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Global Harmonization Center Clinical Trials Webinar Part 1:
ICH E6(R3): Current Status and Implementation of Updated Good Clinical Practice Guideline
Understanding the major amendments in ICH E6 (R3) and the introduced "Proportionality Approach" - June 2026

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Outline

- Overview of ICH E6 (R3) and Proportionality Concepts
- Comparative Analysis: ICH E6 (R2) Vs. ICH E6 (R3)
- Risk Proportionality, Quality by Design and Critical to Quality Factors in Clinical Trials
- Practical Implementation: Use Case(s)
- Stakeholder Roles & Engagement
- Key Messages

Overview of ICH E6 (R3) and Proportionality Concepts



*Link to the ICH E6 (R3) guideline: https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step4_FinalGuideline_2025_0106_ErrorCorrections_2025_1024.pdf

- ICH E6 (R3)* is a revision of the ICH E6 (R2) guideline and does **not** introduce a new standalone section or formal definition of "proportionality.“
- Instead, it **strengthens and encourages** existing concepts of a **risk-based and proportionate approach** to the conduct of a clinical trial.
- Principle 7: Clinical trial processes, measures and approaches should be implemented in a way that is **proportionate to the risks** to participants and to the importance of the data collected and that avoids unnecessary burden on participants and investigators.

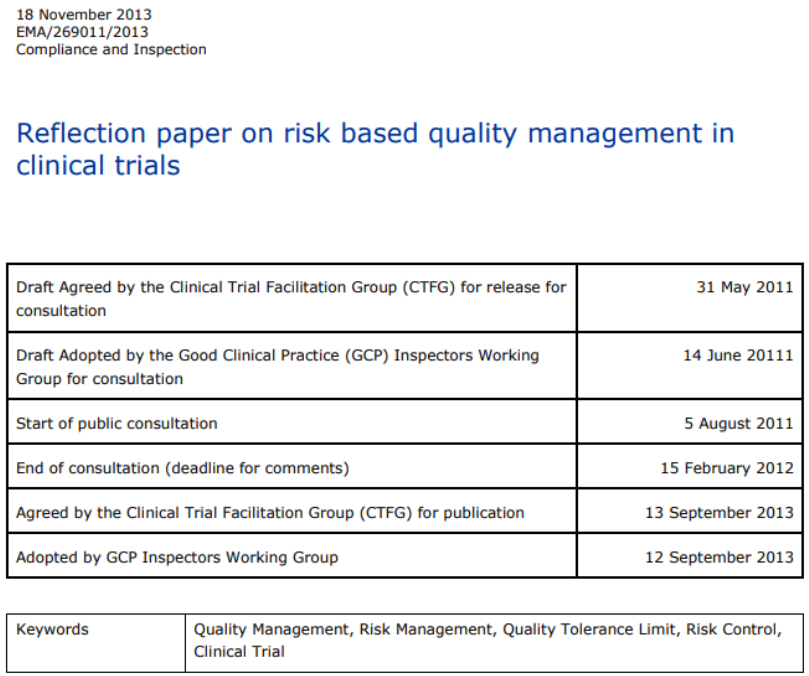


Rationale for Proportionality

- Proportionality balances clinical trial efforts based on participant risk and data importance
  - 7.1 Trial processes should be proportionate to the risks inherent in the trial and the importance of the information collected. Risks in this context include risks to the rights, safety and well-being of trial participants as well as risks to the reliability of the trial results.
- Proportionality safeguards trial integrity by aligning activities with risk and data criticality.
- 7.2 The focus should be on the risks associated with trial participation. For clinical trials involving patients, the focus should be on risks that go beyond those associated with usual medical care.
- Applying proportionality helps optimize (limited) resources while maintaining compliance with regulatory standards

(CTCG) Reflection paper on risk based quality management in clinical trials (2013)

- Source: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-risk-based-quality-management-clinical-trials_en.pdf
- „The current manner in which **some elements of a quality system are implemented** by sponsors and their agents (CROs etc.) is generally acknowledged to be time-**consuming** and constitutes a major proportion of the cost of development of medicines."
- "**risk aversion** – society and its institutions (public and private) is increasingly risk averse, often with little appreciation of the actual or relative risk of different activities, leading to imbalanced or disproportionate risk mitigation;"



18 November 2013
EMA/269011/2013
Compliance and Inspection

Reflection paper on risk based quality management in clinical trials

Draft Agreed by the Clinical Trial Facilitation Group (CTFG) for release for consultation	31 May 2011
Draft Adopted by the Good Clinical Practice (GCP) Inspectors Working Group for consultation	14 June 20111
Start of public consultation	5 August 2011
End of consultation (deadline for comments)	15 February 2012
Agreed by the Clinical Trial Facilitation Group (CTFG) for publication	13 September 2013
Adopted by GCP Inspectors Working Group	12 September 2013

Keywords	Quality Management, Risk Management, Quality Tolerance Limit, Risk Control, Clinical Trial

- "poor risk identification and poor risk mitigation – a lack of use or understanding of risk-management tools and techniques, is often associated with a reactive, fire-fighting approach to problem management. This results in p**rocesses** largely based on **corrective rather than preventive** actions;

(CTCG) Risk proportionate approaches in clinical trials

Risk proportionate approaches in clinical trials

Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use

25 April 2017

Table of contents

1. Introduction 3
2. Scope 3
3. Low intervention clinical trials 4
4. Risk proportionate approaches in clinical trials 6
4.1. Risk based quality management 5
4.2. Safety reporting 8
4.3. IMP management 10
Traceability and accountability 10
4.4. Trial management 11
Monitoring 11
4.5. Trial documentation 12
Content of the Trial Master File (TMF) 12
5. References 14

- Source: https://health.ec.europa.eu/system/files/2017-08/2017_04_25_risk_proportionate_approaches_in_ct_0.pdf

Focus on what matters

- "Everything should be made as simple as possible, but not simpler." - Albert Einstein
- "If we knew what it was we were doing, it would not be called research, would it?" - Albert Einstein

- It is not about being perfect
  - Strengthen critical thinking
    - Clinical trials should generate data of sufficient quality to provide confidence in the results for good decision making
      - Moving away from checklists*
        - The pharmaceutical sector has a reputation to be risk avert

Don’t be afraid

- "Anyone who has never made a mistake has never tried anything new." - Albert Einstein

- “Hazel, like nearly all wild animals, was unaccustomed to look up at the sky. What he thought of as the sky was the horizon, usually broken by trees and hedges.” - Richard Adams

A rather **philosophical approach** to regulatory compliance rather than a quantitative mathematical proportionality?

This could means that:

- Low-risk trials require less intensive oversight and documentation.
- High-risk trials (e.g., first-in-human, complex biometrics, vulnerable populations) require more rigorous monitoring, data integrity measures, and sponsor oversight.
- Annex 1: 3.10 Quality management
- The sponsor should implement an appropriate system to manage quality throughout all stages of the trial process. Quality management includes the design and implementation of efficient clinical trial protocols, including tools and procedures for trial conduct (including for data collection and management), in order to ensure the protection of participants' rights, safety and well-being and the reliability of trial results. The sponsor should adopt a proportionate and risk-based approach to quality management, which 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 Clinical Study Reports).

Risk-Based, proportionate oversight: Trial design and conduct to generate data of **sufficient quality** (not perfect)



- The guidance promotes adjusting oversight and monitoring based on (continuous) risk assessments in trials. – proportionate to the risks
- Annex 1 3.9.5: The range and extent of oversight measures should be fit for purpose and tailored to the complexity of and risks associated with the trial. The selection and oversight of investigators and service providers are fundamental features of the oversight process.
- Annex 1 3.9.6: The sponsor should ensure appropriate and timely escalation and follow-up of issues to allow the implementation of appropriate actions in a timely manner.

Comparative Analysis: ICH E6(R2) Vs. ICH E6(R3)



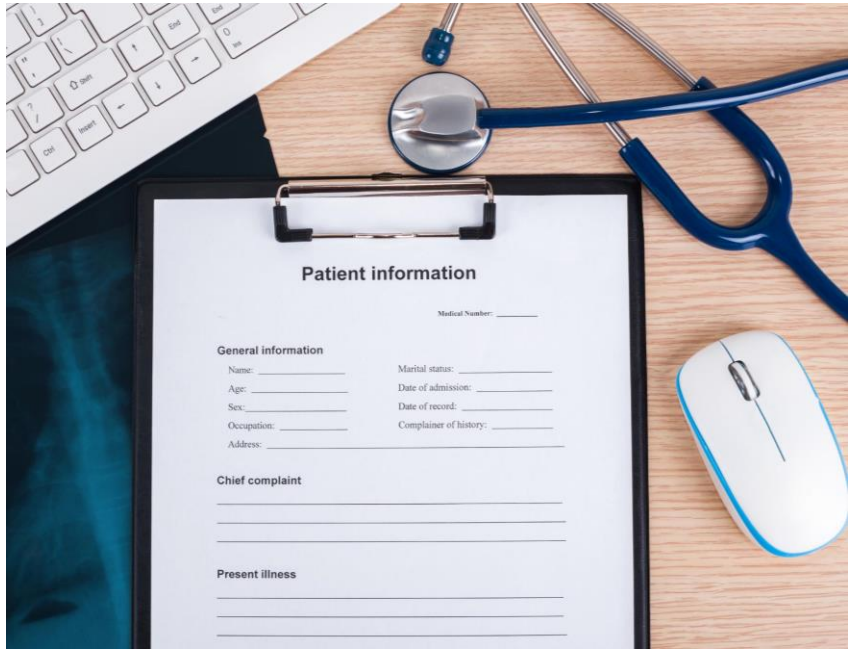
- **Risk-Based Approach Guidance (including Risk management Annex 1 3.10.1)**
- **Expanded Oversight Guidance**
- **Proportionality**
- **Data governance – investigator and sponsor**
  - **Sufficient quality**
    - **Address trial objectives, provide confidence in the trial's results and support good decision making.**

Risk Management and Proportionality



- ICH E6 (R3) further integrates proportionality into risk management, enabling flexible adjustments based on risk levels/assessments and complexity.
- Tailored oversight
  - Service providers
  - Monitoring
  - Creation and retention of essential records

Implications for Clinical Trial Conduct and Documentation



A proportinate approach towards whether a record is essential or not based on criteria as outlined in Appendix C.

- Planning, Conduct and Execution
  - Ongoing processes, re-assessments and adjustments
- Documentation and Compliance
  - ICH E6 (R3) Appendix C.1.1.” The nature and extent of those records generated and maintained are dependent on the trial design, its conduct, application of risk proportionate approaches and the importance and relevance of that record to the trial.”
  - Appendix C.1.3“The essential records permit and contribute to the evaluation of the conduct of a trial in relation to the compliance of the investigator and sponsor with GCP (…)
  - The essential records are used as part of the investigator oversight and sponsor oversight (including monitoring) of the trial. These records are used by the sponsor’s independent audit function and during inspections by regulatory authority(ies) to assess the trial conduct and the reliability of the trial results. (…)”

Essential ~~documents~~ records – (mis)used as checklist

- ICH E6 (R2): e.g. section 8.3 (extract)

8.3. During the Clinical Conduct of the Trial

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available

	Title of Document	Purpose	Located in Files of	
			Investigator /Institution	Sponsor
8.3.1	**INVESTIGATOR'S BROCHURE UPDATES**	To document that investigator is informed in a timely manner of relevant information as it becomes available	X	X
8.3.2	**ANY REVISION TO:** - protocol/amendment(s) and CRF - informed consent form - any other written information provided to subjects - advertisement for subject recruitment (if used)	To document revisions of these trial related documents that take effect during trial	X	X

- ICH E6 (R2): 8.1 ADDENDUM (extract)

ICH E6 (R3) – Appendix C. Essential records

- C.1.2 Determining which records are essential will be based on consideration of the guidance in this appendix
- C.3.1. The assessment of whether a record is essential and has to be retained should take into account the criteria below. Such assessment, whilst important, is not required to be documented.

- Question: Risk based, proportionate approach and fit for purpose?
  - Old inspector/QA saying: “If it is not documented, it does not exist!”

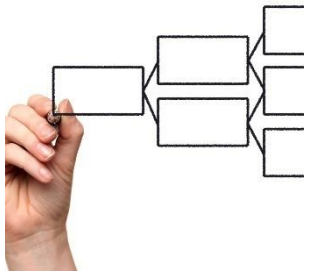
How will sponsors approach and implement e.g. the guidance on essential records?

- Sponsor
  - Justification of decisions?
  - Transparency?
  - Level of documentation
    - Based on importance, criticality
      - Impact, risk

- Inspector:
  - No “one size fits all approach”
  - Make their own assessment
  - Review and evaluate the steps and actions taken and any (negative) effects on the data and/or rights, safety of the trial participants.

How to address divergent opinions, interpretations during inspections?

Risk Proportionality and Intended Use in Clinical Trials



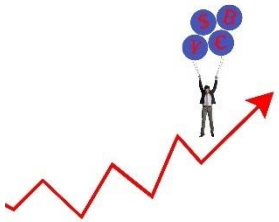
Systematic Risk Assessment

ICH E6 (R3) encourages a structured approach to identify potential risks in data and processes systematically.



Identification of Critical Data

Critical data and processes should be identified to focus attention on elements that impact quality and compliance significantly.



Proportional Resource Allocation

Resources for monitoring and oversight are allocated proportionally based on the level of identified risk.

Examples of Risk-Based Proportionality Application



Monitoring Plans Optimization

Applying proportionality in monitoring plans helps focus resources on high-risk areas to enhance trial efficiency and compliance.

Streamlined Documentation

Proportional documentation reduces unnecessary (paper)work and prioritizes and focuses on critical information and records.

Framework: Integrating QbD and Proportionality

Concept	Application	Quality by Design (QbD Tool
Key Drivers of Trial Success	Define **Critical-to-Quality (CTQ)** factors and **Critical Risk Factors**	*Exploring the CTQ Factors*
Risk Identifikation & Mitigation	Implement proportinate oversight activities (monitoring,	Risk Assessment Matrix
Control Strategy	Tailor monitoring plans and data management plans to CTQs	Proportional monitoring and data handling plans
Continuous Learning	Dynamic risk assessment and timely corrective and/or preventive actions	Communication/escalation plans and feedback loops and updates on key information

E.g. The Clinical Trials Transformation Initiative (CTTI) has published recources on CTQs https://ctti-clinicaltrials.org/

Risk based QMS for clinical trials

- Most, if not all organisations have a high level procedure
  - What about the trial specific adjustments, modifications
    - Protocol and Protocol Amendments and other related records
- By inspectors:
  - Assessment of the sponsor‘s RBQM approaches and their implementation
  - Adequacy of sponsor‘s risk assessment Usually focus on identified critical areas
    - But not necessarily limited (in case inspectee did not identify an area as critical)
- Figure taken from the EU IWG Reflection paper on risk based quality management in clinical trials (2013)

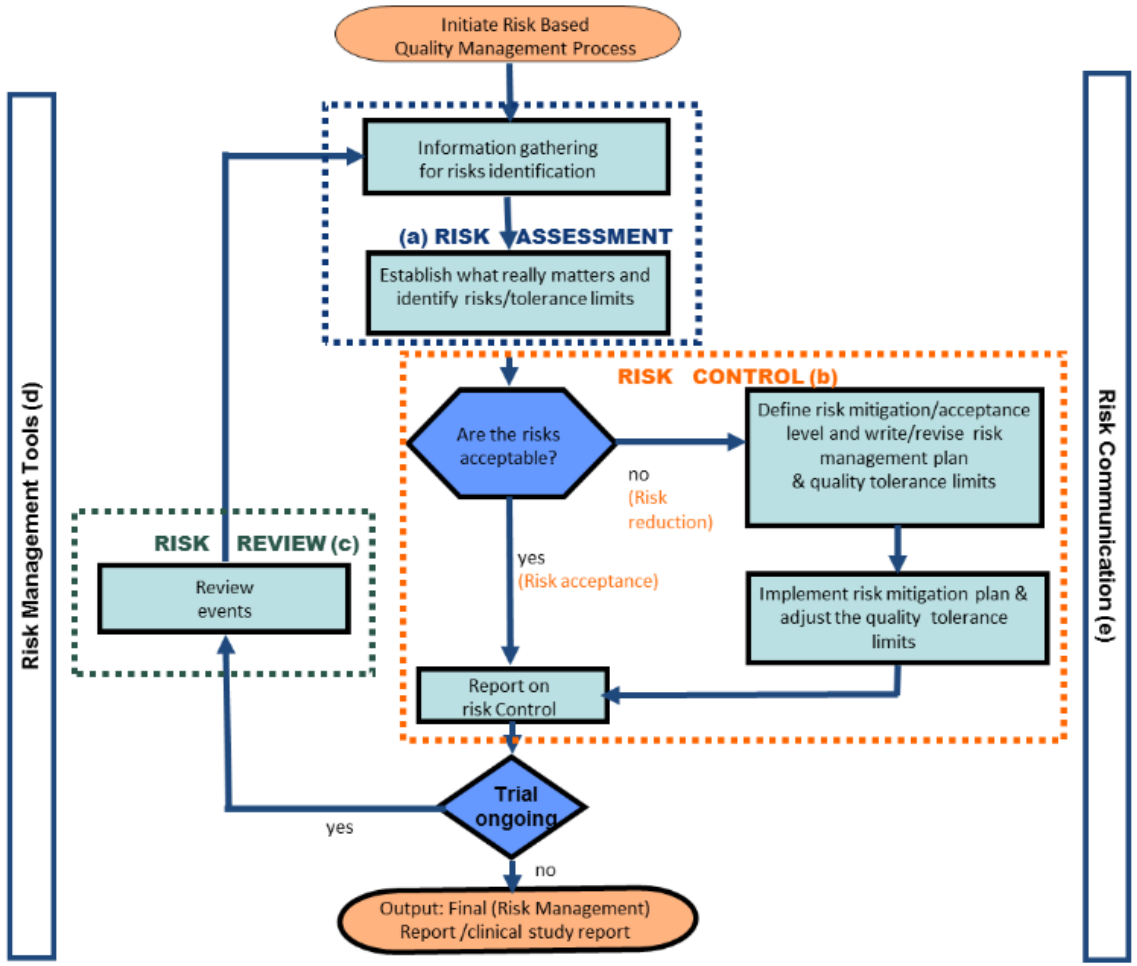


Figure 1: Illustration of a risk based quality management system for clinical trials

Practical Implementation: Use Cases and Good Practices



Case Study: Proportionality in Protocol Development:

- **Guiding Protocol Design**

Proportionality helps prioritize critical elements in trial protocols to ensure focus and relevance.

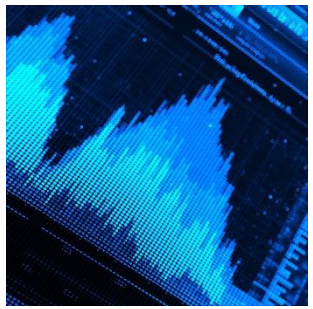
Streamlining Procedures

Applying proportionality streamlines procedures, reducing complexity and improving trial efficiency.

Enhancing Compliance

Proportional protocol design supports better compliance with regulations and standards.

Case Study: Adaptive Monitoring Strategies



Adaptive Oversight Intensity

Monitoring strategies dynamically adjust oversight based on (real-time) risk evaluations to ensure efficiency and safety.



Improved Resource Allocation

Adaptive approaches optimize the use of resources by focusing efforts where risk is highest/critical, ensuring effective management.



Protecting Trial Participant Safety

Ongoing risk assessment allows early detection and response to safety signals/concerns, protecting trial participants effectively.

Case Study: Proportional Record Keeping and Reporting



Balanced Documentation Management

Proportional documentation reduces workload while maintaining essential records for regulatory evaluations.



Regulatory Compliance Assurance

Ensuring that the essential records meets applicable regulatory requirements.



Data Integrity Preservation

Maintaining accuracy and consistency of essential records despite reducing documentation volume.

Case study

- Observation: Caps lock was ON which resulted that several were characters where mistyped.
  - Preventive action proposed: disable all Caps locks and replace all keyboards
    - Pragmatic? Grading? impact?
      - Scenario A) some words were written in all capital letters which did – by a certified linguist - not affect the readability
      - Scenario B) incidence rates of serious ADRs were affected.
- Review of critical data
  - Part of risk mitigation
    - You can not eliminate all risks
      - Have adequate procedures in place (and in effect)

How to present and inspect/verify QbD, risk proportionality during an inspection?

- Everything new due to ICH E6 (R3)?
  - Not really.

- No glossary term for proportionality in ICH E6 (R3)
  - Ensure all stakeholders have the same understanding and interpretation

- Let’s have a look at some low hanging(?) fruits

Use Case Illustrating Proportional application:

Context: Study Type: Phase I/IIa, First-in-Human (FiH), healthy volunteers. Primary objective: Assess safety, tolerability and dose finding.

Element	„traditional“ approach	Proportinal approach
Monitoring	100% Source Data Verifcation (SDV) at all clinical sites during on site visits	Combination of central monitoring of critical data and trends; 25% SDV focused on critical data (e.g. (S)AE causality and signals relevant for dose escalation decisons
Data Validation	Full range data edit checks for all data points	Targeted edit checks for critical data (e.g. primary safety endpoints)
…		

- **Risk-Based Justification:** Proportional decisions should be documented. Linking to oversight activities to the identified risk.
- Dynamic Assessment: Proportionality is not static. Not a one-off activity and adjustments as necessary

Review of the Informed Consent Process

- Review/verification of 100% of all records from all trial participants needed?
  - What about re-consents?
- Points to consider?
  - Who is involved in the process?
  - Adaptive approach?
  - Re-consents: assess the relevance of the actual changes/implications of the updated information.
- Informed Consent is – without dispute – a critical area
  - But apply a risk-based apporach as well
    - E.g. In vaccine CTs there may be thousands of trial participants (plus re-consents)
    - Monitoring plan(s)

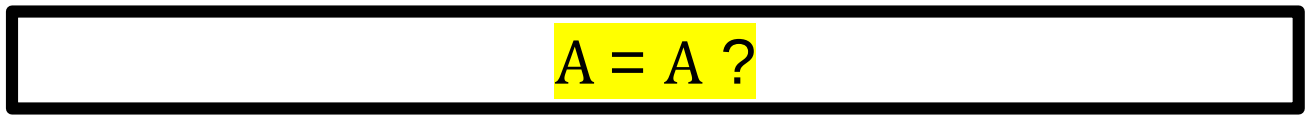
Prior and Concomitant Medications / eligibility criteria

- Time spent to verify actual start date?
  - Relevance of specific date known as required by the protocol?
    - Wash out periods vs. non-steroidal anti-inflammatory drug (NSAID) 8 years ago.
      - And time (hh:min)? As required in the electronic data capture system

- Focus on key eligibility criteria
  - Case by case
  - Encourage to discuss with the clinical investigator and where considered appropriate with sponsor representative in case of uncertainties
    - Different interpretations/lack of clarity in the protocol
    - Be conscious which eligibility criteria have been modified during the course of the clinical trial

Does it matter / Does it make a difference?

- What procedures were in place, which actions have been taken?
  - Were those adequate?
- Impact assessment and issue management?
  - Company culture?



Stakeholder Roles and Recommendations



- Regulators:
  - provide clear and detailed guidance to ensure proper understanding and compliance with rules provide clear and detailed guidance to ensure proper understanding and compliance with rules
  - Regulators oversee proportionality in applying regulations balancing compliance and enabling innovation and clinical research.
  - Promoting harmonization across multiple regions to enable multi-regional clinical trials.

Investigators: Adapting (Site) Practices and Engagement



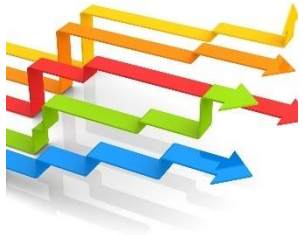
- Adapting to Clinical site workflows
  - Decentralised clinical trial elements
  - Patient’s centricity
  - Cooperation and oversight of service providers, where applicable and relevant
  - Computerised systems and digitalisation

Sponsors (and Service Providers): Optimising operational processes and proactive engagement with key stakeholders



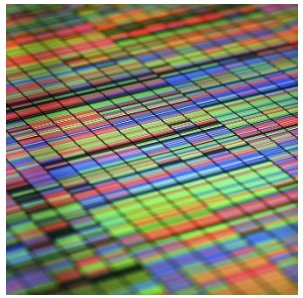
- **Optimizing Operational Workflows**
  - Avoid unnecessary burden to investigators and trial participants
- **Leveraging Technology**
  - New Data Governance section in ICH E6 (R3)

Visualization and Communication Tools



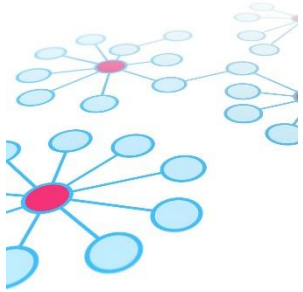
Use of Flowcharts

Flowcharts help break down processes into clear, sequential steps for easier comprehension.



Incorporating Risk Matrices

Risk matrices visually can represent risk levels to aid quick assessment and decision-making.



Layered Diagram Usage

Layered diagrams organize complex information in stacked, easy-to-understand segments.

- **Risk identification**
- **CTQ Factor Definition**
- **Proportinal Oversight** Strategies
- **Dynamic Adjustments** (continious improvement)

Tools to Visualize Risk Proportionality and Implementation Steps



Dashboard Visualization

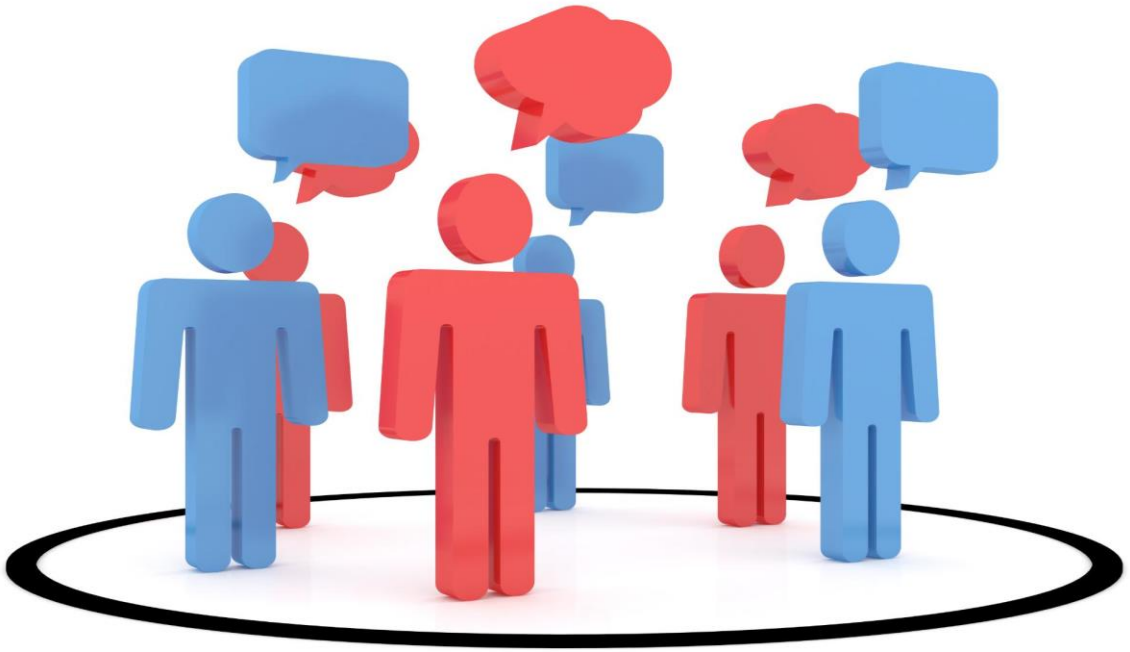
Dashboards provide a (real-time overview) of risk proportionality metrics to support decision-making.

Interactive Models

Interactive models can support to explore implementation steps and monitor progress dynamically.

Media neutral

Strategies for Effective Stakeholder Engagement and Communication



Clear Messaging

Delivering messages clearly ensures stakeholders understand important and critical information without confusion.

Consistent Communication

Maintaining consistent messages across channels builds trust and reinforces understanding among stakeholders.

Tailored Engagement

Customizing communication to stakeholder needs enhances engagement and supports effective implementation.

Conclusion: Embracing Proportionality in Clinical Trials

Enhancing Trial Quality	Ensure Efficiency	Protecting Participants	Collaborative Efforts
Proportionality approach improves overall quality and integrity of clinical trials by tailoring processes appropriately	Applying proportionality streamlines trial operations, increasing efficiency by focusing on activities critical to achieving the trial objectives.	Participant safety and protection are enhanced by proportional application of regulatory requirements and oversight.	“Success*” depends on strong collaboration among regulators, investigators, academic/ industry and patient representative stakeholders.
- For its intended use.	- Focus on what matters.	- Safety comes first.	

- “This guideline encourages a risk-based and proportionate approach to the conduct of a clinical trial.”
- “proportionality means doing the **right amount** of oversight on the **right risks**, not necessarily **less** oversight overall”.

Take away message

- The **proportionality approach** in ICH E6 (R3) is not a "one-size-fits-all" reduction in oversight. It is a **strategic, risk-based allocation of resources** to ensure the sufficient quality data where it matters most.
- By integrating principles for risk identification and **QbD framework** for CTQ definition, sponsors can design efficient, compliant, and scientifically robust clinical trials.

THANK YOU VERY MUCH

FOR YOUR ATTENTION