Advanced Good Clinical Practice ICH E6 (R3) Masterclass

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Organisations are encouraged to consult additional sources and conduct a thorough review of ICH E6(R3) to ensure a comprehensive understanding of the changes and their implications.

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Key course elements

- ICH GCP E6 (R3) – Summary of key updates
  - Principles of GCP
  - Annex 1 (all sections)
    - Impact of the changes and implementation requirements
  - Appendices (Essential Records, Protocols, Investigator Brochures)
  - Annex 2
- Comparison with ICH E6 (R2)
- Risk-Based Approaches: Emphasizing quality by design and proportionate risk management
- Leveraging tools to meet updated data governance and monitoring standards

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Agenda – Day 1

2 breaks of 15 mins each will be added when needed

12:55 - Online meeting room opens

13:00 - Welcome note, introduction and agenda outline

- 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

13:10 - ICH E6 R3 Development, timelines and implementation

- Overview of the ICH E6 R3 development process
- Outline of planned enforcement
- Implementation recommendation and discussion

13:30 - Summary of ICH E6 R3 key messages and changes in terminologies

13:40 - New ICH E6 R3 Key GCP principles

- Analysing the foundations of new GCP principles and expectations

14:15 - Annex 1 (Responsibilities of Ethics and Investigator) – changes compared to ICH E6 R2, implications, and how to implement

- Reviewing Annex 1 and assessing the impact of the changes (Ethics Committees, Investigators)
- Best practices for implementation of the new guideline
- Overcoming the challenges
- Team discussions
- GCP test

17:00 - End of Day 1

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Agenda – Day 2

2 breaks of 15 mins each will be added when needed

12:55 Online meeting room opens

13:00 Discussion of any open questions from Day 1

13:10 ICH E6 R3 Annex 1 (Sponsor Responsibilities) – changes compared to ICH E6 R2, implications, and how to implement

- Reviewing Annex 1 and assessing the impact of the changes (Sponsor)
- Best practices for implementation of the new guideline
- Overcoming the challenges
- Team discussions
- GCP test

15:15 Risk Management

- Quality risk management principles
- Quality By Design, Critical to Quality Factors and relevant implementation
- ICH E6 R3 link with ICH E8
- Risk Management Plan (development of a Risk Registry)
- Team discussions

- **17:00 - End of Day 2**

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Agenda – Day 3

2 breaks of 15 mins each will be added when needed

12:55 Online meeting room opens

13:00 Discussion of any open questions from Day 1 and 2

13:10 ICH E6 R3 Annex 1 (Data Governance)

- Reviewing Annex 1 and assessing the impact of the changes (Data Governance)
- Correlation with EMA GCP Guideline on Computerised Systems and electronic Data in Clinical Trials
- Team discussions
- GCP test

15:30 ICH E6 R3 Appendices

- Essential Document management including TMF inspection observations
- Investigator Brochure and Protocol development
- ICH E6 R3 link with ICH M11

16:30 Questions and Answers/Discussion

- Additional practical Implementation Steps

- **17:00 End of training**

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ICH E6 (R3) Development and Enforcement

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ICH Guidelines – common technical standards Reminder

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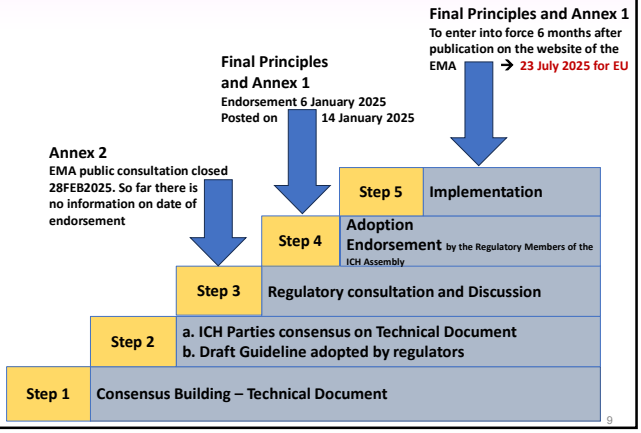
ICH E6 (R3) Development Process



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ICH E6 (R3) enforcement - EMA region

- **ICH E6 (R3) Principles and Annex 1 have entered into force in the EU on 23 July 2025**
  - All clinical trial application submissions and major amendments for trials in the EMA region from that date **must** reflect E6(R3) Principles & Annex 1
    - Even if sponsors are located outside of the EMA region

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ICH E6 (R3) enforcement - outside of EMA region

- **Each regulator decides whether/when to adopt ICH E6 R3 into law, guidance, or annotated local guidance. Timelines therefore vary.**
  - **Switzerland has adopted Principles & Annex 1 on 15 August 2025**
  - **Brazil has formally adopted revision on the date of endorsement according to ANVISA Board Resolution No 945, 29NOV2024**
  - **FDA published final guidance implementing E6(R3) for industry (Federal Register notice Sept 2025). The FDA guidance provides expectations; FDA historically does not set a single "legal" global enforcement date but issues "guidance"**
  - **UK implementation will coincide with its updated clinical trial regulations to come into force on 28 April 2026. Until then, ICH E6(R2) remains the applicable standard**
  - **Health Canada's planned implementation is effective 1 April 2026**
  - **Japan - PMDA / MHLW actively engaged in ICH E6 R3 development and is preparing local implementation documents, however has not set a single fixed national "effective date" published publicly**

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ICH E6 (R3) implementation

- **In the period since January 2025, the responsible parties** (sponsors, investigators, service providers, Ethics Committees) **are/were expected to prepare themselves for the relevant future implementation and take proactive steps**
  - **Recommend (documented) self-reading – set aside some time**
  - **Perform a process gap analysis** to identify areas that need improvement or change – make a list of what is needed and compare with what you already have
  - **Update and/or create processes and procedures to ensure they are aligned with the evolving principles of ICH E6 R3** – prioritise → focus on topics such as quality by design, risk management, and data governance - use Process Owners to support – update your protocols
  - **Work with your vendors and investigators to initiate the changes** – start tailoring documentation for trial needs
  - **align ongoing and planned clinical trials with the new expectations**

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ICH E6 (R3) implementation

- **CONT…**
  - Ensure a risk-based approach is embedded in your trials (should be from the start of a trial as per ICH E8) – ensure the availability of risk management plans and records – Develop/amend risk mitigation strategies aligned with the principles of E6 (R3)
  - **Identify new or revised training requirements for new and ongoing trials** - invest in training, comprehensive training will be crucial

- **Be prepared for potential resistance** - Transitioning from R2 to R3 isn't something that can happen overnight. It requires a willingness to change and do things differently. This can be challenging for stakeholders who are comfortable with "the way things have always been done."
- **Implement change management initiatives -** Change isn't easy, but it's not something to be afraid of either. Do everything you can to foster a company culture of collaboration, innovation, and openness. Specifically, think of ways to enhance communication between various departments. Encourage leadership to get involved and plan for ongoing monitoring and adaptation.

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ICH E6 (R3) implementation

GCP inspectors may evaluate this gap analysis during GCP inspections and assess whether the training requirements of ICH E6 R3 are adequately implemented and documented

Reference: Danish Medicine Agency

https://laegemiddelstyrelsen.dk/en/licensing/clinical-trials/gcp-inspection/ich-gcp-training/

As part of this implementation, Health Canada expects sponsors to clearly identify Critical to Quality Factors with their associated risks and mitigation measures in their protocols.

Health Canada encourages all stakeholders to begin preparations promptly to ensure full compliance by the implementation date.

Reference: Health Canada

Health Canada implementation of the ICH E6(R3) guideline: Notice to stakeholders - Canada.ca

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Implementing ICH E6 R3 – Example questions

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

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ICH E6 (R3) implementation - some helpful references

- **Trancelerate:**

https://www.transceleratebiopharmainc.com/assets/ich-e6-asset-library/

https://www.transceleratebiopharmainc.com/assets/interpretation-of-clinical-guidances-regulations-solutions/#_msocom_1-accordionTab

- **Danish Medicine Agency**

Live streaming of the Danish Medicines Agency's after-work meetings on the revised ICH GCP guideline (ICH E6 R3)

- **EMA**

ACT EU Workshop https://www.youtube.com/watch?v=d1rx1BNZAuc

https://www.ema.europa.eu/en/events/act-eu-workshop-ich-e6-r3-principles-annex-1#presentations-day-1-74523

- **ACRO**

https://www.acrohealth.org/initiatives-hub/interpreting-ich-e6r3/

https://www.acrohealth.org/resource/data-flow-diagram-framework-template/

- **ICH**

https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step%204_Presentation_2025_0123.pdf

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ICH GCP renovation, ICH E6 (R3) revised structure and Key messages

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ICH GCP Renovations

ICH efficacy guidelines are an **integrated set of guidances** for planning, design, conduct, safety, analysis and reporting and should be used in a **holistic way**

E8 – integrating QbD into study design and conduct

E6 – Applying the foundation of E8 to the conduct of clinical trials

∴ Do not read E6(R3) in isolation !!

Also mentioned in ICH E6 R3 are: E9 Statistical Principles; E11 Paediatric Population; E2A Clinical Safety Data Management; E3 Study Report

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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

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ICH E6 (R3) Structure

Overarching Principles that Apply across the Board

Annex-1

GCP for Interventional clinical trials

Considerations for non-traditional interventional clinical trials

Annex-2

Annex-1
Reflects the concepts in E6(R2) (with updates and refinements as needed)

Annex-2
Additional considerations for non-traditional interventional clinical trials not addressed in Annex-1

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Revised structure

ICH E6 R2:
- Glossary
- Principles
- IRB/IEC
- Investigator
- Sponsor
- Protocol
- IB
- Essential Documents

ICH E6 (R3)

I. Introduction
II. Principles of ICH GCP
III. Annex 1
I. IRB/IEC
II. Investigator
III. Sponsor
IV. Data Governance - Investigator & Sponsor NEW!
Appendices
A. Investigator's Brochure
B. Clinical Trial Protocol & Protocol Amendment(s)
C. Essential Records for the Conduct of Clinical Trial
Glossary

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Revised structure – Annex 2

The (currently) 12 pages in the draft Annex 2 provides additional GCP Considerations, focusing on examples of trials that incorporate:

Decentralised Elements	• **Trial-related activities conducted outside the investigator's location.** • *E.g., trial visits conducted at participant's home / local healthcare centre / mobile medical units; or data acquisition is performed remotely using digital health technologies (DHTs).*
Pragmatic Elements	• **Trials that integrate aspects of clinical practice into the design and conduct of the trial.** • *E.g., simplified protocols with streamlined data collection.*
Real World Data (RWD)	• **Use of data relating to patient health status collected from a variety of sources outside of clinical trials.** • *E.g., electronic health records (EHRs), registries, claims data.*

Regardless of the operational approaches and data sources used, a quality by design (QbD) approach should be used in clinical trials as stated in Annex 1.

Source: ich-e6-r3-annex-2_overview-of-step-2-draft-(22jan2025).pdf

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Why the change to Revision 3?

- **Lack of consideration of** emerging technologies, innovations in trial design, variety of data sources and acquisition tools (i.e. not just CRFs used for data collection), diversity in testing facilities, service providers and record keeping → **Clinical Trials evolve** with new designs and innovations and this was not reflected in R2
- R2 was seen as a "one-size-fits-all" approach to clinical trials → **GCP requirements were being applied where they were not applicable**
- Study feasibility was not considered consistently → **patient needs were not considered in trial design**
- **Requirements of advancing the concept of a proportionate risk-based approach to design and conduct of clinical trials** → R3 re-enforces the R2 quality risk approaches and stresses the need for justified risk proportionate actions

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The new approach - Summary…

1. **New structure** and clarification of the scope
2. Includes language to **facilitate new clinical trial designs, technology and operational approaches**
3. **Builds on key concepts of ICH E8 (R1)** - **encourages fit-for-purpose approaches = Risk-based and proportionate approach** with a focus on the clinical trial's **critical to quality factors** (i.e., whose integrity is fundamental to safety of participants and the reliability of trial results)
   - This includes **fostering a quality culture** and **proactively designing quality into clinical trials** and drug development planning
   - **Engaging interested parties**, such as patients and their communities, patient advocacy groups and healthcare professionals can help to improve feasibility and the likelihood of meaningful outcomes
   - Requires **critical thinking**
4. **Encourages transparency** by clinical trial registration and result reporting

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The new approach

- **The GCP Principles are top level and open to interpretation**, therefore the **Annexes provide the detail and guidance about how to apply the GCP principles**
  - The Annexes provide the basis for the **appropriate interpretation and application of the principles** and should therefore be appropriately considered
  - **Various approaches to the provisions in the Annexes may be considered if they are justified and achieve the intended purpose** of the application of the principles

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Key messages

- "Focus is on protection of the rights, safety and well-being of trial participants and the reliability of the trial results by **paying attention to risk mitigation** and **processes relating to those factors that impact on this** and to do so is **implementing a proportionate, quality by design and risk-based approach**"

Source: Andy Fisher MHRA, 26MAY2023 ICH E6 (R3) Good Clinical Practice - MHRA Inspectorate (blog.gov.uk)

- Focus on fit for purpose clinical trial quality (QbD and proportionate, risk-based approaches), Innovation, Efficiency & Engagement

Source: Danish Health Authority https://laegemiddelstyrelsen.dk/en/news/2025/live-streaming-of-the-danish-medicines-agencys-after-work-meetings-on-the-revised-ich-gcp-guideline-ich-e6-r3-/~/media/C0DDF67E95194EA686613DE3CD1A7B51.ashx

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References

- ICH E6 (R3) Good Clinical Practice - MHRA Inspectorate (blog.gov.uk)
- Recording of Public Web Conference Now Available: Listen to ICH E6 Guideline for Good Clinical Practice (GCP) – Update on Progress - CTTI (ctti-clinicaltrials.org)- May 18 & 19, 2021
- https://laegemiddelstyrelsen.dk/en/licensing/clinical-trials/gcp-inspection/ich-gcp-training/
- https://acrpnet.org/wp-content/uploads/2025/01/Updated-ICH-E6-Principles-012825.pdf
- https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/research-transparency/informing-participants/
- https://www.hra.nhs.uk/planning-and-improving-research/best-practice/publication-and-dissemination-research-findings/
- https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/gdpr-guidance/templates/transparency-wording-for-all-sponsors/
- https://laegemiddelstyrelsen.dk/en/news/2025/live-streaming-of-the-danish-medicines-agencys-after-work-meetings-on-the-revised-ich-gcp-guideline-ich-e6-r3-/~/media/C0DDF67E95194EA686613DE3CD1A7B51.ashx
- https://www.ich.org/news/ich-reflection-gcp-renovation-modernization-ich-e8-and-subsequent-renovation-ich-e6

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Changes in Terminology

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Terminology changes and additions (1)

- **"Trial Participant"** replaces Trial Subject; Trial participant and participant are used interchangeably
- "**Service provider**" replaces "contract research organisation" reflecting the range of other parties involved in clinical trials
- **"Essential records"** replaces "essential documents" to reflect the wider range of records that need to be kept
  - Essential records are the documents **and data (and relevant metadata**), in any format, that facilitate the ongoing management of the trial and **collectively allow the evaluation of the methods used, the factors affecting a trial and the actions taken during the trial conduct** to determine the reliability of the trial results produced and the verification that the trial was conducted in accordance with GCP and applicable regulatory requirements (see **Appendix C**).
- A new term **'essentiality'** of trial records has been introduced
  - An assessment of whether a record is essential

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Terminology changes and additions (2)

- **Clarification for ADR**
  - If the ADR is suspected to be medicinal product-related with a high level of certainty, it **should be included in the reference safety information (RSI) and/or the Investigator's Brochure (IB)**
- **Addition of Glossary terms** "SUSAR"; "Agreement"; "Assent", "Data Acquisition Tool", "Data Integrity", "Meta Data", "Monitoring Plan", "Reference Safety Information", "Signature", "Trial Participant Identification Code", "Computerised Systems Validation"
- **Clarification of "Audit Trail"**
  - **Metadata records** that allow the appropriate evaluation of the course of events by capturing details on actions (manual or automated) performed relating to information and data collection and, where applicable, to activities in computerised systems.

    The audit trail should show activities, initial entry and changes to data fields or records, by whom, when and, where applicable, why.

    In computerised systems, the audit trail should be secure, computer-generated and time stamped

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Terminology changes and additions (3)

- Addition of "**Investigator site**" to Glossary (nothing new here), however
  - Where an investigator/institution is referenced, it describes expectations that may be applicable to the investigator **and/or** the institution in some regions. **Where required by the applicable regulatory requirements, the "investigator" should be read as "investigator and/or the institution."**
- **Clarification of "Sponsor"**
  - An individual, company, institution or organisation that takes responsibility for the initiation, management **and arrangement of the financing of a clinical trial.** Where a documented agreement does not specify to which sponsor a given responsibility is attributed, that responsibility lies with all sponsors.
- **Clarification of Source Records**
  - Original documents or data **which includes relevant metadata**, certified copies of the original documents or data, irrespective of the media used. This may include trial participants' medical/health records/notes/charts

    Data provided/entered by trial participants (e.g., **electronic patient-reported outcomes (ePROs)**); healthcare professionals' **records from pharmacies, laboratories and other facilities** involved in the clinical trial; and **data from automated instruments, such as wearables and sensors.**

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Terminology changes and additions (4)

- Introduction of **"acceptable ranges"** in risk control (3.10.1.3)
  - Where relevant, the sponsor **should set pre-specified acceptable ranges (e.g., quality tolerance limits at the trial level) to support the control of risks to critical to quality factors**

    These pre-specified ranges reflect limits that when exceeded have the potential to impact participant safety or the reliability of trial results. Where deviation beyond these ranges is detected, an evaluation should be performed to determine if there is a possible systemic issue and if action is needed.
- Clarification of **"Certified Copy"**
  - A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information as the original, **including relevant metadata**, where applicable
- Clarification of **"Quality Control"**
  - The operational techniques and activities undertaken to verify that the requirements for quality of the trial-related activities have been fulfilled
- Clarification of **"Monitoring Report"**
  - A documented report following **site and/or centralised monitoring activities**

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Principles of GCP under ICH E6 (R3)

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Change in the definition of GCP….

R2:
A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

R3:
A standard for the planning, initiating, performing, recording, oversight, evaluation, analysis and reporting of clinical trials that provides assurance that the data and reported results are reliable and that the rights, safety and well-being of trial participants are protected.

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Principles of ICH E6 (R3) - overview

- The principles outline the required approaches to trial design and conduct
- **The principles may be satisfied using differing approaches and should be applied to fit the intended purpose of the clinical trial**
- **Annex 1 is intended to provide information on how the Principles can be applied to clinical trials**
- **Clinical trial processes and risk mitigation strategies should be proportionate to the importance of the data being collected and the risks to trial participant safety and the reliability of trial results**
- Trial designs should be operationally feasible and **avoid unnecessary complexity**

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Principles of ICH E6 (R3)

The principles are interdependent and should be considered in their totality

1. Ethical Principles
2. Informed Consent
3. IRB/IEC Review
4. Science
5. Qualified Individuals
6. Quality NEW !
7. Risk Proportionality NEW !
8. Protocol
9. Reliable Results NEW !
10. Roles and Responsibilities NEW !
11. Investigational Product

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NEW !

New GCP principles

- **ICH E6(R3) introduces four new principles that were not documented in ICH E6(R2)**
  1. Quality should be built into the (6) scientific and operational design and conduct of clinical trials; The quality and amount of the information generated should support good decision making.
  2. Clinical trial processes, measures, and (7) approaches should be proportionate to the risks of participants and to the reliability of trial results
  3. Clinical trials should generate reliable (9) results
  4. Roles, tasks and responsibility (10) definitions

Big messages

- Flexible framework for trial conduct, adaptable for innovation
- Quality evaluation of each trial, QbD, CtQ
- Engage stakeholders
- Avoid unnecessary complexity
- Risk based approach
- Transparency

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Building quality into design/conduct of trials

6 NEW !

- **Factors critical to the quality of the trial should be identified**
  - **Quality factors are critical** because, if they were to be undermined by errors of design or conduct, the ethical basis of the trial and reliability of results could also be undermined
- **Quality by design sets out to ensure that the quality of a trial is driven proactively by designing quality into the study protocol and processes**
- **Quality by design must be implemented to identify the factors (i.e., data and processes) that are critical to ensuring trial quality and the risks that threaten the integrity of those factors and ultimately the reliability of the trial results**
  - This may involve the use of a prospective, multidisciplinary approach to promote the quality of protocol and process design, and clear communication of how this will be achieved
  - Quality by design approaches **must** be applied across the clinical trial and supporting processes
- **Strategies must** be implemented to avoid, detect, address and prevent recurrence of serious noncompliance with GCP, the trial protocol and applicable regulatory requirements

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Risk proportionate approach

7 NEW !

- **Processes, measures, and approaches should be "proportionate to the risks" that are inherent in the trial and the importance of the information collected**
  - For example, study monitoring should focus on those risk factors that impact participant rights, safety, wellbeing, the importance of the data collected (i.e., risk-based monitoring) and risks to the reliability of the trial results
  - The focus should be on risks that go beyond those associated with usual medical care
  - Risks to critical to **quality factors should be managed proactively and adjusted when new or unanticipated issues arise** once the trial has begun
  - **Trial processes should be operationally feasible and avoid unnecessary complexity, procedures and data collection**
  - Unnecessary burden on participants and investigators should be avoided

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Some selected wording from the Principles to illustrate

- "6.1 - **Quality** of a clinical trial is considered in this guideline as **fitness for purpose**"
- "6.2 - **Factors critical to the quality** of the trial should be **identified prospectively**"
- "7.4 - Trial processes should be **operationally feasible** and **avoid unnecessary complexity**, procedures and data collection"
- "9.1 - The **quality and amount of the information generated** in a clinical trial **should be fit for purpose** and sufficient to **provide confidence** in the trial's results and support good decision making"
- "9.3 - **Computerised systems used in clinical trials should be fit for purpose** (e.g., through risk-based validation, if appropriate), and **factors critical to their quality should be addressed in their design or adaptation** for clinical trial purposes to ensure the integrity of relevant trial data"

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Generation of reliable results (1)

9 NEW !

- ? Haven't we always wanted to generate reliable results"?
- In E6 R2 this principle does not exist as such, but the closest equivalent is "Ensure all data is recorded accurately and can be verified." → **The focus shifts from verifying all data to ensuring reliable results for data that matter**
  - "The quality and amount of the information generated in a clinical trial should be fit for purpose and sufficient to provide confidence in the trial's results and support good decision-making."
- **Systems and processes** for data capture, management and analyses, and those that help ensure the quality of the information generated, should be fit for purpose, and should capture the data required by the protocol → **Trial processes should support the key trial objectives**
- **Computerised systems** should be fit for purpose (e.g., through risk-based validation, if appropriate). **Factors critical to their quality** should be **addressed in their design or adaptation for clinical trial purposes** to ensure the integrity of trial data

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Generation of reliable results (2)

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- Clinical trials should incorporate **efficient and robust processes for managing records and data to help ensure that record/data integrity and traceability are maintained** and that personal information is protected
- **Essential records should be available** to regulatory authorities, monitors, auditors and IRBs/IECs (as appropriate) **upon request**
- The transparency of clinical trials includes **timely registration on publicly accessible and recognised databases and the public posting of clinical trial results**
- Communicating trial results to participants should be considered

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Roles, tasks and responsibilities

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- ? Again, what is new here?

- E6 R2 only calls out physicians and dentists, while E6 R3 refers to other roles
  - R3 acknowledges that while physicians will always be a vital part of running trials, **other expertise may be needed** such as nurses, pharmacists, scientists, ethicists, trial coordinators, monitors, auditors, biostatisticians and technology experts (e.g., for using tablets, apps etc.)
    → The rising usage of electronic data sources is addressed in E6 (R3)

- **The sponsor and investigator** may delegate their tasks, duties or functions ("activities"), **but retain overall responsibility** for respective activities, **including quality and integrity of the trial data**
- **Agreements must clearly define the roles, activities and responsibilities**
- Maintenance of **appropriate oversight by sponsor and investigator** is expected

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Further (new) clarifications within the principles

1 Ethical Principles
- The safety of the participants should be reviewed **in a timely manner** (rather than annually as per R2)
- Do not unnecessarily exclude particular participant populations
- Participant selection must be **representative of the population groups that the investigational product is intended to benefit**
- Delivery of medical care and decisions can be carried out **by appropriately qualified healthcare professionals**

2 Informed Consent
- Information provided needs to be **clear and concise**
- In the event that a minor is a participant, **assent should be collected** from that minor in accordance with local regulatory requirements - see ICH E11(R1)
- The potential use of technology to inform participants is mentioned here

3 IRB/IEC review
- **Periodic review** of the trial by the IRB/IEC should be conducted in accordance with applicable regulatory requirements (instead of "at least once per year" as per R2)

4 Science
- There should be **periodic review** of current scientific knowledge and approaches to determine whether modifications to the trial are needed

5 Qualified individuals
- Individuals with different expertise and training may be needed across all phases of a clinical trial – see previous slide re roles, tasks and responsibilities

6 7 Quality, Risk proportionality - See last slides

8 Protocol
- Protocols should be clear, concise, scientifically sound and operationally feasible
- **This also applies to plans or documents for the protocol execution** (e.g., statistical analysis plan, data management plan, monitoring plan)

9 10 Reliable results, Roles, responsibilities - See last slides

11 Investigational Product
- Measures should be in place to ensure that the IP provided to participants retains its quality
- **Appropriate processes should be implemented** for the handling, shipping, storage, dispensing, returning and destroying or alternatively disposing of the investigational product.

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Comparison to ICH E6 (R2)

ICH E6(R3) PRINCIPLE	TOPIC	ICH E6(R2) PRINCIPLE
1	Ethical Principles	2.1, 2.2, 2.3, 2.7, 2.11
2	Informed Consent	2.9
3	IRB/IEC Review	2.6
4	Science	2.4, 2.5
5	Qualified Individuals	2.8
6	Quality	2.13
7	Risk Proportionality	N/A
8	Protocol	2.5
9	Reliable Results	2.10
10	Roles and Responsibilities	N/A
11	Investigational Products	2.12

Source: ICH Website Microsoft PowerPoint - ICH_E6(R3)_Step 4_Presentation_2025_0123.pptx

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Annex 1

→ Notes in green represent the resulting impact and implementation requirements

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Structure of Annex 1

79 pages in R3 vs 60 pages in R2

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Section 1 – Institutional Review Board/ Independent Ethics Committee (IRB/IEC)

48

Comparison to ICH E6 (R2)

ICH E6(R3) Section	ICH E6(R2) Section
1.1 – *Submission and Communication* *In R3, added global language about reporting to IRB/IEC and regulatory authorities*	N/A NEW !
1.2 – Responsibilities	3.1
1.3 – Composition, Function and Operations	3.2
1.4 – Procedures	3.3
1.5 – Records	3.4

As per "Glossary": The legal status, composition, function, operations and regulatory requirements pertaining to IRBs/IECs **may differ among countries** but should allow the IRB/IEC to act in agreement with GCP as described in this guideline → **this allows some flexibility for IRBs/IECs but it may require updates of sponsor procedures**

Source: ICH Website Microsoft PowerPoint - ICH_E6(R3)_Step 4_Presentation_2025_0123.pptx

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IRB/IEC Key Changes (1)

- Requirements for the IRB/IECs should **be read in conjunction with local regulatory requirements** → **knowledge of relevant local regulations is required**
- **Submissions or communication** can be combined with those to regulatory authority and **can be made by investigator/institution and/or by sponsors (as applicable locally)** → **agreement is needed to define who does what**
- If minors are to be included in a trial, IRB/IEC should review the **assent information considering the age, maturity and psychological state of the minor population** intended to be enrolled, and applicable regulatory requirements → **assent is now a required process in ICH E6 R3**

50

IRB/IEC Key Changes (2)

- **IRB/IEC should review a description of the media through which trial related information will be provided** → **change in IRB/IEC submission requirements**
- The investigator, **investigator site staff and/or sponsor** may provide information on any aspect of the trial (but can't vote) → **the sponsor may get involved with IRB/IECs**
- Clarified that "reasonable" costs reimbursements to participants are not considered coercive

51

IRB/IEC Key Changes (3)

- Continuing review of ongoing trials should be **at intervals** appropriate to the degree of risk to participants (**removal of annual review requirement**, but note that local requirements still apply) → **change in processes may be needed**
- Clarification of **safety reporting expectations**:
  - **All suspected unexpected serious adverse reactions (SUSARs) in accordance with applicable regulatory requirements** (instead of all adverse drug reactions (ADRs) that are both serious and unexpected), and as before – requirements to report new information that may adversely affect the safety of the participants or the conduct of the trial

  → **change in processes is needed**
- Record retention by IRB/IEC **as per local regulations** (rather than at least 3-years after completion of the trial)

Section 2 Investigator Responsibility

→ **…new training needs for sites must be considered**

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Comparison to ICH E6 (R2)

ICH E6(R3) Section	ICH E6(R2) Section
2.1 – Qualifications and Training	4.1
2.2 – Resources	4.2
2.3 – Responsibilities	4.1, 4.2
2.4 – Communication with IRB/IEC	4.4, 4.10
2.5 – Compliance with Protocol	4.1
2.6 – Premature Termination or Suspension of a Trial	4.12
2.7 – Participant Medical Care and Safety Reporting	4.3, 4.11
2.8 – Informed Consent of Trial Participants	4.8
2.9 – End of participation in a clinical trial	4.3
2.10 – Investigational Product Management	4.6
2.11 – Randomisation Procedures and Unblinding	4.7
2.12 – Records	4.9
2.13 – Reports	4.13

Source: ICH Website Microsoft PowerPoint - ICH_E6(R3)_Step 4_Presentation_2025_0123.pptx

Comparison to ICH E6 (R2)

Overview: This document provides a summary of investigator-focused changes to Good Clinical Practice Version set out in ICH E6 (R3) compared to the provisions in (R2). The document allows interested parties to explore changes to different topics relating to investigators as well as understanding if section changes are new or updated guidance.

Pillar	Topic	ICH E6(R3) Section (Annex 1)	Prior Text in ICH E6(R2)	New or Updated Text	Summary of Change
Communication	IRB/IEC	2.4.1	4.4	New	It is now specifically stated that "submission to the IRB/IEC can be made by the investigator/institution or sponsor in accordance with applicable regulatory requirements"
Communication	IRB/IEC	2.4.4	4.4.3	New	It is now specifically stated that "as the trial progresses, the investigator/institution or sponsor should provide any updates to the participant information to the IRB/IEC in accordance to applicable regulatory requirements"
Communication	IRB/IEC	2.4.5	4.10.2	New	It is now specifically stated that "the investigator or the sponsor should submit documented summaries of the trial status to the IRB/IEC in accordance with local regulatory requirements or upon request."
Communication	IRB/IEC	2.4.6	4.10.2	New	It is now specifically stated that the "investigator or the sponsor should promptly communicate to the IRB/IEC and where applicable, the institution about any changes significantly affecting the conduct of the trial and/or increasing the risk to participants"
Communication	IRB/IEC	2.6.3	4.12.2	Updated	If the sponsor prematurely terminates or suspends the trial, the investigator or sponsor should promptly inform the IRB/IEC and regulatory authorities.
Communication	Medical Care of Participants	2.7.1 (d)	4.3.3	Updated	The investigator should inform the participants primary physician about the participants involvement in the trial if the participant agrees. Previously it was only recommended to inform.
Communication	Medical Care of Participants	2.9.3	4.3	New	New language that the investigator should inform the participant as per their preference of the trial results and treatment received (after blinding).
Communication	IRB/IEC	1.1	3	New	A new section has been added providing global guidance on communication with IRB/IEC and regulatory authorities.
General	Principles of ICH GCP	II	2	Updated	The thirteen principles of ICH E6 R2 have been reorganized into eleven more detailed principles, each including a main statement and accompanying sub-points.
Operations	Unblinding	2.11	4.7	Updated	A new requirement in unblinding: In the case of an emergency, to protect patient safety, the investigator should be prepared and capable from the start of the trial to perform unblinding.
Operations	Reporting	2.12.1	4.9	New	There is a new expectation that the Investigator should ensure data integrity when generating, recording and reporting trial data under their responsibility.
Operations	Reporting	2.12.5	4.9.1	Updated	New language on the expectation for Investigators to review and endorse reported data at milestones agreed with the Sponsor. The investigator should ensure accuracy, completeness, legibility and timeliness of the data reported to the sponsor in the data acquisition tools provided by the sponsor.

Source: https://www.transceleratebiopharmainc.com/assets/ich-e6-asset-library/#Investigators

Section 2 - Investigator

- 2.1 Qualification and Training
- 2.2 Resources
- 2.3 Responsibilities — NEW !
- 2.4 Communication with IRB/IEC
- 2.5 Compliance with Protocol
- 2.6 Premature Termination or Suspension
- 2.7 Medical Care and Safety Reporting
- 2.8 Informed Consent — Revised
- 2.9 End of Participation — NEW !
- 2.10 Investigational Product Management
- 2.11 Randomisation procedures and unblinding
- 2.12 Records — Revised
- 2.13 Reports

ICH E6 R3 – major changes for investigators…. (1)

- Easing of restriction that only qualified physicians and dentists can be solely responsible for trial related medical care and decisions - allows other qualified healthcare professionals **in line with clinical activities and local regulatory requirements to be involved** (1.5)
  - → **this needs knowledge of local regulatory requirements** NEW !

ICH E6 R3 – major changes for investigators…. (2)

- The investigator **retains the final decision on service provider selection**, i.e. whether the **service provider intended to support the investigator** is appropriate based on information provided by the sponsor (2.3.1) NEW !
- (also see 3.6.5 - The sponsor should provide information to the investigator on any service provider identified by the sponsor to undertake any activities under the responsibility of the investigator. The responsibility for such activities remains with the investigator) → **site "approval" should be documented**

→ **Investigator oversight requirements extend beyond site staff to "parties" undertaking delegated activities** (2.3)

→ **Requires clear communication with the investigator regarding responsibilities and training considerations !!**

58

Impact

→ **Strong emphasis on investigator responsibility**

- **All** relevant individuals at the trial site must be trained (and documentation available)
- **All** relevant individuals at site must have evidence that they are qualified
- **All** relevant individuals at site must be supervised (incl. pharmacy, laboratories etc., **and the parties provided by the sponsor intended to support the investigator**)

See also 2.10.2: When the investigator/institution delegates some or all of their activities for investigational product(s) management to a pharmacist or another individual in accordance with local regulatory requirements, the delegated individual should be under the oversight of the investigator/institution

BUT…

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Clarification regarding Investigator Oversight (1)

- **The level** of investigator oversight should depend on the **nature of the delegated activities** and **be proportionate to the importance of the data** being collected and **the risks to trial participant safety and data reliability** → **Risk proportionate oversight**

- Trial-related training should correspond to what is necessary for persons/ parties to fulfil their delegated trial activities **that go beyond their usual training and experience** → **trial-related training is only needed for activities that are above standard job responsibilities, thus "standard" responsibilities must be clear**

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Clarification regarding Investigator Oversight (2)

- Site staff must be adequately informed about **relevant aspects of the protocol**, **the investigational product(s)** and **their assigned trial activities** → **Training should be focussed on IMP, staff specific assignments and related protocol sections**
- **Delegation documentation for routine clinical practice activities may not be required** → **delegation documentation should be proportionate to the significance of the trial-related activities**

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Clarification regarding Investigator Oversight (3)

Research Nurse	Trial Specific Training	Delegation Log
Measuring Blood Pressure of Trial Participant for Routine Trial Visit	No – not if there is anything outside usual training and experience	No – not if there is anything outside normal clinical practice
New Trial Specific ePRO device – Smartwatch that requires participant specific settings.	Yes	Yes

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Some selected wording from Section 2 to illustrate

- "2.3.1…The level of investigator oversight of the delegated activities should depend on the nature of the delegated activities and be proportionate to the importance of the data being collected and the risks to trial participant safety and data reliability"
- "2.3.2 Trial-related training to persons assisting in the trial should correspond to what is necessary to enable them to fulfil their delegated trial activities that go beyond their usual training and experience"
- "2.3.3 Documentation of delegation should be proportionate to the significance of the trial related activities. In situations where the activities are performed as part of clinical practice, delegation documentation may not be required"

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What is meant by Oversight ?

- Adequate investigator oversight could for example include:
  - Documented Meetings with the staff and "parties"
  - Implemented procedures and associated documented training
  - Documented review of the performance of delegated task
  - Timely correction and documentation of problems identified
  - Visible involvement in the conduct of the trial

Lack of evidence of oversight of trial related activities can raise concern about adequacy of protection of trial participants enrolled, and about the integrity of data generated by the site

64

ICH E6 R3 – major changes for investigators…. (3)

- Strengthening of the text relating to informing the participant's GP of patient trial participation, **when the participant consents** to this - it is **no longer just a recommendation** (2.7.1 d)
  → **this requires clarity in the consent documentation**

NEW !

- **Agreements made by the investigator/institution with service providers for trial-related activities should be documented** (2.3.4)
  → **This may include internal trial services within the institution (e.g. MRIs, Radiology etc)**

65

ICH E6 R3 – major changes for investigators…. (4)

- **Responsibility for investigational product(s) management, including accountability, handling, dispensing, administration and return, rests with the investigator/institution** (2.10)
  - Delegated individuals should be under the oversight of investigator/institution
  - Level of investigator oversight depends on factors such as characteristics of the IMP, route and complexity of administration, level of existing knowledge about the IMP and marketing status
  - The investigational product may be shipped to the participant's location or supplied to/dispensed at a location closer to the participant (e.g., at a local pharmacy or a local healthcare centre)

→ **Clarifications re IMP management and responsibilities**
→ **Acceptance of direct IMP shipments to patients**

66

ICH E6 R3 – major changes for investigators….(5)

- Requirement to provide updated information **to the IRB/IEC according to local requirements** (2.4.1) – see also Principle 3 (IRB/IEC review)

  → **needs knowledge of these local requirements**

  - For example:
    - any changes significantly affecting the conduct of the trial and/or increasing the risk to participants
    - the updated IB version (or product information brochure)
    - updates to the participant information
    - documented summaries of the trial status

– the sponsor may also make submissions to the IRB/IEC (2.4 – see also 3.8.1)

→ **requires documented clarification in the protocol/project plans/site plans/agreements who will do this**

NEW !

67

ICH E6 R3 – major changes for investigators….(6)

NEW !

- The investigator should **document all protocol deviations and also review deviations communicated to them by the sponsor** (2.5.3)

→ **requires that the sponsor provides deviation listings to the PI – see Monitor responsibilities** (3.11.4.5.1)

- For **important deviations** (see 3.9.3 - a subset of protocol deviations that may significantly impact the completeness, accuracy and/or reliability of the trial data or that may significantly affect a participant's rights, safety or well-being.)**, the investigator should explain the deviation and implement appropriate measures to prevent a recurrence** (2.5.3)

→**Site CAPAs need to be reviewed by the monitor** (see 3.11.4.5.1 b)

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ICH E6 R3 – major changes for investigators….(7)

- The investigator should have **timely access** to and **be responsible for the timely review** of data, **including relevant data from external sources** (e.g., **central laboratory data**, **centrally read imaging data**, other institution's records and **electronic patient-reported outcome (ePRO) data**)

- The investigator should ensure the accuracy, **completeness**, legibility and **timeliness** of the data reported to the sponsor **in the data acquisition tools completed by the investigator site** (e.g., case report form (CRF)) and in all required reports)

→ **Confirms the need for PIs to ensure timely data entry and to review all data in a timely manner**

→ **Thus PI needs to have access to ALL data (also to e.g. centrally read data)**

69

The investigator should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects.

Source data should be attributable, legible, contemporaneous, original, accurate, and complete. = ALCOA

70

Impact

→ Source data

- should be ALCOA ++ ? *

ALCOA++ are attributes of quality of data accuracy and consistency

- Thus, ICH E6 changes makes investigator responsibility for source data explicit → training needs should be considered

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ALCOA ++ ?

And…

Traceable
Any changes to the data should not obscure the original information and should be explained, if necessary. Changes should be documented as part of the audit trail

*

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Changes to source data should be traceable, should not obscure the original entry and should be explained if necessary (via an audit trail).

→ Source data changes should have clarifications via audit trails

Inspectors are reviewing the audit trails at investigational sites – we should too!

73

ICH E6 R3 – major changes for investigators….(8)

- **Substantial changes relating the records/data/computerised systems –**

NEW !

… the investigator should……: (2.12.1 to 2.12.9)

- ensure data integrity for data under their responsibility
- **define source records, methods of data capture and data locations at the site prior to starting the trial** and should update this when needed
- **avoid unnecessary transcription** of data source record and the data acquisition tool
- have **timely access to all data** relating to a trial participant including data from external sources (e.g. ePRO, centrally read data, lab data)
- **endorse the clinical trial reported data at milestones agreed with the sponsor**

→ SD agreements must be in place before FPI

→ Sponsor must ensure investigator has access to all data all the time

→ CRF design must allow that investigators sign CRFs not just at the end of the study ! Timelines for this need to be agreed

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ICH E6 R3 – major changes for investigators….(9)

NEW !

When **computerised systems** in a clinical trial are deployed by the investigator/institution, **the investigator/institution should do the following:** (2.12.10) For example:

- **ensure** that appropriate individuals have secure and attributable access → ensuring means checking…
- **ensure that the requirements for computerised systems in Section 4 [Data Governance – Investigator and Sponsor] are addressed;** → investigator responsibility continues in Section 4, that is also applicable to the sponsor
- where equipment for data acquisition is provided to trial participants, ensure that traceability is maintained and participants are provided with appropriate training → participant training must be documented
- ensure that incidents in the use and operation of computerised systems, which in their judgement may have a significant and/or persistent impact on the trial data, are reported to the sponsor and, where applicable, to the IRB/IEC → to be checked by monitors (should be mentioned in the monitoring plan)

75

NEW !

- **NOTE:** ICH E6 R3 **requires the sponsor to assess** whether **Computer systems** deployed by the investigator/institution **that contain source records** in the trial (*e.g., electronic health records, imaging systems used, investigator site files*) **are fit for purpose** in the context of the trial or whether known issues can be appropriately mitigated

→ **This assessment must occur during the process of selecting clinical trial sites** (3.16.1 vi) (including data security, measures for backup, user management and audit trails) and be proportionate to the importance of the data managed in the system
This assessment must be documented, thus needing changes in visit report templates

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Investigators and Informed Consent (Section 2.8)

1. Approaches to obtaining informed consent

- The information should be as clear and concise as possible, use simple language and **avoid unnecessary volume and complexity** (2.8.1(b))
- **Varied approaches to the provision of information and the discussion about the trial may be used** (e.g. providing text in different formats, images, videos, via computerised systems) but this needs to consider the characteristics of the trial population (2.8.1 (c)) → **paper back-up should be in place when computerised consent process is in place**
- Obtaining consent **remotely** may be considered "when appropriate" (2.8.1 (d)) → **if used, a justification is required**
- Whether the informed consent process takes place in person **or remotely**, the investigator should **assure** themselves of the **identity of the participant** (2.8.1 (e)) → **clear process for remote ID confirmation needs to be in place**
- **Informed consent can be taken as an electronically signed record** (2.8.7)
- **The consent process must be approved by IRB/IEC** (1.2.2b) → **details in IRB/IEC submissions will need to be amended**

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Investigators and Informed Consent (Section 2.8)

2. For "New" information

- **Communication of new information and confirmation of the willingness to continue trial participation must be documented** (2.8.2) → **this applies to sharing information BEFORE the actual re-consent is conducted**
- **New information should be assessed to determine if written re-consent is needed**, for example considering the stage of the trial and whether new information is relevant to existing participants (2.8.2) → **justification for not re-consenting needs to be documented if applicable, however communication of new information to participants is still required**
- **New information should be clearly identified** in the revised informed consent materials (2.8.2) → **new information must be highlighted (tracked changes) for participants and for IRB/IEC**

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Investigators and Informed Consent (Section 2.8)

3. Enrolment of minors

- Where a minor is to be included as a participant, **age-appropriate assent information** must be provided and discussed with the minor as part of the consent process
- **A process for consent should be considered if during the trial, the minor reaches the age of legal consent**, in accordance with applicable regulatory requirements

→**new processes may be required**

4. Informed Consent content update

- "a to v" – compared to "a to t" in R2. For example: explanation of follow-up procedures; clarification that the trial may be registered on publicly accessible databases;

→**Sponsor "informed consent checklists" may need to be updated**

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Further (new) clarifications in Section 2

2.1 Qualification and Training

- Expectation of investigator CV removed and replaced with "evidence of qualifications".
- Removal of GCP awareness here – but stating in 2.5.1 "The investigator should comply with the protocol, GCP and applicable regulatory requirements."

2.7 Medical Care and Safety Reporting

- Other qualified HCPs may be the investigator or be involved in medical care and decisions in line with their normal activities and in accordance with local regulatory requirements
- Unfavourable medical events before investigational product administration (e.g., during screening) should be considered and reported to the sponsor if required by the protocol
- SAE causality assessment is required
- The investigator can delegate safety reporting but remains responsible

2.9 End of Participation in a Clinical Trial

- Discussions with participants recommended to determine if there are ways to address the concerns so that participants may reconsider withdrawal
- Provision of instructions how to avoid loss of already collected data in case of withdrawals
- Trial results and treatment received should be shared with participants when this information is available

2.11 Unblinding

- Included language that investigators should be prepared and capable from the start of the trial to perform unblinding without undue delay and hindrance in the case of an emergency, to protect participant safety

2.12 Records

- Direct access to records is required
- Need to keep sponsor informed of the responsible person for record retention
- Measures required to ensure availability, accessibility, readability, prevent unauthorised access, premature destruction, and follow regulatory requirements

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Section 3 Sponsor Responsibility

The responsibility of the sponsor entails the implementation of risk-proportionate approaches to ensure the rights, safety and well-being of the trial participants and the reliability of the trial results throughout the clinical trial life cycle

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Comparison to ICH E6 (R2) (1)

ICH E6(R3) Section	ICH E6(R2) Section
3.1 – Trial Design	5.0, 5.4
3.2 – Resources	N/A
3.3 – Allocation of activities	5.7
3.4 – Qualification and Training	5.3, 5.4
3.5 – Financing	5.9
3.6 – Agreements	5.1, 5.2, 5.6, 5.9, 5.23
3.7 – Investigator Selection	5.6
3.8 – Communication with IRB/IEC and Regulatory Authority(ies)	5.10, 5.11
3.9 – Sponsor Oversight	N/A

Source: ICH Website Microsoft PowerPoint - ICH_E6(R3)_Step 4_Presentation_2025_0123.pptx

Comparison to ICH E6 (R2) (2)

ICH E6 (R3) Section	ICH E6 (R2) Section
3.10 – Quality Management	5.0
3.11 – Quality Assurance and Quality Control	5.1, 5.18, 5.19
3.12 – Noncompliance	5.20
3.13 – Safety Assessment and Reporting	5.16, 5.17
3.14 – Insurance/Indemnification/Compensation to participants and investigators	5.8
3.15 – Investigational Product(s)	5.12, 5.13, 5.14
3.16 – Data and Records	5.5, 5.15
3.17 – Reports	5.21, 5.22

Source: ICH Website Microsoft PowerPoint - ICH_E6(R3)_Step 4_Presentation_2025_0123.pptx

Section 3 - Sponsor

Trial Design

3.1

Revised and NEW !

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Sponsor Key Changes (1) - 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)

NEW !

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)**

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Sponsor Key Changes (2) – Trial Design

3.1

- All aspects of the trial must be operationally feasible and should **avoid unnecessary complexity, procedures and data collection** (3.1.4) → **focus on your research question**
  - **Do not place unnecessary burden on participants and investigators**
- When planning trials, data from real-world sources should also be considered if available (3.1.1)

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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

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→ 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 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?

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Resources 3.2
and
Qualification and Training 3.4

NEW !

90

Sponsor Key Changes (3) – Resources & Qualification

3.2 3.4

- **Sponsor should have adequate resources (this was previously only noted in the Investigator section !!)** (3.2)

NEW !

- Sponsor should **utilise appropriately qualified individuals** for the activities to which they are assigned (e.g., biostatisticians, clinical pharmacologists, physicians, data scientists/data managers, auditors and monitors).
- **Medical personnel should be readily available** to advise on specific trial-related medical questions or problems (3.4)

→**Be prepared for questions regarding your own staff selection, qualifications and experience**

91

Agreements

3.6

NEW !

92

Agreements (1)

3.6

- **Although the information may not be entirely new, it now has its own section (3.6) to stress the importance**
- Agreements made with **all** parties (including independent data monitoring committee (IDMC), adjudication committees) must be documented **prior to initiating the activities**
  - **The requirement for agreement updates is stressed → incorporate regular (documented) contract reviews into your work processes → Ensure contract review timelines are clarified and reviews are indeed conducted and documented**
    - Amendments/modifications of the protocol occur; Regulations may change; Responsibilities may change; Nature of partnerships may change
  - If service providers subcontract contracted tasks to other service providers, these **subcontracted service providers must be bound to the same**

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Agreements (2) 3.6

- The sponsor must obtain **agreements from investigators and service providers to permit monitoring and auditing by sponsors**, inspections by regulatory authorities (domestic and foreign), **including providing direct access to source records and facilities**

→**direct access to SOPs, validation records, facilities etc. can no longer be denied, BUT access requirements must be specified in the contract**

→ see also 3.6.8 **The sponsor must have access to relevant information (e.g., SOPs and performance metrics) for selection and oversight of service providers – a service provider is not just a CRO, it means ALL "vendors"**

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Agreements (3) 3.6

- Any **of the sponsor's trial-related activities that are transferred to and assumed by a service provider must be documented in an agreement,** ultimate responsibility remains with the sponsor

→ **this requires details of all activities in contracts (e.g. document management and document retention)**

- Sponsor is responsible for **assessing the suitability of service providers and selecting the service provider to ensure that they can adequately undertake the activities transferred to them**

→**Service provider selection process is essential, including documented assessment of suitability (a sponsor process is required)**

see also 3.6.10 Service provider's quality management processes need to be fit for purpose in the context of the trial. **Trial-related activities performed by service providers should be conducted in accordance with relevant GCP requirements.**

95

Agreements (4) 3.6

- Sponsor must ensure **appropriate oversight of important trial-related activities** that are transferred to service providers, **including activities further subcontracted by the service provider**

→**Requires a defined sponsor oversight process and/or plans (including definition of "important" activities)**
→**Requires oversight over subcontractors**

- If a coordinating committee and/or coordinating investigator(s) are to be utilised in multicentre trials, their organisation and/or selection are the sponsor's responsibility, and their **roles and responsibilities should be documented prior to their involvement in the trial** (3.7.1)

→**The role of a coordinating investigator or committee(s) should be defined in an agreement**
→ **The selection process should be defined and documented**

96

→ Contracts – should contain at least (1)

- Clear identification of the study or studies to which the contract applies
- Services and Deliverables description
  - Study-level tasks including Study team/Governance meetings, Risk Management, communication plan etc.
  - Budget and Payment Schedules
- Timeframes for mutual provision of information (or may otherwise be agreed in other defined documents e.g. study plans)
- Applicable laws, regulatory standards, SOPs, etc.
- Access arrangements for SOPs
- Service provider training requirements (e.g. GxP; therapeutic indication; study documents)
- Statements regarding precedence between contracts and the trial protocol, i.e. that compliance with the protocol and regulations supersedes the contract and any internal procedures or vice versa as applicable
- Subcontracting clause, i.e., how the sponsor maintains oversight of any service providers subcontracted by the CRO/ service provider

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→ Contracts – should contain at least (2)

- If electronic systems are used for handling trial data, contracts should state that these must be validated and that records are available for audit and inspection
- Trial Master File details (if managed by service provider)/or detailed TMF plan*
- Records Management/Archiving arrangements/Transfer to sponsor
- Clearly delineated roles and responsibilities
- Granting regulatory bodies and sponsor QA function to inspect/audit
- Notification of quality issues to the sponsor, incl. non-compliance, deviations, potential serious breaches
- Portfolio/Project Performance Metrics (KPIs and KQIs), and Quality/Technical Agreements as necessary

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→ Contracts (3)

- **Detailed project specific contractual stipulations may also include:**

- **Project Level Governance specification**
- Governance aims to ensure oversight of project milestones, performance management, issue escalations, risk mitigations, budget tracking, and invoicing
  - Governance may involve Steering Committee meetings and regular Commercial and Operational Management Team reviews
- **Quality Alignment clarification**
  - Quality alignment may be maintained through a service provider risk oversight committee that is monitoring supplier risks, Portfolio level Quality Standards, and management of Corrective Action Requests
  - Service provider Project Plans define communication strategies, issue escalations, key milestones, deliverables, and risk-mitigations for effective project management

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→ Contracts - TMF details

- Structure and indexing of the TMF;
- Access arrangements for all involved parties;
- eTMF - details of the system and change control management;
- Lists of applicable procedures to be followed and training requirements;
- Type of documents that each party should retain;
- Arrangements for managing correspondence;
- How the TMF would be made available to the competent authorities and auditors;
- Arrangements for Quality Control reviews by the service provider;
- Arrangements for oversight of the TMF performed by the sponsor
- Arrangements for when the trial is completed;
- Document/TMF retention times;
- Access to TMF after archiving;
- Procedures in case of an involved party closing down its business.

100

Sponsor Oversight

3.9

NEW !

101

Sponsor oversight

NEW !

3.9

- **According to ICH E6 R3**, the term "trial conduct" includes processes from planning to reporting, including planning, initiating, performing, recording, **oversight**, evaluation, analysis and reporting activities" (Section 1)

and

- **GCP** is defined as "a standard for the planning, initiating, performing, recording, **oversight**, evaluation, analysis and reporting of clinical trials that provides assurance that the data and reported results are reliable and that the rights, safety and well-being of trial participants are protected" (Glossary)

  - **Thus, "oversight" is part of the regulated clinical trial conduct**

"Oversight" requirements are spread across ICH E6 R3….
ICH E6 (R3) mentions the word "oversight" 23 times (vs. 3 times in ICH E6 R2)

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Sponsor oversight

3.9

- **This section clarifies that:**
  - the sponsor should ensure that the range and extent of **oversight measures are fit for purpose and tailored to the complexity and risks associated with the trial** (3.9.5)

→**oversight measures should be proportionate to individual trials and must fit the complexity and risks of the service provider/investigational site → no more "cut and paste" of oversight plans → risk proportionate approach …**

  - **the oversight of facilities outside of investigator sites, e.g., central image reading facilities, should be part of the overall QC strategy**

→ **a defined overall oversight strategy should be in place**

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Sponsor oversight

3.9

- Sponsor should **determine necessary trial-specific criteria for classifying protocol deviations as important** (3.9.3)
  - **Important** protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy and/or reliability of the trial data or that may significantly affect a participant's rights, safety or wellbeing

→**Deviation Plans are required defining deviation classification. Terminology now matches ICH E3. Avoid using the term "major" deviations → change in processes/plans**

- **Decisions** related to the trial should be appropriately **assessed for their impact and** suitably **managed throughout the planning, conduct and reporting of the trial** (3.9.4)

→**It is now essential to document decisions – and to add impact assessments and justifications throughout all the trial activities**

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Sponsor oversight

3.9

- Sponsor should **ensure appropriate and timely escalation and follow-up of issues** to allow the implementation of appropriate actions **in a timely manner** (3.9.6)

→**Escalation processes are required (e.g. in project plans)**

→ **Clarification of sponsor expectations regarding escalation should be in service provider/investigator contracts/study plans**

- **Committees** (e.g. IDMC, endpoint assessment/adjudication committee) that could impact participant safety or the reliability of trial results must include members with relevant expertise and with managed conflicts of interest, **have written operating procedures** (e.g., charters) and **document their decisions** (3.9.9).
  - **Committees should typically be blinded to assigned treatments when performing their assessments, regardless of whether the trial itself is conducted in a blinded manner**

  → **This may require changes in committee set-ups and related processes/SOPs**

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3.11

Quality Assurance and Quality Control

Revised

106

Quality Assurance and Quality Control

3.11

1. Quality Assurance (3.11)

- Quality assurance should be **applied throughout the clinical trial**
- QA includes **implementing risk-based strategies to identify potential or actual causes of serious noncompliance** with the protocol, GCP and/or applicable regulatory requirements to enable their corrective and preventive actions

→**QA is not just meant to conduct audits**

→**QA requires a strategy how to identify serious non-compliance**

- **Audits should be risk based**

→**The "every 3 years" audit approach is no longer appropriate**

- The sponsor's **audit plan, program and procedures** for a trial audit should be guided by level of risks, problems, number of participants in the trial, the type and complexity of the trial

→**Audit programme, audit plan and relevant procedures should be trial specific**

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Quality Assurance and Quality Control

3.11

- **Quality assurance and quality control processes should be implemented in the oversight of investigators and service providers**

→ **Processes defining "Quality Control" are also required**

2. Quality Control

- 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**. 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).

→**Quality control activities include Data Management and Monitoring. This must also cover service providers (e.g. data reviews, visits (not audits), governance measures, KPI reviews) and Centralised Monitoring** (see 3.11.4.2)

→ a **Risk Based Monitoring Strategy supports trial oversight**

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3.11.4

Monitoring

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Monitoring

Monitoring may include site monitoring (performed on-site and/or remotely) and centralised monitoring, depending on the monitoring strategy and the design of the clinical trial.

The sponsor should determine the appropriate extent and nature of monitoring based on identified risks. Factors such as the objective, purpose, design, complexity, blinding, number of trial participants, investigational product, current knowledge of the safety profile and endpoints of the trial should be considered.

Monitoring is one of the principal quality control activities

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Centralised Monitoring

- **Centralised monitoring** is an evaluation of accumulated data, performed in a timely manner, by the sponsor's qualified and trained persons (e.g., medical monitor, data scientist/data manager, biostatistician)
- Centralised monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of site monitoring or be used on its own
- 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.

ICH E6 R3: 3.11.4.2

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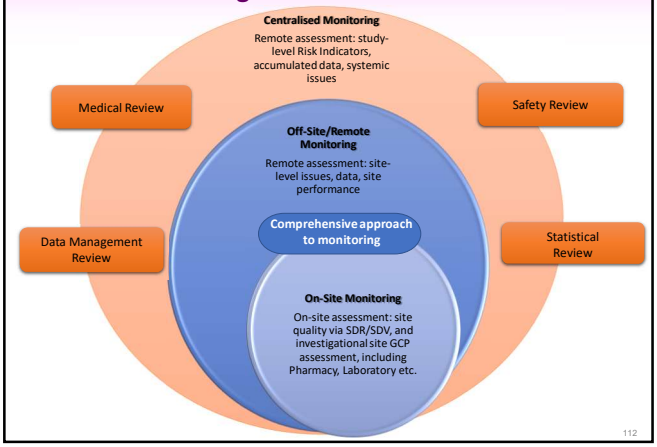
RBM - Monitoring Execution



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The "new" Monitoring

- **The monitoring approach should consider the activities and services involved, including decentralised settings, and be included in the monitoring plan.**

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Monitoring

The sponsor should document the **rationale** for the chosen **monitoring strategy** (e.g., in the monitoring plan)

The **monitoring plan needs to be tailored** to the specific human subject protection and **data integrity risks** of the trial

The **frequency of monitoring activities should be determined based on identified risks**. Monitoring activities and their frequency should be modified as appropriate using knowledge gained

Monitoring may include **secure, remote, direct read-only access to source records, other data acquisition tools and essential record retention systems**

114

Monitoring Plan – minimum requirements

The Plan should describe
- the monitoring strategy
- the monitoring activities of **all** parties involved
- the various monitoring **methods and tools** to be used, and **the rationale for their use**

Tailored to study risks (safety, reliability of data, data quality)

Focus on aspects that are critical to quality, safety and endpoints

Reference the sponsor's applicable policies and procedures

Address the monitoring of key data and processes performed outside the investigator site (e.g., central reading facilities, central laboratories)

115

Monitoring Plan

Identified potential safety risks, risks to data quality, and any other risks impacting the reliability of trial results should guide the nature and the extent of the monitoring strategy selected

- **The monitoring plan that is developed should be focused on aspects that are critical to quality**

By taking such a risk-based approach decisions are made prospectively

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

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Monitoring Report

Reports of monitoring activities should include a **summary of what was reviewed**, a **description of significant findings**, **conclusions and actions required to resolve them** and **follow-up on their resolution** including those not resolved in previous reports.

The requirements of monitoring reports (including their content and frequency) should be described in the sponsor's procedure

→ **Ensure you have reviewed (evidence needed) and approved any CRO procedures**

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Monitoring Report

Monitoring results should be provided to the sponsor (including appropriate management and staff responsible for trial and site oversight) in a timely manner for review and follow up

Results of monitoring activities should be documented in sufficient detail to allow verification of compliance with the monitoring plan

Outcomes of any centralized monitoring should also be reported

The report should describe findings requiring escalation for action and resolution

The sponsor should decide on the appropriate action to be taken, and these decisions and the resolution of the actions involved, where needed, should be recorded

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Note – some clarification of monitoring responsibilities as per ICH E6 R3

(i) verify that the data required by the protocol and identified as critical in the monitoring plan are consistent with the source

(ii) identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations

(iii) examine data trends, such as the range, consistency and variability of data within and across sites

And also: Identifying significant errors in data collection and reporting at a site or across sites, potential data manipulation and data integrity problems

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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"

  * For example: processes how to review MVRs, how many, how to provide feedback to CRO, how to document CRO responses; escalation processes for issues. Ensure MP review timelines are defined.

- Off-site Monitoring and On-site Monitoring reports are required, with evidence of Central Monitoring activities
- The sponsor must confirm that all reports contain sufficient information
- The monitoring strategy must be formulized and plans are **no longer optional** or "good practice"

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Sponsor Oversight Summary - MHRA Grey Guide

"The sponsor is responsible that the trial complies with the legislation and GCP.

Trial Management and an effective quality management system provide a means of oversight of all functions, whether undertaken in-house or subcontracted"

https://www.tsoshop.co.uk/product/9780117081079/Medical/MHRA/Good-Clinical-Practice-Guide-Paperback/?TrackID=000039

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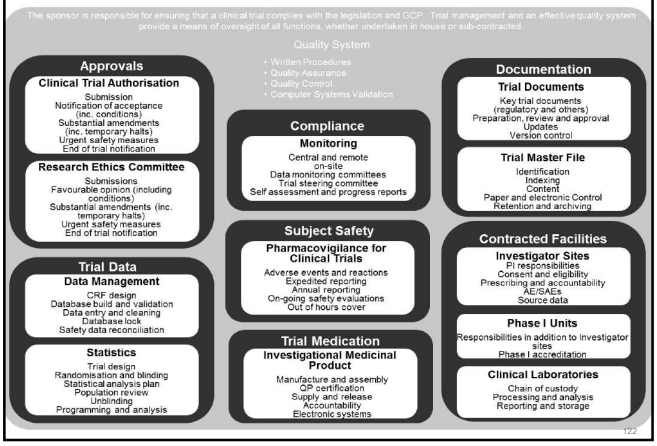
Sponsor Oversight Summary



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Noncompliance

3.12

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Noncompliance

- **When noncompliance is discovered that has the potential to significantly affect rights, safety or well-being of trial participant(s) or the reliability of trial results the sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions and confirm their adequacy unless otherwise justified**

- **If significant noncompliance is identified on the part of an investigator/institution or service provider that persists despite efforts at remediation, the sponsor should consider terminating the investigator's/institution's or service provider's participation in the trial.**

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Impact

- **Expands on CAPAs to confirm their adequacy unless otherwise justified → ensure documented justification if adequacy of CAPAs is not checked**
- Issue that are likely to significantly impact the rights, safety or well-being of the trial participant(s) or the reliability of trial results (i.e., serious noncompliance), the **sponsor must notify the regulatory authority and/or IRB/IEC and/or investigator as appropriate and as per applicable regulatory requirements → know your requirements, processes should be in place**

Note: **EU Regulation 536/2014 Article 52 requires sponsors to report Serious Breaches within 7 calendar days of awareness within Europe – see Serious Breach Guidance**
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-notification-serious-breaches-regulation-eu-no-536/2014-clinical-trial-protocol_en.pdf

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3.10

Quality Management

Identify your study's most important data and critical to quality success factors to get to the right level of oversight for your staff, your service providers and sub-contractors

127

Quality Management

3.10

Limited changes compared to ICH E6 R2 Section 5 – mainly clarifications….

- Clarified that **risks must be considered** across **all processes and systems**, **including computerised systems** (3.10.1.1) e.g. trial design, participant selection, informed consent process, randomisation, blinding, investigational product administration, data handling and service provider activities
- Further clarified the **requirements for "critical to quality factor" assessment and management** (factors that are likely to have a meaningful impact on participants' rights, safety and well-being and the reliability of the results) (3.10)
- Term "Harm/hazard" replaces "errors" (3.10.1.2 "Risk Evaluation")
- Introduction of the term **"prespecified acceptable ranges"** that need to be set by sponsor (**example: quality tolerance limits at the trial level**)
  - **Where deviation beyond these ranges is detected, an evaluation must be performed to determine if there is a possible systemic issue and if action is needed** 3.10.1.3
- **Clarified that sponsor must describe** the quality management approach, summarise important quality issues, including instances in which acceptable ranges are exceeded, and the remedial actions taken **in the CSR** (3.10 and 3.10.1.6)

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→ Impact

Limited changes compared to ICH E6 R2 Section 5 – mainly clarifications….

- **Sponsor responsibility 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**

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→ Impact

- Re-enforcement of 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, thereby protecting human subjects and ensuring the reliability of study results

*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

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Risk Management Steps

1. Critical Process/System 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 R3 Section 3.10

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1. Critical Process/System and Data Identification

- **During protocol development**, the sponsor should
  - identify processes/systems **(including computerised systems)** and data that are critical

  to assure **human subject protection and the reliability of study results (Critical to Quality Factors)** 3.10.1.1

  → **Highlighting the need for assessing processes/systems as well as data and determine if they are critical**
  → **Computerised systems must be part of risk identification**
  → **Defining, rationalizing and documenting those critical processes/systems and data (Critical to Quality Factors)**

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Critical data and processes

Critical Data	Critical Processes/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 and Systems 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

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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

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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

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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

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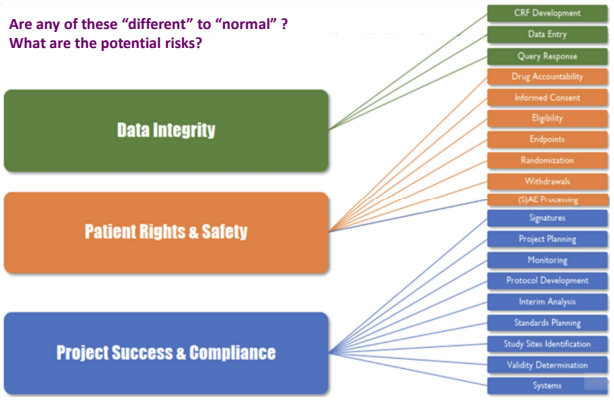
Other Examples - Critical to Quality Factors

Are any of these "different" to "normal" ?
What are the potential risks?



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Quality by Design of Clinical Studies

Quality by design involves focusing on 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**

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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

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2. Risk Identification

- The sponsor should **identify risks** that may **have a meaningful impact on critical to quality factors** (3.10.1.2)
- Risks should be considered across the processes/systems used in the clinical trial, including computerised systems (e.g., trial design, participant selection, informed consent process, randomisation, blinding, investigational product administration, data handling and **service provider activities**)
  - → Clarifying the need for assessing processes as well as data
  - → Highlighting the need to define "**"Prespecified Acceptable Ranges"**

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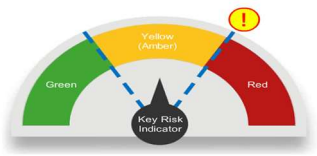
Setting "Prespecified Acceptable Ranges" e.g. quality tolerance limits at the trial level

Concept of Acceptable Ranges is introduced in R3, which expands the QTL concept

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



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Quality Tolerance Limits

3.10.1.3: **pre-specified acceptable ranges (e.g., quality tolerance limits at the trial level) to support the control of risks to critical to quality factors**.
These pre-specified ranges reflect limits that when exceeded have the potential to impact participant safety or the reliability of trial results.
Where deviation beyond these ranges is detected, an evaluation should be performed to determine if there is a possible systemic issue and if action is needed.

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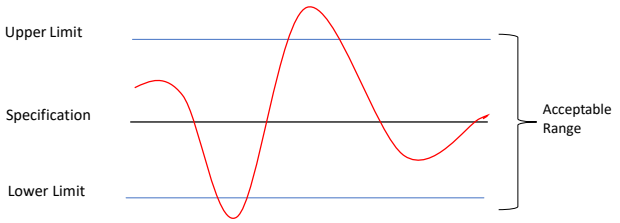
What are QTL?

- 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



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Acceptable ranges (Quality Tolerance Limits) …And then….

- **The Risk Management Plan and related activities as part of the Sponsor Oversight** should include strategies for monitoring acceptable ranges/QTLs, determining the root cause of deviations, and addressing deviations
- **Acceptable ranges/QTLs and justification of changes must be documented in the CSR**

→ **Sponsor Oversight includes risk management**

Suggested reading: Risk-Based Quality Management - TransCelerate

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3. Risk Evaluation

- Identified risks should be evaluated by considering:
  - (a) Likelihood of harm/hazard occurring

    [consider existing risk controls and mitigations]
  - (b) Impact/severity of harm/hazard

    [on human subject protection and data integrity]
  - (c) Detectability of harm/hazard

    [the state/extent/likelihood of the errors being observed]

Harm/hazard terminology introduced in R3 to prioritize risks that may have a meaningful impact

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Transfer risk evaluation into practice…

Development of a Risk Registry

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Example Risk Registry

Risk Identification			Risk Analysis				
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 from Column B of the 'Risks Library' tab*	Risk Details *Provide details about why this risk applies to this study*	Quality Impact (1-5)	Likelihood (1-5)	Detectability (1-3)	RPN (2Lx2Lx2D)	Quality Impact Category

Risk Evaluation		Risk Control	
Accepted?	Justification for Decision *(Mandatory for accepted high Quality Impact Category risks)*	Risk Mitigation Plan *For unaccepted risks - enter details of new controls/mitigations that will be implemented to protect against the risk - see 'Guidance' tab for more details*	Risk Mitigation Owner *Enter who has responsibility for ensuring the new control/mitigation is implemented*

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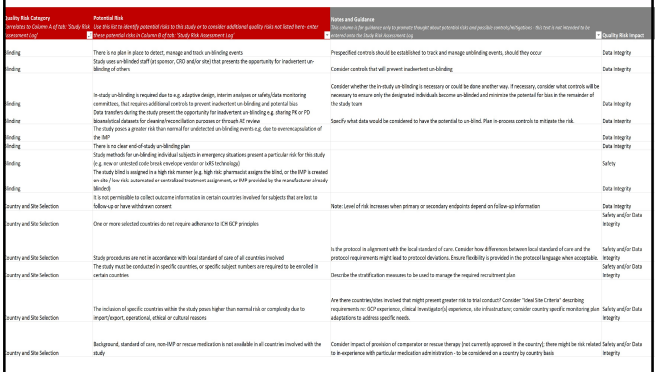
Example Risk Registry – the "risk library"



Quality Risk Category (correlates to Column A of risk '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 risk 'Study Risk Assessment Log')	Notes and Guidance (Any column is for guidance only to promote thought about potential risks and possible controls/mitigations - this tool is not intended to be entered onto 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 an unblinded staff (an 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 clinical/reconciliation purposes or through AC 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 unintected 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. new or untested code break envelope vendor or IVRS technology)		Safety
Blinding	The study blind 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)		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 adherance 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 adaptations to address specific needs.	Safety and/or Data Integrity
Country and Site Selection	Background, standard of care, non-IMP or rescue medication 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)

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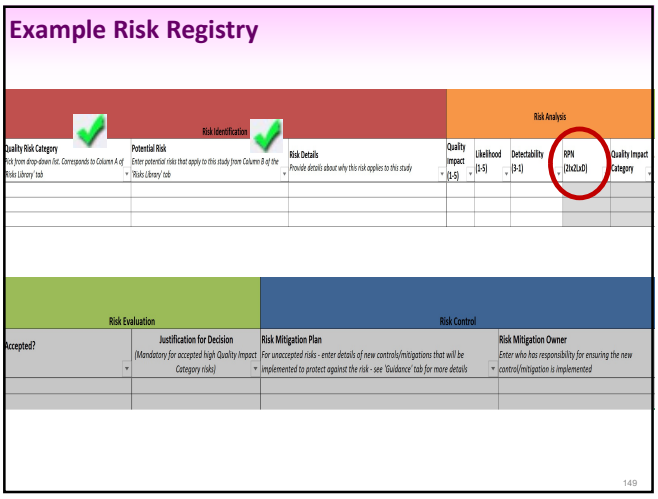
Example Risk Registry



Risk Identification			Risk Analysis					
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 from Column B of the 'Risks Library' tab)	Risk Details (Provide details about why this risk applies to this study)	Quality Impact (1-5)	Likelihood (1-5)	Detectability (1-3)	RPN (2lx2Lx3)	Quality Impact Category	

Risk Evaluation		Risk Control	
Accepted?	Justification for Decision (Mandatory for accepted high Quality Impact Category risks)	Risk Mitigation Plan (For unaccepted risks - enter details of new controls/mitigations that will be implemented to protect against the risk - see 'Guidance' tab for more details	Risk Mitigation Owner (Enter who has responsibility for ensuring the new control/mitigation is implemented

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Risk Analysis – Risk Priority Number

1. Risk Class

Impact (x4) \ Likelihood (x1)	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	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)

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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 and risk acceptability should be assessed by the Study Team**
- Approach used to reduce risk to an acceptable level should be proportionate to the significance of the risk

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4. Risk Control

- Sponsor should identify those risks that
  - can be accepted

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

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

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Risk Control (2)

- **ICH E6 R3:**
  - **Risk control should be proportionate** to the importance of the risk to participants' rights, safety and well-being and the reliability of trial results
  - **Risk mitigation** activities may **be incorporated** in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, training 3.10.1.3
    - [also consider systematic safeguards to ensure adherence to SOPs]

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Examples of Risk Mitigation activities

- 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

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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]

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5. Risk Communication

- Identified risks and mitigation activities must be
  - **documented** and
  - **communicated to stakeholders**
    - **….to those who are involved in taking action or are affected by such activities**

to facilitate risk review and continual improvement during clinical trial execution 3.10.1.4

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

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6. Risk Review

- Sponsor must **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
  - Additional risk control measures may be implemented as needed → Revising the risk plan and documentation based on relevant changes

→ **We need for example: Risk Assessment Plan; Meetings discussing risk assessments; risk registry with version control**

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7. Risk reporting

- **Sponsor must [in the Clinical Study Report]**
  - **summarise and report important quality issues**
  - **instances in which acceptable ranges are exceeded, as detailed in section 3.10.1.3) and**
  - **the remedial actions taken**

[ICH E3, Section 9.6 Data Quality Assurance]

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Impact

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

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How to include risks in the protocol design

Refer to DRAFT ICH M11 template
https://www.ema.europa.eu/en/documents/scientific-guideline/ich-m11-template-step-2b_en.pdf

for suggested protocol wording

Adoption planned for Nov 2025

DRAFT M11 Guideline:
https://www.ema.europa.eu/en/documents/scientific-guideline/ich-m11-guideline-clinical-study-protocol-template-technical-specifications-step-2b_en.pdf

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How to include risks in the protocol design (1)

- **Protocol template sections** ICH M11 (selected section for this presentation)
  - **Section 2.2 Summary of Benefits and Risks**
    - Trial Specific Discussion of **intervention** Risks and Mitigation
      - Trial Intervention – Discuss risks related to trial-specific treatments and interventions. For the protocol, focus discussion only 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.

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How to include risks in the protocol design

- **Protocol template sections** ICH M11 (selected section for this presentation)
  - **Section 2.2 Summary of Benefits and Risks (CONT)**
    - Trial Specific discussion of **procedure(s)** Risks and Mitigation
      - Trial Procedures – Consider risks associated with the trial design and procedures specific to this trial (for example, biopsies) or design (for example, placebo arm), and any measures to control 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. As above, provide a brief description of strategies to mitigate identified risks or provide a cross-reference to the relevant protocol section.

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How to include risks in the protocol design

- **Protocol template sections** ICH M11 (selected section for this presentation)
  - **Section 2.2 Summary of Benefits and Risks (CONT)**
    - 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.

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How to include risks in the protocol design (2)

- **Protocol template sections** ICH M11 (selected section for this presentation)
  - **Section 11 General Considerations: Risk Management and Quality Assurance**
    - **Quality Tolerance Limits**
      - Indicate aspects of the trial design which attend to the principles of Quality by Design, such as clear trial objectives, meaningful endpoints, and selection of appropriate trial population.
      - **Indicate where Quality Tolerance Limits will be predefined, how they will be monitored during the trial, and expected discussion in the clinical trial report.**

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Other

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Further (new) clarifications in Section 3

3.8 Communication with IRB/IEC
- IRB/IEC submissions by investigator OR sponsor per regulatory requirements

3.12 Noncompliance
- Appropriate and proportionate actions to secure compliance
- **CAPA adequacy to be confirmed**
- Report serious noncompliance to regulatory authorities and actions to minimise impact

3.13 Safety assessment & reporting
- Sponsor review in timely manner of relevant safety information including any reported unfavourable medical events occurring **before** IMP administration (e.g., during screening)
- Reporting of SUSARs to investigators and IRB/IEC should be in a manner that reflects the urgency of action required and per local regulations (urgent safety issues requiring immediate attention or action must be reported without undue delay)
- Alternative arrangements for safety reporting should be prospectively agreed with regulatory authorities/ IRB/IEC, and described in the protocol

3.15 IMP
- Sponsor may supply IMP to trial participants in accordance with applicable regulatory requirements

3.17 Reports
- Where a coordinating investigator is involved in a trial, consideration should be given to them being a signatory on the clinical trial report
- Once trial is unblinded and analyses/ conclusions are completed, sponsor should make **trial results publicly available**; provide the investigator with information about the treatment taken by their participants and the trial results.
- **Trial results for participants** should be non-technical, understandable to a layperson and non-promotional.

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3.16

Data and Records

Revised

Read this in parallel with Section 4 – Data Governance

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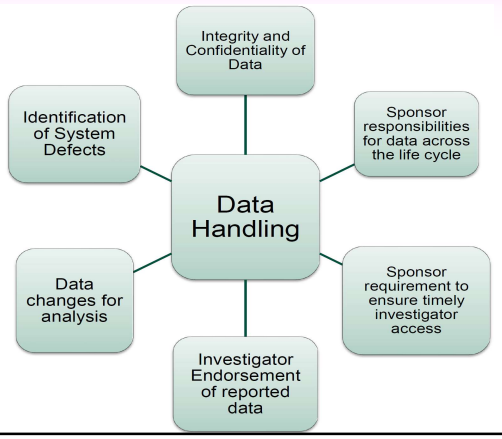
Data Handling – see also Section 4 (Data Governance)

3.16



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Data Handling – important requirements for sponsors (1)

- ❑ Apply quality control to the relevant stages of data handling - focus quality assurance and quality control activities, including data review, on data of higher criticality **and relevant metadata**
- ❑ Where necessary, additional details, including a **data flow diagram**, should be contained in a protocol related document (e.g., a data management plan)
- ❑ **Data acquisition tools must be fit for purpose and validated and ready for use prior to their required use in the trial**
- ❑ Provide guidance to investigators/institutions, service providers and trial participants (if applicable) on the **expectations for data capture, data changes, data retention and data disposal**
- ❑ **Do not make changes to data** entered by the investigator or trial participants unless justified and agreed upon in advance by the investigator and documented

Data Handling – important requirements for sponsors (2)

- ❑ **Data corrections by site and participants should be possible but justified and supported by source records around the time of original entry**
- ❑ Do not have exclusive control of data captured in data acquisition tools
- ❑ Ensure that the **investigator has access** to the required data for retention purposes
- ❑ Seek **investigator endorsement** of their reported data **at predetermined milestones**
- ❑ Describe the process by which participant data will be handled when participant withdraws or discontinues from the trial
- ❑ **Have processes and procedures in place** for reporting to relevant parties, including regulatory authorities, incidents (including security breaches) that have a significant impact on the trial data

Data Handling – computerized systems (1)

- ❑ **Have a record of the important computerised systems used in a clinical trial**
  - **This must include: the use, functionality, interfaces and validation status, who is responsible for its management, a description of implemented access controls and internal and external security measures**
- ❑ Ensure that the requirements for computerised systems (e.g., requirements for validation, audit trails, user management, backup, disaster recovery and IT security) are addressed and implemented and that **documented procedures and adequate training are in place to ensure the correct development, maintenance and use of computerised systems in clinical trials**
- ❑ Maintain a record of the individual users who are authorised to access the system, their roles and their access permissions
- ❑ Ensure that access permissions granted to investigator site staff are in accordance with delegations by the investigator and visible to the investigator
- ❑ Ensure that there is a process in place for service providers and investigators to inform the sponsor of system defects identified

Data Handling – computerized systems (2)

- ❑ **Assess whether systems containing source records in the trial,** (e.g., electronic health records, imaging systems used or deployed by the investigator/institution and any other record keeping systems for source data collection and investigator site e-files) **are fit for purpose** and whether the risks from a known issue(s) can be appropriately mitigated
  - ❑ **Assessments must be performed before being used in the trial**
  - ❑ **Assessments must occur during the process of selecting clinical trial sites**
  - ❑ **Assessments should be proportionate to the importance of the data managed in the system**
  - ❑ **Factors such as data security (including measures for backup), user management and audit trails, which help ensure the protection of confidentiality and integrity of the trial data, should be considered as appropriate**
  - ❑ **Assessments must be documented**

→Change in monitoring procedures – discuss with the CRO that this is covered

What questions to ask when reviewing computerised systems - References

Use available checklists:

Research Quality Association - Auditing Computerised Systems (to purchase online)

PICS Good Practices for Computerised Systems in Regulated GXP environments Microsoft Word - PI 011-3 Recommendation on Computerised Systems.doc (picscheme.org)

The eSOURCE-READINESS ASSESSMENT TOOL (eSRA) eClinical Forum January 2024 eSRA V2024 (eSource-Readiness Assessment) Handbook and Questionnaire (eclinicalforum.org)

Technical Guide on Information System Audit Microsoft Word - Initial.doc (icai.org) (at the moment not accessible though, feel free to request from jQAGCP@gmail.com)

IT Audit Manual - United Nations Development Programme https://www.undp.org/sites/g/files/zskgke326/files/migration/al/IT-AUDIT-MANUAL.pdf

A Beginner's Guide to IT System Inspection Readiness – ISPE https://ispe.org/pharmaceutical-engineering/may-june-2021/beginners-guide-it-system-inspection-readiness

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Some references re CSV

- **EMA Guideline on computerised systems and electronic data in clinical trials (March 2023)** https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-computerised-systems-electronic-data-clinical-trials_en.pdf
- **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) (Question 9)** 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
- **EMA Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials (June 2010)** https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/reflection-paper-expectations-electronic-source-data-data-transcribed-electronic-data-collection_en.pdf

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Other References

- MHRA **Electronic health records** Electronic health records - MHRA Inspectorate (blog.gov.uk)
- Guidance: **Access to Electronic Health Records by Sponsor representatives in clinical trials -** jointly developed by the Heath Research Authority (HRA) and MHRA, in consultation with the Information Commissioners Office (ICO), on behalf of the UK https://www.gov.uk/guidance/on-site-access-to-electronic-health-records-by-sponsor-representatives-in-clinical-trials
- 21 CFR # 11 – Electronic Records; Electronic Signatures
- 21 CFR # 820 – FDA Quality System Regulations
- Guidance for Industry: Computerised Systems in Clinical Investigations, May 2005
- Guidance for Industry and FDA Staff: General Principles of Software Validation, January 2002
- FDA: Guide to Inspections of Computerised Systems in Drug Processing, 1983
- OECD Advisory Document: The Application of the Principles of GLP to Computerised Systems, 2016 (see attachment A) https://www.oecd.org/en/publications/application-of-glp-principles-to-computerised-systems_e3c9cda5-en.html
- GAMP 5
- PIC/S – PI 011-3: Good Practices for Computerised Systems in Regulated GXP Environments, September 2007 https://picscheme.org/docview/3444

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Section 4 Data Governance

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Data Governance Definition

- **Oversight and control of clinical trial-related information to ensure the identification, purpose, availability, usability, traceability, integrity, security and quality of data throughout its lifecycle**
  - **Essential for generating valid and reliable clinical trials results as well as ensuring the protection of participant safety, privacy, and rights**
  - **Involves data identification, data ownership, and accountability, and linking data to critical to quality factors**
  - **Requires oversight and control mechanisms to ensure compliance with policies, standards, regulations, and best practices**
- An effective data governance strategy aims to establish **accountability, transparency, and consistency in data-related decision-making processes** across the organisation

- EMA "Guideline on computerised systems and electronic data in clinical trials" explains as follows: "The **total of activities, processes, roles, policies, and standards** used to **manage and control the data** during the entire data lifecycle, while adhering to **ALCOA++ principles**" (see section 4.5.).

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Content and focus of the new section

Provides guidance for investigators and sponsor (as responsible parties) on appropriate management of data integrity, traceability and security, to allow the accurate reporting, verification and interpretation of clinical trial-related information

Reference to individual responsibilities in investigator and sponsor sections, but data governance requirements is applicable to all

Clarifies the meaning of a "data lifecycle"

→ **Requires systems and processes for Data protection of confidential participant data; Management of Computerised Systems; Safeguarding of essential elements of the trial (e.g. randomisation, blinding); Processes to support key decision making (e.g. allocation to analysis data sets, changes in clinical trial design)**

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ICH E6 R3 - New section 4 - section overview (1)

4.0 Clarification of Key processes that are required - Processes for:

- ensuring the protection of the confidentiality of trial participants' data;
- managing computerised systems to ensure that they are fit for purpose and used appropriately;
- safeguarding essential elements of the clinical trial, such as randomisation, dose adjustments and blinding;
- supporting key decision making, such as data finalisation prior to analysis, unblinding, allocation to analysis data sets, changes in clinical trial design and, where applicable, the activities of, for example, an IDMC.

For details see section 4.3

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ICH E6 R3 - New section 4 - section overview (2)

4.1 Safeguard Blinding in Data Governance
4.2 Data Life Cycle Elements
4.3 Computerised Systems
- **4.3.1** Procedures for the Use of Computerised Systems
- **4.3.2** Training
- **4.3.3** Security
- **4.3.4** Validation
- **4.3.5** System Release
- **4.3.6** System Failure
- **4.3.7** Technical Support
- **4.3.8** User Management

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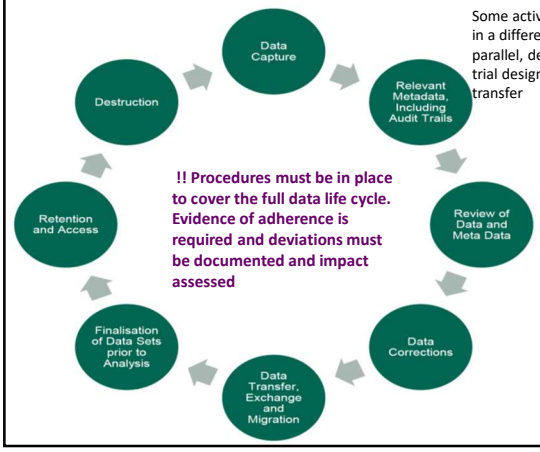
4.2 Data Life Cycle Elements



Some activities may occur in a different order or in parallel, depending on the trial design, e.g., data transfer

4.2 Data Lifecycle – some important aspects (1)

- **Acquired data from any source**, including **data directly captured** in a computerised system (e.g., a data acquisition tool), **must be accompanied by relevant metadata** 4.2.1

→ Define the metadata you require
→ Define the metadata which will require review and retention
→ Define the data archive that allows for retrieval and readability, protected from unauthorised access and alterations throughout the retention period
→ Create a data flow diagram - A clinical study data flow diagram is a visual representation of how data moves within a clinical trial, from its capture, review, finalization and archiving. It illustrates the flow of information between stakeholders, systems, and processes involved in the study

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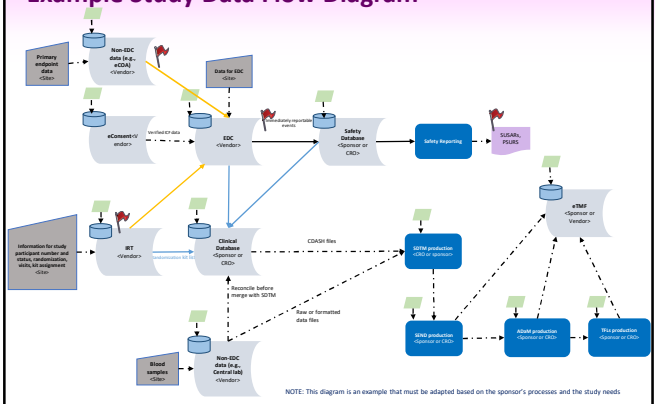
Example Study Data Flow Diagram



Source: https://www.acrohealth.org/wp-content/uploads/2025/01/Study-Data-Flow-Diagram-Template-ACROTransCelerateResource.pdf

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4.2 Data Lifecycle – some important aspects (2)

- **Evaluate the system for the types and content of metadata available to ensure that:** 4.2.2
  - Computerised systems maintain logs of user account creation, changes to user roles and permissions and user access
  - Systems are designed to permit data changes in such a way that the initial data entry and any subsequent changes or deletions are documented, including the reason for changes
  - Systems record and maintain workflow actions in addition to direct data entry/changes into the system

→ **Document the system evaluation**

- **Ensure that audit trails, reports and logs are not disabled, are interpretable, support review and are unambiguous (e.g. time, dates)**

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4.2 Data Lifecycle – some important aspects (3)

- **Procedures for review of trial-specific data, audit trails and other relevant metadata must be in place as a planned activity**
  - Extent and nature of review should be risk-based, adapted to the individual trial and adjusted based on the experience during the trial
- **There must be processes to correct data errors that could impact the reliability of the trial results**
  - Corrections must be attributed to the person or computerised system making the correction. Corrections must be justified and supported by source records around the time of original entry and performed in a timely manner
- **Validated processes and/or other appropriate processes such as reconciliation must be in place to ensure that electronic data, including relevant metadata, transferred between computerised systems retains its integrity and preserves its confidentiality**
  - The data exchange/transfer process or system migration must be documented to ensure traceability.
  - Data reconciliation must be implemented as appropriate to avoid data loss and unintended modifications

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→ Important considerations

- **Despite these very detailed requirements, remember to focus on those defined data that matter (i.e. how critical are the data, are they part of the key objective, are they essential for decision making, safety data) and thus determine the extend of data verification required here**
- **Consider how critical data are implemented, evaluated, accessed and managed**
- **Consider which metadata require review and attention**
- **Consider the timing and extend of audit trail reviews (e.g. before a key milestone, suspected mismanagement) depending on criticality of data, what is it used for and the impact if the data are incorrect**

→ This must form part of the trial risk assessment

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4.1 Safeguarding Blinding (1)

- When designing systems, ensure that the blind will be protected (e.g. by management of user accounts/roles; provision of data access, data transfers, review of data prior to analysis)
- **Roles and responsibilities and procedures for access to unblinded information must be defined and documented** (e.g. in Project Plans, Data Management Plans or Statistical Analysis plans, site delegation records)
- **Potential for unblinding must be part of the trial risk assessment**

→ Map out the data flow of blinded information, identify where the risks are and how to mitigate

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4.1 Safeguarding Blinding (2)

- The sponsor must put procedures in place to describe unblinding

→ An SOP needs to be in place to describe management of unblinding

- **Documentation** of any planned, emergency or unplanned unblinding is required **(also requires description in the CSR)**
  - Who were unblinded
  - At what timepoint
  - For what purpose
  - Who should remain blinded
  - The safeguards in place to preserve the blinding
- **Any emergency or unplanned unblinding must be assessed for its impact on the trial results**

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4.3 Computerised Systems

When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

…… Maintain SOPs/processes for using these systems

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The SOPs/processes should describe

- system validation,
- functionality testing,
- data collection and handling,
- system maintenance,
- system security measures and controls,
- change control,
- data backup,
- (disaster) recovery,
- contingency planning,
- decommissioning

In addition

- Data protection
- How to manage systems to ensure they are fit for purpose and used appropriately
- How to safeguard essential elements of the trials e.g.,
  - Randomisation, Dose adjustments, Blinding
- How to support key decision making e.g.,
  - Data finalisation, unblinding, allocation of analysis data sets, changes in trial design, IDMC (as applicable)
- Audit trail management
- User management
- adequate training process to ensure the correct development, maintenance and use of computerised systems

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For the individual computer systems, procedures should cover:

- system design
- validation
- functionality testing
- release
- system setup
- installation
- use
- change control
- decommissioning

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4.3 Computerised Systems

- **Expectations are based on the system purpose and importance**
- **Responsibilities with respect to a computerised system must be clear and documented**

Trial-specific systems (including updates resulting from protocol amendments) must only be implemented, released or activated for individual investigator sites after all approvals for the clinical trial relevant to that investigator site have been received

→ **Have a record of the important computerised systems used in a clinical trial. This should include the use, functionality, interfaces and validation status of each computerised system, and who is responsible for its management**
→ **The record should also include a description of implemented access controls and internal and external security measures - see 3.16.1 (i)**

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4.3 Computerised Systems Expectations (1)

- ❑ **The responsible party must ensure that those developing computerised systems for trials are aware of the intended purpose and the regulatory requirements that apply to them so that the system is compliant → GCP awareness of IT/Vendors)**
  - ❑ There should be mechanisms (e.g., help desk support) to document, evaluate and manage issues with the computerised systems (e.g., raised by users)
  - ❑ There should be periodic review of cumulative issues to identify those that are repeated and/or systemic
- ❑ Involve representatives of participants and HCPs in the design of the system to ensure that computerised systems are suitable for use by the intended user population (recommendation) → **User Involvement**
- ❑ **Procedures must be in place to ensure appropriate use of computerised systems for essential activities related to data collection, handling and management → User Management**
  - The responsible party must ensure that those using computerised systems are trained in their use → **Training requirements**

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4.3 Computerised Systems Expectations (2)

Security: - measures should be periodically tested – a lot of defined requirements … **for further reading…**

1. **Procedures must cover system security measures, data backup, disaster recovery, user authentication requirements, password management, firewall settings, antivirus software, security patching, system monitoring, penetration testing**
2. **Controls should include user management, access control, attributability and ongoing measures to prevent, detect and/or mitigate security breaches, prevention of loss, lack of accessibility**
3. **Authorised users and access permissions should be clearly documented, maintained and retained. These records should include updates to a user roles, access permissions and time of access permission being granted (e.g., time stamp).**
4. **A process should be in place to ensure that user access and assigned roles and permissions are periodically reviewed**
5. **The responsible party should maintain adequate backup of the data**

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4.3 Computerised Systems Expectations (3)

Validation – a lot of defined requirements … for further reading – must be done before the use of the system even if owned by a third party and records must be in the TMF

1. The approach to validation should be based on a risk assessment that considers the intended use of the system, the purpose and importance of the data/record that are collected/generated, maintained and retained in the system and the potential of the system to affect the well-being, rights and safety of trial participants and the reliability of trial results.
2. Validation should demonstrate that the system conforms to the established requirements for completeness, accuracy and reliability and that its performance is consistent with its intended purpose.
3. Systems should be appropriately validated prior to use.
4. Subsequent changes to the system should be validated based on risk and should consider both previously collected and new data in line with change control procedures.
5. Periodic review may be appropriate to ensure that computerised systems remain in a validated state throughout the life cycle of the system.
6. Both standard system functionality and protocol-specific configurations and customisations, including automated data entry checks and calculations, should be validated.
7. Interfaces between systems should also be defined and validated.
8. Different degrees of validation may be needed for bespoke systems, systems designed to be configured or systems where no alterations are needed.
9. Validation procedures (until decommissioning) should cover the following: system design, system requirement, functionality testing, configuration, release, setup, installation and change control.
10. The responsible party should ensure that the computerised systems are validated as fit for purpose for use in the trial, including those developed by other parties.
11. They should ensure that validation documentation is maintained and retained.
12. Validation should generally include defining the requirements and specifications for the system and their testing, along with the associated documentation, to ensure the system is fit for purpose for use in the trial, especially for critical functionality, such as randomisation, dosing and dose titrations and reductions, and collection of endpoint data.
13. Unresolved issues, if any, should be justified and, where relevant, the risks identified from such issues should be addressed by mitigation strategies prior to and/or during the continued use of the system.

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Impact

- **SOPs need to be evaluated regarding computer systems** used for electronic trial data handling and/or remote electronic trial data systems,
  - including SOPs for system upgrades and migration to ensure **data integrity** when making changes
- Computerised systems should be clear, and users should be provided with training → **training needs analysis !!**

→ **Computer systems should be listed in the "Risk Identification" section and require evaluation, mitigation and management of risks**

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Impact

- Sponsors must establish requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation) for electronic trial data handling systems
- **Note that inspectors request a list of all computerized systems used in the trial and validation status documentation – INCLUDING vendor systems used for the study**

ICH E6 R3 now clearly states: The responsible party should ensure that the computerised systems are validated as fit for purpose, **including those developed by other parties.**
They should ensure that validation documentation is maintained and retained. 4.3.4 g

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Note that the material presented here is only an extract of ICH E6 R3 changes regarding Computer Systems
Refer also to ICH E6 (R3) Good Clinical Practice - MHRA Inspectorate (blog.gov.uk) and **EMA Guideline on computerised systems and electronic data in clinical trials (March 2023)** https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-computerised-systems-electronic-data-clinical-trials_en.pdf

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EMA GCP Guideline on Computerised Systems and electronic Data in Clinical Trials

- Rather long document – 52 pages
- Final version adopted by the GCP IWG on 7 March 2023; came into effect on 6 September 2023
- **Focusses on**
  - **Data integrity**
  - **Data lifecycle management**
  - **Risk based decision making**
  - **Protection and security**
  - **Validation of computerised systems**
  - **GCP considerations and principles**
- The scope are computerized systems, (including instruments, software and 'as a service') used in the creation/capture of electronic clinical data and systems used in the control of other processes - all with the potential to affect participant protection and reliability of trial data in the conduct of a clinical trial. This includes life systems AND retired systems

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FDA Regulatory Observation

- **Not capturing the complete document audit trail which is a critical component of data integrity**
- *"Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying,"* [FDA 21CFR11.10]

  - **Full audit trail features would be for example**
    - Who has logged into the system and when
    - At the individual file level a record of access, downloads and whether it has been modified, including changes to the metadata and retention rules
    - A log of the reason for changes to the files and associated metadata
    - The audit trail is maintained regardless of any changes to the file (for example across preservation)
    - Simple and complete reporting on the audit trail

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Appendix C - Essential Records

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Essential Records - Appendix C

- **Guidance on what makes a record essential** (Such assessment, whilst important, is not required to be documented)
- **Provides clarity on the content and maintenance of essential records**
- **Contains a table of examples of essential records, e.g., protocols, investigator brochure or basic product information, informed consent forms, necessary approvals/opinions**
- **Provides guidance about access by the sponsor and investigator/institution to one another's relevant essential records in order to fulfil their respective responsibilities**

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Essential Records - Appendix C

No changes to these requirements:

- Timeliness and organisation of filing
- Completeness of records
- Avoid duplications
- Retention
- Readily available and direct access
- Certified copies
- Essential records that are not specific to a trial and used in multiple trials must follow same requirements but can be retained outside the trial-specific repository (e.g., related to the investigational product, facilities or processes and systems, including computerised systems such as Investigator's Brochure, master services agreements, standard operating procedures, validation records

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Comparison to ICH E6 (R2)

ICH E6(R3) Section	ICH E6(R2) Section
C.1 – Introduction	8.1
C.2 – Management of Essential Records	N/A – Major Revamp
C.3 – Essentiality of Trial Records	

https://www.ema.europa.eu/en/documents/presentation/presentation-session-2-essential-records-conduct-clinical-trial-susanne-norskov_en.pdf

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Essential Records – some highlights

- The sponsor should ensure that the investigator has control of and continuous access to the data reported to the sponsor
- The sponsor should not have exclusive control of those data
- Version history should be identified - records should include authors, reviewers and approvers as appropriate, along with dates and signatures (where necessary) - Alteration to essential records should be traceable
- The sponsor and investigator/institution should maintain a record of the location(s) of their respective essential documents → TMF/ISF index
- For activities that are transferred or delegated to service providers, arrangements should be made for the access and management of the essential records throughout the trial and for their retention following completion of the trial → Essential record management should be in an agreement

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Essential Records – changes in ICH E6 R3 – extract only (1)

- ICH E6 R3 describes the "essentiality" of Trial Records (C3.1)
  - Listing 28 "essentiality" criteria, for example:
    - Relevant correspondence or documentation of meetings related to important discussions and/or trial-related decisions that have been made related to the conduct of the trial and the processes being used;
    - Demonstrates that a trial-specific computerised system is validated and that non-trial-specific systems have been assessed as fit for purpose for their intended use in the trial;
    - Documents that sponsor personnel involved in the trial conduct and individuals performing trial-specific activities on their behalf are qualified by education, training and experience to undertake their activities;
    - Contains the data as well as relevant metadata that would be needed to allow the appropriate evaluation of the conduct of the trial;
    - Documents that laboratory activities and other tests used in the trial are fit for purpose;

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Essential Records – changes in ICH E6 R3 – extract only (2)

- **Listing 28 "essentiality" criteria, for example (CONT):**
  - **Documents that service providers are suitably qualified for conducting their delegated or transferred activities;**
  - **Documents sponsor oversight of investigator site selection and monitoring and audit of the trial;**
  - **Provides information on arising issues/non-compliance and deviations detected and implementation of corrective and preventative actions;**
  - **Documents the collection, chain of custody, analysis and retention or destruction of biological samples;**
  - **Documents processes and activities relating to unblinding;**
  - **Documents the recruitment, pre-trial screening and consenting process of trial participants and their identity and chronological enrolment as appropriate;**
  - **Defines processes/practices in place in the event of a security breach in order to protect participants' rights, safety and well-being and the integrity of the data;**

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Essential Records – changes in ICH E6 R3 – extract only (3)

Applying the criteria in section C.3.1, trial records that are considered essential are listed in the Essential Records Table, and **these should be retained when produced** (not an exhaustive list, and other trial records may also be considered essential by sponsor or investigator)

Table 1 – Essential Records for All Trials

- Essential Records Table
  - Highlights what should be in place prior to the start of the trial (represented by asterisks)

Emergency decoding procedures for blinded trials*
Master randomisation list*
Instructions for use of important trial-specific systems (e.g., interactive response technologies (IRTs) user manual, electronic CRF (eCRF) manual)*
Records demonstrating fitness for purpose (e.g., maintenance and calibration) for equipment used for important trial activities*
Site monitoring reports (including site selection,* initiation,* routine and close-out)
Documentation of trial-specific computerised system validation (e.g., specifications, testing, validation report, change control)*
Documentation of the assessment of fitness for purpose for non-trial-specific computerised systems used in the trial (e.g., clinical practice computerised systems)*

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Impact

- **TMFs remain a "hot topic" for inspectors**

- EMA **guidance** (2018) on expectations of organisation and content of TMF remains effective https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-content-management-archiving-clinical-trial-master-file-paper/electronic_en.pdf
- Any related record that helps to **reconstruct and evaluate the trial** must be filed in the TMF, **irrespective of whether it is explicitly listed in guidelines**
- Essential records are used as part of the investigator oversight and sponsor oversight (including monitoring) of the trial

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Sponsor Responsibilities in Relation to Essential Records

- Sponsor's Monitor confirming the investigator is maintaining the essential records and the arrangement for the retention of the essential records
- The sponsor (or subsequent owners of the data) should retain all of the sponsor-specific essential records pertaining to the trial in conformance with the applicable regulatory requirement(s).
- The sponsor should inform the investigator(s)/institution(s) and service providers, when appropriate, in writing of the need for essential records retention and should notify the investigator(s)/institution(s) and service providers, when appropriate, in writing when the trial-related records are no longer needed.
- The sponsor should report any transfer of ownership of the essential records to the appropriate authority(ies) as required by the applicable regulatory requirement(s).

Source: A Joint US-FDA | MHRA-UK | Health Canada Good Clinical Practice & Pharmacovigilance Symposium - February 13-15, 2024
Day 1, Session 1 https://sbiaevents.com/fda-mhra-hc-2024/#files

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Type and Quality of

- Identifiable
- version controlled
- include authors, reviewers and approvers as appropriate
- Include date and signature (electronic or wet ink), where necessary
- Alteration to the essential records should be traceable
- a copy is used to permanently replace the original, it should fulfil the requirements for certified copies
- Certain essential records may not be specific to a trial but may be related to the systems and processes involved in running multiple trials and retained outside the trial-specific repositories

Sharing of Records

- In order to fulfil their responsibilities in the conduct of the trial, the sponsor and investigator/institution may need access to or copies of one another's relevant essential records before, during and after the trial is completed. This will determine whether the record resides in the repositories of the sponsor, the investigator/institution, or both
- There should be careful consideration of sharing of records subject to data protection legislation and blinding considerations in line with applicable regulatory requirements

Use of Service

- For activities that are transferred or delegated to service providers by the sponsor or investigator/institution respectively, arrangements should be made for the access and management of the essential records throughout the trial and for their retention following completion of the trial

Source: A Joint US-FDA | MHRA-UK | Health Canada Good Clinical Practice & Pharmacovigilance Symposium February 13-15, 2024
Day 1, Session 1 https://sbiaevents.com/fda-mhra-hc-2024/#files

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Appendix A - Investigator Brochure

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Comparison to ICH E6 (R2)

ICH E6(R3) Section	ICH E6(R2) Section
A.1 – Introduction	7.1
A.2 – General Considerations	7.2
A.3 – Contents of the Investigator's Brochure • A.3.6 (b) – In R3, added frequency and nature of AEs should be included to determine expectedness of Serious Adverse Reactions.	7.3

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Investigator Brochure – Appendix A - changes

- Added that a list of adverse reactions identified as the reference safety information, including information on their frequency and nature, should be included
- Reorganised the order of language for clarification
- Examples of title page and table of contents removed as same information can be read in the text of the guideline

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Appendix B - Clinical Trial Protocol and Protocol Amendments

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Comparison to ICH E6 (R2)

ICH E6(R3) Section	ICH E6(R2) Section
B.1 – General Information	6.1
B.2 – Background Information	6.2
B.3 – Trial Objectives and Purpose	6.3
B.4 – Trial Design	6.4
B.5 – Selection of Participants	6.5
B.6 – Discontinuation of Trial Intervention and Participant Withdrawal from Trial	6.5
B.7 – Treatment and Interventions for Participants	6.6
B.8 – Assessment of Efficacy	6.7
B.9 – Assessment of Safety	6.8
B.10 – Statistical considerations	6.9

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Comparison to ICH E6 (R2)

ICH E6(R3) Section	ICH E6(R2) Section
B.11 – Direct Access to Source Records	6.10
B.12 – Quality Control and Quality Assurance	6.11
B.13 – Ethics	6.12
B.14 – Data Handling and Record Keeping	6.4, 6.13
B.15 – Financing and Insurance	6.14
B.16 – Publication Policy	6.15

Please do not forget to refer to (draft) ICH M11 regarding the new (planned) protocol template. For summary of M11 refer to:
https://database.ich.org/sites/default/files/ICH%20M11_Step_2_Presentation_2022_09_27.pdf

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Protocol and Amendments – Appendix B - changes

- Design to minimise unnecessary complexity, encourage simplicity and clarity (clear, concise and operationally feasible protocol)
- Build adaptability into the protocol, for example, by including acceptable ranges for specific protocol provisions, which can reduce the number of deviations or requirements for a protocol amendment
- Description of identified critical to quality factors, associated risks and risk mitigation strategies in the trial is required - mitigate or eliminate important risks to the rights, safety, and well-being of trial participants and reliability of data

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Protocol and Amendments – Appendix B - changes

- Summary of the monitoring approaches that are part of the quality control process for the clinical trial
- Description of the process for the handling of noncompliance with the protocol or GCP
- Identification of data to be recorded directly into the data acquisition tools (i.e., no prior written or electronic record of data) and considered to be the source record
- Address the implication for withdrawal of consent or discontinuation by the investigator
- Broaden the statistical section to include statistical inference methodologies (e.g., Bayesian design and estimands – see ICH E9 R1)

- **Some of the information listed may be contained in other protocol referenced documents**

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- **Clinical Trials Transformation Initiative. Effective and efficient monitoring as a component of quality** https://www.ctti-clinicaltrials.org/project-topics/study-quality/effective-and-efficient-monitoring-as-a-component-of-quality
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- 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)

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Other Reading Lists (3)

- **A Joint US-FDA | MHRA-UK | Health Canada Good Clinical Practice & Pharmacovigilance Symposium**
  February 13-15, 2024 Day 1, Session 1 https://sbiaevents.com/fda-mhra-hc-2024/#files
- https://www.pda.org/docs/default-source/website-document-library/chapters/presentations/missouri-valley/data-integrity-issues-concernse703e9d7a8c4657391feff0000cd242a.pdf?sfvrsn=4 Slide 1 (pda.org)1 (pda.org)

- https://www.ema.europa.eu/en/events/act-eu-workshop-ich-e6-r3-principles-annex-1#presentations-day-1-74523

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