

ICH Good Clinical Practice E6 (R3) :

What we need to Know & Do to optimize trial management

Clinical Quality Assurance (CQA)

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3 Dec 2024



ICH E6 R3 - We love to hear from
you



Talking Points



ICH GCP E6 R3 –
Where are We now?



Key Changes &
Implications



Next Steps



Discussions

R3: Approaches, Innovation & Quality

ICH E6 – Finalized in 1996
Version 1



ICH E6 R2
Revision effective in 2016



ICH E8 R1
Effective in 2021



E6 (R3):

- Use of a proportionate Risk-based approaches
- Quality by design and CtQF
- Flexibility... "NOT one size fits all"
- Critical thinking
- Incorporate new technological advancement
- 'Decentralized' and 'pragmatic' clinical trial elements
- Stakeholder engagement
- Study Quality right from the start & meaningful trial outcomes
- Expectations for data quality through all data lifecycles
- Use of computerized systems
- Selection and oversight of Service providers
- Responsibilities for Investigators & Sponsors

Fundamentals of R3

- Annex 1
 - 1) IRB/EC
 - 2) Investigator
 - 3) Sponsor
 - 4) Data Governance

- Appendixes
 - A) Inv Brochure
 - B) Clinical Trial Protocol & Amendments
 - C) Essential Records



- Annex 2

Decentralised Elements & Real-world Evidence (RDE)

Key Areas – ICH E6 (R3)



Roles & Responsibilities (Section 2 & 3) –

Service providers Selection & Oversight,

Pragmatic protocol,

Qualification/supervision of non-site staff



Data Governance (Section 4) –

Computerized systems responsibilities for Sponsor/Inv,

Sponsor review of site systems (e.g EHR) to ensure FFP



Documentation & Records (Appendix C) –

Essential records using RBA



ICH E6 R3 Principles

Quality

New
Risk Proportionate

Protocol

Reliable Results

New
Roles and Responsibilities

Investigational Product

Informed Consent

Ethical Principles

IRB/IEC Review

Science

Qualified Individuals

New Principles in ICH E6 R3

Principle 7 (Risk Proportionality)

- Clinical trial processes, measures and approaches proportionate to the **risks to participants** and to the importance of the **data collected**.
 - The focus is on any risks to participants beyond those associated with standard medical care.
- Risks to **critical quality factors** should be managed prospectively & updated as new issues arise.

Principle 10 (Roles & Responsibilities)

- Roles and responsibilities should be clearly documented
- The Sponsor & Investigator retain overall responsibility for their respective activities (**including contracted/sub-contracted**) and should maintain appropriate oversight /supervision
- Any **agreements** should clearly define roles and responsibilities and should be documented appropriately.

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Decentralised Elements & Real-world Evidence (RDE)

Updates Annex 1 (Section 1 IRB/IEC)

- **NEW - Section: 1.5 Submission and Communication to RA**
(Submissions to IRB/IEC and Regulatory Authority(ies) can be combined per regulatory requirements)
- Updated wording around **Compensation of Participants**
(IRB/IEC should review amount of compensation and method of payment to assure that neither presents problems of coercion or undue influence)
- Review of the consent process includes **description of consent process / media used**
- Risk-based **continuing** review
- Revision of **safety reporting expectations**
- **Record retention** per applicable Regulatory requirements

Updates Annex 1 (Section 2 Investigator)- Significant Updates

NEW - Section: 2.3 (Responsibilities)

- Investigator may delegate trial-specific activities to other persons or parties. Sponsor may identify service provider, however, **final decision** on utilizing the **service provider** remains with the investigator.
- Investigator should ensure persons or parties have been delegated trial-specific activities are appropriately **qualified, supervised, and are knowledgeable** about the study activities. This includes staff provided by **other parties** (for example, home nurses arranged by the sponsor).
- In situations where clinical trial activities are performed in accordance with routine clinical care, delegation documentation **may not be required**.
- **Trial-related training** focused on delegated activities beyond usual training/experience
- Submission to IRB/IEC by Investigator **or Sponsor**
- Important deviations should be explained with **measures implemented** to prevent recurrence

Updates Annex 1 (Section 2 Investigator)- Significant Updates

NEW - Section 2.9 (End of participation in a Clinical Trial)

- Investigator is expected to follow the protocol and other sponsor instructions to determine appropriate follow-up measures, when a **participant ends participation** (due to withdraw, study completion, etc).
- The investigator may include instructions to **avoid unnecessary loss** of already collected critical data, in accordance with applicable regulatory requirements.
- Where relevant, the investigator should **inform the participant** about the trial results and treatment received, when the information is available from the sponsor.

Updates to Annex 1 (Section 2 Investigator)

- **Unblinding** without delay available from trial start
- Responsibility for integrity of data **irrespective of media** used
- Define source, methods of data capture & location **prior to starting** the trial
- Investigator **ongoing access** to/review of data
- **Data acquisition tools** used as intended
- Measures to protect **privacy/confidentiality** of participants
- Responsibilities for **computerised systems** use/management

- Delegation of **safety reporting** but retain overall responsibility
- Clear and concise **consent** information
- **Varied approaches** to informed consent
- **Assent** and process for **re-consent**
- Management of **critical data** when participant withdraws
- Trial results and treatment received **shared** with participants
- Sponsor may facilitate IP accountability process

Updates to Annex 1 (Section 3 Sponsor)- Significant Updates

- **Section 3.2 (Resources):** Sponsor to ensure that there are **sufficient resources** to appropriately conduct the study.
- **Section 3.4 (Qualification and Training):** The sponsor should utilize **appropriately qualified** individuals for the activities which they are assigned throughout the trial process (e.g biostatisticians, physicians, auditors, monitors...)
- **Section 3.9 (Sponsor Oversight):** Ensure trial design and conduct, processes undertaken, and information/data generated are **sufficient in quality** to ensure reliable trial results, trial participant safety, and appropriate decision making.
 - Determine **trial-specific criteria** for classifying **important protocol deviations**.
 - Ensure **appropriate and timely escalation** and follow-up of issues to allow for the implementation of appropriate actions in a timely manner.
 - **Risks** related to participant's rights, safety and well-being, and the reliability of trial results should be suitably **managed throughout** the planning, conduct, and reporting of the trial.

Updates to Annex 1 (Section 4 Data Governance)

- Relates to both the Investigator and the Sponsor
- Maintain integrity of the blind across the full data life cycle
- Planned review of data and **metadata** (including audit trails)
- Defines the approach to be used for implementing, evaluating, accessing, managing, and reviewing the relevant metadata data associated with critical data
- Discusses **data correction processes** and the requirement for validation of data transfers
- Defines that **security controls** should be maintained for computerized systems.
- The responsible party is responsible for the **validation** status of the system throughout its life cycle and must be validated prior to use.
- **Access rights** to computerized systems must be aligned to delegated functions
- System related Issue management with periodic review of cumulative issues

Section	Topic
4.1	Safeguard Blinding in Data Governance
4.2	Data Life Cycle Elements
4.3	Computerised Systems
4.4	Security of Computerised Systems
4.5	Validation of Computerised Systems
4.6	System Failure
4.7	Technical Support
4.8	User Management

Appendices

A) Inv Brochure

B) Clinical Trial Protocol & Amendments

C) Essential Records –

- Expectations for maintenance (filing and access) of essential records – **Timeliness!**
- What makes a record essential – Safety of Participants, Data, Sponsor, Inv, Provider oversight, Regulatory/ IEC approvals & updates
- Potential Essential Records

How are you embracing these changes?

- **Familiarisation:** Understand the core principles & proposed changes to allow identification of areas for current practice adjustments.
- **Risk Assessments:** Identify critical risks specific to trials that affects patient safety or data integrity. Develop risk mitigation strategies based on the principles of QbD
- **Review & Update SOPs, protocols:** Revise standard operating procedures (SOPs) to reflect the emphasis on QbD, Risk management, & data governance.
- **Training:** Ensure your team receives training on the key updates not limited to risk management, data integrity and QbD principles.
- **Embrace New Technologies:** Explore and implement technology solutions that can enhance data management, risk mitigation & overall trial efficiency.

Comments, Questions ?

[ICH E6 R3 Draft Guidelines ; E6\(R3\) GOOD CLINICAL PRACTICE \(GCP\)](#)

[Comparison document R2 x R3 \(AVOCA\)](#)

[ICH presentation](#)

[ICH Video](#)

[Andy Fisher blog , MHRA inspectorate](#)

