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International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6(R2) – Integrated Addendum to Good Clinical Practice (GCP) Guideline

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Good Clinical Practice

Clinical research regulation timeline

Why does it concern me?

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> Legally binding in most countries!

Art. 5 Rules of Good Clinical Practice

[1] Clinical trials must be conducted in accordance with the rules of Good Clinical Practice, as specified in Annex 1 number 2.

[2] A clinical trial covered by Chapter 4 may be conducted in accordance with other rules which are recognised in the specialty in question, provided that the protection of participants and data quality and security are guaranteed.

[3] The measures and precautions required in accordance with the rules of Good Clinical Practice must be adapted to the extent of the risks to which participants are exposed. Depending on the extent of these risks, there may be certain deviations from the rules of Good Clinical Practice. Any deviations must be recorded in the protocol. The protection of the participants and data quality and security must be guaranteed in all cases.

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…R, TRAINING AND EXPERIENCE, AUXILIARY MEDI-
…TS

Article 47

Compliance with the protocol and good clinical practice

The sponsor of a clinical trial and the investigator shall ensure that the clinical trial is conducted in accordance with the protocol and with the principles of good clinical practice.

Without prejudice to any other provision of Union law or Commission guidelines, the sponsor and the investigator, when drawing up the protocol and when applying this Regulation and the protocol, shall also take appropriate account of the quality standards and the ICH guidelines on good clinical practice.

The Commission shall make publicly available the detailed ICH guidelines on good clinical practice referred to in the second paragraph.

Definition of ICH-GCP

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An international ethical & scientific quality standard f
designing, conducting, recording & reporting
involve the participation of huma

What not How!

Specific objectives

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Good Clinical Practice

The rights, safety and well-being of trial subjects are protected.

ICH-GCP 2.1, 2.3

The trial data are complete, accurate and unbiased.

ICH-GCP 2.10

More on GCP in general

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> GCP Refresher

19.05.2017, 14:00 - 17:00

The integrated addendum (R2)

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- Not new
  but
  more detailed explanations/definitions

- An amendment **not** a revision!

Rationale

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- Original version dates back to 1996*
- Clinical trials evolved substantially
  - Methodology
  - Technology
  - Environment

- To keep pace with the scale and complexity of clinical trials
- To ensure appropriate use of technology

* R1 was an irrelevant change

The Good, the Bad and the Ugly

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- ☺ More precise definitions
- ☺ Less room for interpretation
- ☺ More flexibility

- 😐 Less room for interpretation
- 😐 Less flexibility

- ☹ (Implicitly) new requirements
- ☹ Things will not get easier (cheaper)!

Three domains of change

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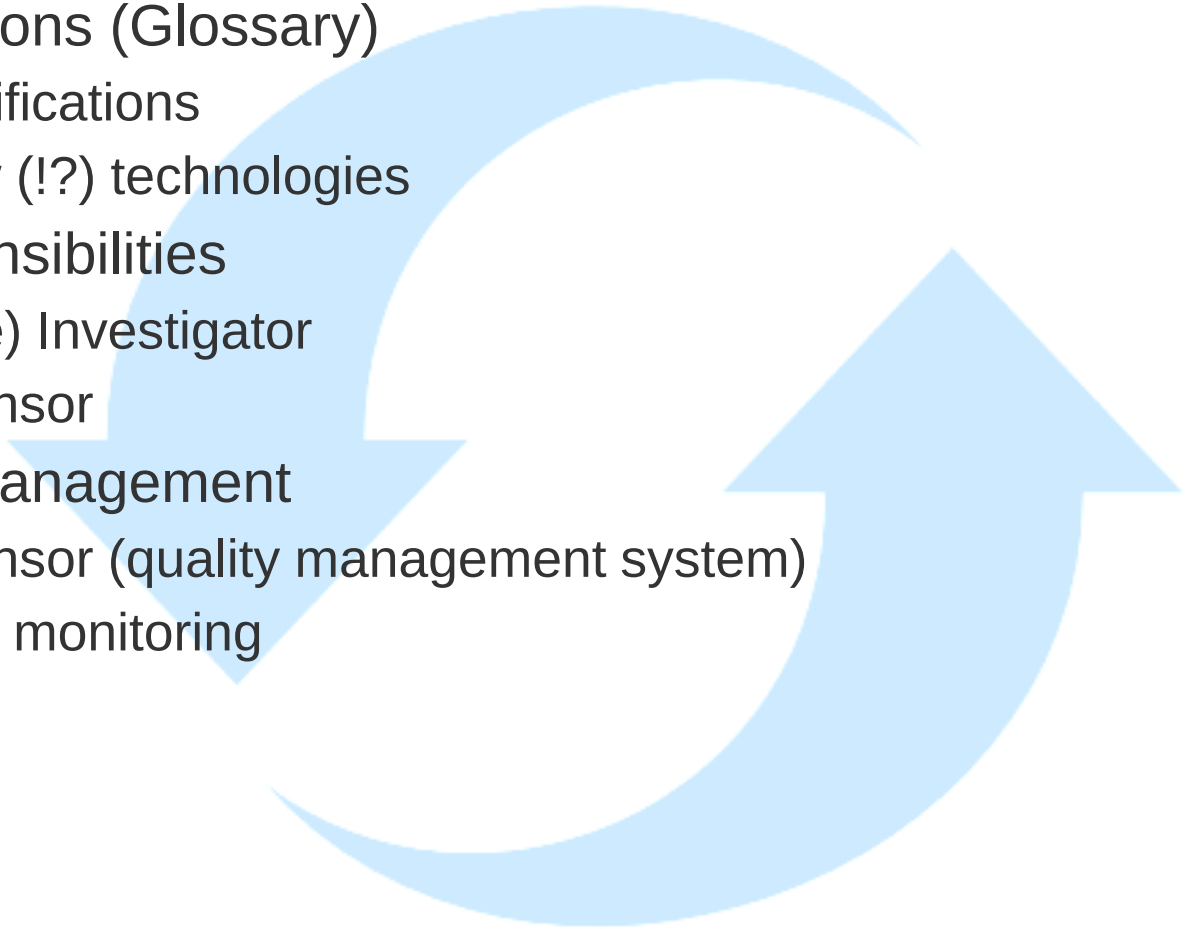
- Definitions (Glossary)
  - Clarifications
  - New (!?) technologies
- Responsibilities
  - (Site) Investigator
  - Sponsor
- Risk management
  - Sponsor (quality management system)
  - Trial monitoring



Source data and related I

- *All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.*
- *Addendum: This principle applies to all records referenced in this guideline, irrespective of the type of media used.* (2.10)

→ GCP principles apply to paper as well as electronic records

Source data and related II

- *Addendum: The investigator/institution 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. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).* (4.9.0)

→ All trial data with adequate source (previous version E6(R1) only mentioned in definitions and indirectly)

→ Audit trail for source (electronic health record/patient chart!)

Source data and related III

> *Addendum: 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, including data that describe the context, content, and structure, as the original. (1.63)

→ Sign and date copies or
have a validated (scan-)process

Relevant for archiving (validation: Addendum 1.65)

Essential documents

> *… Addendum: The sponsor and investigator/institution should maintain a record of the location(s) of their respective essential documents including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.* (8.1)

→ Be able to locate and have access all essential documents at all phases (incl. archiving)

Electronic Data Capturing I

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> *… Addendum: The SOPs should cover system setup, installation, and use. The SOPs should describe system validation and functionality testing, data collection and handling, system maintenance, system security measures, change control, data backup, recovery, contingency planning, and decommissioning. The responsibilities of the sponsor, investigator, and other parties with respect to the use of these computerized systems should be clear, and the users should be provided with training in their use.* (5.5.3 (b))

→ Set of SOPs covering at least 9 domains (sponsor)

→ Training in using the eCRF (documentation!)

Electronic Data Capturing II

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- *… Addendum: Ensure the integrity of the data including any data that describe the context, content, and structure. This is particularly important when making changes to the computerized systems, such as software upgrades or migration of data* (5.5.3 (h))

→ Prove that the system **and** the data is safe at all times (incl. updates and changes e.g. by risk analysis) (sponsor)

Investigator responsibility I

> *Addendum: The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.* (4.2.5)

→ Supervision of all site personnel

Investigator responsibility II

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> *Addendum: If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.* (4.2.6)

→ Ensure to check qualification before outsourcing (documentation!)

→ Process that this is monitored e.g. via audits etc. (documentation!)

Sponsor responsibility I

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> *Addendum: 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. …
(5.0)

→ A quality management system covering all phases (concept → development → set-up → conduct → completion incl. archiving)

Sponsor responsibility II

> *… Addendum: The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s).* (5.2.2)

→ Oversight on outsourced tasks (monitoring; see Investigator responsibility before)

Sponsor responsibility III

> *… Addendum: The sponsor should ensure that the investigator has control of and continuous access to the CRF data reported to the sponsor.* (8.1)

→ Ensure access to the eCRF

Sponsor responsibility IV

> *… Addendum: If noncompliance that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results is discovered [protocol violations], the sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions.* (5.20.1)

→ Clarification regarding actions to be taken for protocol violation:
root-cause analysis and CAPA plan

Risk-based – THE change in R2

Risk management in R2

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- Validation of Electronic Data Capturing system
- Quality Management system
- Monitoring
- Essential documents
- …

More on risk management

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> GCP Refresher

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Risk management in R2 – QM

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> *… Addendum: The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures, and data collection. Protocols, case report forms, and other operational documents should be clear, concise, and consistent* (5.0)

→ Sometimes less is more

→ Feasibility

Risk management in R2 – QM

> *… Addendum: The quality management system should use a risk-based approach as described below.* (5.0)

→ Risk management for **all** (not only data or trial site) sponsor processes

- System/institutional level and
- Trial level

Risk management in R2 – QM (5.0)

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1. Identify critical processes, data, and information
   - To ensure safety of participants
   - To ensure reliability of trial results
2. Identify risks
3. Evaluate risks
4. Measures to control risk
5. Document and communicate
6. Review (and update)
7. Report

Risk-based monitoring

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> *… Addendum: The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials. The flexibility in the extent and nature of monitoring described in this section is intended to permit varied approaches that improve the effectiveness and efficiency of monitoring. The sponsor may choose on-site monitoring, a combination of on-site and centralized monitoring, or, where justified, centralized monitoring. The sponsor should document the rationale for the chosen monitoring strategy (e.g., in the monitoring plan).* (5.18.3)

→ Flexible monitoring strategy (documentation incl. decisions)

→ Central data monitoring and statistical monitoring explicitly mentioned

Caveat!

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- Risk-based/-proportinate approaches do not mean
  - That we can do what suits us best in a given situation
  - That we necessarily safe money
  - That we are allowed to take higher risks
- Rather: conscientious assessment and conscious decisions
  - Structured
  - Comprehensive
  - Documented
- Probably more difficult
- Probably more expansive and time-consuming at trial set-up and hopefully cheaper during conduct

- → Risk management (institutional and trial level)
- → Structured and rationale decision-making e.g. protocol violations (documentation)
- → Principles apply to electronic and paper records
- → Oversight and supervision

Next CTU Lecture

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> **14.02.2017, 12:45**
> **Workshop On-site Monitoring**