Risk-Based Quality Management in Clinical Trials

Implications and Implementation Challenges

Valid on 20–21 April 2026

Jeannette Dixon, jQAGCP Ltd.

jqagcp@gmail.com

Key course elements

- Principles of Risk Based Quality Management
  - Expectations based on ICH E6 R3 and ICH E8 R1
  - Understanding key challenges in risk management and implementation
  - Critical Process and Data Identification
  - Deciding on Critical to Quality Factors for your trials
  - Prospective Risk identification
  - Setting pre-specified acceptable ranges and Quality Tolerance Limits
  - Monitoring and reporting of QTLs
  - Risk assessment tools and development of a risk registry
  - Risk control, communication, review, escalation and reporting
- How risks drive operational decisions
  - Monitoring intensity, risk based monitoring and centralized monitoring
  - Service Provider Oversight
  - Site Selection
- The expectations of regulators
  - GCP inspection outcomes related to Risk Based Quality Management

2

Learning Objectives

- Describe the principles of Risk Based Quality Management (RBQM) in clinical trials
- Developing best practices and implementation of Risk Management processes in clinical trials
- Improving your standard operating procedures covering risk management
- Assess how risks drive operational decisions
- Having full awareness of the potential inspection risks - learn about outcomes of GCP inspections related to RBQM to ensure this will not happen in your company

3

Agenda

DAY 1	
13:55 – 14:00	Online meeting room opens
14:00 – 14:10	Welcome & Introductions • Join with your camera turned on to meet & greet the trainer and participants • Share your expectations on this course and what you would like to learn
14:10 – 14:30	Quality Risk Management Principles – Background and Risk Management Steps
14:30 – 15:15	Critical Process and Data Identification
15:15 – 15:30	Break
15:30 – 16:15	Risk Identification and Quality Tolerance Limit
16:15 – 17:00	Risk Evaluation and development of a Risk Registry

DAY 2	
13:55 – 14:00	Online meeting room opens
14:00 – 14:30	Recap & Key Takeaways from Day 1
14:30 – 15:00	Risk Control, Communication, Review and Reporting
15:00 – 15:15	Break
15:15 – 15:45	Risk based Monitoring
15:45 – 16:45	Expectations of Regulators/Inspection observations
16:45 – 17:00	Implementation, summary and Q&A

4

Disclaimer

The views and statements in this presentation are *my personal views* and do not necessarily represent those of Wehive or other organisations I am involved with.

Nothing in these materials is intended to constitute legal advice. Organisations using or referring to the material are responsible for *ensuring their own compliance with applicable laws and regulations*.

Any party using this information do so entirely at their own risk. jQAGCP Ltd will not bear responsibility or liability for any harm, including indirect or consequential harm, that a user may incur from use of this information.

5

Quality risk management principles

Background

6

Reminder - Why follow ICH GCP E6 (R3)?

Public assurance of:
Protection of the Rights, Integrity and Confidentiality of Human Subjects
Integrity of Data - assurance that the data and reported results are credible and accurate

Allowing:
Increased confidence in Data
Reproducibility of Data
Transparency and uniformity of Conduct

Unified Standard across ICH Countries
Relevant to all studies involving human participants
MUST be followed when generating data that are intended to be submitted to regulatory authorities

7

Reminder - Why follow ICH GCP E6 (R3)?

- **EU - Clinical Trial Regulation 536/2014** refers to ICH in several places
  - Article 47: …sponsor and investigator, when drawing up the protocol and applying CTR and protocol, shall also take appropriate account of the quality standards and the ICH guidelines on GCP
  - **Thus, although not making ICH the law in the EU, it does give it prominence as a quality standard. In force in the EU since 23 July 2025**

- **US -** availability of a final guidance for industry in September 2025. FDA states that guidance documents "represent the agency's current thinking" and are not binding. But do you want to argue with FDA's thinking…..

8

ICH harmonisation for better health

Considerations

ICH E family of guidelines – need to be read together

E8 General Considerations for Clinical Trials

Design and analysis:
E4 Dose-Response Studies
E9 Statistical Principles for Clinical Trials
E10 Choice of Control Group in Clinical Trials
E17 Multi-Regional Clinical Trials

Conduct and reporting:
E3 Clinical Study Reports
E6 Good Clinical Practice

Safety reporting:
E1 Clinical Safety for Drugs used in Long-Term Treatment
E2A - E2F Pharmacovigilance
E14 Clinical Evaluation of QT
E19 Safety Data Collection

Populations:
E5 Ethnic Factors
E7 Clinical Trials in Geriatric Population
E11 - E11A Clinical Trials in Pediatric Population
E12 Clinical Evaluation by Therapeutic Category

Genetics/genomics:
E15 Definitions in Pharmacogenetics / Pharmacogenomics
E16 Qualification of Genomic Biomarkers
E18 Genomic Sampling

9

ICH E6 R3 considerations regarding Trial Design 3.1

- Sponsors should **incorporate quality into the design** of clinical trials by identifying **factors that are critical to the quality of the trial** and by **managing risks to those factors** (3.1.2)

see GCP Principle 6
Quality should be built into the scientific and operational design and conduct of clinical trials

!!! see Appendix B – Protocol – Section B12 **Quality Control and Quality Assurance: B.12.1 Description of identified critical to quality factors, associated risks and risk mitigation strategies in the trial unless documented elsewhere**

- Sponsors should consider **inputs from a wide variety of interested parties** (e.g. HCPs, patients) to support the development plan and clinical trial protocols **as described in ICH E8(R1)** (3.1.3)
  - **also when developing the informed consent materials** and any other participant-facing information

→**Implementation of ICH E6 (R3) into the conduct of clinical trials requires good understanding of ICH E8 (R1)**

10

Quality Management – ICH E6 R3 Section 3.10

almost identical to Section 5.0 in ICH E6 R2 applicable since November 2016

The sponsor should implement a system to manage quality throughout all stages of the trial process, i.e., design, conduct, recording, evaluation, reporting and archiving of clinical trials

- Quality management includes
  - efficient design and implementation of clinical trial protocols (→ discussed in ICH E8 R1),
  - tools and procedures for trial conduct (including data collection and management)
  - collection of information that is essential to decision making (→ TMF)

11

Quality Management – Section 3.10

- Quality Management involves incorporating quality into the design of the clinical trial (i.e., **quality by design**) and **identifying those factors that are likely to have a meaningful impact** on participants' rights, safety and well-being and the reliability of the results (i.e., **critical to quality factors as described in ICH E8(R1)**).
- The sponsor should **describe the quality management approach** implemented in the trial in the clinical trial report (see ICH E3 Structure and Content of **CSRs**)

Quality Management

3.1.2 Sponsors should incorporate quality into the design of the clinical trial by identifying factors that are critical to the quality of the trial and by managing risks to those factors.

- **Methods used to to ensure the protection of participants' rights, safety and well-being and the reliability of trial results should be proportionate to the risks inherent in the trial and the importance of the information collected**

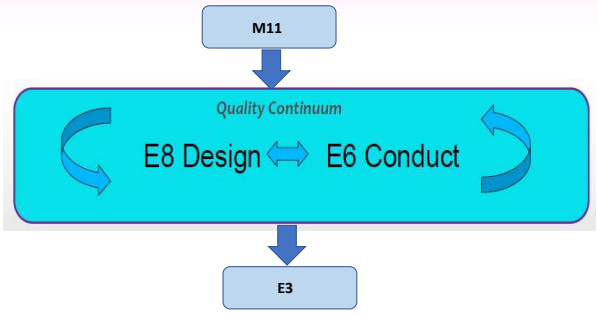
13

Impact

- **Sponsor responsibility - it requires the sponsor to have implemented a System of Quality Management**
- **Requires procedures and evidence on implementation of Risk Management**
- **Requires documented risk assessment before study start and to ensure the correct tools are employed**
- **Requires ongoing and documented risk assessment throughout the study**
- **Requires "reporting" of risks**

14

GCP Renovations



The guidelines should be used in an integrated manner rather than one or the other guideline or subsection being focussed on in isolation of the others

15

Reminder – why follow ICH E8 (R1)

ICH E8 (R1) Objectives:

- Describe internationally agreed upon principles and practices to facilitate regulatory acceptance
- **Provide guidance on the consideration of quality in the design and conduct of clinical studies, including:**
  - **Identification of factors critical to the quality of the study**
  - **Management of risks to those factors during study conduct**
- Provide an overview of the types of clinical studies performed during the product lifecycle, including:
  - **Study design aspects that support the determination of quality factors critical to ensuring the protection of study subjects and ability to meet the study objectives**
- Provide a guide to all of the ICH Efficacy Guidelines

16

ICH E8 (R1)Background

The International Council for Harmonisation has delivered the first of a two-part project to modernize the international good clinical practice framework

General Considerations for Clinical Studies **ICH E8** is regarded as the **foundational document for all clinical trials**

Its implementation is expected to herald a significant shift in how trials should be managed and overseen due to its emphasis on embracing quality by design (QbD) principles

ICH adopted the E8(R1) guideline on 6 October 2021, replacing the version that had been in place since 1997 – **it applied in the EU from 14 April 2022**

Consider reading this as additional background information
https://admin.ich.org/sites/default/files/inline-files/ICHPublicMeetingE8R1PublicMeetingSlides_3019_1209.pdf
Slides 37 to 52

17

Impact

- **Describes approaches for optimizing study quality* which promote the reliability, efficiency, and patient focus of clinical trials**
- **Requires identifying factors that are critical to the quality of a clinical study at the design stage for every study**
  - **The quality of a study is driven proactively by designing quality into the study protocol and processes**
  - **Risks that threaten the integrity of the critical to quality factors should be identified and managed in a proportionate manner**
- **Requires planning the study conduct proportionate to the risks to the identified quality factors**

***ICH E8 (R1) states "Quality of a clinical study is 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

18

What are "risks"?

Risk is defined as the combination of the probability of occurrence of harm, the severity of that harm and how easily that harm can be detected

4 major questions:

1. What might go wrong?
2. What is the likelihood it will go wrong?
3. What are the consequences?
4. How easy it to detect?

19

And what are "issues"?

What is the **difference between a risk and an issue?**

Risk	Issue
Something that *might* happen in the future.	Something that is *currently* happening (or already happened).
Example: The Study Coordinator may resign during the study.	Example: The Study Coordinator resigned, effective immediately. No replacement was assigned yet.

20

Quality risk management principles

Risk Management Steps

21

Risk Management Steps

1. Critical Process and Data Identification
2. Risk Identification – **During protocol development**
3. Risk Evaluation
4. Risk Control – **predefined thresholds for quality**
5. Risk Communication
6. Risk Review
7. Risk Reporting – **report deviations from the predefined thresholds**

[ICH E6 R3 Section 3.10]

22

1. Critical Process and Data 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**
  - The likelihood of a successful trial can be dramatically improved through prospective attention to preventing important errors that could undermine the ability to obtain meaningful information from a trial

Critical to quality factors ?

If their integrity were to be undermined by errors of study design, data sources or conduct, the reliability or ethics of decision-making would also be undermined

Fundamental to
- protection of study participants,
- reliability and interpretability of study results,
- decisions based on study results

Should be considered holistically so that dependencies among them can be identified

Successful application may minimize the need for modifications of the protocol and make adherence throughout the study more likely

24

1. Critical Process and Data Identification

- During **protocol development and before trial initiation**, the **sponsor** needs to
  - identify **processes, systems** and **data** that are critical

  to assure **human subject protection and the reliability of study results**

→ **Highlighting the need for assessing processes as well as data to determine what is important**

→ **Expectation to define, rationalize and document those processes and data**

25

Critical data and processes

Critical Data	**Critical Processes and Systems**
What are the data which are critical to program and/or protocol success? **What Critical Data must be collected in order to satisfy the objectives?**	**What are the Critical Processes that must be done correctly to ensure subject safety, data quality, and GCP/regulatory compliance?** **Are there any Critical Processes in the program and/or protocol which are vulnerable to error?**

Data that support primary & key secondary objectives
• Rationale: why is it critical?
  • Endpoint - primary or secondary
  • Safety - SAEs, events leading to discontinuation of treatment
  • Other (specify)
	Processes that underpin safety or quality
	• Rationale: why is it critical?
	  • Safety/ethical treatment - seeking appropriate medical consultation, investigating clinically significant findings
	  • Data quality – blinding, event adjudication, controlling inter-rater variability
	  • Compliance – GCP, local regulations, protocol

Example: 1) AEs/SAEs 2) Laboratory results	Example: 1) Collection and reporting of AEs/SAEs 2) Collection, storage, shipment of labs

26

ICH E8(R1) Guideline

ANNEX 3: SELECTED EXAMPLES OF CRITICAL TO QUALITY FACTORS

Selected Examples of Critical to Quality Factors	E1	E2A-E2F	E3	E4	E5	E6	E7	E8	E9	E10	E11	E12	E14	E15	E16	E17	E18
Protocol Design																	
Eligibility Criteria						√	√	√	√		√	√	√	√		√	
Randomisation				√		√		√	√	√		√	√			√	
Blinding/Masking						√		√	√	√							
Types of Controls	√			√				√		√			√			√	
Data Quality	√						√	√	√					√			
Endpoints				√	√			√	√	√	√	√				√	
Procedures Supporting Study Endpoints and Data Integrity					√	√		√	√	√	√	√				√	
Investigational Product (IP) Handling and Administration						√							√				
Feasibility																	
Study and Site Feasibility																√	√
Accrual									√		√		√				
Patient Safety																	
Informed Consent						√					√						√
Withdrawal Criteria and Trial Participant Retention			√			√					√		√				

Note: This Annex was available in the DRAFT version of ICH E8 (R1), not in its final version

27

ICH E8(R1) Guideline

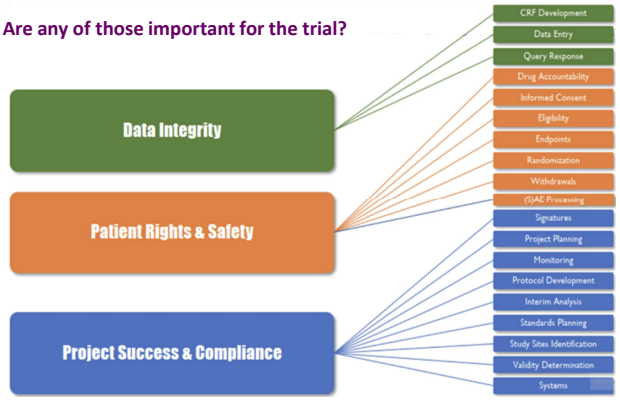
Selected Examples of Critical to Quality Factors	E1	E2A-E2F	E3	E4	E5	E6	E7	E8	E9	E10	E11	E12	E14	E15	E16	E17	E18
Signal Detection and Safety Reporting		√ (B)	√			√						√	√				
Data Monitoring Committee (DMC)/Stopping Rules						√			√	√			√				
Study Conduct																	
Training						√							√			√	√
Data Recording and Reporting		√ (B,C,F)	√	√					√		√		√		√	√	√
Data Monitoring and Management		√ (A,B,D)	√						√						√	√	√
Statistical Analysis			√	√	√				√				√			√	
Study Reporting																	
Dissemination of Study Results		√ (D,F)															√
Third-Party Engagement																	
Delegation of Sponsor Responsibilities						√											
Collaborations						√											

Note: This Annex was available in the DRAFT version of ICH E8 (R1), not in its final version

28

Other Examples - Critical to Quality Factors

Are any of those important for the trial?



29

Other Examples (1) – what are those potential critical to quality factors ?

3.10.1.1 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**)

They are CRITICAL for the success of a trial…

- **Trial population** → correct choice depends on study objectives
- **Number of participants** → sufficient number of participants to make statistical conclusions
- **Dropouts** → retrieving data following treatment discontinuation, definition of treatment effect in the presence of dropouts

30

Other Examples (2) – critical to quality factors

- **Bias** → determine what may affect study progress and course of treatment, e.g., concomitant treatment/AE recording based on participant responses; questionnaires
- **Choice of endpoints** → should be of sufficient accuracy, precision, responsiveness (sensitivity to change) and reproducibility to assess drug effects
- **Comparability between treatment groups** (control group; randomisation) → consider how treatment groups remain comparable, for example, there may be differences in the follow-up patterns between the groups, as participants in one group dropping out because of adverse events or lack of efficacy
- **Adherence to the study protocol** → consider processes of protocol deviation reviews, and management of serious breaches

31

Other Examples (3) – critical to quality factors

Trial data collection and management processes

→determine the manner, timelines, operational checks, statistical surveillance, and appropriate access to data

→determine the required information about trial participants that may be important to understand the benefit/risk of the drug (e.g., age, weight, sex, co-morbidities, history, concomitant therapies)

→use of validated computerised systems for source data provision, data collection and management

32

Quality by Design of Clinical Studies

Quality by design involves focusing on the critical to quality factors of the trial in order to maximise the likelihood of the trial meeting its objectives.

Expectation:

- **involving the use of a prospective, multidisciplinary approach to promote the quality of the protocol and process design proportionate to the risks involved**

  → Ensure all relevant functions have input into the protocol and amendments

  → Ensure study processes and controls match the potential risks of the studies

33

Stakeholder engagement

- Engaging stakeholders within trial development is an important feature of quality by design
- The process of building quality into the protocol may be informed not only by the sponsor but also by those directly involved in completion of the study, **such as service providers, investigators, site staff, and patients (e.g. through patient advocacy groups)**

Quality by Design of Clinical Studies

Expectation:

- **Critical to quality factors should be determined and rationalised for each study**
  - Ensure that for each study the critical to quality factors are determined and documented, including the reason why they are critical
  - Different factors will stand out as critical for different types of studies….(please don't copy and paste)
- **Risks that threaten the integrity of the "critical to quality factors" should be identified, documented and managed in a proportionate manner**
  - For each quality factor, risks must be identified
- **Study procedures should be proportionate to the risks and importance of information collected**

35

Quality by Design of Clinical Studies

Clear communication of how this will be achieved

→ Ensure availability of internal processes (SOPs)

→Ensure 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

→ needs regular reviews and oversight

→ Ensure availability of a Risk Management Plan

36

Risk Management Steps

1. Critical Process and Data Identification ✓
2. Risk Identification – **During protocol development**
3. Risk Evaluation
4. Risk Control – **predefined thresholds for quality**
5. Risk Communication
6. Risk Review
7. Risk Reporting – **report deviations from the predefined thresholds**

[ICH E6 R2 Section 3.10]

37

2. Risk Identification

The sponsor should **identify risks** that may **have a meaningful impact on critical to quality factors** (3.10.1.2)

prior to trial initiation and throughout trial conduct

- **Risks should be considered at**
  - **Programme level**
  - **Clinical trial level**
  - **System/Process level**

38

Risk identification at trial/programme level

Programme level (e.g., investigational product, specific safety requirements or adverse events of special interest, risks inherent to the indication, patient population, and/or therapeutic area, IMP efficacy)

Program Level

- New/unique tools or procedures associated with the program?
- Specific safety requirements or adverse events of special interest?
- Any risks unique for the product such as storage requirements?
- Risks inherent to the indication and/or therapeutic area?
- Risks from a regulatory perspective?

39

Risk identification at trial/programme level

Protocol/Trial Level

- Do the new/unique tools and procedures differ from standard of care?
- Are there safety considerations as a result of comparator drugs or the indication?
- Any competing studies for the study population?
- Are any inclusion/exclusion criteria open to interpretation or unclear for study staff?
- Does the study complexity increase risks?

Clinical trial level (e.g., trial design, data collection and recording, informed consent process)

40

Risk Identification at system/process level

- **System Risk** (facility & people):
- **System Risk** (organisation):
- **Process Risk**:

41

Practical suggestion for CTQ and risk development

1. Following selection of CTQ factors for your trial
2. Establish questions for the selected CTQ factors to support the evaluation of the CTQ's relative importance for your trial
3. Establish issues that did happen with the CTQ factor
4. Use those issues to evaluate the risks to the CTQ factors for your trial

PATIENT SAFETY			
Factor	**Description/Rationale**	**Potential Considerations in Evaluating Relative Importance of CTQ Factor**	**Examples of Issues to Consider in Evaluating Risks to CTQ Factor**
Informed Consent	The clinical investigator has a responsibility to ensure that trial participants' participation in research is informed and voluntary, and that new information that may affect trial participants' willingness to continue in the study is communicated in a timely manner. Informed consent is an ongoing process, and the consent document should be the basis for a meaningful exchange between the investigator (or designee) and the trial participant.	1. What are the key elements of the informed consent process for this study? 2. Have various stakeholders, especially PPAO and treating physicians, been involved in the development of the informed consent document? 3. Does the consent document employ plain language principles, including description of symptoms rather than disease state (e.g., fatigue rather than anemia)? 4. How does the consent process (vs. the document) fit within the study processes? 5. Describe the study population. Is there the potential for: • Vulnerable trial participants? • Trial participants with impaired cognition or diminished capacity to consent, either initially or over time? • Emergency situations in which obtaining consent prospectively may not be feasible?	1. Are key elements of the consent process for the study reflected in the informed consent document? 2. Is the consent form meaningful to the target audience? • Will participants understand the risk? • Will participants understand why following the study procedures is important? • Could the form be shortened to enhance trial participant understanding while still meeting consent requirements in regions in which the study will be conducted? 3. What options does the informed consent document provide for trial participants to withdraw from the investigational product but complete follow-up visits, withdraw from the study but permit access to medical records for necessary follow-up data, or withdraw consent entirely? 4. Do the informed consent and the investigational plan clearly distinguish between withdrawal of consent for the study vs. withdrawal from the investigational product? 5. What is the threshold for amending the consent and the process for ensuring timely provision of new information to trial participants? Who will be responsible for identifying and ensuring appropriate changes to the informed consent document? 6. Are there unique features about the study that will affect the consent process (i.e., emergent conditions, need to obtain assent from pediatric trial participants)?

Practical suggestion for CTQ and risk development

Please refer to your handout

- This document is not intended to serve as a checklist applicable for every trial, nor be all inclusive
- During protocol development, the study team should carefully evaluate whether there are additional CTQ factors that arise from specific trial's scientific and operational design or more generally from the development program
- Historical data from previous trials with the same investigational product or with a similar design may be useful in identifying additional factors

Practical suggestion – create a "Risk Library"

Facility Risk Category (procedures to (column A of tab "Study Risk Assessment Log"	Potential Risk Use this list to identify potential risks to this study or to consider additional quality risks not listed here- enter these potential risks in Column B of tab "Study Risk Assessment Log"	Forms and Guidance This column is for guidance only to promote thought about potential risks and possible controls/mitigations - this text is not intended to be entered into the Study Risk Assessment Log	Quality Risk Impact
Blinding	There is no plan in place to detect, manage and track un-blinding events	Prespecified controls should be established to track and manage unblinding events, should they occur	Data Integrity
Blinding	Study uses un-blinded staff (at sponsor, CRO and/or site) that presents the opportunity for inadvertent un-blinding of others	Consider controls that will prevent inadvertent un-blinding	Data Integrity
Blinding	In-study un-blinding is required due to e.g. adaptive design, interim analyses or safety/data monitoring committees, that requires additional controls to prevent inadvertent un-blinding and potential bias	Consider whether the in-study un-blinding is necessary or could be done another way. If necessary, consider what controls will be necessary to ensure only the designated individuals become un-blinded and minimize the potential for bias in the remainder of the study team	Data Integrity
Blinding	Data transfers during the study present the opportunity for inadvertent un-blinding e.g. sharing PK or PD bioanalytical datasets for cleaning/reconciliation purposes or through AE review	Specify what data would be considered to have the potential to un-blind. Plan in-process controls to mitigate the risk.	Data Integrity
Blinding	The study poses a greater risk than normal for undetected un-blinding events e.g. due to overencapsulation of the IMP		Data Integrity
Blinding	There is no clear end-of-study un-blinding plan		Data Integrity
Blinding	Study methods for un-blinding individual subjects in emergency situations present a particular risk for this study (e.g. now or unlocked code break envelope vendor or IxRS technology) The study (title) is assigned in a high risk manner (e.g. high risk: pharmacist assigns the blind, or the IMP is created on-site / low risk: automated or centralized treatment assignment, or IMP provided by the manufacturer already blinded)		Safety Data Integrity
Country and Site Selection	It is not permissible to collect outcome information in certain countries involved for subjects that are lost to follow-up or have withdrawn consent	Note: Level of risk increases when primary or secondary endpoints depend on follow-up information	Data Integrity
Country and Site Selection	One or more selected countries do not require adherence to ICH GCP principles		Safety and/or Data Integrity
Country and Site Selection	Study procedures are not in accordance with local standard of care of all countries involved	Is the protocol in alignment with the local standard of care. Consider how differences between local standard of care and the protocol requirements might lead to protocol deviations. Ensure flexibility is provided in the protocol language when acceptable.	Safety and/or Data Integrity
Country and Site Selection	The study must be conducted in specific countries, or specific subject numbers are required to be enrolled in certain countries	Describe the stratification measures to be used to manage the required recruitment plan	Safety and/or Data Integrity
Country and Site Selection	The inclusion of specific countries within the study poses higher than normal risk or complexity due to import/export, operational, ethical or cultural reasons	Are there countries/sites involved that might present greater risk to trial conduct? Consider "Ideal Site Criteria" describing requirements re: GCP experience, clinical investigator(s) experience, site infrastructure; consider country specific monitoring plan adjustments to address specific needs.	Safety and/or Data Integrity
Country and Site Selection	Background, standard of care, non-IMP or rescue medications is not available in all countries involved with the study	Consider impact of provision of comparator or rescue therapy (not currently approved in the country); there might be risk related to in-experience with particular medication administration - to be considered on a country by country basis	Safety and/or Data Integrity

Also refer to Microsoft Word - SNAP risk assessment_25jan13_formatted by MHRA 15Feb2013_clean.doc (publishing.service.gov.uk)

Supporting the required control of these risks

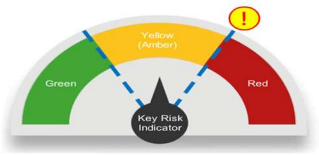
Setting pre-specified acceptable ranges

Quality Tolerance Limits

46

Setting pre-specified acceptable ranges

Risk Indicator	Threshold
Risk indicators are metrics used to monitor identified risk exposures over time	A pre-determined level, point, or value (e.g., number, %, range) associated with a Risk Indicator that indicates the need for a follow-up action



47

Risk Indicator Examples

Safety	• Outliers/trends in number of adverse events per subject visit/site
Investigational Product	• Incidence of temperature excursions
Recruitment/Discontinuation	• Number of screen failures compared to average across sites
Issue Management	• Number of deviations per subject visit/site compared to average across sites
Data Quality	• Abnormal trend or lack of variability in data
On-Site Workload	• Amount of data outstanding for verification or review
Essential Documents	• Number of overdue or missing documents
Staffing, Facilities, Supplies	• Staff turn-over

48

What are QTL? (1)

A QTL is a pre-defined threshold, point, value associated with a parameter that is critical to participant safety or reliability of trial results. When the threshold is crossed, this should trigger an evaluation to determine if there is a possible systemic issue and if corrective actions is needed

A QTL is a **trial-level parameter**, not a site or participant-level parameter

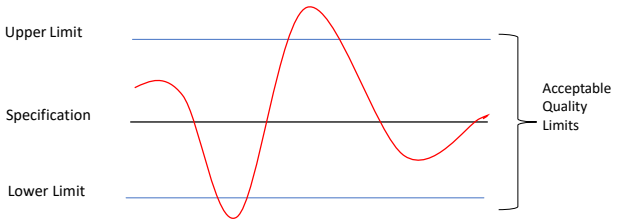
QTLs need to be documented before study start

Source: theavocagroup.com

49

What are QTL? (2)

- QTLs have historically been required for Good Manufacturing Practice (GMP) activities
- Are inferring limits by which significant actions must be taken to ensure the manufactured product achieves quality and usability limits



50

Agreeing on QTLs

- **QTLs should be defined at the planning level of the trial to define the limits that might indicate systemic problems**
- **The recommended number of parameters is 3 to 5 and should include the impact on participant safety and reliability of trial results**
  - Examples include inclusion/exclusion protocol violations, incomplete/missing endpoint data, and AEs/SAEs of special interest

Source: theavocagroup.com

51

Recommended items to be defined and documented for QTLs		
1	Parameter	The subject of the QTL
2	Definition	Definition including how the QTL will be measured
3	Justification for parameter	Rationale and any limitations to the use of the parameter
4	Unit	e.g., number, proportion
5	Expectation	The expected (mean/median) value of errors that are of a random nature (i.e., excluding errors that are due to systematic issues)
6	Justification for expectation	Historical data from previous trials within the organization or published data. When referencing historical data, it is important to state whether systematic issues have been excluded
7	Tolerance limit	(Statistical) Limit (and whether it is one-sided or two sided)
8	Justification for tolerance limit	How the tolerance limit was set. Include the statistical method if used
9	The mitigations/ actions taken and the outcome/impact to the trial	If a QTL is exceeded, explain the deviations. Provide the rationale if the trial results are still regarded to be acceptable (e.g., for submission for marketing authorization, for analyzing the safety profile of a marketed compound). Clearly state if the results are not valid

Source: Transcelerate Risk-Based Quality Management: Quality Tolerance limits and risk reporting 52

Example
defining QTLs (within a functional plan)

Parameter	Definition	Justification for parameter	Unit	Expect-ation	Justification for expectation	Tolerance limit	Justification for tolerance limit
% of randomized subjects not meeting per protocol population criteria	Proportion (%) of randomized subjects with pre-defined important inclusion/ exclusion criteria violation(s) that lead to exclusion from the per protocol population	A high number of subjects not meeting the entrance criteria can have a negative impact on interpretation of the primary endpoint and overall validity of the trial results	%	1.5	Overall number (%) of patients not meeting per-protocol population criteria and excluded from the primary analysis in the reference trial	One-sided upper limit 1.7	Based on maximum reported rate in one of the randomized groups in the reference trial

Source: Transcelerate Risk-Based Quality Management: Quality Tolerance limits and risk reporting 53

Difference between Pre-specified acceptable ranges and Quality Tolerance Limits

- **Pre-specified acceptable ranges** are the *broader concept* in ICH E6(R3), describing the expected, normal operating boundaries for Critical-to-Quality (CTQ) factors
- **QTLs** are a *subset* of these ranges—specific, trial-level thresholds that, when crossed, indicate a **systemic issue** requiring evaluation and potential corrective action and always linked to CTQ factors

- So:
- **All QTLs are acceptable ranges**
- **Not all acceptable ranges are QTLs**

54

Difference between Pre-specified acceptable ranges and Quality Tolerance Limits

Acceptable ranges may include:

- Expected ranges for recruitment rates
- Expected ranges for visit window adherence
- Expected ranges for endpoint completeness

QTLs for critical parameters like missing primary endpoints or eligibility violations

55

Quality Tolerance Limits …And then….

- The **Risk Management Plan** should include strategies for monitoring these parameters, **determining the root cause** and addressing any deviations to QTLs
- Modifications to the QTLs during the clinical trial are acceptable as long as sufficient rationale and documentation are provided
- **QTLs and justification of changes must be documented in the CSR**

Suggested reading: Risk-Based Quality Management - TransCelerate

56

Determining the root cause - the "five whys"

- Genuine human errors happen, but they're cited far more frequently than they should be

- **5 Whys is methodology for uncovering the root cause** of a specific problem by drilling down to the underlying process failure
- **Success depends on data-driven answers** and ensuring the analysis focuses on fixing broken processes rather than blaming people for "human error"

57

Deviation management - root cause - the "five whys"

Begin by asking why the problem occurred. Write down the answer and treat it as the starting point for your investigation.

Example:
Problem: Production output dropped by 15%.
Why #1: Why did production output drop?
Answer: Because the equipment was unexpectedly down for three hours.

At this point, you've likely reached the root cause: the lack of a preventive maintenance schedule

Tip: Test your root cause by asking, *"If we fix this, will the problem stop?"* If the answer is no, dig deeper

- **Why #2:** Why was the equipment down?
  Answer: Because the conveyor belt broke.
- **Why #3:** Why did the conveyor belt break?
  Answer: Because it hadn't been properly maintained.
- **Why #4:** Why wasn't it maintained?
  Answer: Because there's no preventive maintenance schedule.
- **Why #5:** Why isn't there a preventive maintenance schedule?
  Answer: Because we don't have a standardized process for maintenance planning.

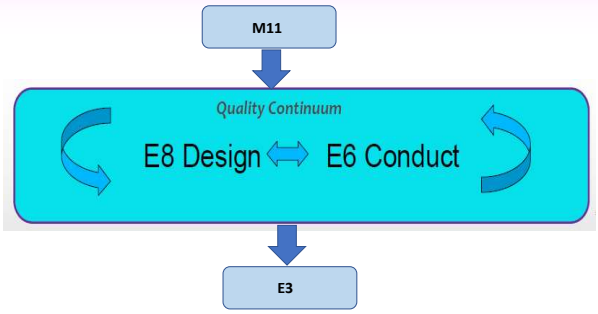
58

How to include risks in the protocol design

→ ICH M11

59

GCP Renovations



The guidelines should be used in an integrated manner rather than one or the other guideline or subsection being focussed on in isolation of the others

60

How to include risks in the protocol design (1)

- **Protocol template sections** ICH M11 (selected section for this presentation)
  - **2.2 Assessment of Risks and Benefits**
  - 2.2.1 Risk Summary and Mitigation Strategy
    - Trial Specific Discussion of **intervention** Risks and Mitigation
      - Trial Intervention – Describe risks related to trial-specific treatments and interventions. For the protocol, focus on the relevant key risks for this trial. Provide a brief description of strategies to mitigate identified risks or provide a cross reference to the relevant protocol section.
    - Trial Specific discussion of **procedure(s)** Risks and Mitigation
      - Trial Procedures – Describe risks associated with the design (e.g., placebo arm) and procedures specific to this trial (e.g., biopsies), and any measures to control or mitigate the risks.
      - Provide a brief description of strategies to mitigate identified risks or provide a cross reference to the relevant protocol section.
      - This is not intended to be an exhaustive list of all possible risks associated with trial procedures but should focus on the unique risks inherent in the design or less common or high-risk procedures.
    - Trial specific Discussion of **other** Risks and Mitigations
      - Other – Consider risks associated with other items (for example, comparators, challenge agents, imaging agents, medical devices). Insert a line for each, as needed.

61

How to include risks in the protocol design (2)

- **Protocol template sections** ICH M11 (selected section for this presentation)
  - **11 Trial oversight and other general considerations**
  - 11.6 Risk-Based Quality Management
    - Describe the identified critical to quality factors, associated risks and risk mitigation strategies for the trial or refer to the location where this information is described and updated during the trial based on emerging data.
  - 11.7 Data Governance
    - Describe the key systems and processes for critical trial integrity, traceability and security including a summary of the approaches enabling accurate data collection, reporting, monitoring, transfer, retention, and access if not addressed in separate agreement(s).

Refer to ICH M11 template ICH_Step4_M11_Final_Template_2025_1119.pdf for suggested wording

Adoption by the Regulatory Members of the ICH Assembly under Step 4. 19 November 2025

M11 Guideline: ICH_Step4_M11_Final_Guideline_2025_1119.pdf

62

Risk-Based Quality Management

example text, Protocol Section 11.6

This clinical trial implements a Quality by Design approach following ICH E8 (R1) General Considerations for Clinical Studies during protocol development to ensure protection of the rights, safety, and wellbeing of trial participants, the generation of reliable and meaningful results.

The trial conduct will be governed by a risk-based quality management approach following ICH E6(R3) Good Clinical Practice guidelines, whereby a systematic risk assessment will be conducted during protocol development and maintained during its conduct. Risk mitigation strategies will be implemented following a risk-proportionate approach.

During protocol development, the Sponsor identified Critical to Quality factors (CTQ factors) which are processes, systems and data that are critical in this trial to assure human subject protection and the reliability of study results. CTQ factors will be documented in the risk management plan for the trial.

Risks to CTQ factors were considered to identify potential issues that could impact (1) the participant safety and tolerability of study procedures; and (2) data integrity processes that could affect the reliability of trial results.

The potential impact, severity, detectability and overall risk priority ratings were described and proposed actions to mitigate these risks in the design of the study were documented.

Pre-specified acceptable ranges were documented as Quality tolerance limits (QTLs) in the risk management tool to allow the identification of systematic issues that can impact participant safety and/or reliability of trial results. These predefined parameters will be monitored during the trial, and important deviations from the QTLs and remedial actions taken will be summarised in the clinical study report.

Risk mitigation efforts will be assessed for continued suitability and effectiveness throughout the trial through the Sponsor's oversight activities and actions taken where Quality Tolerance Limits are exceeded. Risks will also be reassessed at the time of protocol amendments/modifications and at other timepoints during the trial lifecycle as specified by the Sponsor.

All Quality by Design considerations, risk activities, quality thresholds, mitigations, and oversight activities will be documented throughout the clinical trial and archived in the TMF.

Risk Management Steps – where are we so far

1. Critical Process and Data Identification ✓
2. Risk Identification – **During protocol development** ✓
3. Risk Evaluation
4. Risk Control – **predefined thresholds for quality**
5. Risk Communication
6. Risk Review
7. Risk Reporting – **report deviations from the predefined thresholds**

Based on ICH E6 R2 Section 5.0

64

3. Risk Evaluation

- Identified risks should be evaluated by considering:
  - (a) Likelihood of errors occurring
    [consider existing risk controls and mitigations]
  - (b) Impact/severity of errors
    [on human subject protection and data integrity]
  - (c) Detectability of errors
    [the state/extent/likelihood of the errors being observed]

65

Transfer risk evaluation into practice…

Development of a risk registry

66

Risk Identification Refer to Tab 1 Guidance					Risk Analysis See 'Grading Criteria' tab 5 for guidance on scoring Quality Impact, Likelihood and Detectability - refer to tab 6 for calculations					
Risk ID Number UPDATED or NEW risk	Quality Risk Category (Pick from drop-down list. Corresponds to Column A of 'Risks' Library Tab	Potential Risk Enter potential risks that apply to this study. Use Column B of the 'Risks Library' tab as guidance if applicable. Consider documenting the potential risk as: "Risk" "Cause" "Effect" (Copy sample text for full situation)	Risk Details Provide details about why this risk applies to this study	Controls (existing/already in place) Enter details of existing controls/mitigations that will protect against the risk	Quality Impact (1-5)	Likelihood (1-5)	Detectability (1-5)	Risk Priority Number (no entry required) (RPN) (QxLxD)	Risk Impact Category (no entry required) (as category	Critical to Quality (CtQ) Factor?	Quality Tolerance Limit required? If QTL is selected, enter details in the QTL TAB [?]
R1 NEW EXAMPLE 1	Subject Population / Eligibility	▶ Risk: Site enrolls ineligible patients. ▶ Cause: Complex protocol eligibility criteria and screening assessment schedule. ▶ Effect: Ineligible patient enrolled, leading to frustration, resource burden and potential issues around patient safety.	The protocol is in design phase. Complex assessments flagged by several investigators involved in protocol design.	none at this time, discuss inclusion/exclusion criteria at next meeting	5	3	2	120 High		Yes	Yes Percentage or number of subjects not eligible greater than red%
R2 NEW EXAMPLE 2	Informed Consent	▶ Risk: Delay in availability of final ICF and translations. ▶ Cause: Delay in finalisation of the core English ICF - varying local ICF requirements, translations required. Sites or IECs request changes. ▶ Effect: Potential to delay start-up activities for overall study or individual countries/sites.	Contract with Translator has not been finalised.	▶ Finalisation of the core ICF identified as a critical path. ▶ Plan of translations required and lead time to achieve these provided to sponsor. ▶ Process is agreed for review of requests for ICF changes with strict turnaround times.	5	3	1	68 Moderate		No	No
R3 NEW EXAMPLE 3	Subject Accrual	▶Risk: Failure to meet overall enrolment target. ▶Cause: Lack of site motivation due to enrolment hold ▶Effect: Potential impact on LPI (August 2023) and study finalization.	Enrolment hold was recommended by Safety Committee on 15 June 2023 due to potential safety concerns.	Protocol Version 5 is finalised and provided to CI/RA for approval	5	5	1	300 High		No	No
R4 NEW EXAMPLE 4	Protocol Adherence/non-compliance	▶Risk: Failure of sites to correctly follow the protocol for collection and shipment of PK samples ▶Cause: Lack of site staff understanding, error in obtaining and/or processing samples. ▶Effect: Impact on data evaluability.	CRA noted that shipments of PK samples did not contain the number of samples expected.	▶Give particular consideration to site set up when conducting PSVs. Ensure they have the facilities and resource to support the PK sampling. ▶Work closely with sites and conduct PK training with key staff members at SIV. ▶Provide supporting materials to walk site staff through the process.	2	4	1	32 Low		No	No

Risk Analysis – Risk Priority Number

1. Risk Class Score assessment (Impact x Likelihood)

Impact (x2) \ Likelihood (x2)	1	2	3	4	5
5	20	40	60	80	100
4	16	32	48	64	80
3	12	24	36	48	60
2	8	16	24	32	40
1	4	8	12	16	20

2. Risk Priority Number

Risk Class Score \ Detectability (x1)	1	2	3
100	100	200	300
80	80	160	240
64	64	128	192
60	60	120	180
48	48	96	144
40	40	80	120
36	36	72	108
32	32	64	96
24	24	48	72
20	20	40	60
16	16	32	48
12	12	24	36
8	8	16	24
4	4	8	12

3. Quality Impact Category

Score	Grade
Score >=100	High Risk Priority
Score 40-99	Moderate Risk Priority
Score <40	Low Risk Priority

= Risk Priority Number (RPN)

68

Risk Evaluation

- Having completed Risk Analysis and calculated the **Risk Priority Number (RPN)**, the RPN can be ordered into highest to lowest quality risks
- **The scores should be assessed by the Study Team for their acceptability**

69

Risk Management Steps

1. Critical Process and Data Identification ✓
2. Risk Identification – **During protocol development** ✓
3. Risk Evaluation ✓
4. Risk Control – **predefined thresholds for quality**
5. Risk Communication
6. Risk Review
7. Risk Reporting – **report deviations from the predefined thresholds**

[ICH E6 R2 Section 5.0]

70

4. Risk Control
Risk acceptance as part of risk control

Risk acceptance is not:

Inappropriately interpreting data and information
Hiding risks from the regulators
Dodging legal requirements

- Discuss the appropriate balance among benefits, risks, and resources
- Be careful to emphasize the principles: the participants' interests and good science/data

71

Risk acceptance as part of risk control

- In general
  - Low priority risks may be considered Acceptable and High priority risks considered Unacceptable

72

Risk acceptance as part of risk control

- In general low priority risks may be considered Acceptable and high priority risks considered Unacceptable
- However, there is no right or wrong answer, for example:
  - The process of completing the risk assessment may have indicated the need for additional controls/mitigations for Low priority risks
  - In this instance, the risk should be marked Unacceptable and the new controls/mitigations recorded in the next section (Risk Control)
  - Additional controls/mitigations can only change the Likelihood or Detectability scores; the Quality Impact will always remain the same
  - High priority risks may be considered Acceptable if there is no possible or feasible risk reduction method identified

73

Risk Control

Once the sponsor identified those risks that

- can be accepted and/or should be reduced (through mitigating actions)

[→ it is expected that a rational is given either way….]

the approach used is to reduce a risk to an acceptable level that should be proportionate to the significance of the risk

74

Risk Control

- **Pre-specified acceptable ranges** should have been established

as the trigger point for action (remember the earlier discussions?)

- taking into consideration medical and statistical characteristics of the variables
- statistical design of the trial, that can impact subject safety or data integrity

Develop the contingency plan and get it ready to take action should the risk occur

→Define simple and clear triggers and a defined time period for action

75

Risk Control

- Risk Mitigation activities may be incorporated in
  - protocol design and amendments/modifications,
  - monitoring plans,
  - agreements between parties defining roles and responsibilities,
  - systematic safeguards to ensure adherence to SOPs,
  - training in processes and procedures
- Consider resource restrictions and operational inefficiencies

76

Risk Evaluation Refer to Tab 1 Guidance		Risk Control - Mitigation Refer to Tab 1 Guidance				Risk Control - Contingency Refer to Tab 1 Guidance			
Accepted?	Justification for Decision (Mandatory for accepted moderate and high Quality Impact Categories risks; recommended for accepted low Quality Impact Category risks)	Risk Mitigation Plan (initial risk event planning) At least for unaccepted risks - enter details of new/planned controls/mitigations that will be implemented to protect against the risk	Risk Mitigation Timelines enter implementation deadline (MMM/YYYY)	Risk Mitigation implementation outcome Provide details of the outcome of risk mitigation activities - If risks are added/updated, do not delete the existing entry but create a new row/line and update Column A	Risk Owner Enter who has responsibility for ensuring the new controls/mitigation and contingency if applicable is implemented	Trigger Point Start of Contingency Planning Pre-specified Acceptable Ranges	Contingency Plan Action(s) to be Taken if Risk Event Occurs Activated by Trigger Point If a Trigger Point is not considered, justify the decision here	Actions Taken & Outcomes - If risks are added/updated, do not delete the existing entry but create a new row/line and update Column A
No	Not accepted	▶ revise inclusion/exclusion criteria. If considered not possible: ▶ This is a key training issue for monitors and site personnel around key eligibility criteria at the Investigator Meeting/Site Initiation Visit.	Mar-2026	Protocol could not be revised, risk mitigation plan will need to be implemented	Project Manager	Discovery of an ineligible patient being entered.	▶ Flag immediately to Medical Monitor, CRA and site staff. ▶ Medical Monitor to review the case with the PI and decide on appropriate course of action for the patient. ▶ Ascertain whether the patient should be replaced	At this time not applicable
No	Not accepted	▶ Utilise local reg knowledge to ensure the versions provided follow the required format.	Aug-25	Contract with vendor is signed. ICF and translations are completed.	Project Manager	Not applicable	Contract with vendor is signed	Not applicable
No	Not accepted	▶ Upon protocol version 5.0 approval, conduct site webex call to whole staff on protocol changes and address any site concerns that occurred during enrollment hold ▶ Conduct post amendment approval investigator meeting to re-kick off the study and get investigators reenvisioned	Dec-25	▶ Face to Face meeting took place on 17 June 2025 to discuss initial plans on study "restart". ▶ effect to be evaluated	Project Manager	Slow re-start of recruitment / many non-enrolling sites	Obtain buy in from all key stakeholders on extension of enrollment timelines.	Webex trainings meetings and local Inv. Meeting were held in Q1/Q2 in Europe - successful re-start of study.
Yes	PK is not a primary endpoint, thus lack of samples will not have an impact on the overall study outcome. However, risk mitigation steps will be taken to avoid loss of data unnecessarily.	▶ Ship samples on a per patient basis rather than batching so that samples can be tracked and issues flagged by the laboratory early.	Dec-25	Not known yet	CRA	Central lab flag a missed or spoiled PK/ biomarker samples to PM/CRA	▶ Investigate immediately with site staff. Review processes and the reason for potential errors. ▶ Address training and communication where necessary.	Not known yet

Risk Control

- Detection of deviations from the **predefined** acceptable ranges should trigger an evaluation to determine if action is needed

78

Examples of Responses to Risk Thresholds

- Possibly no action needed beyond ongoing monitoring

- Continue central and/or off-site monitoring
- Assess other data remotely
- Contact site to get additional information

- Contact site to get additional information
- Collect site documentation
- Visit site to review documentation not available remotely

Source: Transcelerate: Risk-Based Monitoring Overview, 2016

79

Examples of Responses to Risk Thresholds

Threshold:

Threshold	Examples of Action(s)
+/- 5% more/less than the average reported AE rate (Green)	No action
+/- 5.1 to 15% more/less than the average reported AE rate (Yellow)	No action Assess data remotely (e.g. determine if AE symptoms were listed as separate AEs versus entered as one diagnosis, consider if the site's subject population is associated with a higher than average number of AEs) Call the site Visit the site
Greater than 15% of the average reported AE rate (Red)	Assess data remotely Call the site Visit the site

80

Examples of Responses to Risk Thresholds (2)

- **Risk Indicator:** A site has incorrectly administered IP and more than expected
- **Threshold:** Rate of incorrectly administered IP at a site is > 2 standard deviations more than the average rate across sites
- **Risk Detection:** Central monitoring analytic to flag outlying sites
- **Risk Mitigation:**
  - Monitor to retrain the PI and/or delegate off-site on the importance of IP compliance for subject safety and data integrity
  - Review the process for administering IP at next site visit
  - Other (standard) mitigation efforts, e.g.
    - Query where data is missing in CRFs
    - SDV a sample of the subjects at site visit

81

Risk Management Steps

1. Critical Process and Data Identification ✓
2. Risk Identification – **During protocol development** ✓
3. Risk Evaluation ✓
4. Risk Control – **predefined thresholds for quality** ✓
5. Risk Communication
6. Risk Review
7. Risk Reporting – **report deviations from the predefined thresholds**

[ICH E6 R2 Section 5.0]

82

5. Risk Communication

- Quality management activities should be
  - well **documented** and
  - **regularly communicated to stakeholders**

to facilitate risk review and continual improvement during clinical trial execution

→ **We need for example: Meeting minutes of risk assessments; evidence of risk communication in the TMF; definition and justification of stakeholders**

83

Risk Escalation steps

1. Identify & Document the Signal
- What happened
- When it occurred
- Who was involved
- Impact on safety, data, or compliance
- Whether it is isolated or part of a pattern

2. Classify the Severity to determine the escalation route

- **A. Critical Risks (Immediate Escalation) – Important Deviations -** Anything that threatens:
  - **Participant safety**
  - **GCP compliance**
  - **Data credibility**
    - Examples:
    - Unreported SAEs
    - Enrolling ineligible subjects
    - Suspected data fabrication
    - Missing or invalid informed consent

84

Risk Escalation steps

2. Classify the Severity to determine the escalation route

- **B. Major Risks (e.g., escalate within 24–48 Hours) -** Issues that could become critical if not addressed:
  - Repeated protocol deviations
  - Systematic data entry delays
  - Poor IP accountability
  - Staff turnover affecting trial conduct

  Example action: Notify the project manager, lead CRA, and site management team; Document in monitoring report and issue a CAPA request
- **C. Minor Risks (Routine Escalation) -** Operational inefficiencies or isolated errors:
  - Occasional missing data
  - Minor documentation gaps
  - Visit window deviations without safety impact

  Example Action: Address with site staff, document in follow-up letter, and monitor for recurrence

85

Risk communication methods

- **1. Immediate Verbal Escalation for critical risks**
  - Phone call → email confirmation → documentation.
- **2. Written Escalation**
  - Follow-up letters
  - Monitoring visit reports
  - Email alerts
  - Risk log entries
- **3. Formal Quality Processes**
  - CAPA management
  - Deviation reports
  - Quality incident reports
  - Audit recommendations
- **4. Central Monitoring Integration -** feeding risk signals into:
  - KRIs
  - Data trend dashboards
  - Risk review meetings

86

Risk communication to sponsors

1. The Risk Itself

- What the risk is
- How it was detected
- Which critical-to-quality factors it affects
- Whether it is emerging, active, or escalating

2. The Evidence

- KRIs/KPIs
- Monitoring findings
- Protocol deviation trends
- Recruitment or data-entry metrics
- Central monitoring outputs
- Site performance comparisons

87

Risk communication to sponsors

3. The Impact to quantify the consequences
- Patient safety
- Data integrity
- Regulatory compliance
- Timelines and budget
- Probability × severity x detectability

4. The Decision Options
- Mitigate
- Accept
- Escalate further (e.g., report as breach)
- Implement CAPA
- Increase monitoring intensity

5. The Recommended Action - Sponsors want a clear recommendation, not just a list of problems

88

Risk Management Steps

1. Critical Process and Data Identification ✓
2. Risk Identification – **During protocol development** ✓
3. Risk Evaluation ✓
4. Risk Control – **predefined thresholds for quality** ✓
5. Risk Communication ✓
6. Risk Review
7. Risk Reporting – **report deviations from the predefined thresholds**

[ICH E6 R2 Section 5.0]

89

6. Risk Review

- 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 and assessing residual risks
- [Revise the risk plan and documentation based on those changes]
- → **We need for example: Risk Assessment Plan; Meetings discussing risk assessments; risk registry with version control**

90

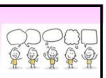
Risk Review in practice – identifying risk signals (1)

- **Risk detection is not a single activity — it's an ongoing analytical mindset applied before, during, and after every monitoring interaction**
- CRAs can detect risk signals by integrating **source data review**, **protocol compliance checks**, **safety surveillance**, and **data trend analysis** to spot deviations, inconsistencies, or emerging patterns that indicate potential threats to trial quality or participant safety
- KRIs such as query rates and unresolved inconsistencies are widely used to detect issues early
- Delayed data entry KRIs help flag operational risks before they disrupt timelines
- Protocol deviations are often the earliest indicator of deeper site issues

Classic early warning signs that require immediate escalation → see next slides

91

Risk Review - How to identify risk signals (1)



A. Patient Safety Signals

- Unexpected spikes in **adverse events** or **SAEs**
- Delayed or incomplete **safety reporting**
- Missing or incorrect **informed consent** documentation
- Protocol procedures skipped that could compromise safety (e.g., labs, ECGs)

B. Data Integrity Signals

- High **query rates** or repeated data inconsistencies
- Missing source documentation
- Transcription errors between source and EDC
- Patterns suggesting fabrication or "copy-paste" entries

92

Risk Review - How to identify risk signals (2)

C. Protocol Compliance Signals

- Site is enrolling ineligible subjects
- Visit windows are repeatedly missed
- Unapproved changes to procedures
- Investigators not following the investigational plan

D. Operational & Site Performance Signals

- Slow recruitment or sudden recruitment surges
- Staff turnover affecting study continuity
- Poor IP accountability

93

Risk Review - How to identify risk signals – the methods (1)

- **Source Data Verification (SDV) & Source Data Review (SDR) -** a cornerstone of risk detection
  - CRAs compare source documents with EDC entries to detect:
    - Inconsistencies
    - Missing data
    - Safety events not reported
- **Trend & Pattern Analysis using KRIs -** to look beyond individual datapoints
  - AE patterns across subjects
  - Repeated deviations
  - Outlier values
  - Sites performing differently from others

94

Risk Review - How to identify risk signals – the methods (2)

- **Site Engagement & Interviews**
  - Risk signals often surface through human interaction:
    - Staff expressing confusion about the protocol
    - Overworked coordinators
    - Poor communication from the PI
- **Review of Essential Documents**
  - Gaps here often correlate with other compliance risks
    - Delegation logs
    - Training records
    - IP accountability
    - Regulatory binders

95

Risk Management Steps

1. Critical Process and Data Identification ✓
2. Risk Identification – **During protocol development** ✓
3. Risk Evaluation ✓
4. Risk Control – **predefined thresholds for quality** ✓
5. Risk Communication ✓
6. Risk Review ✓
7. Risk Reporting – **report deviations from the predefined thresholds**

[ICH E6 R2 Section 5.0]

96

7. Risk reporting

- Sponsor should [in the Clinical Study Report]
  - **describe** the quality management approach implemented in the trial
  - **summarise** important deviations from the predefined quality tolerance limits

[ICH E3, Section 9.6 Data Quality Assurance]

97

Recommended items to be reported on QTLs (e.g. attachment in CSR)		
1	Parameter	The subject of the QTL
2	Justification for parameter	Rationale and any limitations to the use of the parameter
3	Unit	e.g., number, proportion
4	Tolerance limit	(Statistical) Limit (and whether it is one-sided or two sided)
5	Actual Occurrence	Occurrence at the end of the trial
6	The mitigations/ remedial actions taken	If a QTL is exceeded, explain the deviations and which actions had been taken if applicable
7	Impact to Data Integrity/Quality	Provide the rationale if the trial results are still regarded to be acceptable (e.g., for submission for marketing authorization, for analyzing the safety profile of a marketed compound). Clearly state if the results are not valid

Source: Transcelerate Risk-Based Quality Management: Quality Tolerance limits and risk reporting

98

Example

reporting on QTLs (within the CSR/appendix) Note – each set QTL needs summarising

Parameter	Justification for parameter	Unit	Tolerance limit	Actual occurrence at end of the trial	Mitigation/Remedial Actions Taken	Impact to Data Integrity/Quality
% of randomized subjects not meeting per protocol population criteria	A high number of subjects not meeting the entrance criteria can have a negative impact on interpretation of the primary endpoint and overall validity of the trial results.	%	1.7	1.0	During trial conduct, when 9000 of planned 20000 subjects were randomized, 162 subjects (1.8%) did not meet eligibility criteria. An assessment of individual cases revealed consistent misinterpretation of inclusion criterion #24. As a result, the protocol was revised to clarify inclusion criterion #24. In addition, refresher sessions were held with all sites to address compliance with inclusion/exclusion criteria. Result of actions brought parameter value below QTL by the end of the enrollment period (201 of 20000 subjects randomized [1.0%])	Analysis reveals no potential impact on patient safety and trial objectives

Source: Transcelerate Risk-Based Quality Management: Quality Tolerance limits and risk reporting

99

Risk Management Steps

1. Critical Process and Data Identification
2. Risk Identification – **During protocol development**
3. Risk Evaluation
4. Risk Control – **predefined thresholds for quality**
5. Risk Communication
6. Risk Review
7. Risk Reporting – **report deviations from the predefined thresholds**

[ICH E6 R2 Section 3.10]

100

Summary - Quality by Design

Refers to a systematic, proactive approach to ensuring quality is built into the design and conduct of a clinical trial from the outset—rather than relying on retrospective checks or fixes.

🔍 **Key Principles of QbD in Clinical Trials:**

1.Prevention over Detection:
Focus is on **preventing errors** that matter to patient safety and data integrity, rather than detecting and correcting them after they occur.

2.Critical to Quality (CTQ) Factors:
Identify and prioritize **key trial attributes** that are critical to delivering reliable results and protecting participants (e.g., proper randomization, adherence to inclusion criteria, accurate outcome measurement).

3.Risk-Based Thinking:
Apply **risk assessment** early in trial planning to identify where quality issues are most likely to occur and would have the highest impact.

4.Cross-functional Planning:
Involve stakeholders (sponsors, investigators, patients, regulators) from the beginning to ensure trial design is **feasible, ethical, and scientifically sound**.

5.Continuous Improvement:
Quality is monitored and refined throughout the trial using **risk-based monitoring (RBM)** and adaptive strategies

101

→ Quality by Design Checklist

1. Identify Critical to Quality (CTQ) Factors
- Have you identified primary objectives and endpoints clearly?
- Are key eligibility criteria directly linked to trial objectives?
- Have risks to patient safety and data reliability been prioritized?
- Are source data and measurement methods for endpoints clearly defined?

2. Protocol Design and Feasibility
- Is the protocol scientifically sound and operationally feasible?
- Have potential burdens on sites and patients been minimized?
- Are assessments and visits essential and logically scheduled?
- Has input been obtained from investigators and patients?

3. Risk Assessment and Mitigation
- Has a risk assessment been conducted?
- Are acceptable ranges/quality tolerance limits agreed?
- Are mitigation strategies in place for high-impact risks?
- Are monitoring strategies aligned with identified risks?

4. Study Tools and Training
- Are Data Collection Tools (e.g. CRFs) designed to collect only necessary data?
- Is staff training aligned with CTQ factors and risk areas?
- Are job aids and checklists available for complex procedures?

5. Oversight and Monitoring
- Does the monitoring plan focus on CTQ (Critical to Quality) processes and data?
- Are quality indicators in place to track performance over time?
- Is there a feedback loop for continuous improvement?

102

Overall Impact

- **Requires new procedures and evidence of implementation**
- Risk assessment is not a static event but **must be reviewed periodically, with relevant evidence**
- Risk assessment and mitigation plans are **required** regardless of whether Risk Based Monitoring is being utilised

103

Overall Impact

Some additional thoughts:

- Procedural risk assessment can be performed by going step-wise through patient-centred procedures and general study processes asking "What can go wrong?" in an interdisciplinary brainstorming session
- Be specific - following checklists and guidelines blindly is a major risk in risk analysis

ICH E6 R3 is similar to EMA **2013** risked based quality management of clinical trials proposal to set and document "quality tolerance limits" 18 November 2013 EMA/269011/2013 Compliance and Inspection Reflection paper on risk based quality management in clinical trials Reflection paper risk based quality management in clinical trials (europa.eu)

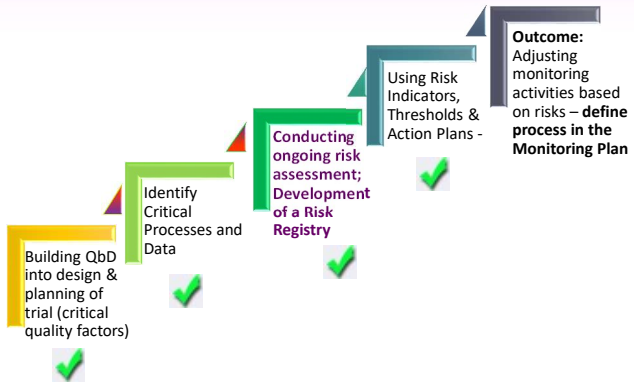
104

Quality risk management principles - implementation

How risks drive operational decisions

105

Risk Management Tools



106

Quality by Design (QbD) and Risk Based Monitoring Concept

Build Quality into the scientific and operational design and conduct of clinical trials to:

- Effectively & efficiently answer intended questions about benefits/risks
- Identify fit for purpose data
- Focus on key risks to Patient safety & data integrity
- **Design efficient Monitoring Plans to rapidly detect/correct issues**

Identify risks at the program, study, & site level to **apply the appropriate level of monitoring** through:

- Mapping the risks to appropriate monitoring plans
- Monitor important parameters (Central & Off-site monitoring activities)
- Implement effective oversight
- Targeted on-site interventions

107

ICH E6 R3 - Monitoring (also see ICH E6 R3 3.11.4)

Quality control should be applied using a risk-based approach to each stage of the data handling to ensure that data are reliable and have been processed correctly. Within clinical trials, monitoring and data management processes are the main quality control activities. Where appropriate, quality control activities may also be applied to facilities outside of investigator sites (e.g., central image reading facilities).

Planning is the key to implementing risk-based monitoring

For example:

- extent of source document verification and review
- the extent of remote monitoring
- risk indicators/signals and their associated risk mitigation strategies

By taking a risk-based approach, decisions are made **prospectively**

108

Monitoring Plan (1) (also see ICH E6 R3 3.11.4.3)

The plan should
describe the monitoring strategy that should ensure appropriate oversight of trial conduct considering site capabilities and the potential burden

- Describe the monitoring **responsibilities and activities** of all the parties involved
- Describe the various monitoring **methods** and tools to be used **and the rationale for their use**
- Describes the range of different types of monitoring visits [OnSite/Remote/ Centralised] and when they should be used

The monitoring plan must be tailored to the identified potential safety risks, the risks to data quality and/or other risks to the reliability of the trial results

The plan should
provide those involved in monitoring with adequate information to effectively carry out their duties

109

Monitoring Plan (2) (also see ICH E6 R3 3.11.4.3)

The plan should
describe what should be done at each type of visit and under what circumstances you might switch from one visit type to the next – **describe your triggers**

- **Focus on aspects that are critical to quality** (Remember !!!)

The plan should
address 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)

Particular attention should be given to aspects not routine clinical practice and that require additional training

The plan should
reference the applicable policies and procedures

110

Monitoring Plan (3) (also see ICH E6 R3 3.11.4.3)

All sponsor and CRO personnel who may be involved with monitoring, including those who review and/or determine appropriate action regarding potential issues identified through monitoring, should review the monitoring plan → **ensure evidence of this**

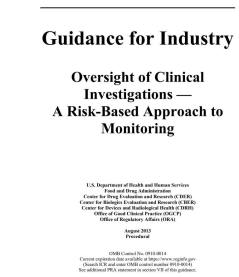
Monitoring Reports should be sufficiently detailed to demonstrate compliance with the plan

111

Monitoring

- Also refer to FDA Guidances

- Whilst FDA CFR parts are legally binding, guidance documents are not
- Guidance documents do provide the "current thinking" of the regulators
- Deviating from these guidelines should therefore be done with caution and with justification

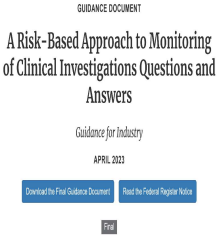

Guidance for Industry

Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Combination Products (OCP)
Office of Regulatory Affairs (ORA)

August 2013
Procedural

OMB Control No. 0910-0014
Current expiration date available at https://www.reginfo.gov
(Search ICR and enter OMB control number 0910-0014)
See additional PRA statement in section VII of this guidance.


GUIDANCE DOCUMENT

A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers

Guidance for Industry

APRIL 2023

Download the Final Guidance Document | Read the Federal Register Notice

Final

[Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring | FDA]

[A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers | FDA]

112

The "new" Monitoring – why

- No single approach is appropriate for every clinical trial, therefore a **risk-based monitoring approach -**
  - Provides strategy for on-site, off-site and centralized monitoring
  - Allows sponsor to monitor the right data (Identified Risks)
  - Addresses the risks of the study (Risk Mitigation Plan)
  - Allows better quality of data per ALCOA Principles
  - Allows quick identification and issue escalation in real time
  - Results in better utilization of resources

…flexibility… to permit varied approaches …. improve effectiveness and efficiency of monitoring…

113

ALCOA ?

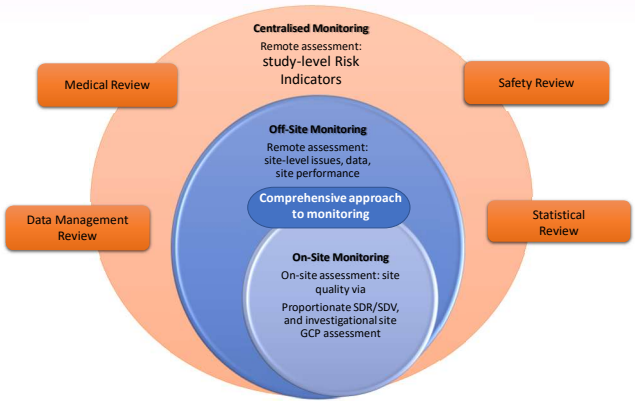
114

The "new" Monitoring – how

- **A combination of on-site, off-site and centralised monitoring** activities may be appropriate (with extend and nature described in the monitoring plan)

115

RBM - Monitoring Execution



116

Off-site Monitoring

Is a remote evaluation of ongoing and/or cumulative data collected from trial sites:

- **Data Errors:** identify systematic or significant errors in data collection and reporting at a site, potential data manipulation, data integrity problems
- **Data Analysis:** identify data trends such as the range and consistency of data at a site
- **Outlier oversight:** identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations
- **Performance review:** analyse site characteristics and performance metrics
- **Target sites:** select processes for targeted on-site monitoring

117

Centralised Monitoring 3.11.4.2

Evaluation of accumulated data by the sponsor's qualified and trained persons (e.g., medical monitor, data scientist/data manager, biostatistician)

- Provides additional monitoring capabilities that can complement and reduce the extent and/or frequency of site monitoring or be used on its own
- Use of centralised data analytics can help identify systemic or site-specific issues, including protocol noncompliance and potentially unreliable data
- Centralised monitoring may support the selection of sites and/or processes for targeted site monitoring

118

Key Features of RBM Methodology

- Monitoring is customized to sites/trials needs
- Schedule is flexible to comply with sites needs
- Identifies risks proactively
- Shares monitoring responsibilities across many functional areas
- Relies more heavily on central and off-site monitoring

119

How risk drives operational decisions in clinical trials (1)

Monitoring Intensity

- **Risk-based monitoring (RBM):** Monitoring frequency and depth are tailored to the level of risk (e.g., patient safety, data integrity, protocol complexity)
- **Critical data focus:** High-risk endpoints (primary efficacy, safety data) receive more frequent and detailed review than non-critical data
- **Site risk stratification:** Sites with higher risk (e.g., inexperienced staff, high enrolment, past issues) get more intensive monitoring
- **Central vs on-site monitoring balance:** Lower-risk trials rely more on centralized/remote monitoring; higher-risk trials require more on-site visits

120

How risk drives operational decisions in clinical trials (2)

Monitoring Intensity

- **Adaptive monitoring plans:** Monitoring intensity is adjusted throughout the trial based on emerging risks, trends, and findings
- **Key Risk Indicators (KRIs):** Site Metrics (e.g., protocol deviations, query rates) trigger increased monitoring when thresholds are exceeded
- **Reduced Source Data Verification (SDV):** Low-risk data may undergo partial or no SDV, while high-risk data undergo 100% SDV
- **Patient safety prioritization:** Trials with higher safety risks (e.g., first-in-human studies) demand more frequent and detailed monitoring

121

Impact

- **Processes need to be developed by the sponsor (not just by CRO !) to define a "systematic, prioritized, risk-based approach to monitoring clinical trials"**
- **Off-site Monitoring and On-site Monitoring reports required**
- **Evidence of Central Monitoring activities and reports required**
- The sponsor must confirm that all reports contain sufficient information to
  - allow verification of compliance with monitoring plan,
  - contain a summary of what was reviewed,
  - significant findings, deviations and deficiencies,
  - conclusions and actions recommended or taken to secure compliance

122

Impact

- The **monitoring strategy** should be formulised and plans are **no longer optional** or "good practice"
- EU CTR 536/2014 does not explicitly define a "monitoring plan", however Article 48 states that "extent and nature of the monitoring shall be determined by the sponsor on the basis of an assessment… " and Annex 1.D.17 (AD) does require that the protocol includes "a description of arrangements for monitoring the conduct of the clinical trial"

123

References

TransCelerate Risk Based Monitoring Project
Risk Based Monitoring Solutions - TransCelerate (transceleratebiopharmainc.com)

FDA Guidance for Industry Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring [Final]
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf

EMA Reflection Paper on Risk Based Quality Management in Clinical Trials (EMA/INS/GCP/394194/2011)
https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-risk-based-quality-management-clinical-trials_en.pdf

Clinical Trials Transformation Initiative. Effective and efficient monitoring as a component of quality
CTTI Recommendations: Effective and Efficient Monitoring as a Component of Quality Assurance in the Conduct of Clinical Trials - CTTI

124

How risk drives operational decisions in clinical trials (3)

Service Provider Oversight

Risk-based selection: Service Providers are chosen based on their ability to manage specific risks (e.g., lab accuracy, data handling, geographic coverage)
Critical Service Provider oversight: Service Providers supporting high-impact activities (e.g., central labs, EDC systems) must receive greater oversight
Oversight intensity proportional to risk: High-risk Service Providers are subject to more frequent audits, meetings, and performance reviews
Performance metrics tracking: KPIs (e.g., turnaround time, error rates) are monitored closely, especially for high-risk services

125

How risk drives operational decisions in clinical trials (4)

Service Provider Oversight

Contractual risk controls: Service level agreements include stricter requirements and penalties for Service Providers
Data integrity assurance: Service Providers handling critical data are subject to stricter validation, access controls, and compliance checks
Issue escalation pathways: Faster and more formal escalation processes are in place for high-risk Service Providers issues
Continuous risk assessment: Service Providers risk profiles are reassessed throughout the trial, adjusting oversight as needed

126

How risk drives operational decisions in clinical trials (5)

Investigational Site Selection

Patient safety risk assessment: Sites are selected based on their ability to safely manage the study population (e.g., access to emergency care, experience with similar patient groups)
Investigator experience & qualifications: High-risk trials (e.g., complex protocols, first-in-human) prioritize highly experienced investigators and well-trained staff
Protocol complexity fit: Sites must demonstrate capability to handle complex procedures, specialized equipment, or intensive visit schedules
Historical performance data: Past metrics (e.g., enrolment rates, protocol deviations, audit findings) are used to avoid high-risk or underperforming sites
Infrastructure and resources: Adequate staffing, facilities, pharmacy capabilities, and data systems are critical—gaps increase operational risk

127

How risk drives operational decisions in clinical trials (6)

Investigational Site Selection

Patient population access: Sites with reliable access to the target population reduce recruitment risk and timeline delays
Regulatory and compliance history: Sites with prior inspection findings or compliance issues are considered higher risk and may be excluded or closely managed
Geographic and geopolitical risk: Location-based risks (e.g., political instability, regulatory variability, logistics challenges) influence site inclusion and contingency planning
Competing trials and workload: Overburdened sites may pose risks to data quality and timelines, leading to lower prioritization

128

How risk drives operational decisions in clinical trials (7)

Investigational Site Selection

Technology readiness: Ability to use EDC, ePRO, remote monitoring tools is essential—lack of readiness increases operational risk
Start-up timelines: Sites with historically slow ethics/regulatory approvals may be deprioritized to mitigate timeline risk
Quality culture and training: Sites demonstrating strong adherence to GCP and proactive quality management are preferred for higher-risk studies
Risk-based site mix strategy: Sponsors balance high-performing "core" sites with newer sites to manage both performance risk and enrolment scalability
Ongoing risk reassessment: Site risk is continuously evaluated during the trial, influencing continued participation, monitoring intensity, or early termination

129

The expectations of regulators

GCP inspection outcomes related to Risk Based Quality Management

130

How can QRM activity be inspected

- **Inspectors might review :**
  - Whether the quality risk management performed is integrated in the Quality System of the organization
  - Traceability, transparency
  - Were risks/QTLs defined and monitored
  - How were the decisions made
  - Were the decisions justified and based on scientific knowledge
  - Were the appropriate functions involved
  - How was risk and risk management communicated
  - How were risk mitigation decisions taken
  - **Is documentation available to reconstruct the actions**

131

FDA Inspection Processes

Bioresearch Monitoring Program (BIMO) Compliance Programs

Share | Tweet | LinkedIn | Email | Print

Compliance Program Manual

Program #	Compliance Program Title	On-line Availability	
7348.003	In Vivo Bioavailability-Bioequivalence Studies - Clinical		PDF
7348.004	In Vivo Bioavailability-Bioequivalence Studies - Analytical		PDF
7348.007	Inspection of Nonclinical Laboratories Conducting Animal Rule-Specific Studies		PDF
7348.808	Good Laboratory Practice (Nonclinical Laboratories)		PDF(117 kb)
7348.808A	Good Laboratory Practice Program (Nonclinical Laboratories) EPA Data Audit Inspections	HTML	PDF(38 kb)
7348.809	Institutional Review Board		PDF(293 kb)
7348.809A	Radioactive Drug Research Committee		PDF (155 kb)
7348.810	Sponsors and Contract Research Organizations		PDF
7348.811	Clinical Investigators and Sponsor-Investigators		PDF
7353.001	Postmarketing Adverse Drug Experience (PADE) Reporting Inspections		PDF (335 kb)
7353.001C	Risk Evaluation and Mitigation Strategies (REMS) Reporting Inspections		PDF

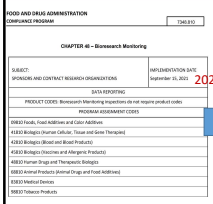
Content current as of: 10/17/2022

Topic(s) Compliance

Bioresearch Monitoring Program (BIMO) Compliance Programs | FDA

132

FDA Inspection Processes


FOOD AND DRUG ADMINISTRATION
COMPLIANCE PROGRAM

7345.810

CHAPTER 48 – Bioresearch Monitoring

SUBJECT: SPONSORS AND CONTRACT RESEARCH ORGANIZATIONS	IMPLEMENTATION DATE: September 15, 2021
DATA REPORTING	
PRODUCT CODES: Bioresearch Monitoring inspections do not require product codes	
PROGRAM ASSIGNMENT CODES	
03B30 Foods, Food Additives and Color Additives	
41B30 Biologics (Human Cellular, Tissue and Gene Therapies)	
42B30 Biologics (Blood and Blood Products)	
45B30 Biologics (Vaccines and Allergenic Products)	
46B30 Human Drugs and Therapeutic Biologics	
56B30 Animal Products (Animal Drugs and Food Additives)	
85B30 Medical Devices	
99B30 Tobacco Products	

2021

Page 26

H. MONITORING PROCEDURES AND ACTIVITIES

Regulations state that sponsors are required to ensure proper monitoring of the study (21 CFR 312.50 and 812.40) and to select monitors qualified by training and experience to monitor the study (21 CFR 312.50, 312.53(d), 511.1(b)(8)(ii), 514.117, and 812.43(d)). However, regulations are not specific about how sponsors are to conduct such monitoring (e.g., it may be onsite, remote, and/or involve centralized monitoring practices).

Sponsors may utilize a systematic, prioritized, risk-based approach in monitoring practices appropriate to a given study.[19] No single approach to monitoring is appropriate or necessary for every clinical study. As such, the extent and nature of monitoring may vary.

Each sponsor should design a monitoring plan that is tailored to the specific risks of the trial. In general, monitoring activities should focus on preventing or mitigating important and likely sources of error in the conduct, collection, and reporting of critical data (e.g., efficacy endpoint data, safety data) and processes necessary for subject protection and trial integrity.

Review the sponsor's procedures (e.g., written SOPs or stated practices), and study-specific plans for studies under review, for the following:

Bioresearch Monitoring Program (BIMO) Compliance Programs | FDA

133

FDA Inspection Metrics (2021)

Common Sponsor/CRO Inspectional Observations*

- Failure to submit an Investigational New Drug (IND) application
- Failure to select qualified investigators and/or monitors, ensure proper monitoring of the study and ensure the study is conducted in accordance with the protocol and/or investigational plan
- Failure to maintain and/or retain adequate records in accordance with 21 CFR 312.57; accountability for the investigational product; Investigator Statement (Form FDA 1572); Financial disclosures

However, available FDA metrics do not provide details

*Most common observations collected from issued FDA Form 483s

14

PowerPoint Presentation (fda.gov)

134

Expectations - MHRA


Version: 10th October 2011

MHRA

MRC/DH/MHRA Joint Project

Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products

Table of Contents

Titles	Page
Executive summary	1
Background to the project	2
Risk in clinical trials	2
Risk assessment	3
Appendix 1: Guidance on risk adapted approaches within the scope of the Clinical Trials Directive	6
Appendix 2: Guidance on risk-proportionate approaches to the management and monitoring of clinical trials	19
Appendix 3: Membership of Ad-hoc Working Group and Risk-stratification Sub-group	30

Executive Summary


GOV.UK

Home > Clinical trials and investigations > Risk-Adapted Approach to clinical trials and Risk Assessments

Medicines & Healthcare products Regulatory Agency

Guidance

Risk-Adapted Approach to clinical trials and Risk Assessments

Published 28 January 2022

Contents

Risk Assessment Process

When and how to undertake the risk assessment

Risk Assessment Process

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.

MRC/DH/MHRA Joint Project (publishing.service.gov.uk)

Risk-Adapted Approach to clinical trials and Risk Assessments - GOV.UK (www.gov.uk)

135

MHRA Inspectorate Blog


GOV.UK

Blog

MHRA Inspectorate

Organisations: Medicines and Healthcare products Regulatory Agency

Risk Adaption in Clinical Trials of Investigational Medicinal Products (CTIMPs)

Kath Meely, 16 November 2017 - Compliance matters, Good clinical practice

Hello and welcome to the first blog written jointly by Kath Meely from the GCP Inspectorate and Lisa Campbell from the Clinical Trials Unit (CTU) about risk adaption in clinical trials of Investigational Medicinal Products (CTIMPs).


GOV.UK

Blog

MHRA Inspectorate

Organisations: Medicines and Healthcare products Regulatory Agency

Search results for Risk

About the MHRA Inspectorate Blog

Risk Adaption in Clinical Trials of Investigational Medicinal Products (CTIMPs) - MHRA Inspectorate (blog.gov.uk)

136

MHRA Inspectorate Blog

Source 23 August 2022: Innovation, Quality & Transparency – a Compliance Team 1 Perspective - MHRA Inspectorate (blog.gov.uk)

…Uptake in the right direction, with industry and academia reviewing how they can be as transparent as possible with regulators on their risk assessments for trials; what the most important risks are, how they are mitigated, and what the issues were.

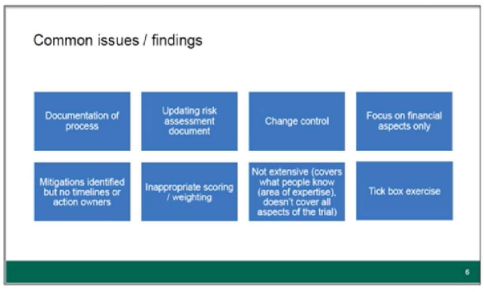
Some have already moved to submitting this information directly through marketing authorisation applications internationally…. and look to push risk adaptation into the forefront of planning and managing clinical trials.

We are in the early stages of seeing this type of activity, but from the MHRA perspective - quality input built into these risk assessments and transparent release of this detail to regulators is exactly what is required to support innovation.

137

MHRA Inspection Metrics

MHRA Presentation at Industry Meeting



Source: Mandy Budwal-Jagait [Head of GCP, MHRA]. *Implementation of ICH E8 (R1) - An Inspector's perspective*. DIA Annual Global Meeting - June 2022.

138

MHRA Inspection Observations – Documentation

Documentation of risk management process

It should be clearly documented: who has participated in the risk assessment - those involved could change as the planning and conduct of the trial progresses

Documentation of the risk assessment is essential – it is an important document which will influence the conduct and management of the trial. It is for the sponsor to decide upon the best way to document the areas considered, the risks identified and any mitigations/adaptations.
MHRA recommends a tabular format for the assessment, and an example is provided in Appendix 2 of the risk-adaptive approach

It is strongly recommended that the risk assessment is a separate document in its own right. The documented risk assessment should be subject to appropriate version control

The sponsor is responsible for selecting or defining a suitable process to define the risk for the various areas assessed

The risk assessment should be kept in the Trial Master File (TMF)

Risk-Adapted Approach to clinical trials and Risk Assessments - GOV.UK (www.gov.uk)

139

MHRA Inspection Observations – Risk Scoring

Inappropriate scoring/ weighting

Whilst an overall risk score can give a useful indication of the trial's risk, the aim of the risk-adapted approach is to identify specific vulnerabilities within the trial and take appropriate actions for these
Specific high risk areas within the trial could potentially be overlooked by assigning a risk category to the entire trial

Risk-Adapted Approach to clinical trials and Risk Assessments - GOV.UK (www.gov.uk)

140

MHRA Inspection Observations – Updates

Updating the risk assessment document

It is expected that the sponsor undertakes a continual review of the risk assessment, which is particularly important when new information becomes available
For example, the risk assessment should be re-examined following a protocol amendment or when new data is obtained (new SmPC, related pre-clinical/clinical trial results are released, a data monitoring committee meeting or interim analysis takes place)
If the risk assessment is reviewed and it is not updated, the sponsor should document that the review has taken place

It is important when applying a quality risk management process that systems are in place for identification of new or unanticipated risks and taking appropriate actions
For example, a serious breach may occur and this may result in an amendment to the risk assessment with additional, changed or new mitigating actions required, such as changes to the type and/or frequency of monitoring

Risk-Adapted Approach to clinical trials and Risk Assessments - GOV.UK (www.gov.uk)

141

MHRA Inspection Observations – Mitigation management

Mitigations identified but no timelines or action owners are identified

The risk assessment should be kept in the trial master file (TMF), but it is important that the sponsor and, where appropriate, site staff are aware of the content of the risk assessment
Therefore there should be a process to ensure that the risk assessment and are provided to the relevant personnel

It is strongly recommended that one person has the responsibility for ensuring that the mitigations/actions that are planned from the risk assessment have been implemented and undertaken
For example, ensuring the requirements for specific aspects of monitoring identified in the risk assessment are subsequently captured in the trial monitoring plan (or other trial procedure)
This would typically be the responsibility of the Project Manager

Risk-Adapted Approach to clinical trials and Risk Assessments - GOV.UK (www.gov.uk)

142

MHRA Inspection Observations – Personnel

Lack of personnel involvement

Area of expertise does not cover all aspects of the trial

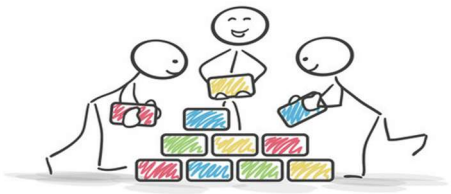
Relevant personnel undertaking the risk assessment would typically include:

- Medic with understanding of the therapeutic area and the therapeutic use of the proposed IMP
- Pharmacist/ toxicologist/pharmacologist who has a detailed understanding of the IMP;
- Statistician with relevant experience of medical statistics;
- Person with an appropriate level of understanding of applicable regulatory, legal and GCP requirements (e.g. Regulatory Affairs/Quality Assurance/Lawyer/Research Governance personnel);
- 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;
- Also try to include a suitable patient advocate/ representative in the risk assessment

Risk-Adapted Approach to clinical trials and Risk Assessments - GOV.UK (www.gov.uk)

143

Implementation



144

Mindsets and expectations

- 'I am not involved, our QMS manages it'
- 'The Vendor will inform us of any data irregularities'
- 'It's not my job to do this'

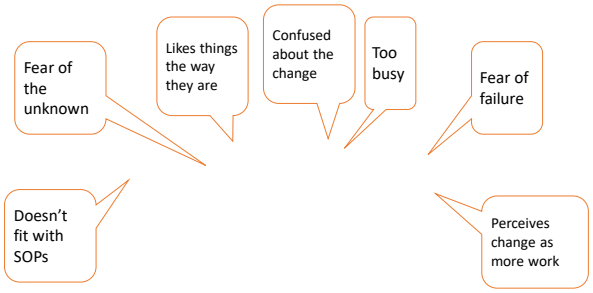
Instead

- Companies should create the right environment to enable data integrity controls to be effective
- There should be a Data Integrity Policy
- Governance measures should be employed, e.g. audits on data integrity failures
- When weaknesses are identified, CAPAs must be implemented across all related activities
- Ensuring data integrity is the responsibility of everyone who produces, manages, analyses, reports and archives data
  - No one should say "it's not my responsibility"

145

Challenges with Change

- Cultural – We've always done it this way
- Systems – The systems we have require that we do it this way

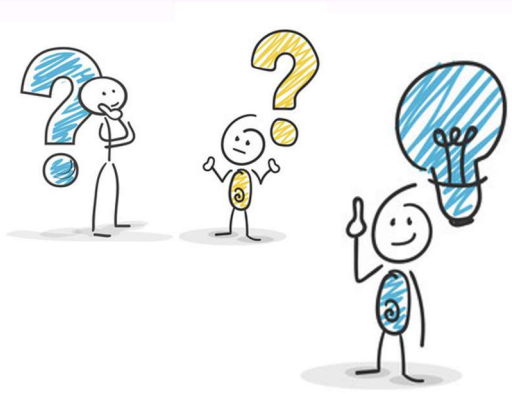


146

Questions to ask

- Do our policies and procedures adequately address risk?
- Do our practices incorporate the focus on quality control?
- Can our teams monitor leading quality indicators and potential risks?
- Have we adopted methods that can help pinpoint risks when they show up amid reams of data?
- Do our teams understand how to use relevant technology, and how to incorporate it into trial designs?
- Have we taken measures to ensure the quality and diversity of data generated by technology (e.g., apps, tables, wearable devices, etc.)?
- Do we have the expertise and technology to support remote and central monitoring?
- Can our processes implement Risk Based Monitoring?

147



148

Jeannette Dixon, jQAGCP Ltd. jqagcp@gmail.com

149

Additional References

- TransCelerate Home Page https://www.transceleratebiopharmainc.com/
- FDA Guidance for Industry Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring [Final] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf.
- Clinical Trials Transformation Initiative. Effective and Efficient Monitoring as a Component of Quality Assurance in the Conduct of Clinical Trials https://ctti-clinicaltrials.org/about/ctti-projects/quality-by-design/ctti-recommendations-effective-and-efficient-monitoring-as-a-component-of-quality-assurance-in-the-conduct-of-clinical-trials/
- EMA Quality By Design Guidance documents Quality: Quality by Design (QbD) | European Medicines Agency (EMA)
- GCP Inspectors Working Group https://www.ema.europa.eu/en/human-regulatory-overview/research-development/compliance-research-development/good-clinical-practice/good-clinical-practice-inspectors-working-group

150

Additional References

- EMA Data Integrity Q&A (2016) https://www.ema.europa.eu/en/news/data-integrity-key-public-health-protection
- https://rx-360.org/wp-content/uploads/2018/08/2016-EMA-QA.pdf
- WHO Annex 4. Guideline on data integrity https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/inspections/trs1033-annex4-guideline-on-data-integrity.pdf?sfvrsn=6218a4e6_4&download=true&utm_source=copilot.com
- MHRA Oversight and monitoring activities (JAN2022) https://www.gov.uk/government/publications/oversight-and-monitoring-of-investigational-medical-product-trials/oversight-and-monitoring-activities
- MHRA Guidance on GxP data integrity https://www.gov.uk/government/publications/guidance-on-gxp-data-integrity

151

Additional References

- MRC/DH/MHRA Joint Project Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Risk-adapted_approaches_to_the_management_of_clinical_trials_of_investigational_medicinal_products.pdf
- EMA Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational_en.pdf

152

Additional References

- EMA Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic) (December 2018) https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-content-management-archiving-clinical-trial-master-file-paper/electronic_en.pdf
- MHRA Forum FAQ for Trial Master Files (TMF) and Archiving https://forums.mhra.gov.uk/showthread.php?1665-MHRA-produced-FAQs-for-Trial-Master-Files-(TMF)-and-Archiving
- Trial Master File Reference Model https://tmfrefmodel.com/

153

Additional References

- EMA Notice to sponsors on validation and qualification of computerised systems used in clinical trials (April 2020) https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/notice-sponsors-validation-qualification-computerised-systems-used-clinical-trials_en.pdf
- EMA Q&A: Good clinical practice (GCP) (April 2020) https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp
- EudraLex Volume 4 (GMP) Annex 11: Computerised Systems (effective June 2011) https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/annex11_01-2011_en.pdf
- Council of Europe Revised: "Validation of Computerised Systems" Guideline (effective August 2018) https://www.edqm.eu/en/news/revised-validation-computerised-systems-guideline

154

Additional References

- European Commission - Clinical trials - Regulation EU No 536/2014 https://ec.europa.eu/health/human-use/clinical-trials/regulation_en
- EMA Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials (June 2010; superseded) https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/reflection-paper-expectations-electronic-source-data-data-transcribed-electronic-data-collection_en.pdf
- EMA Guideline on computerised systems and electronic data in clinical trials Guideline on computerised systems and electronic data in clinical trials
- EudraLex - Volume 10 - Clinical trials guidelines https://ec.europa.eu/health/documents/eudralex/vol-10_en
- Clinical efficacy and safety guidelines https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-efficacy-safety-guidelines
- **Data Integrity in Global Clinical Trials:** Discussions From Joint US Food and Drug Administration and UK Medicines and Healthcare Products Regulatory Agency Good Clinical Practice Workshop CLINICAL PHARMACOLOGY & THERAPEUTICS VOLUME 00 NUMBER 0; Month 2020

155

Additional References

- MHRA BLOG Sponsor oversight
  - https://mhrainspectorate.blog.gov.uk/2018/07/26/sponsor-oversight-part-1/
  - https://mhrainspectorate.blog.gov.uk/2018/09/25/sponsor-oversight-part-2/
- EMA Q&A: https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp
- Cornell Law School, Legal Information Institute: https://www.law.cornell.edu/cfr/text/21/part-312/subpart-D
- Health Canada Clinical Trial Inspections: https://www.drug-inspections.canada.ca/gcp/searchResult-en.html?lang=en&sponName=&contNum=&region=&drugName=&phase=&startDate=&rating=NC&cat=2
- WHO Essential Medicines and Health Products Information Portal (digicollections.net) https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/essential-medicines-lists?utm_source=copilot.com

156

Other Reading Lists (1)

- Regulation (EC) No. 1394/2007 on advanced therapy medicinal products
- Directive 2001/83/EC on the community code relating to medicinal products for human use
- Directive 2009/120/EC relating to medicinal products for human use as regards advanced therapy medicinal products
- Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006)
- Guideline on xenogeneic cell therapy medicinal products (EMEA/CHMP/CPWP/83508/2009)
- Reflection Paper on stem cell-based medicinal products (EMA/CAT/571134/2009)
- European Pharmacopoeia, general chapter 5.14
- Draft Guideline on the risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to Advanced Therapy Medicinal Products (EMA/CAT/CTWP/686637/2011)

157

Other Reading Lists (2)

- Guideline on non-clinical studies required before first clinical use of gene therapy medicinal products (EMEA/CHMP/GTWP/125459/2006)
- Guideline on non-clinical testing for inadvertent germline transmission of gene transfer vectors (EMEA/273974/2005)
- Guideline on follow-up of patients administered with gene therapy medicinal products (EMEA/CHMP/GTWP/60436/2007)
- Guideline on safety and efficacy follow-up – risk management of advanced therapy medicinal products (EMEA/149995/2008)
- Eudralex Volume 10 of The Rules Governing Medicinal Products in the European Union – Clinical trials
- Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products (CHMP/GTWP/125491/2006)

158