Clinical Research in Resource Limited Settings: Mission Impossible or Role Model for Future Drug Development?

Risk Management in Clinical Trials in Today’s ICH-GCP(R2) Framework

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Introduction

● The changes are introduced as an **Integrated Addendum** to the existing ICH E6 (R1) guideline

● Date for coming into effect: **14 June 2017**

● It is the new approved standard for the European Union, Japan, United States, Canada, China, South Korea and Switzerland
Rationale for Updating ICH E6

20 years ago, at the time of ICH E6 (R1) release, clinical trials were largely paper-based.

Since 1996,

- major evolutions in technology happened with an increasing use of electronic data in reporting and recording.
- scale, complexity, territories involved, and cost of clinical trials have strongly increased.

This revision encourages implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting. Standards regarding electronic records and essential documents have also been updated.
Criticism on the Updated ICH E6

Much criticism was expressed during the consultation period about the limited extend of the planned GCP guideline revision, e.g.,

- No attention to the needs of clinical trials in different cultural and economic settings
- No attention to the needs of innovative use of electronic tools in the organisation of clinical trials like decentralised trials or patient-initiated trials
- No attention to vulnerabilities in data protection

This criticism is justified. ICH announced already that work on a major revision in version R3 has been started but this will take time.
Criticism on the Updated ICH E6

Beside the focus on quality improvement strategies on sponsor’s side also at the investigator site

more professionalism and flexibility

is encouraged.

Will this Addendum really help to make a difference?
E6 (R2): Relevant Changes

4. Investigator: update on sections

- **4.2.5 Supervision and delegation**

  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.

- **4.2.6 Assurance of qualification and quality performance of service providers**

  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.
Relevant for the site:

- **New**: strong focus on a functioning delegation and supervision process
  - Formal delegation procedure
  - Documented supervision procedure

- **New**: the investigator is responsible for the qualification of the individuals or parties providing the service
  - Documented verification of qualification
  - Documented quality supervision procedure

How to apply this to, e.g., the lab, the pharmacy, etc.?
E6 (R2): Relevant Changes

6. Essential Documents (Appendix 8)

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Essential documents for the trial should be supplemented or may be reduced where justified (in advance of trial initiation) based on the importance and relevance of the specific documents to the trial.
E6 (R2): Addendum Section 5: Sponsor

● **5.0 Quality Management**
  ➢ Risk-based Quality Management System
  ➢ Operational feasibility - Simplification of procedures

● **5.2 CROs / oversight incl. sub-contractors**

● **5.5 Data Handling, Record Keeping**
  ➢ Risk-based validation of electronic systems
  ➢ SOPs and training for using electronic systems

● **5.18 Monitoring**
  ➢ Systematic risk-based approach to monitoring / Monitoring Plan
  ➢ Centralized Monitoring
  ➢ Reporting

● **5.20 Noncompliance**
  ➢ Root cause analysis and CAPA

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5.0 Quality Management (1)

Sponsor’s obligations:

- Implementation of a **system** to manage **quality** throughout all stages of the trial process

- **Focus** on trial activities that are essential to ensure **human subjects protection** and **reliability of trial results**

- **Design of efficient** clinical trial protocols, tools and procedures for data collection and processing as well of information essential to decision making
5.0 Quality Management (2)

Sponsor’s obligations:

- The methods used to assure and control quality should be proportionate to the risks inherent in the trial and the importance of the information collected.

- Protocols, CRFs, and other operational documents to be clear, concise and consistent.
How does risk-based quality management work?
5.0 QM: Risk-based Approach (1)

5.0.1 Critical Process and Data Identification:

During protocol development, the sponsor should identify those processes and data that are critical to assure human subject protection and the reliability of study results.

5.02 Risk Identification

The sponsor should identify risks to critical trial processes and data. Risks should be considered at both system level (e.g., SOPs, computerized systems, personnel) and clinical level (e.g., trial design, data collection, informed consent process)
5.0 QM: Risk-based Approach (2)

5.0.3 Risk Evaluation

The sponsor should evaluate the identified risks, against existing risk controls by considering:

a) The likelihood of errors occurring

b) The extent to which such errors would be detectable

c) The impact of such errors on human subject protection and reliability of study results
5.0 QM: Risk-based Approach (3)

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.

Risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, system safeguards to ensure adherence to SOPs, and training in process and procedures.
5.0 QM: Risk-based Approach (4)

5.0.4 Risk Control (ff)

*Predefined quality tolerance limits* should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial results.

Detection of *deviations* from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.
5.0 QM: Risk-based Approach (5)

5.0.5 Risk Communication

The sponsor should **document** quality management activities. The sponsor should **communicate** quality management activities to those who are involved in or affected by such activities, to facilitate risk review and continual improvement during clinical trial execution.
5.0 QM: Risk-based Approach (6)

5.0.6 Risk Review

The sponsor should *periodically review risk control measures* to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience.

5.0.7 Risk Reporting

The sponsor should *describe the quality management approach implemented in the trial* and *summarize important deviations from the predefined quality tolerance limits* and remedial actions taken in the clinical study report.
5.18 Risk-based Monitoring (1)

5.18.3 Extent and Nature of Monitoring

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 efficacy of monitoring.**

- The sponsor may choose on-site monitoring, a combination of on-site monitoring 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 Risk-based Monitoring (2)

5.18.3 Extent and Nature of Monitoring

Addendum:

- **On-site monitoring** is performed at the sites at which the clinical trial is conducted.

- **Centralized monitoring** is a remote evaluation of accumulating data, performed in a timely manner, supported by appropriately qualified and trained persons (e.g., data managers, biostatisticians).

- **Centralized monitoring processes** provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring and help distinguish between reliable data and potentially unreliable data.
5.18 Risk-based Monitoring (3)

5.18.3 Extent and Nature of Monitoring

Addendum:

- Review, that may include statistical analyses, of accumulating data from centralized monitoring can be used to:
  - Identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations.
  - Examine data trends such as the range, consistency, and variability of data within and across sites.
  - Evaluate for systematic or significant errors in data collection and reporting at a site or across sites; or potential data manipulation or data integrity problems.
  - Analyze site characteristics and performance metrics.
  - Select sites and/or processes for targeted on-site monitoring.
Addendum:

5.18.7 Monitoring Plan

- The sponsor should develop a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial.
- The plan should describe the monitoring strategy, the monitoring responsibilities of all parties involved, the various monitoring methods to be used, and the rationale for their use.
- The plan should also emphasize the monitoring of critical data and processes.
- Particular attention should be given to those aspects that are not routine clinical practice and that require additional training.
- The monitoring plan should reference the applicable policies and procedures.

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5.20 Root Cause Analysis

Addendum:

*If noncompliance that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results is discovered, the sponsor should perform a *root cause analysis* and implement appropriate *corrective and preventive actions*. 
Will this Addendum really help to facilitate clinical research in resource-limited settings?
I think : yes

GCP now means to adapt the efforts and activities to the level of risks for patients and data quality.

This means there is not anymore “THE” GCP-conform approach but we can adapt to the type of study and to the environmental conditions as long as we are reliably able to protect the patients and data quality.
I think: yes

GCP now means to move away from control and disaster management to proactive risk identification and mitigation.

This means: Staff is not there to do primarily “Policing/Controlling” the data generation process but to avoid problems, identify the cause if problems happen and avoid that mistakes are made twice.
I think: yes

GCP now means moving away from blind obedience to application of common sense.

This means: we need to educate all team members to think, plan, analyse and focus on constant improvement

GCP now means to intelligently apply technology to reduce costs.

This means we need to jointly identify efficient, reliable technology suitable to support research in resource-limited settings and promote their use/make it available.
The problem will be to achieve the mind change

We need to train and encourage sponsors and investigators

- to dare to individualize their approaches to the needs of the particular trial
- to think in terms of risk management
- to plan and implement processes more strategically and
- to have the courage to defend the chosen strategies and processes

We need to communicate with regulators, auditors, and inspectors to accept consistently well-defined GCP(R2)-conform resource-saving strategies.
Thank you for your attention!