset, during the study design and planning stage, using sound scientific understanding and proactive risk management. This approach enables sponsors to 'de-risk' the protocol upfront by identifying Critical to Quality (CtQ) factors and potential risks to those factors, ensuring that the study design is optimized to prevent foreseeable issues.

RBQM builds on this foundation by applying risk assessments and mitigation strategies throughout study conduct. RBQM ensures that risks are continuously evaluated and managed across the entire study lifecycle. QbD and RBQM are closely interconnected components of a unified approach to achieve fit for purpose clinical study quality. QbD lays the foundation by embedding quality into the study from the outset, while RBQM ensures that quality is maintained, and risk controls are appropriate and adapted dynamically as the study progresses.

This quality framework operates at both an organizational and a study level. At an **organization level**, "*the sponsor should implement an appropriate system to manage quality throughout all stages of the trial process*" [1]. At **a clinical study level**, it includes *"the design and implementation of efficient clinical trial protocols, including tools and procedures for trial conduct (including for data collection and management), in order to ensure the protection of participants' rights, safety and well-being and the reliability of trial results*" [1]. As illustrated in the figure below, considering these four dimensions is essential to establish a robust rb-CDM framework that aligns with risk-based quality management practices.

Figure 1 – rb-CDM Framework

This risk-based quality framework moves beyond tools and checklists to foster prospective planning, critical thinking, and flexible, proactive, study-specific strategies in study design and conduct. It explicitly discourages one-size-fits-all approaches, advocating instead for tailored, risk-proportionate strategies that support quality throughout the study[2].

As sponsors increasingly adopt a quality framework with **QbD** and **RBQM**, early and ongoing collaboration across all relevant functions within the organization is essential. The QbD process should be led by a cross-functional and multidisciplinary team that might include as an example, representatives from clinical operations, data management, biostatistics, medical, regulatory affairs, pharmacovigilance, digital data technology (or equivalent), drug supplies, and quality assurance. Each function and each discipline bring a unique perspective to identifying CtQ factors and potential risks. These teams can collaboratively define quality objectives and risk mitigation strategies, as well as QTLs and KRIs. Additionally, engaging external stakeholders (e.g., patients, patient's advocacy groups, healthcare providers and clinical investigators) can play a vital role in ensuring that clinical studies are scientifically valid, operationally feasible, ethically sound, and patient-centered.

In summary, the overall quality framework aims to apply to all drug development stakeholders involved and ensures participants protection and reliability of study results throughout the clinical study lifecycle (i.e., starting from protocol design and extending through study conduct, evaluation, and reporting phases). Important risks that cannot be eliminated through study design may be mitigated and managed through the study's operational plans, processes, and procedures. These plans, processes, and procedures should be implemented in a way that is proportionate to the risks to study participants and the importance of the data collected.

5.2) Organizational considerations

As previously discussed, Risk Management (incl. QbD and RBQM) and its rb-CDM component should ideally be recognized as a multidisciplinary and cross-functional responsibility supported by a leadership driven culture "*that values and rewards critical thinking and open, proactive dialogue about what is critical to quality for a particular study or*

development programme"[2]. It is therefore recommended to follow a systematic, cross-functional approach to define and embed the right culture, policies, processes and training in order to adopt new ways of working, build new skills, prevent siloed RBQM delivery and build trust in new tools and techniques.

Below are some of the elements that could be considered when creating an RBQM Framework, with a particular emphasis on rb-CDM:

1. **Aligning on core principles** – Leadership and stakeholders should align on definitions of core principles such as 'risk proportionate ways of working', 'errors that matter', and the definition of 'clean data'. Aligning on these principles ensures organizations are thinking about this in the same way, growing their capabilities in a complementary way, and then supporting implementation.

2. **Building a preventative rather than corrective mindset** – instilling a 'get it right first time' data quality mindset and a focus on improving critical processes at the site, at all service providers (incl. central laboratories, central imaging, eCOA Providers, CROs, etc.) and within the study team. This could include a systematic and regular review of EDC forms and ePRO instruments with sites and study participants to improve of data collection and data flow, or it could include a review of recent studies to understand the root causes of historical protocol deviations that could be avoided through protocol design or more tailored protocol training at the site. Moving QBD and development of the risk assessment upstream into protocol development can also foster a more preventative mindset.

3. **Skillsets, Training, and Change Management** – new skills may be required across all the functional groups to reinforce the RBQM Framework. This should be a combination of analytical skills such as critical thinking and root cause analysis techniques, and technical knowledge such regulatory guidance's (i.e., minimum requirements) and the development of comprehensive corrective and preventative action plans. Formal training should be supplemented by a comprehensive mentoring program so that key concepts and rb-CDM principles can be applied in a consistent yet flexible way, and reinforced through a variety of communication and shared-learning techniques including lessons learned and the sharing of successes. Change Management should pay particular attention to emphasizing the risks of continuing with a one-size-fits all approach, and that "going beyond sole reliance on tools and checklists, is encouraged"[2]

4. **Processes, SOPs and Roles** – processes should be re-assessed to ensure teams are applying QbD from the earliest stage of protocol development onwards and that appropriate focus is placed on RBQM and rb-CDM activities during the study. Process flows, SOPs, job descriptions and training curriculums should all align to the new ways of working and explicitly state expectations for RBQM and rb-CDM, as guided by the core principles above, to ensure RBQM does not become a tick box exercise adding unnecessary burden to study teams.

- Establish a standard library, for example, of CtQ factors, KRIs, QTLs and risk assessments.

  Note: Consider leveraging established industry references such as:

  - The CtQ categories and factors from the Clinical Trial Transformation Initiative (CTTI)[10].
  - The TransCelerate Risk Assessment Categorization Tool (RACT) [11] and risk indicator library[12]

- Consider creating compound specific library that can be used across similar studies with buy in from all stakeholders.

5.3) Study Level considerations

The figure below highlights the core elements to implement in a study level rb-CDM life cycle framework i.e., designing quality into clinical studies and risk-based quality management.

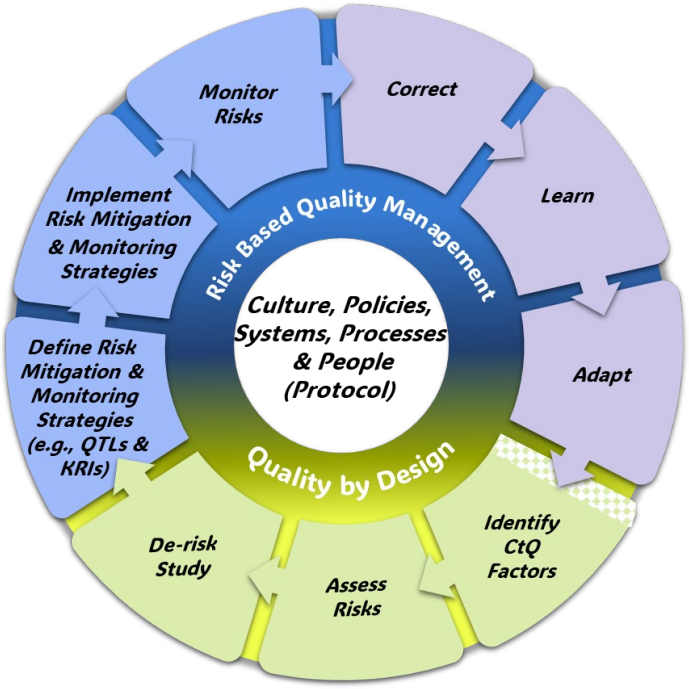


Figure 2 – rb-CDM study life Cycle

First and foremost, even though this GCDMP chapter focuses on rb-CDM, it is essential that all risk management related activities (i.e., risk identification, risk evaluation, risk control, risk communication, risk review and risk reporting) incorporate input from the cross-functional and multidisciplinary team. This team may represent a variety of critical disciplines and functions. Expertise required may cover but would not be limited to clinical operations, data management, biostatistics, medical, regulatory affairs, pharmacovigilance, digital data technology (or equivalent), drug supplies, and quality assurance.

This collaborative approach should be applied regardless of the operational model—whether in-house or outsourced—ensuring comprehensive expertise and alignment throughout the rb-CDM process.

It is essential to consider all external parties (e.g., Clinical research Organizations (CROs), technology and service providers) as **risk identification** should "*be considered across … service provider activities)*"[1] and **risk mitigation** *"activities may be incorporated, for example, in … agreements between parties defining roles and responsibilities*"[1].

When engaging with external parties in risk management activities, the following elements should be considered:

1. Establishing clear roles & responsibilities (e.g., documented using RACI matrix)
2. Aligning Standard Operating Procedures (SOPs) and work instructions
3. Leveraging technology to reduce burden; ensure prompt oversight and limit risk of transcription error. Service providers may as an example supply tools for centralized monitoring, data visualizations, system to system integration.
4. Ensuring the integrity of the data chain of custody
5. Defining a governance and communication framework to track service provider performance based on KPIs and key metrics
6. Training and continuous improvement on rb-CDM principles and tools
7. At study level, performing a jointed risk assessment and share lessons Learned

The rb-CDM Life Cycle focuses on core data-related components within the QbD and RBQM framework. Aligned with the ICH E6 (R3)[1], it begins with QbD by identifying CtQ factors and associated risks, followed by the application of the **six risk management steps described** in its section 3.10.1, "Risk Management".

1. Risk identification
2. Risk evaluation
3. Risk control
4. Risk communication
5. Risk review
6. Risk reporting

This approach ensures that data quality is proactively designed and continuously monitored throughout the clinical study lifecycle, supporting regulatory compliance and improving participant protection and data reliability.

Below are considerations, diving into the six risk management steps described in ICH E6 (R3)[1]:

1 - Risk Identification: "Identify risks that may have a meaningful impact on critical to quality factors **prior to study initiation and throughout study conduct.** "*Risks should be considered across the critical processes and systems",* that matter most to the overall reliability of trial results and participant safety, *"including computerised systems used in the*

clinical trial (e.g., trial design, participant selection, informed consent process, randomisation, blinding, investigational product administration, data handling and service provider activities)." [1]

- Identifying **Critical to Quality Factors** (i.e., critical data, processes, and systems) considering the study design and objectives
- Identifying potential risks to the **integrity and quality of the critical data**
- Identifying risks to the data that could jeopardize the **evaluation and management of participant's rights, safety and well being**
- Identifying risks to the data that could jeopardize the **reliability of the study results**

2 - Risk Evaluation: Assess identified risks, and existing controls in place to mitigate the risk considering its likelihood of occurrence, its detectability and its impact.

- Evaluate risks to critical data, processes, and systems that are the most vulnerable to errors or deviations to understand the potential consequences of those risks.

- Evaluate which risks could most significantly impact the study outcomes and participant's protection.

- Document the risk evaluation in the risk assessment plan and proactive mitigations in relevant functional plans including role-based review and monitoring strategies.

Note: The risk evaluation should consider:

a) The likelihood of harm/hazard occurring
b) The extent to which such harm/hazard would be detectable
c) The impact of such harm/hazard on study participant protections and the reliability of study results.

3 - Risk Control: Establish robust risk proportionate approaches to monitoring, validation, and management of risks to the CtQ factors (i.e., critical data, processes, and systems) while remaining flexible and adaptive to emerging risks. Those risk proportionate controls should be fit for purpose, reflecting the importance of the data, in ensuring participant's protection and the reliability of study results.

- The most efficient risk control is to prevent it, if possible, by proactively **de-risking the study,** with QbD in mind**,** during protocol development.

  This entails incorporating feedback from study personnel, health care providers, participants, and participant advocates, in the study design to reduce unnecessary protocol complexity, for example by eliminating the collection of non-essential data, simplifying and/or reducing visit schedules and study procedures, and leveraging technology for data collection.

- Build pro-active measures to mitigate remaining risks that could have not been fully de-risked (i.e., risk that could not be fully prevented). This includes the ability to

monitor risks and prevent and/or limit their occurrences such as ensuring appropriate validation , access controls, audit trails and trainings for critical systems.

- It also means, building risk-based mitigation strategies into study related plans. While study plans span across multiple functions, Clinical Data Managers/Scientists may specifically contribute to the Data Management Plan (DMP), the Centralized Monitoring Plan (CMP) and/or the Integrated Quality Risk Management Plan (IQRMP) as appropriate in their organization. This may include:

  - Incorporating automated validations into the data collection systems such as edit checks in Electronic Data Capture (EDC) and patient alerts for missing data in electronic Clinical Outcome Assessment (eCOA)

  - Defining KRIs at site and country level as well as "*pre-specified acceptable ranges (e.g., QTL at the trial level)*"[1]

  - Set-up systems to perform signal detection and analysis

- Implement cross-functional mitigation strategies to manage risks. This includes leveraging clinical data and metadata to identify emerging risks during study conduct, using KRIs, QTLs, and other data-driven approaches, such as data analytics and automated data validations to flag inconsistencies and missing data patterns.

4 - Risk Communication:

- The anticipated CtQ risks identified, the outcome of their assessment as well as mitigating strategies resulting from the prior three steps, should be communicated to and agreed with all impacted stakeholders, ideally prior to initiating participant enrollment.

- When monitoring risks, any identified occurrences should be documented and communicated to the appropriate stakeholders (e.g., site staff, site monitor, medical monitor). Relevant context should be provided to guide corrective and preventive actions, such as whether the risks are emerging or anticipated, isolated or widespread, any known or potential root causes, and areas that may require further investigation.

5 - Risk review:

- It should be also noted that risk assessment and management is a continuous process. While risk identification and mitigation are initiated at the time of protocol development, the steps above should also be repeated at regular intervals, ideally pre-defined within the process and any time a protocol is amended, or systemic issues are identified.

- The study team should learn by "*periodically reviewing risk control measures to ascertain whether the implemented quality management activities remain effective*

and relevant, taking into account emerging knowledge and experience. Additional risk control measures may be implemented as needed"[1].

- Adapt to prevent further re-occurrence i.e.,

  - Updating the study plans to include measures preventing systematic emerging risks to re-occur

  - Adapt systems and processes accordingly

6 – Risk Reporting

Important quality issues impacting participant protection and/or the reliability of study results should be summarized and reported *"(including instances in which pre-defined acceptable ranges are exceeded)"*[1] with the corresponding remedial actions taken. Those should be documented in the clinical study report[1].

5.4) rb-CDM Process Implementation Considerations

The adoption of rb-CDM approaches has a deep impact on our traditional CDM ways of working, as shown in the process flows in this section. Through this section, examples of process flows have been added where risk-based process steps (in green) have been added to the traditional CDM steps (in blue) to illustrate the end-to-end nature of risk-based approaches. In addition, each rb-CDM activity has been positioned in its overall life cycle to illustrate the QbD, risk management nature of rb-CDM.

A. Study Design and Study Planning Considerations

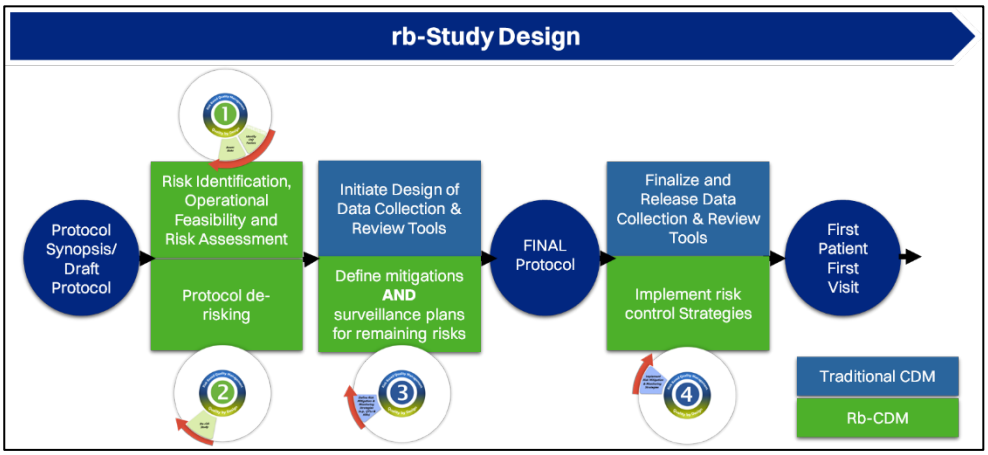


Figure 3: Example of rb-CDM Set-Up Process

As CDM experts, the following activities should be performed during the **risk-based study design phase** to embed QbD principles, ensure data quality, and manage risks effectively.

The following steps have also been summarized as a checklist in Appendix B.

A.1 - Risk Identification, Operational Feasibility and Risk Assessment

Risk management is a core component of QbD and RBQM, encompassing the proactive identification, assessment, and control of risks throughout the clinical study lifecycle. It begins with risk prevention, by identifying threats prior to the first participant being enrolled into the study, which have the potential of leading to errors that could negatively impact participant protection, the credibility and reliability of the study results. As such, a sound scientific protocol, operationally feasible and without unnecessary burden to sites and participants is the foundation of study execution.

But first and foremost, it is critical to engage the appropriate cross-functional, multi-disciplinary, internal and external experts to manage all risks through their entire life cycle.

1 - Engage Stakeholders & Align on Protocol Design

- Actively **identify and engage with internal and external, multidisciplinary, cross-functional stakeholders** (e.g., Clinical, Biostatistics, Safety) during protocol development to ensure alignment on protocol design.

- Evaluate **data and data management risks** related to the entire data flow and processing of **primary/secondary endpoints and safety data**.

- Ensure the **protocol is operationally feasible** and especially that the **data flow does not introduce risks to data** (e.g., leading to data capture, interpretation, and/or transformation errors).

  Note: Ensure that protocol sections intended to serve as the basis for data-driven activities are **clear, complete, and unambiguous**. For example, **the lists of inclusion and exclusion criteria** and **prohibited medications** directly support automated detection **of protocol deviations**. The more precisely these sections are defined, the more robust and reliable the automation will be, in identifying such deviations.

2 - Identify & Document Critical to Quality (CtQ) Factors

- Identify and document **Critical to Quality (CtQ) factors** prior to protocol finalization (i.e. **critical data, systems and processes**, including data review strategies).

Note: The CTTI introduced the CtQ factors in 2015 and organized them around the six major categories below. Those can be used as a guide to define the study specific CtQ Factors CtQ[10].

CtQ Categories	CtQ factors
Protocol Design	Eligibility Criteria Randomization Masking Types of Controls Data Quantity Endpoints Procedures Supporting Study Endpoints and Data Integrity Investigational Product (IP) Handling and Administration
Feasibility	Study and Site Feasibility Accrual (i.e., Enrollment Strategy)
Patient Safety	Informed Consent Withdrawal Criteria and Trial Participant Retention Signal Detection Safety Reporting Data Monitoring Committee (DMC) / Stopping Rules (if applicable)
Study Conduct	Training Data Recording and Reporting Data Monitoring and Management Statistical Analysis
Study Reporting	Dissemination of Study Results
Third-party Engagement	Delegation of Sponsor Responsibilities and Collaborations

Figure 4 - CTTI Critical to Quality categories and factors[7]

3 - Conduct Study Risk Assessment

While many risks would be evaluated and accounted for by the multidisciplinary and cross-functional study team, some risks related to areas such as the 5Vs of the clinical data[13] (i.e., Volume, Variety, Velocity, Veracity, and Value), the data flow's complexity, the extent of service providers involved, and planned technologies used through the data life cycle would be the primary focus of CDM.

- Perform a study **risk assessment** of the identified CtQs. There are many risk areas associated with the CtQ factors, including but are not limited to the:

  A. Complexity of protocol designs such as umbrella, basket, platform, master and adaptive

  B. Vulnerability of the participant population (e.g., elderly, pediatric)

  C. Complexity of enrollment procedures (e.g., consent, eligibility, stratification and randomization)

  D. Deviations from standard of care

  E. Characteristics of the participating countries (e.g., standard of care, customs, dialects)

  F. Planned rate and distribution of enrollment

  G. Number, profile and experience of the study sites and countries

H. Nature of the protocol-required procedures, with specific emphasis on the burden they may place on participants and sites (e.g., hourly blood draws, long clinic visits)

I. Organization of the study (e.g., site-centric vs. decentralized) with telemedicine and home nursing

J. Planned technologies used to collect data, including when participants bring their own device

K. Complexity of the data flow, including variety of the data sources

L. Oversight of the capture and modification of the eSource data owned by the sites

M. Number and experience of the data and operational Service Providers

N. Any other study execution activities which may lead to data errors that could negatively impact the credibility and reliability of the study results (e.g., central readers, decentralized study procedures)

A.2 - Protocol de-risking

- Based on the risk assessment, CDM should collaborate with the cross-functional and multidisciplinary study team to assess, whether or not, the protocol design introduces unnecessary risks due to its complexities and recommend **simplification opportunities** to reduce those risks (i.e., "De-risk" the protocol).

A.3 - Define mitigations and surveillance plans for remaining risks

1 - Design Data Review & Validation Strategy

- Develop a **cross-functional, multidisciplinary and CDM-specific data review and validation strategy** proportionate to risks.
    - Define approaches for managing **critical vs. non-critical data**.
    - Identify data and associated strategies that will require **site monitoring** including **Source Data Verification (SDV)** and **Source Data Review (SDR)**.

      Note: While this GCDMP chapter focuses rb-CDM, the parallels between SDV and data review are important to highlight. Increasingly, CDM organizations are configuring EDC systems to dynamically adjust SDV requirements based on strategies outlined in the study monitoring plan. As a result, CDM SMEs should have a clear understanding of the SDV process and its implications for overall data quality.

      Important considerations:

      Some publications, such as the 2014 TransCelerate publication on "*Evaluating Source Data Verification as a Quality Control Measure in Clinical Trials*" [14] and the 2021 SCDM publication on "*Risk-based Quality Management in CDM*" [15] have highlighted that Queries and SDV seem to have a low impact on study data corrections and study results, when evaluated as an overall study measure (e.g., as study level QTL).

Those publications showed that at study level, the industry median of eCRF data correction due to SDV was only 1.1%[14] and those from auto-queries varied from 0.9%[15] to 1.4%[14].

This does **not** suggest that SDV and query management lack value or should be eliminated from our traditional processes. With 100% SDV, all mistakes can theoretically be corrected. However, when assessing data corrections following SDV, at eCRF forms, sites, countries and Therapeutic Areas (TAs) level, it could highlight variability in the rate of data corrections across those dimensions. As an example, the median of eCRF data change rate due to SDV in Oncology was 2.7%[14] and only 0.5% for Pharmacokinetic studies[14].

So, while a study may show an overall low data change rate resulting from SDV, some sites may exhibit significantly higher rates—indicating potential issues with source data control. It means, that correcting all transcription errors through SDV, is not addressing the root cause, but only correcting errors retrospectively.

An efficient risk-adapted SDV approach should prioritize evaluating whether data quality meets predefined targets, rather than simply correcting individual transcription errors. It relies on a meaningful, data-driven sampling strategy to assess quality at both the study and site levels. When deficiencies are identified, proportionate corrective actions should follow to safeguard overall data integrity. Risk-adapted SDV is not designed as a mechanism for fixing isolated transcription errors; rather, it serves to detect and address underlying, systematic issues that require resolution.

Therefore, a risk-based SDV and query strategies should ensure focus on activities, where they are most needed, proportionally to risks, without compromising data quality or participant protection.

As such, a sound approach should therefore apply **proportionate SDV** based on objective (i.e., data and fact driven) information such as (but not limited to):

- Pre-defined study and site-specific sampling strategies considering, as examples:
  - historical performance of the site,
  - site experience in clinical research,
  - complexity of the data collected,
  - whether study procedures comply with country specific standard of care
- During study, study and site level SDV may be adjusted considering, as examples:
  - Staff turnover
  - SDV findings from initial sampling
  - Protocol amendment

Note: Site monitoring frequency should not be dictated by SDV efforts. A risk-based SDV approach does not necessarily mean fewer site monitoring visits, either on-sire or remote, but rather a shift in focus to critical risk areas (e.g., SDR, protocol compliance, adherence to procedures). Frequency of monitoring visits may align with the minimum frequency necessary for broader oversight, with triggered monitoring visits, based on findings and/or workload (e.g. SDR, drug reconciliation, etc.), beyond SDV alone.

- Similarly, **data reviews** need a well defines risk-proportionate strategy ensuring participant protection and the reliability of study results. It should rely on an objective and holistic measures, not just on Queries.

- As an example, while data review plans **should primarily focus on edit checks and the validation of critical data points**, it **is equally important to have a strategy in place to monitor the quality of non-critical data**. This can be achieved through methods such as targeted sampling, trend analyses, and statistical techniques to detect atypical patterns or outliers.

- Although considered non-critical, recurring or emerging data trends at the form, site, or even country level may indicate underlying issues that could compromise the reliability or credibility of study outcomes. Such signals may warrant further investigation or corrective actions to safeguard the overall integrity of the study.

- Consider risks to data and data related **activities performed by external service and technology providers.**

- Evaluate the risk of **eliminating non-critical data validation** if other safety nets exist (e.g., aggregated data trending or statistical monitoring of non-critical data.

2 - Define Quality Control & Risk Mitigation Plan

- Establish a **quality control and risk mitigation plan**, including the definition of targeted **data acceptability targets to demonstrate reliability of study results (**e.g., rate of missing data for primary end point)
  - "Pre-specified acceptable ranges (e.g., **Quality Tolerance Limits (QTLs)** at study level)"[1] to monitor CtQ factors.
  - **Key Risk Indicators (KRIs)** for ongoing risk management.
  - Risk based review of metadata including **Audit Trail** is expected according to ICH E6 (R3) which states the "*Procedures for review of trial-specific data, audit trails and other relevant metadata should be in place*"[1]. identify issue that are not otherwise easily detectable as "*beyond the reconstruction of the data events, audit trails can also provide critical insights on how the data is being collected*"[16]. "*Potential objectives of risk-based audit trail may review includes*"[16].
    1. investigation of data integrity issue

2. identification of suspicious justification and/or fraudulent data
3. identification of alternative source data implemented by sites
4. unauthorized accesses and data events
5. oversight on changes to critical data
6. process improvements based on trends
7. performance of users

Example Use Cases and Risk Scenarios includes:

1. Unauthorized Access or Lack of Access Control Management
2. Limited of clinical investigator system access potentially indicating lack of clinical investigator oversight
3. High proportion of Data Changes potentially indicating high proportion of transcription errors
4. High proportion of changes specific to inclusion/exclusion (I/E) criteria data, primary efficacy, key secondary having the potential affecting the reliability of study results
5. Data not collected per protocol timing or collected at "unanticipated/suspicious" time

For a more comprehensive list of scenarios, please refer to appendix 3 of the SCDM and eClinical Forum Position paper on Audit Trail Review[16].

3 - Specify Reporting & Analytics Requirements

- Define **specifications for reports, analytics, monitoring metrics, and risk indicators and dashboards** to monitor Critical Data and Processes.
- Define how and to which extent non-critical data and process will be monitored

A4 – Implement risk control strategies

- Ensure mitigations all above are developed and implemented ideally prior to the first participants entering the study.

A5 – Additional considerations

1 - Define milestones-based deliverables and compliance monitoring

- Specify the extent of data review needed for specific study milestones (i.e., Interim Data Deliverables) such as **Interim Analyses (IAs), Data Safety Monitoring Board (DSMB) reports, and Development Safety Update Reports (DSUR)**.
- Define and implement **ongoing data compliance reports** to monitor data quality and completeness.

2 – Consideration when outsourcing CDM activities

- Conduct Knowledge Transfer (KT) & secure the service provider collaboration (if applicable)
- Ensure KT to newly onboarded CDM Study Experts (included in the context of outsourced studies). This includes but not limited to:
    - the QbD principles applied to the study design and conduct
    - the list of prioritized data to review and the purpose of the review
    - the expected risks to watch which have identified at study start or emerged during study conduct
- Require the **service provider SMEs to perform an independent risk assessment** based on the KT and encourage the service provider SMEs to raise questions or share additional insights.

👉 **Key Takeaway:** These start-up activities position CDM experts as **proactive risk managers and data quality stewards** from the earliest study stages, aligning with risk-based and quality-focused study execution.

B. Risk-based Study Execution Considerations

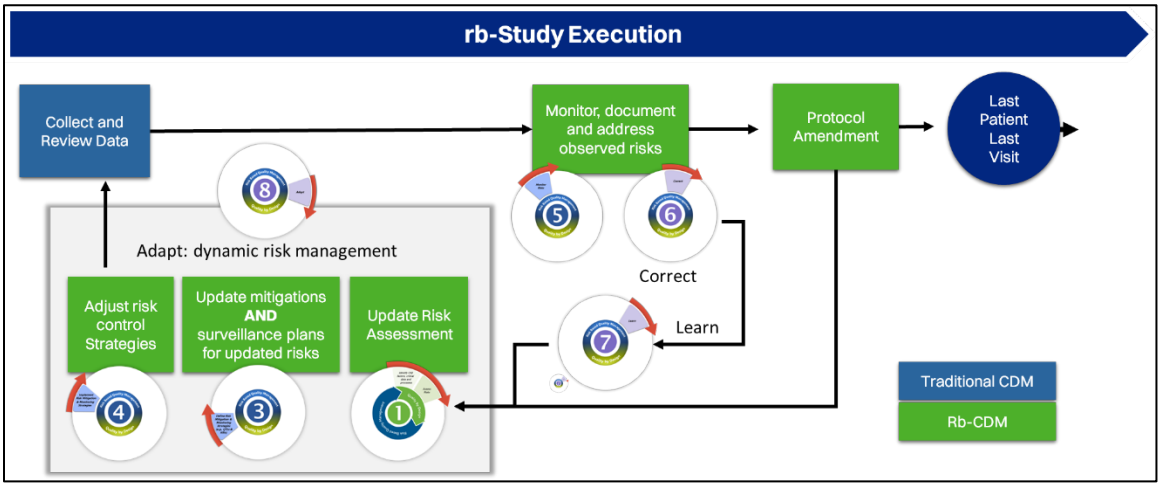


Figure 5: Example of rb-CDM Study Execution Process

During the **study execution phase**, CDM experts should focus on the following key activities to ensure data quality and manage risks effectively. The following steps have also been summarized as a checklist in Appendix C.

B1 - Monitor, document and address observed risks

1 - Conduct tailored data review proportional to risk

- Perform data reviews commensurate with the level of risk identified during the study start-up according to the corresponding strategy pre-defined upfront. As an example, non-critical data may be only reviewed through trending analysis or other means.

- Prioritize the review of **critical data**, ensuring it is reviewed **promptly and with heightened scrutiny** as soon as possible upon data collection.
- **Monitor KRIs and QTLs**. "*These pre-specified ranges reflect limits that when exceeded have the potential to impact participant safety or the reliability of trial results. Where deviation beyond these ranges is detected, an evaluation should be performed to determine if there is a possible systemic issue and if action is needed*"[1].
- **Identify systematic or process driven data issues** including those stemming from study design and study conduct factors such as rate of enrollment, technologies used, etc. The key will be to efficiently and reliably monitor such risks through the holistic review of **all** clinical and operational data (i.e., finding data patterns and anomalies across studies, countries, sites, participants and eCRF forms).
- **Monitor trends in non-critical data as identified through the risk assessment (i.e., data not associated with CtQ, data related to tertiary efficacy)**
    - Conduct **periodic trend reviews of non-critical data** to detect emerging risks or issues.
    - Documents with the appropriate justification issues that do not present risks to participant's right, safety, well-being nor reliability of study results.
    - Increase monitoring level of **non-critical data similar to critical data** when trend analysis or risk indicators suggest increased risk requiring heightened focus.

2 - Review critical data and associated metadata

- Ensure the review of **critical data includes associated metadata**—for example, reviewing **audit trail** to confirm appropriate and justified data modifications.

3 - Monitor for the possible emergence of any new risks

This includes but is but not limited to:

- Disasters and **p**ublic **h**ealth **e**mergencies (PHEs) such as "*hurricanes, earthquakes, military conflicts, infectious disease outbreaks, or bioterrorist attacks*" [17].
- Database availability delays which could delay study start
- Study timelines and data flow delays which could negatively impact the availability of study data and/or results for safety reviews, the potential submission and product approval
- Protocol amendments
- Protocol deviations
- Investigative site attrition

4 - Monitor critical processes during study execution

- Perform ongoing oversight of **critical processes**, including processes tied to **endpoint data collection, protocol amendments, and Independent Review Committee (IRC) activities**.

5 - Ensure synergetic oversight across stakeholders

- Ensure alignment of **sponsor and Service Provider oversight strategies and reporting** to support **timely assessment of data quality and study progress**.
- **Conduct data integrity assessments**
    - Schedule and conduct **regular data integrity assessments of CtQ factors, critical risks, and critical processes**.
    - Adjust the frequency of these assessments based on the outcome of the monitoring of **risk assessment, QTL, and KRIs**.

6 – Signal Review

- Once a signal is determined to have moved from a risk to an issue, the underlying process or data issue needs to be addressed. Lastly, to close the loop, teams should follow up to make sure the issue has been fully resolved.

  Below are some examples of signals that can be found with the potential responses made by teams.

  1. At a site in Puerto Rico, all enrolled participants are Hispanic. While this may appear statistically atypical when compared to other sites outside South America, it is not unexpected given the site's geographic and demographic context. No immediate action is required; however, the study team should continue monitoring enrollment at the site to assess whether this pattern persists through the end of recruitment
  2. Many participants at a site have the same respiratory rate: Rather than questioning if the value was correctly entered into the source document, teams should think about how this lack of variability occurred. It is possible, but highly unlikely, that many participants at a site have the same respiratory rate. It is more likely that something was wrong with how the measurements were taken and/or recorded. Thus, the process for collecting and recording the rate should be reviewed. The importance site compliance, accurate data collection and recording should be reiterated to the site personnel. Since the existing data is not going to change, any issue with the process in taking measurements should be addressed, fixed, and monitored moving forward.
  3. Participants on an oncology study have either no or a very low number of adverse events (AEs): This is statistically unlikely. The study team should ensure the site personnel understand how to collect AEs, and increase the SDR to check for unreported AEs. The site personnel may need retraining, and the study team should follow up to make sure the situation is resolved. Current data might not change, but the process should be fixed and then tracked for ongoing correctness.

  To address the examples above, the CDM SMEs and the study team should dig deep into the data to understand the root cause of the issues. They need to perform detailed root cause analysis (RCA) and data review findings to resolve them. Occasionally, the team will need to go through multiple iterations of RCA and follow-up to fully understand the root cause. This requires a focus on details and strong

communication skills as most findings will not result in queries, but rather in addressing systematic process issues and site behaviors.

B2 – Adapt by maintaining a dynamic risk management

- Proactively solicit feedback from **newly onboarded team members** to benefit from fresh perspectives or therapeutic area insights.
- **Regularly update the risk assessment, risk monitoring and mitigation strategies** throughout study execution, based on learnings and issues identified.
- Assess the effectiveness of the implemented risk mitigations and adapt risk assessment as well as risk mitigation strategies.
- Ensure the focus remains on the **most relevant risks as the study progresses**, allowing for targeted risk mitigation.

B3 – Protocol Amendments or major study update (e.g., urgent safety measure)

1 - Continuous Review & Protocol Amendments

- Ensure all above activities are reviewed and updated in case of **protocol amendments**.
- Evaluate all protocol or major study update (e.g., within Investigator Brochure) for their impact on the risk assessment and mitigations required.

👉 **Key Takeaway:** These activities empower CDM experts to maintain proactive oversight of data quality, ensuring that critical data and processes are continuously monitored and managed in alignment with study risks**.**

C. Risk-based study close-out Considerations

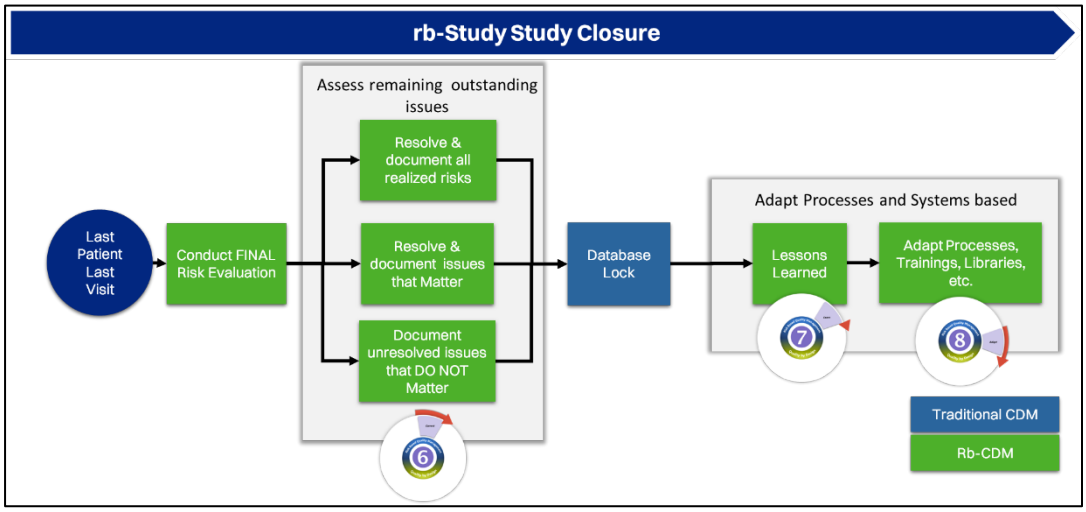


Figure 6: Example of rb-CDM Study Closure

At the **close-out phase** of a clinical study, CDM experts should ensure the following activities are completed to confirm data integrity, regulatory compliance, and risk mitigation. The following steps have also been summarized as a checklist in Appendix D.

C1 - Conduct a final risk evaluation

- Perform a comprehensive **final review of all occurrences of issues related CtQ factors (anticipated or not in the risk assessment)** that have been observed to confirm that all identified issues associated with those risks have been appropriately addressed.
- Ensure any **newly identified risks are mitigated, if necessary, prior to database lock**.
- Conduct a **final data quality assessment focused on CtQ factors, QTLs and KRIs,** thus evaluating the impact of all observed issues on 1) regulatory and protocol compliance, 2) participant protection and 3) the reliability of study results.

C2 - Assess remaining outstanding issues

1. **Review and close outstanding issues**

- Resolve remaining issues impacting participant's rights, safety and well-being, the reliability of study results and regulatory and protocol compliance.
- Formally close **any remaining issues that do not impact participant protection or the reliability of study results** with clear justification and documentation.

2. **Document process completion and compliance**

- Prepare documentation confirming completion of close-out activities and adherence to the study's quality plan.
- Examples of documentation include:
    - **CtQ assessments**
    - **KRI and QTLs assessments**
    - **Corrective Action and Preventive Action (CAPA) outcomes**
    - Other relevant compliance records

C3 - Adapt Processes and Systems based on Lessons learned

- Perform cross-functional and multidisciplinary lessons learned by Assessing the following:
    - the outcome of the final data quality evaluation,
    - the risks realized in the studies,
    - the effectiveness of mitigations,
    - related audits and inspections.

- Evaluates the need to adapt and to update organization or TA level trainings, processes and/or systems as a preventative mitigation for future studies.

CDM SMEs and study teams should leverage the lessons learned during study execution and adapt the processes. They should prevent further reoccurrence of the same issues in the study and in future studies. For systematic issues, the mitigation of a specific risk may involve a need to define CAPAs.

Although there is often a CAPA process owned by the Quality function in most organizations, CDM SMEs can (and should) drive the definition of actions (corrective and/or preventative) based on rb-CDM observations. They, as SMEs in the risk management lifecycle, should also be contributing to the process through the characterization of the risk and suggesting pragmatic and robust remediations and preventive actions.

👉 **Key Takeaway:** These close-out activities ensure a high-quality, compliant database lock and clear documentation of risk management outcomes.

5.5) Practical rb-CDM Study examples for CDM Experts

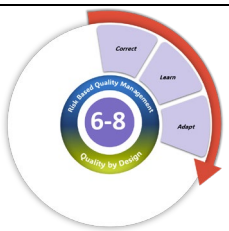
Below are 2 study level implementation examples of the rb-CDM process, highlighting some of the complexities such as those involved in pediatric clinical studies.

Example #1 - Age-Specific Protocols

This scenario highlights some of the complexities involved in pediatric clinical studies, particularly those involving inflammatory bowel disease. Here's a breakdown of the key points to be considered when implementing a risk-based approach.

	**Risk Identification and Risk Assessment** **CtQ Factors** may evolve around key elements such as participant protection, data flow, data integrity and protocol adherence. This example does not intend to provide an exhaustive list of CtQ Factors for this study but highlight a few to follow through their life cycle. In this example we focused on Patient-Reported Outcome (PRO) Completion. The corresponding CtQ Factor may be defined as "*Primary Efficacy Endpoint measurement and **consistency of administration** (e.g., Accuracy and consistency of patient-reported IBS-SSS, diary compliance, handling of Missing Data: Processes to minimize missing PRO entries and ensure proper imputation rules)*" **<u>Protocol Specific Element to evaluate:</u>** **Age-Specific Protocols**: The study design includes specific interventions and assessments at different ages: • At age 8, one PRO is administered. • At age 9, a second PRO is added.

	• At age 12, participants can self-administer the Investigational Medicinal Product (IMP). • At age 13, a daily diary is introduced. **Evaluation of the consistency in PRO Administration:** Despite participants aging during the study, new PROs are not introduced beyond what was initially administered at the first visit. This means that some participants may not have certain PROs even if they reach the age defined in the protocol. **Risk implications for the PRO Collection:** This approach can lead to gaps in data collection, as not all participants will have the same set of PROs. This could affect the comprehensiveness of the data and potentially the study's outcomes.
	**De-risk Study Considerations:** • Include participant-centric approach to minimize participant burden and improve compliance and retention. • Design the protocol to be flexible, adaptive and allow modifications to address participant aging during the study. **Suggestions may include:** • Change protocol design so that a 'baseline' ePRO is done at any point the participant joins the study, not just at age 8. • Add participant burden questionnaire or interview during the study to determine if ePRO requirements need to change (link to drop out KRI, etc.) • Investigate previous protocols to understand prevalence of PDs for this age-related data collection requirement and previous mitigations to add to QbD discussions at protocol design.
	**Define risk mitigation and Control Strategies** • **Risk Management:** The study design should include a risk assessment to understand the impact of these gaps on the study's validity and reliability. • **Control Strategy:** Implementing a control strategy to monitor and address any inconsistencies in data collection could help mitigate potential issues. **Example:** Define age specific KRIs on ePRO Completion Compliance in parallel of having a study wide QTL on ePRO Compliance.

	**Implement risk mitigation and Control Strategies** Focus resources on critical aspects of the studies that could impact data quality • Implement QTL and KRIs • Train site staff specifically on this requirement • Create age-specific data entry guidelines and consider adjusting terminology accordingly. Although the age gap between an 8-year-old and a 13-year-old may seem small, their cognitive and comprehension levels can differ significantly, warranting differentiated guidance. Additionally, the guidelines should take into account both site workflows and participant interaction patterns to ensure usability and relevance. • Include edit checks to verify if previous ePRO occurred for this participant and add a prompt in the ePRO • Add to SDR checks and guidelines
	**Monitor risks** • Monitor if daily ePROs is linked to other compliance issues to understand participant burden implications • Review KRIs and QTL at specifies frequency. Assess how they are trending over time.
	**Correct, Learn & Adapt** • Take and document corrective action (e.g., add ePRO reminders friendly to 8-to-9 years old participants in case we observe a lower compliance rate in that age population) • Learnings from continuous monitoring may lead to adjustments throughout the study that can ensure that the quality of data remains high despite the varying ages and interventions. Note: Adjust the risk assessment, risk controls and mitigations based on learning Implement a Plan-Do-Check-Act cycle to continuously monitor, adapt and improve the study design and data collection process

Example #2 – Endpoint-Specific Protocols

This scenario highlights challenges in a Phase II asthma study, focusing on data quality risks for critical endpoints and acute exacerbations of chronic obstructive pulmonary disease (COPD).

CtQ Identification and Risk Assessment

CtQ Factors may evolve around key elements such as participant protection, data flow, data integrity and protocol adherence. This example does not intend to provide an exhaustive list of CtQ Factors for this study but highlight a few to follow through their life cycle.

In this example we focused on the reporting of acute exacerbation of COPD. The corresponding CtQ Factors may include "***Accuracy and consistency for the reporting of* acute exacerbation of COPD** *(incl., Accurate Severity grading by Investigator – Timeliness and Completeness of symptom reporting by participants)*" AND "***upfront investigator/clinician training of assessing COPD exacerbations per protocol***"

Protocol Specific Element to evaluate:

Primary Objective: The primary objective for this clinical study, is to assess the reduction of the rate of "acute exacerbation of COPD".

The assessment of those exacerbations is reported in the eCRF by the investigator. In addition, participants complete daily eDiaries symptom scale questions in the EXAcerbations of Chronic Pulmonary Disease Tool (EXACT) instrument and complete a COPD Assessment Test (CAT) to measure the effects of the disease on their wellbeing and daily life.

The protocol defines the evaluation of exacerbation as "moderate" or "severe" through a complex set of criteria:

- Evaluation of the acute worsening of respiratory symptoms reported by participants
- "Moderate" acute exacerbations require systemic corticosteroids and/or antibiotics
- "Severe" acute exacerbations must meet the Serious adverse events criteria.
- Investigation validation: need to differentiate whether the episode is an ongoing COPD or a new exacerbation event (>=14 days between any event)

For this scenario, the key CtQs are:

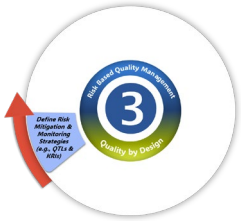
CtQ factors: Procedures supporting study endpoints and data integrity

Specific consideration(s):

- Accurate reporting of acute exacerbation of COPD across participants in eDiary
- Timely reporting in eDiary

Risk(s):

- "Acute worsening" lacks measurable thresholds, increasing diagnostic variability.

	• Requiring ≥14 days between exacerbation events (counted from treatment end) ignores symptom persistence after treatment end, fragmenting ongoing events as different episodes.
	**De-risk Study Considerations:** Simplify definitions & processes for critical endpoints and implement technical controls for data quality. **Suggestions may include:** **Reporting episodes of acute exacerbation of COPD:** Simplify criteria and enforce real-time reporting needs to mitigate risk to ensure prompt safety acute COPD exacerbations. • Symptoms quantification: Define worsening more specifically (e.g. ≥2-point CAT increase within 48hr). • Prioritize symptom resolution: Replace fixed intervals with define new events only after symptoms return to baseline and remain stable >=7 days.
	**Define risk mitigation and Control Strategies** KRI was designed for monitoring study risk related to reporting of acute exacerbation of COPD. **Potential Acute Exacerbation of COPD (KRI):** • **Purpose:** Monitor site-level reporting of acute exacerbation of COPD to detect potential under-reporting or over-reporting. • **Method:** Calculate the rate of acute exacerbation of COPD per participant visit at each site.
	**Implement risk mitigation and Control Strategies** • **KRI & DQA Setup:** Program the designed KRI to enable active monitoring. • **Assign Ownership:** Designate medical manager as primary reviewers for KRI alerts and ongoing oversight. • **Trigger Response:** Low rates triggering eCRF completeness checks; high rates prompting safety assessments.

	• **Lifecycle Management:** Continuously review KRI outputs and dynamically adjust mitigation tactics (e.g., retraining focus, threshold refinement) throughout the study.
	**Monitor risks** Below is an example, created based on real life risk escalations: **Observing a low reporting rate of acute exacerbation of COPD: Site A** had a lower KRI rate than the study average of 0 compared 0.64 episodes of acute exacerbation of COPD per participant across the study. Over 3 years of treatment had passed without any exacerbation being reported and close to 10 participants were randomized to this site. **Evaluation of the finding:** Clinical Data Management, Medical Monitoring, and Project Management functions, have collectively conducted a thorough review of the exacerbation reporting process. Four potential risk categories that could influence the reporting of exacerbation of COPD. Amongst these, two have been determined to be potential root cause contributing to the low reporting rate: **Category #1:** Site related process: • Root cause: Site misunderstood the protocol and used inconsistent assessment methods. Site applied subjective judgment when determining whether episodes were acute or not, which biased the outcome when identifying exacerbations of COPD episodes. Note: When approached, the Investigator acknowledged the risk and fully collaborated to its resolution. **Category #2:** Participant Reporting Factors • Not a root cause: Since the entire site has low reporting rates (not isolated participant), participant related issues were ruled-out. Additionally, the timeliness and completeness of participant eDiaries at Site A were consistent with other sites. **Category #3:** Data Collection Failures • Root cause: Inefficient site workflows led to delayed or missing eCRF entries for observed exacerbation of COPD events. **Category #4**: Systemic process or system Issues

	• Not a root cause: Systemic process or system problems were ruled out because only site A had low reporting rates, while others function normally.
	**Corrective Action** Immediate corrective measures were implemented: **Corrective Actions**: • All acute exacerbation of COPD cases, including those initially missed, were ultimately documented in the eCRF through retrospective review of source data and eDiaries. • Onsite retraining covered: 1. Precise identification of acute exacerbation of COPD 2. Real-time reporting per protocols 3. Data collection workflow optimization **Outcome:** Reporting compliance showed sustained improvement after interventions, demonstrating successful risk mitigation while preserving data integrity.
	**Lessons Learned** Key insights emerged from this incident: **Critical Training Timing:** Training for critical processes (like reporting of endpoint) should be *refreshed regularly*, not just at study start. **Mitigation risk since beginning:** Identify potential risk when designing the protocol can decrease complexity and reduce site/participant burden.
	**Adapt (i.e., Preventative Action** **Enhanced Training:** Regular training program becomes standard practice **Key Outcome:** Focus on preventing risks proactively through these improvements rather than reactively fixing sites.

5.6) Additional considerations

First and foremost, we need to clearly understand what adopting rb-CDM approaches means.

It means:

- De-risking protocols across functions and disciplines at the design stage (i.e., building quality into the study) by streamlining the design and simplifying data collection and

procedures to be conducted, hence making study conduct more feasible and less burdensome.

- Proactively focusing data review activities on what matters most and avoiding disproportionate focus on activities which have no meaningful impact on participant protection or the study results.

- Adopting a Risk Management Framework to Identify, Evaluate, Control, Communicate and Review risks to participant protection and to the reliability of the study results.

It does **not** mean:

- Taking risk nor promoting risk.
- Asking other functions to increase their data oversight to perform activities CDM is no longer planning to perform (or not performing as historically performed).

Adopting rb-CDM does requires a deep change in mindset. It means "***creating a culture that values and rewards critical thinking*** *and open, proactive dialogue about what is critical to quality for a particular study or development programme,* ***going beyond sole reliance on tools and checklists***"[2]

As such, "*Inflexible, one size fits all approaches should be discouraged*" [2], Even though "*standardized operating procedures are necessary and beneficial for conducting good quality clinical studies … study specific strategies and actions are also needed to effectively and efficiently support quality in a study*"[2].

In conclusion, we need to move away from inflexible operating standards such as performing uniform review and query process regardless of the criticality of the data and continuing performing 100% Quality Control (QC).

6) SOP Considerations

The relevant SOP may vary from company to company. There might be an overarching SOP and then associated job aids or work instructions, or it may spread across various SOPs. However, the following areas should be covered by process document(s):

1. **Risk Assessment, Categorization and Prevention SOP(s)**

   Purpose: Define a structured approach to identify, assess, and mitigate data-related risks.

   Key elements:

   - Identification and categorization of data-related risks at the protocol and system level.
   - Identification and Documentation of CtQ factors
   - Definition of mitigations and risk-surveillance strategies

2. **Data Management Plan (DMP) Development SOP**

Purpose: Ensure the DMP reflects risk-based data strategies.

Key Elements:

- Integration of risk-based data strategies into the DMP
- Mapping of critical data flows with associated system and data risks
- Inclusion of risk-informed roles, responsibilities, and data review strategies.
- References to KRIs, QTLs, and mitigation procedures.

3. **Risk-Based Data Review and Validation SOP(s)**

Purpose: Ensure the DMP reflects risk-based data strategies.

Key Elements: Define risk-informed approaches to data validation, and review

- Risk-prioritized review of critical data elements and processes
- Query strategy aligned with risk levels and CtQ factors.
- Metadata and operational data review processes.
- Use of centralized monitoring techniques and technologies.
- Review of trends, outliers, KRIs, and QTLs.
- Action thresholds and trigger-based follow-up procedures.

4. **Signal Detection and Escalation SOP**

Purpose: Standardize how potential data quality issues or anomalies are detected and acted upon.

Key Elements:

- Proactive signal detection via statistical and visual analytics.
- Decision-tree for determining whether findings are isolated, systemic, or critical.
- Escalation pathways to clinical, quality, or regulatory teams.
- Time-bound escalation handling and documentation procedures.

5. **Risk Management and CAPA SOP**

Purpose: Govern how emerging risks and deviations are investigated and managed.

Key Elements:

- Ongoing review and update of the risk assessment, risk monitoring and mitigation strategies
- Identification of systematic or process driven data related issues
- Documentation and resolution of data-related risk signals

- Root cause analysis and preventive action

6. **Protocol Deviation and Data Anomaly Handling SOP**

   Purpose: Clarify classification, triage, and resolution of unexpected data issues.

   Key Elements:

   - Differentiating between protocol deviations, data inconsistencies, and fraud
   - Triage framework based on participant's protection and reliability of trial results
   - Documentation and follow-up of confirmed anomalies

7. **Oversight and Governance of Risk-Based Data Management SOP**

   Purpose: Establish governance and ownership for ongoing risk-based data oversight.

   Key Elements:

   - Definition of cross-functional roles and responsibilities
   - Documentation of decision-making processes and risk sign-offs
   - Governance model for ongoing review of risk strategy effectiveness

8. **Database Lock SOP**

   Purpose: pre-DB Lock checks with risk-based quality control emphasis

   Key Elements:

   - Conduct a final data quality assessment focused on CtQ factors
   - Documentation of any open issues, their justification, or resolution
   - Confirmation of protocol-defined quality acceptance criteria before lock

9. **Audit Trail and Documentation SOP**

   Purpose: Ensure audit readiness and traceability of risk-based decisions and activities.

   Key Elements:

   - Risk-prioritized review of audit trail to assess risks to critical data and processes.
   - Traceability of risk-related decisions and data oversight activities

7) Revision History

Publication Date	Comments

September 2025	Final DRAFT for public review

8) References

[1] ICH, January 2025, Integrated Addendum to ICH E6(R2): Guideline for Good Clinical Practice E6 (R3). Available at https://www.ich.org/page/efficacy-guidelines#6-2

[2] ICH, October 2021, ICH E8 (R1), General Considerations for Clinical Trials, Available at https://database.ich.org/sites/default/files/E8-R1_Guideline_Step4_2021_1006.pdf

[3] Association of Clinical Research Organizations (ACRO), January 2023, Risk-Based Monitoring in Clinical Trials: 2021 Update. Available at Risk-Based Monitoring in Clinical Trials: 2021 Update - PMC

[4] SCM, SCDM Competency Framework, Available at https://scdm.org/cdm-competency-framework/

[5] FDA, August 2013, Guidance for Industry, Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring. Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/oversight-clinical-investigations-risk-based-approach-monitoring

[6] MHRA, March 2018, 'GXP' Data Integrity Guidance and Definition', Available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/687246/MHRA_GxP_data_integrity_guide_March_edited_Final.pdf

[7] MHRA, January 2022, Oversight and monitoring, available at https://www.gov.uk/government/publications/oversight-and-monitoring-of-investigational-medical-product-trials/oversight-and-monitoring-activities

[8] FDA, April 2023, A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers, available at https://www.fda.gov/media/121479/download

[9] SCDM, September 2022, Position Paper on how to create a Clinical Data Science Organization, available at https://scdm.org/wp-content/uploads/2024/03/SCDM-Position-Paper-Evolution-into-Clinical-to-Data-Science-V9.0.pdf

[10] CTTI, May 2015, Quality by Design (QbD) Project, Critical to Quality Factors Principles document, Available at https://ctti-clinicaltrials.org/wp-content/uploads/2021/07/CTTI_QbD_Workshop_Principles_Document.pdf

[11] TransCelerate, February 2013, The Risk Assessment Categorization Tool (RACT) template, Available at https://www.transceleratebiopharmainc.com/assets/risk-based-monitoring-solutions/

[12] TransCelerate, February 2019, The Risk Indicator Library, available at https://www.transceleratebiopharmainc.com/wp-content/uploads/2019/02/TransCelerate-RBM-Risk-Indicator-Library_Final-21Feb2019.xlsx

[13] SCDM, May 2022, The 5Vs of Clinical Data, available at https://scdm.org/wp-content/uploads/2024/03/SCDM-The-5Vs-of-Clinical-Data-FINAL.pdf

[14] TransCelerate, Sep 2014, Evaluating Source Data Verification as quality Control Measure in Clinical Trials. Available at https://journals.sagepub.com/doi/pdf/10.1177/2168479014554400

[15] Stokman and al, 2021, Risk-based Quality Management in CDM An inquiry into the value of generalized query-based data cleaning, Journal of the Society for Clinical Data Management, available at a https://www.jscdm.org/article/20/galley/40/download/

[16] SCDM and eClinical Forum, April 2021, Audit Trail Review: A Key Tool to Ensure Data Integrity. Available at https://scdm.org/wp-content/uploads/2024/07/2021-eCF_SCDM-ATR-Industry-Position-Paper-Version-PR1-2.pdf

[17] FDA, September 2023, Considerations for the Conduct of Clinical Trials of Medical Products During Major Disruptions Due to Disasters and Public Health Emergencies, Available at https://www.fda.gov/media/172258/download

8) Acronyms

Acronym	Description
AE	Adverse Event
ALCOA	Attributable, Legible, Contemporaneous, Original and Accurate
CAPA	Corrective Action and Preventive Action
CAT	COPD Assessment Test
CDM	Clinical Data Management
CDS	Clinical Data Science
CMP	Centralized Monitoring Plan
COPD	Chronic Obstructive Pulmonary Disease
CRO	Clinical Research Organization
CtQ	Critical to Quality
DMP	Data Management Plan
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
eCOA	electronic Clinical Outcome Assessment
EDC	Electronic Data Capture
EMA	European Medicine Agency
EXACT	EXAcerbations of Chronic pulmonary disease Tool
FDA	Food and Drug Administration
GCDMP	Good Clinical Data Management Practice
GCP	Good Clinical Practice
IA	Interim Analysis
ICH	International Conference of Harmonization
IQRMP	Integrated Quality Risk Management Plan
IRC	Independent Review Committee
KRI	Key Risk Indicator
KT	Knowledge Transfer
PHE	Public Health Emergency
QbD	Quality by Design
QC	Quality Control
QTL	Quality Tolerance Limit
RACI	Responsible, Accountable, Consulted & Informed
RACT	Risk Assessment Categorization Tool
rb-CDM	risk-based Clinical Data Management
RBQM	Risk-Based Quality Management
RCA	Root Cause Analysis
SCDM	Society for Clinical Data Management
SDR	Source Data review
SDV	Source Data Verification
SME	Subject Matter Expert
SOP	Standard Operating Procedure
TA	Therapeutic Area

Appendix A - The minimum standards (i.e., Regulations)

Important passages from the following six regulatory guidance's have been summarized below and organized around six main concepts:

Regulations

- August 2013, FDA guidance on “A Risk-Based Approach to Monitoring[5]
- March 2018, MHRA ‘GXP’ Data Integrity Guidance and Definition[6]
- October 2021, ICH E8 (R1), General Considerations for Clinical Trials[2]
- January 2022, MHRA Oversight and monitoring activities[7]
- April 2023, FDA, A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers[8]
- January 2025, ICH E6 (R3), Guideline for Good Clinical Practice[1]

Topics:

- Risk-based approaches
- Fit for purpose considerations
- Data integrity and quality
- Quality by Design (QbD)
- Critical data, processes and Critical to Quality (CtQ) factors
- Risk management

Some regulatory sections apply to multiple concepts and maybe repeated in each table where necessary.

1077 # A.1 Risk-based approaches

Regulation/ Guidance	Section #	Section Name	Regulatory Concept
FDA, April 2023, RBM Q&A	II	Background	*"Sponsors should implement a system to manage, throughout all stages of the clinical investigation, both risks to participants (e.g., a safety problem) and to data integrity (e.g., incomplete and/or inaccurate data)"*
FDA, August 2013, A Risk-Based Approach to Monitoring	B	Rational for RBM	*"There is a growing consensus that risk-based approaches to monitoring, focused on risks to the most critical data elements and processes necessary to achieve study objectives, are more likely than routine visits to all clinical sites and 100% data verification to ensure subject protection and overall study quality".*
FDA, August 2013, A Risk-Based Approach to Monitoring	II	Background	*"A risk-based approach to monitoring does not suggest any less vigilance in oversight of clinical investigations. Rather, it focuses sponsor oversight activities on preventing or mitigating important and likely risks to data quality and to processes critical to human subject protection and trial integrity"*
ICH E6 R3, January 2025	I	Introduction	ICH E6 (R3) *"builds on key concepts outlined in ICH E8(R1) General Considerations for Clinical Studies. This includes fostering a quality culture and proactively designing quality into clinical trials and drug development planning, identifying factors critical to trial quality, engaging interested parties, as appropriate, and using a proportionate risk-based approach."* and *"encourages a risk-based and proportionate approach to the conduct of a clinical trial".*
ICH E6 R3, January 2025	II	Principles of ICH GCP	"*Clinical trial processes and risk mitigation strategies implemented to support the conduct of a trial should be proportionate to the importance of the data being collected and the risks to trial participant safety and data reliability. Clinical trial processes and risk mitigation strategies implemented to support the conduct of the trial should be proportionate to the importance of the data being collected and the risks to trial participant safety and the reliability of trial results" Furthermore, "The overarching principles provide a flexible framework for clinical trial conduct."*

Regulation/ Guidance	Section #	Section Name	Regulatory Concept
ICH E6 R3, January 2025	II (Sub-Section 6)	Principles of ICH GCP	This section emphasizes the need to focus on *"**the protection of participants, the reliability and interpretability of the trial results and the decisions made based on those trial result**",* quality by design, and the use of risk-based approaches. Additionally, *"Factors critical to the quality of the trial should be identified prospectively."* and *"Strategies should be implemented to avoid, detect, address and prevent serious non-compliance with GCP, the trial protocol and applicable regulatory requirements."*
ICH E8 R1 *October 2021*	3.1	Quality by Design of Clinical Studies	*"The likelihood that a clinical study will answer the research questions while preventing important errors can be dramatically improved through prospective attention to the design of all components of the study protocol, procedures, associated operational plans and training."* The paragraph continues in questioning the robustness of traditional processes mentioning that *"activities such as document and data review and monitoring, where conducted retrospectively, are an important part of a quality assurance process; but, even when combined with audits, they are not sufficient to ensure quality of a clinical study."*
ICH E8 R1 *October 2021*	3.3.1	Establishing a Culture that Supports Open Dialogue	"Establishing a Culture that Supports Open Dialogue" sets a fundamental shift in our approaches to conducting clinical trials. It signifies the end of one-size-fit all. It states ***"Creating a culture that values and rewards critical thinking and open, proactive dialogue about what is critical to quality for a particular study or development programme, going beyond sole reliance on tools and checklists, is encouraged. Open dialogue can facilitate the development of innovative methods for ensuring quality."*** *It elaborates further by stating that* ***"Inflexible, "one size fits all" approaches should be discouraged. Standardised operating procedures are necessary and beneficial for conducting good quality clinical studies, but study specific strategies and actions are also needed to effectively and efficiently support quality in a study."***

Regulation/ Guidance	Section #	Section Name	Regulatory Concept
ICH E8 R1 *October 2021*	3.3.2	Focusing on Activities Essential to the Study	*"Consideration should be given to eliminating nonessential activities and data collection from the study to increase quality by simplifying conduct, improving study efficiency, and targeting resources to critical areas. Resources should be deployed to identify and prevent or contr*ol errors that matter."
ICH E8 R1 *October 2021*	3.3.4	Reviewing Critical to Quality Factors	*"Accumulated experience and knowledge, together with periodic review of critical to quality factors should be used to determine whether adjustments to risk control mechanisms are needed, because new or unanticipated issues may arise once the study has begun."*
ICH E6 R3, January 2025	II (Sub-Section 8)	Principles of ICH GCP	The role of the data management plan, as an example, is captured in this section as having a part to play in documenting operational execution and its feasibility. *"The clinical trial protocol as well as the plans or documents for the protocol execution (e.g. statistical analysis plan, data management plan, monitoring plan) should be clear, concise and operationally feasible."*
ICH E6 R3, January 2025	II (Sub-Section 9)	Principles of ICH GCP	It is clear that generating reliable clinical trial results has to be accomplished through systems and processes "*that aid in data capture, management and analyses ... that help ensure the quality of the information generated from the trial"* should be fit for purpose. Furthermore, "*Computerised systems used in clinical trials should be fit for purpose (e.g., through risk-based validation, if appropriate), and factors critical to their quality should be addressed in their design or adaptation for clinical trial purposes"*
ICH E6 R3, January 2025	3.11.4	Monitoring	*"The monitoring approach should consider the activities and services involved, including decentralised settings, and be included in the monitoring plan."* Furthermore, "Monitoring activities may include site monitoring (performed on-site or remotely) and centralised monitoring, depending on the monitoring strategy and the design of the clinical trial.". Last but not least *"The appropriate extent and nature of monitoring"* should be *"based on identified risks. Factors such as the objective, purpose, design, complexity, blinding, number of trial participants, investigational product, current knowledge of the safety profile and endpoints of the trial should be considered."*

Regulation/ Guidance	Section #	Section Name	Regulatory Concept
ICH E6 R3, January 2025	3.11.4.2	Centralised Monitoring	*"Centralised monitoring is an evaluation of accumulated data, performed in a timely manner, by the sponsor's qualified and trained persons (e.g., medical monitor, data scientist/data manager, biostatistician)."* *"Centralised monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of site monitoring or be used on its own. Used of centralised data analytics can help identify systemic or site-specific issues, including protocol non-compliance and potentially unreliable data."* *"Centralised monitoring may support the selection of sites and/or processes for targeted site monitoring."*
ICH E6 R3, January 2025	3.11.4.5.4	Monitoring of Clinical Trial Data	*"Verifying that the investigator is enrolling only eligible trial participants"* *"Checking the accuracy, completeness, and consistency of the reported trial data against the source records and other trial-related records and whether these were reported in a timely manner. This can be done on the basis of using samples and supported by data analytics, as appropriate. The sample size and the types of data or records may need adjustment based on previous monitoring results or other indications of insufficient data quality. Monitoring should:* *(i) verify that the data required by the protocol and identified as data of higher criticality in the monitoring plan are consistent with the source;* *(ii) identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations;* *(iii) examine data trends, such as the range, consistency and variability of data within and across sites;"* *"**Identifying significant errors in data collection and reporting at a site or across sites, potential data manipulation and data integrity problems**."*

Regulation/ Guidance	Section #	Section Name	Regulatory Concept
ICH E6 R3, January 2025	3.11.4.6	Monitoring Report	*"Reports of monitoring activities should include a summary of what was reviewed, a description of significant findings, conclusions and actions required to resolve them and follow-up on their resolution including those resolved in previous reports. The requirements of monitoring reports (including their content and frequency) should be described in the sponsor's procedures."* *"Reports of investigator site* ***and/or centralised monitoring*** *should be provided to the appropriate sponsor staff as described in the sponsor's procedures in a timely manner for review and follow up."* *"When needed, the report should describe findings requiring escalation for action and resolution. The sponsor should decide on the appropriate action to be taken, and these decisions and the resolution of the actions involved, where needed, should be recorded."*
ICH E6 R3, January 2025	3.11.4.3	Monitoring Plan	*"The sponsor should develop a monitoring plan that is* ***tailored to the identified potential safety risks, the risks to data quality and/or other risks to the reliability of the trial results****. Particular attention should be given to procedures relevant to participant safety and to trial endpoints. The plan should describe the monitoring strategy, the monitoring activities of all the parties involved, the various monitoring methods and tools to be used, and the rationale for their use. The monitoring strategy should ensure appropriate oversight of trial conduct and consider site capabilities and potential burden. The plan should focus on aspects that are critical to quality. The monitoring plan should reference the sponsor's applicable policies and procedures."*
MHRA GxP Data Integrity *March 2018*	2.6	Introduction	*This guidance aims to promote a risk-based approach to data management that includes data risk, criticality and lifecycle. Users of this guidance need to understand their data processes (as a lifecycle) to identify data with the greatest GXP impact. From that, the identification of the most effective and efficient risk-based control and review of the data can be determined and implemented.*

Regulation/ Guidance	Section #	Section Name	Regulatory Concept
MHRA GxP Data Integrity *March 2018*	3.6	The principles of data integrity	*The effort and resource applied to assure the integrity of the data should be commensurate with the risk and impact of a data integrity failure to the patient or environment.*
MHRA GxP Data Integrity *March 2018*	6.15	Data Review and Approval	*The approach to reviewing specific record content, such as critical data and metadata, cross-outs (paper records) and audit trails (electronic records) should meet all applicable regulatory requirements and be risk-based (…) Data review should also include a risk-based review of relevant metadata, including relevant audit trails records*
ICH E6 R3, January 2025	4.2.3	Review of Data and Metadata	*"Procedures for review of trial-specific data,* ***audit trails and other relevant metadata*** *should be in place. It should be a planned activity, and the extent and nature should be* risk-based, *adapted to the individual trial and adjusted based on experience during the trial."*
MHRA Oversight and monitoring activities *January 2022*	N/A	Central monitoring of a clinical trial	*"It is recommended that the data validation activities are recommended to be focused on the data that is critical to the reliability of the trial results as identified by the risk assessment rather than excessive resource spent on raising data queries whose resolution makes little or no impact on the quality of the trial, the safety of the participants and reliability of the results. This is similar to the approach taken for proportionate source data verification (SDV)."*

A.2 - Fit for purpose considerations

Regulation/ Guidance	Section #	Section Name	Regulatory Concept
ICH E6 R3, January 2025	II (Sub-Section 6)	Principles of ICH GCP	This section states that *"Quality of a clinical trial is considered in this guideline as fit for purpose".*
ICH E6 R3, January 2025	II (Sub-Section 9)	Principles of ICH GCP	*"****The quality and amount of the information*** *generated in a clinical trial should be* ***fit for purpose and sufficient*** *to provide confidence in the trial's results and* ***support good decision making****."*
ICH E6 R3, January 2025	N/A	GLOSSARY	***"Data integrity*** *includes the degree to which data fulfil key criteria of being attributable, legible, contemporaneous, original, accurate, complete, secure and reliable such that data are fit for purpose."*

ICH E8 R1 *October 2021*	2.2	General Principles	Section considers Quality of Clinical Studies ***"as fitness for purpose**. The purpose of a clinical study is to generate reliable information to answer the research questions and support decision making while protecting study participants. **The quality of the information generated should therefore be sufficient to support good decision making."***
MHRA GxP Data Integrity *March 2018*	7	Glossary	*Defines Data Quality as "the assurance that data produced is exactly what was intended to be produced and fit for its intended purpose. This incorporates ALCOA"*

1080

1081 ## A3 - Data integrity and quality

Regulation/ Guidance	Section #	Section Name	Regulatory Concept
ICH E8 R1 *October 2021*	5.7	Study Data	*Data quality attributes include **consistency** (uniformity of ascertainment over time), **accuracy** (correctness of collection, transmission, and processing), and **completeness** (lack of missing information).*
MHRA GxP Data Integrity *March 2018*	2.7	Introduction	*States that data integrity is not data quality as "the controls required for integrity do not necessarily guarantee the quality of the data generated"*
MHRA GxP Data Integrity *March 2018*	6.4	Definition of terms and interpretation of requirements	*Data integrity is the degree to which data are complete, consistent, accurate, trustworthy, reliable and that these characteristics of the data are maintained throughout the data life cycle. The data should be collected and maintained in a secure manner, so that they are attributable, legible, contemporaneously recorded, original (or a true copy) and accurate. Assuring data integrity requires appropriate quality and risk management systems, including adherence to sound scientific principles and good documentation practices.*
MHRA GxP Data Integrity *March 2018*	4.4	Establishing data criticality and inherent integrity risk	*Reduced effort and/or frequency of control measures may be justified for data that has a lesser impact to product, patient or the environment if those data are obtained from a process that does not provide the opportunity for amendment without high-level system access or specialist software/knowledge.*

Regulation/ Guidance	Section #	Section Name	Regulatory Concept
MHRA Oversight and monitoring activities *January 2022*	N/A	The importance of accuracy of the clinical trial data	*"It is not the accuracy of the individual trial data that is important, but the reliability and robustness of the trial results."*
MHRA Oversight and monitoring activities *January 2022*	N/A	The importance of accuracy of the clinical trial data	*"The aim of the management, monitoring and data management activities is recommended to focus on the data and activities that are critical to the reliability of the trial results, for example, the endpoint for the primary objective of the trial or key design aspects (e.g. randomisation) These would be identified during a risk assessment of the trial. It is recommended to aim for a high level of accuracy in these areas identified and potentially accept some degree of error in other areas. Consideration for defining such acceptability in terms of tolerance limits is recommended."*

1082

1083 ## A4 - Quality by Design (QbD)

Regulation/ Guidance	Section #	Section Name	Regulatory Concept
ICH E8 R1 *October 2021*	2.2	General Principles	Quality by Design (QbD) *"in clinical research sets out to ensure that the quality of a study **is driven proactively by designing quality into the study protocol and processes**. This involves the use of a prospective, multidisciplinary approach to **promote the quality of protocol and process design in a manner proportionate to the risks involved**, and clear communication of how this will be achieved*."
ICH E8 R1 *October 2021*	3	Designing Quality into Clinical Studies	*"Quality by design involves focusing on **critical to quality factors** to ensure the protection of the rights, safety, and wellbeing of study participants, the generation of reliable and meaningful results, and the **management of risks to those factors using a risk-proportionate approach**. The approach is supported by the establishment of an appropriate framework for the identification and review of critical to quality factors at the time of design and planning of the study, and throughout its conduct, analysis, and reporting."*

Regulation/ Guidance	Section #	Section Name	Regulatory Concept
ICH E8 R1 *October 2021*	3.1	Quality by Design of Clinical Studies	*"The likelihood that a clinical study will answer the research questions while preventing important errors can be dramatically improved through prospective attention to the design of all components of the study protocol, procedures, associated operational plans and training."* The Paragraph continues in questioning the robustness of traditional processes mentioning that *"activities such as document and data review and monitoring, where conducted retrospectively, are an important part of a quality assurance process; but, even when combined with audits, they are not sufficient to ensure quality of a clinical study."*
ICH E8 R1 *October 2021*	3.1	Quality by Design of Clinical Studies	Concludes by stating that "*Good planning and implementation of a clinical study also derive from attention to the design elements of clinical studies".*
MHRA Oversight and monitoring activities *January 2022*	N/A	The importance of accuracy of the clinical trial data	*"The design of the trial can assist in reducing or mitigating the impact of missing or incorrect data, for example, the results of large blinded, randomised trials with high power are unlikely to be affected by increased variability/omissions of the data, particularly as the errors/omissions would not be differential on a treatment basis (biased).* *Small blinded and randomised trials may suffer from reduced power with increased data variability/omissions and there is potential to increase the risk of a false negative result. Open trials are more at risk from bias, as errors and omissions could be potentially differential for the treatment groups. This issue is recommended to be evaluated as part of the risk assessment to determine what level of SDV (and other monitoring checks) is needed to mitigate any concerns about the reliability of the trial results."*

A5 - Critical data, processes and Critical to Quality (CtQ) factors

Regulation/ Guidance	Section #	Section Name	Regulatory Concept
FDA, April 2023, RBM Q&A	II	Background	*"FDA recommends that at the protocol design stage, sponsors identify the critical data and processes necessary for human subject protection and maintaining data integrity for the investigation."*
ICH E6 R3, January 2025	I	Introduction	*"Clinical trials vary widely in scale, complexity and cost. Careful evaluation of critical to quality factors involved in each trial and the risks associated with these factors will help ensure efficiency by focusing on activities critical to achieving the trial objectives."*
ICH E6 R3, January 2025	3.11.4.3	Monitoring Plan	*"Monitoring of important data and processes (e.g., those related to primary endpoints and key secondary endpoints and processes intended to ensure participant safety) performed outside the investigator site (e.g., central image reading facilities, central laboratories) should be addressed in the monitoring plan."*
ICH E8 R1 *October 2021*	3.2	Critical to Quality Factors	Critical to Quality Factors are defined as "***attributes of a study whose integrity is fundamental to the protection of study participants, the reliability and interpretability of the study results, and the decisions made based on the study results.*** *These quality factors are considered to be critical because, if their integrity were to be* ***undermined by errors of design or conduct****, the reliability or ethics of decision-making based on the results of the study would also be undermined." …* *"Having identified those factors, it is important to determine the risks that threaten their integrity and decide whether they can be accepted or should be mitigated, based on their probability, detectability and impact".*

Regulation/ Guidance	Section #	Section Name	Regulatory Concept
ICH E8 R1 *October 2021*	3.2	Critical to Quality Factors	Elaborates on the risk of striving for perfection instead on focusing on what matters by stating *"**Perfection in every aspect of an activity is rarely achievable or can only be achieved by use of resources that are out of proportion to the benefit obtained. The quality factors should be prioritised to identify those that are critical to the study**, at the time of the study design, and study procedures should be proportionate to the risks inherent in the study and the importance of the information collected."* … ***"The critical to quality factors should be clear and should not be cluttered with minor issues (e.g., due to extensive secondary objectives or processes/data collection not linked to the proper protection of the study participants and/or primary study objectives)."*** This is the genesis of risk-based approaches where on critical data and process is paramount.
ICH E8 R1 *October 2021*	3.3	Approach to Identifying the Critical to Quality Factors	Provides further guidance to Clinical Data Managers when designing data collection solutions by stating that ***"Study designs should be operationally feasible and avoid unnecessary complexity. Protocols and case report forms/data collection methods should enable the study to be conducted as designed and avoid unnecessary data collection."***
ICH E8 R1 *October 2021*	5.7	Study Data	Data quality attributes include **consistency** (uniformity of ascertainment over time), **accuracy** (correctness of collection, transmission, and processing), and **completeness** (lack of missing information). These aspects should be proactively considered during study planning by **identifying the factors, critical to the quality of the study, associated with data sourcing, collection, and processing.**
ICH E6 R3, January 2025	3.10	Quality Management	This section now references ICH E8 (R1) for description of critical to quality factors *"likely to have a meaningful impact on participant's rights, safety and well-being and the reliability of the results"*

Regulation/ Guidance	Section #	Section Name	Regulatory Concept
MHRA GxP Data Integrity *March 2018*	4.1	Establishing data criticality and inherent integrity risk	*Data has varying importance to quality, safety and efficacy decisions. Data criticality may be determined by considering how the data is used to influence the decisions made.*
MHRA Oversight and monitoring activities *January 2022*	N/A	The importance of accuracy of the clinical trial data	*"The aim of the management, monitoring and data management activities is recommended to focus on the data and activities that are critical to the reliability of the trial results, for example, the endpoint for the primary objective of the trial or key design aspects (e.g. randomisation)."*

1087

1088 **A6 – Risk Management**

Regulation/ Guidance	Section #	Section Name	Regulatory Concept
MHRA Risk-Adapted approach *January 2022*	N/A	Risk Assessment	*"It is recommended that a risk assessment is undertaken for all clinical trials. Identification of potential risks to trial participants and to the reliability of the trial results on a trial basis and taking actions to mitigate those risks can only be beneficial for the quality of any clinical trial."*
MHRA Risk-Adapted approach *January 2022*	N/A	When and how to undertake the risk assessment	*The risk assessment should be done as early as possible.*

Regulation/ Guidance	Section #	Section Name	Regulatory Concept
MHRA Risk-Adapted approach *January 2022*	N/A	When and how to undertake the risk assessment	*The relevant personnel undertaking the risk assessment would typically include* • *a medic with understanding of the therapeutic area and the therapeutic use of the proposed investigational medicinal products (IMP)* • *a statistician with relevant experience of medical statistics and a person with an appropriate level of understanding of applicable regulatory* • *it would be usual to include data management personnel, trial monitors or project/study managers in the multidisciplinary team conducting the risk assessment, as these individuals would be important with respect to defining feasible mitigation/adaptations.* • *it may be considered appropriate by the sponsor to include a suitable patient advocate/representative in the risk assessment.*
ICH E6 R3, January 2025	3.10.1.1	Risk Identification	*"The sponsor should identify risks that may have a meaningful impact on critical to quality factors* ***prior to trial initiation and throughout trial conduct****. Risks should be considered across the processes and systems, including computerised systems, used in the clinical trial (e.g., trial design, participant selection, informed consent process, randomisation, blinding, investigational product administration, data handling and service provider activities)."*
ICH E6 R3, January 2025	3.10.1.2	Risk Evaluation	"The sponsor should evaluate identified risks and existing controls in place to mitigate the risk by considering (a) The likelihood of harm/hazard occurring. (b) The extent to which such harm/hazard would be detectable. (c) The impact of such harm/hazard on trial participant protection and the reliability of trial results."
ICH E6 R3, January 2025	3.10.1.3	Risk Control	"*Risk control should be proportionate to the importance of the risk to participants' rights, safety and well-being and the reliability of trial results. Risk mitigation activities may be incorporated, for example, in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, and training*."

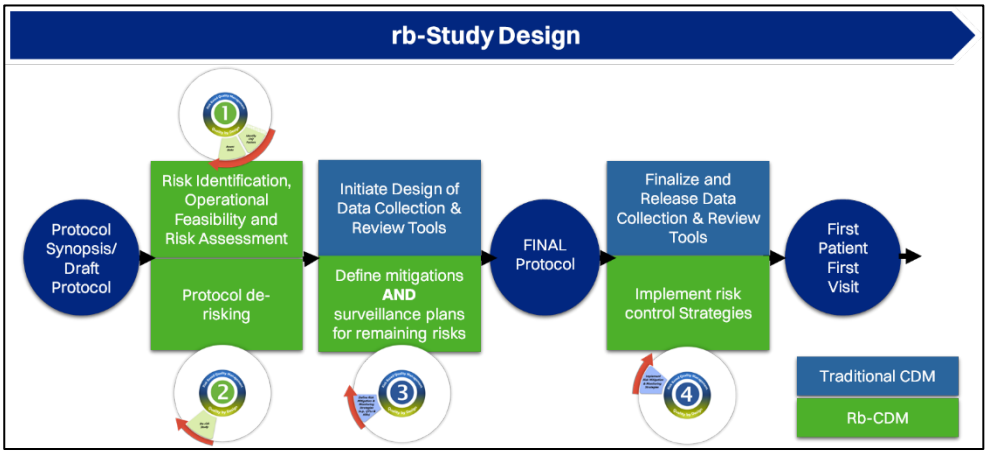
Regulation/ Guidance	Section #	Section Name	Regulatory Concept
ICH E6 R3, January 2025	3.10.1.3	Risk Control	"*Where relevant, the sponsor should set pre-specified acceptable ranges* ***(e.g., quality tolerance limits at the trial level)*** *to support the control of risks to critical to quality factors. These pre-specified ranges reflect limits that when exceeded have the potential to impact participant safety or the reliability of trial results. Where deviation beyond these ranges is detected, an evaluation should be performed to determine if there is a possible systemic issue and if action is needed".*
ICH E6 R3, January 2025	3.10.1.4	Risk Communication	*rights, safety or well-being of trial participant(s) The sponsor should document and communicate the identified risks and mitigating activities, if applicable, to those who are involved in taking action or are affected by such activities. Communication also facilitates risk review and continual improvement during clinical trial conduct."*
ICH E6 R3, January 2025	3.10.1.5	Risk Review	*"The sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience. Additional risk control measures may be implemented as needed."*
ICH E6 R3, January 2025	3.10.1.6	Risk Reporting	*"The sponsor should summarise and report important quality issues (including instances in which acceptable ranges are exceeded, as detailed in section 3.10.1.3) and the remedial actions taken and document them in the clinical trial report (see ICH E3)."*
ICH E6 R3, January 2025	3.12.2	Noncompliance	*"If noncompliance that significantly affects or has the potential to significantly affect the rights, safety or well-being of trial participant(s) or the reliability of trial results is discovered, the sponsor should perform a root cause analysis, implement appropriate corrective and preventive actions and confirm their adequacy unless otherwise justified."*

Regulation/ Guidance	Section #	Section Name	Regulatory Concept
MHRA GxP Data Integrity *March 2018*	3.4	The principles of data integrity	*Organisations are expected to implement, design and operate a documented system that provides an acceptable state of control based on the data integrity risk with supporting rationale. An example of a suitable approach is to perform a data integrity risk assessment (DIRA) where the processes that produce data or where data is obtained are mapped out and each of the formats and their controls are identified and the data criticality and inherent risks documented.*
MHRA GxP Data Integrity *March 2018*	4.5	Establishing data criticality and inherent integrity risk	*The data integrity risk assessment (or equivalent) should consider factors required to follow a process or perform a function. It is expected to consider not only a computerised system but also the supporting people, guidance, training and quality systems.* *Therefore, automation or the use of a 'validated system' (e.g. e-CRF; analytical equipment) may lower but not eliminate data integrity risk. Where there is human intervention, particularly influencing how or what data is recorded, reported or retained, an increased risk may exist from poor organisational controls or data verification due to an overreliance on the system's validated state.*
FDA, April 2023, RBM Q&A	N/Z	Question 7	*"Significant issues should be thoroughly evaluated in a timely manner at the appropriate levels (for example, sponsor, clinical sites) as described in the monitoring plan. A root cause analysis followed by appropriate corrective and preventive actions should be undertaken promptly to reduce the impact of the identified issue on the rights, safety, and welfare of participants in the clinical investigation and/or the integrity of the data"*
FDA, April 2023, RBM Q&A	N/Z	Question 7	*"Significant issues identified through monitoring and oversight activities and the actions to be taken should be documented and communicated to the appropriate parties, which may include, but are not limited to (1) sponsor management; (2) sponsor teams; (3) clinical sites; (4) institutional review boards; (5) other relevant parties (for example, DMCs and relevant contract research organizations); and (6) applicable regulatory agencies, including FDA, when appropriate"*

1089

1090

Appendix B – rb-study design process consideration checklist for CDM Experts



Risk Identification, Operational Feasibility and Risk Assessment

1 Engage Stakeholders & Align on Protocol Design

2 Identify & Document Critical to Quality (CtQ) Factors

3 Conduct Study Risk Assessment

Protocol de-risking

Define mitigations and surveillance plans for remaining risks

1 Design Data Review & Validation Strategy

2 Define Quality Control & Risk Mitigation Plan

3 Specify Reporting & Analytics Requirements

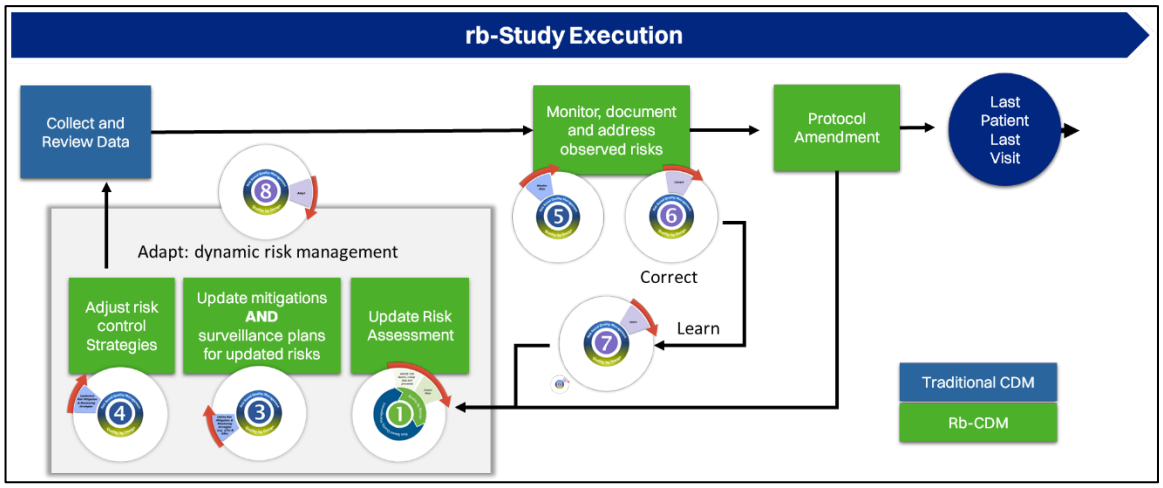
Implement risk control strategies

Additional considerations

1 Define milestones-based deliverables and compliance monitoring

2 Conduct Knowledge Transfer & secure CRO Collaboration

Appendix C – rb-study execution process consideration checklist for CDM Experts



Monitor, document and address observed risks

1 Conduct tailored data review proportional to risks

- Prioritize the review of critical data
- Identify systematic or process driven data issues
- Monitor trends in non-critical

2 Review critical data and associated metadata

3 Monitor for the possible emergence of any new risks

4 Monitor critical processes during study execution

5 Ensure synergetic oversight across stakeholders

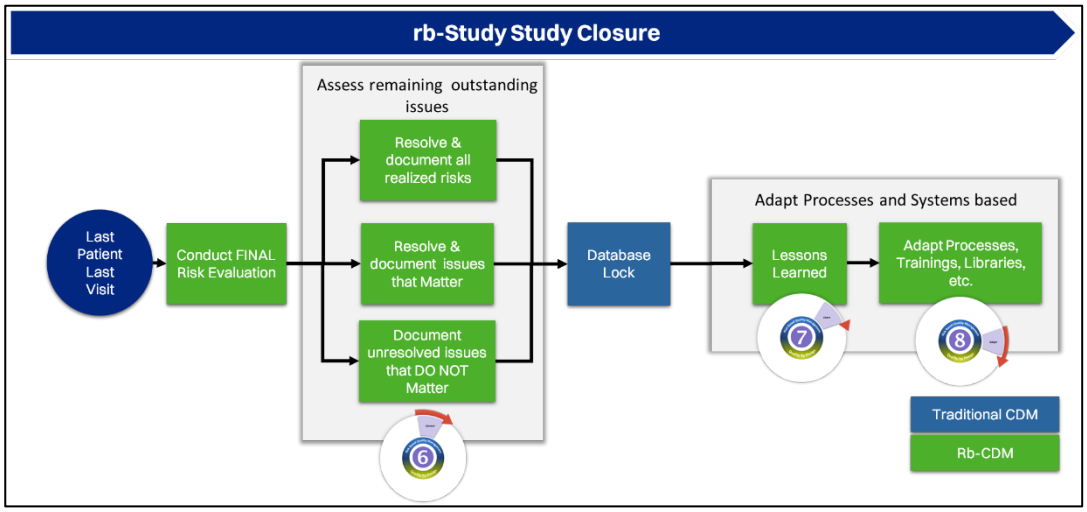
Adapt by maintaining a dynamic risk management

1 Regularly review and update the risk assessment, risk monitoring and mitigation strategies

Protocol Amendments

1 Continuous Review & Protocol Amendments

Appendix D – rb- study close-out Checklist for CDM Experts



Conduct a final risk evaluation

Conduct a final risk evaluation

1. Perform a final **review of all occurrences of issues** related CtQ Factors
2. Conduct a final **data quality assessment** focused on CtQ Factors

Assess remaining outstanding issues

1. Review and close outstanding issues
2. Document process completion and compliance

Adapt Processes and Systems based on Lessons learned