Federal Institute for Drugs and Medical Devices

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Day 1, Session 1: ICH E6(R3) Key Concepts

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Outline

ICH E6(R3) Key Concepts

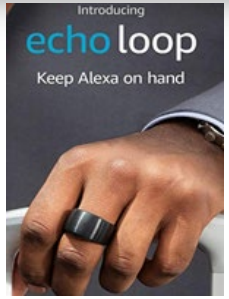
- Introduction
- Short presentation of the key concepts
- Illustration of their development and the links between ICH E8(R1) and ICH E6(R2) and (R3)
- Examples of the application of the key concepts in (R3)
- Summary

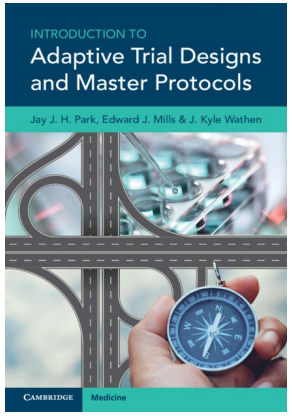
Key Concepts of ICH E6(R3)
What is included?

Source: depositphotos.com

- Quality by design, incl. fitness-for-purpose
- Operational feasibility
- Avoidance of unnecessary complexity
- Avoidance of unnecessary burden on participants and investigators
- Risk-based quality management
- Proportionality

Key Concepts of ICH E6(R3)
Applicability to a Variety of Designs and Technologies





Key Concepts of ICH E6(R3)
Quality-by-Design (1)

- **This concept is based on ICH E8(R1) 'General Principles for Clinical Studies', subsection 3.1**

  Quality is a primary consideration […]. The likelihood that a clinical study will answer the research questions while preventing important errors can be dramatically improved through **prospective attention to the design of all components of the study protocol, procedures, associated operational plans and training**. Activities such as document and data review and monitoring, where conducted retrospectively, are an important part of a quality assurance process; but, even when combined with audits, they are not sufficient to ensure quality of a clinical study. […]

Key Concepts of ICH E6(R3)
Quality by Design (2)

- **New Principle 6, aligning ICH E8(R1) with ICH E6(R3)**

  6. **Quality should be built into the scientific and operational design and conduct of clinical trials.**

  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. These factors are attributes of a trial that are fundamental to the protection of participants, the reliability and interpretability of the trial results and the decisions made based on those trial results. **Quality by design involves focusing on critical to quality factors of the trial in order to maximise the likelihood of trial meeting its objectives.**

  6.3 […]

Key Concepts of ICH E6(R3)
Operational Feasibility, Avoidance of Unnecessary Complexity & Avoidance of Unnecessary Burden

- **Annex 1, chapter 3: Sponsor, section 3.1 Trial Design**

  3.1.4 The sponsor should ensure that **all aspects of the trial are**

  - **operationally feasible** and
  - should **avoid unnecessary complexity, procedures and data collection.**

  Protocols, data acquisition tools and other operational documents should be

  - **fit for purpose**, clear, concise and consistent.

  The **sponsor should not place**

  - **unnecessary burden on participants and investigators.**

Key Concepts of ICH E6(R3)
Fitness For Purpose – Examples From the Guideline

Source: wired.com

- Annex 1, 3.9.5. The **range and extent of oversight measures** should be fit for purpose and tailored to the complexity of and risks associated with the trial. […]
- Annex 1, 3.16.1 (d): The sponsor should ensure that **data acquisition tools** are fit for purpose and designed to capture the information required by the protocol. They should be validated and ready for use prior to their required use in the trial.
- Annex 1, 3.16.1. (v) for **systems deployed by the investigator/institution**, assess whether such systems, if identified as **containing source records** in the trial […] are fit for purpose or whether the known issue(s) can be appropriately mitigated.

Key Concepts of ICH E6(R3)
Avoidance of Unnecessary Burden – Examples From the Guideline

Source: thedesignera.in

Avoidance of unnecessary burden on trial participants

- **Annex 1, 2.8 Informed Consent of Trial Participants**

  (b) The information should be as clear and concise as possible, use simple language and **avoid unnecessary volume and complexity**. […]

  (c) […] The **characteristics of the potential trial population** (e.g., participants may lack familiarity with computerised systems) and the **suitability of the method** of obtaining consent should be taken into consideration when developing the informed consent materials and process. When computerised systems are used to obtain informed consent, trial participants may be given the option to use a paper-based approach as an alternative.

Key Concepts of ICH E6(R3)
Avoidance of Unnecessary Burden – Examples From the Guideline

Avoidance of unnecessary burden on investigators (1)

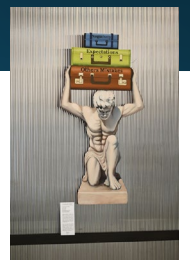
- **Annex 1, 3.11.4.3 Monitoring Plan**

  […] The **monitoring strategy** should ensure appropriate oversight of trial conduct and **consider site capabilities and the potential burden.**

- *See **European 'Recommendation Paper on Decentralised Elements in Clinical Trials', Version 01, 13 December 2022, chapter 7 Trial Monitoring***

  *[…] When establishing remote access for the purpose of monitoring, the principles of necessity and proportionality should always be adhered to. **The monitoring strategy chosen should not unduly burden the site.** […]*

Key Concepts of ICH E6(R3)
Avoidance of Unnecessary Burden – Examples From the Guideline



Avoidance of unnecessary burden on investigators (2)

- **Draft Annex 2, section 3.9 Safety Assessment and Reporting**

  3.9.1 **Safety information in clinical trials with decentralised and/or pragmatic elements** may […] come from **multiple sources**. For example, some trials may capture information via remote visits, DHTs, EHRs, in-person visits or a combination thereof. […] The safety information should be provided in an **actionable manner** that **provides the investigator with an overview** on the health status of the trial participant to **allow for medical decision making**.

- ***See European 'Recommendation Paper on Decentralised Elements in Clinical Trials', Version 01, 13 December 2022, Subsection 'Considerations on keeping oversight on incoming data'***

  *The review of safety data should be planned with a risk-based perspective, which **may include** […] **the use of notifications and alerts**. […]* without creating an unacceptable burden for the investigator and/or the trial participant.

Key Concepts of ICH E6(R3)
ICH E6(R2) 'Risk-based Quality Management' Concept

- **ICH E6(R2), coming into effect in the EU 14 June 2017, initiated the implementation of risk-based considerations to the processes used to manage a clinical trial.**

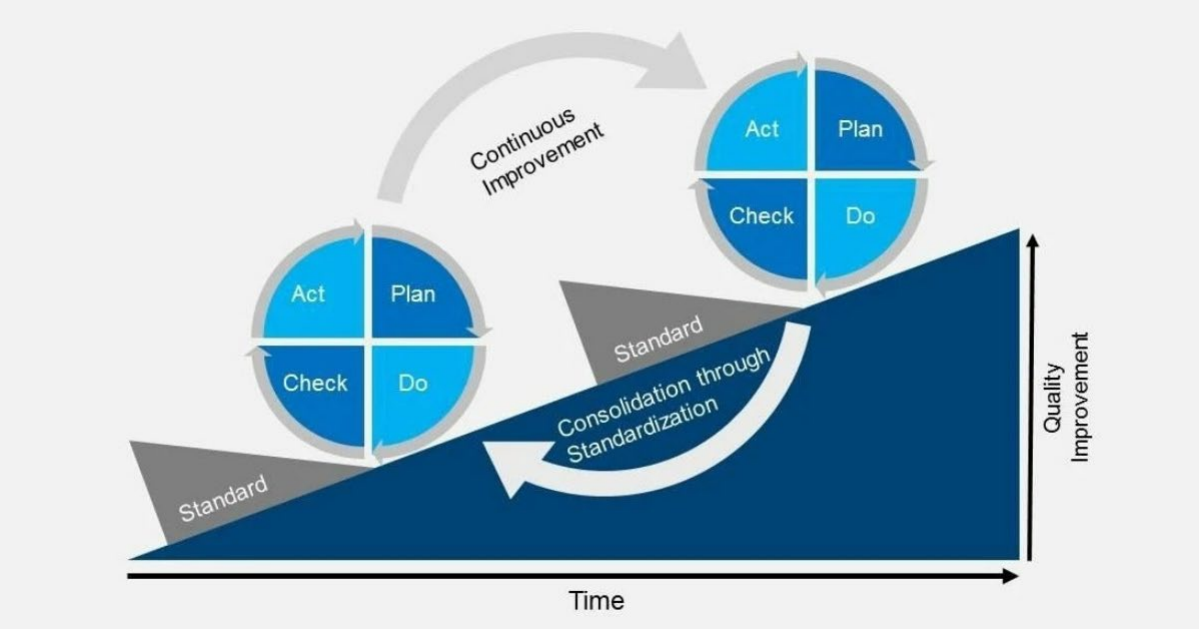
  5.0 Quality Management

  The sponsor should implement a system to **manage quality throughout all stages of the trial process**.
  Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results. Quality management includes the **design of efficient clinical trial protocols and tools and procedures** for data collection and processing, as well as the collection of **information that is essential to decision making**.
  The methods used to assure and control the quality of the trial should be **proportionate to the risks** inherent in the trial **and** the **importance of the information collected**.

Key Concepts of ICH E6(R3)
Linking ‘Risk-based Quality Management’ with ‘Quality By Design’

- **ICH E8(R1), coming into effect in the EU 14 April 2022, complemented the E6(R2) requirement in relation to the ‘design of efficient clinical trial protocols’ by implementing critical-to-quality factors for study design**
  - Engagement of stakeholders (including patients)
  - Benefit/risk of the investigational product and trial interventions
  - Study objectives & meaningful clinical study design, e.g. relevant eligibility criteria, feasibility
  - Protection of participants' rights and safety (Informed Consent, IRB/IEC approval …)
  - Qualification/training needs
  - Data collection needed to meet the study objectives
  - Minimization of bias (randomization, blinding)

Key Concepts of ICH E6(R3)
Risk-based Approaches to Trial Management



Source: https://cyntegrity.com/whats-the-difference-between-rbqm-and-qrm-in-clinical-trials/

Continuation of the E6(R2) RBQM concept

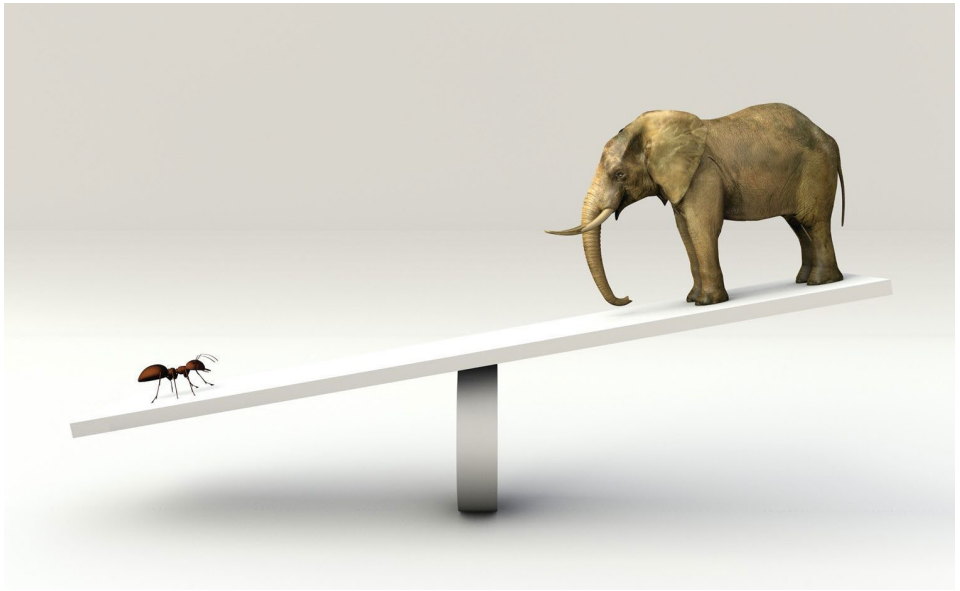
Annex 1, section 3. Sponsor, introduction

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.**

Key Concepts of ICH E6(R3)
Risk-based Approaches – Examples From the Guideline

- 3.11.1 **Quality assurance** […] includes implementing **risk-based strategies** to identify potential or actual causes of serious non-compliance with the protocol, GCP and/or applicable regulatory requirements to enable their corrective and preventive actions.
- 3.11.3 **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. […]
- 4.2.3 **Procedures for review of trial-specific data, audit trails and other relevant metadata** […] should be **risk-based**, adapted to the individual trial and adjusted based on experience during the trial.

Key Concepts of ICH E6(R3)
Proportionality



Source: https://www.heurekasoftware.com/achieve-proportionality/

Re-emphasis of the E6(R2) proportionality concept

ICH E6 (R2)

5.0.4. Risk control: The sponsor should decide which risks to reduce and/or which risks to accept. The approach used to reduce risk to an acceptable level should be **proportionate** to the significance of the risk.

ICH E6(R3), introduction

[…] **Clinical trial processes** and **risk mitigation strategies** implemented to support the conduct of the trial should be **proportionate** to the **importance of the data** being collected and the **risks to trial participant safety** and **data reliability**. […]

Key Concepts of ICH E6(R3)
Proportionality – Examples From the Guideline

- Annex 1, subsection 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**.
- Annex 1, subsection 3.11.4.5.1 (d) **Actions taken in relation to the deviations, errors or omissions** should be **proportionate to their importance**.
- Annex 1, subsection 3.12.1 **Noncompliance** with the protocol, SOPs, GCP and/or applicable regulatory requirement(s) […] **should lead to appropriate and proportionate action** by the sponsor to secure compliance.
- Annex 1, subsection 3.16.1 (ii) […] **requirements for computerised systems** (e.g., requirements for validation, audit trails, user management, backup, disaster recovery and IT security) […] should be **proportionate to the importance of the computerised system and the data or activities** they are expected to process

Key Concepts of ICH E6(R3)
Summary

- The key concepts contained in ICH E6(R3) are for the most part not new, but have already been addressed in (R2), although they have been further developed and included more often and in more detail in (R3)
- They are formulated at a high level, similar to the principles, are overarching and should be applied in every clinical trial
- Their implementation generally requires sound and well-considered decisions and rationale.

Thank you very much for your attention!

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