ICH E6(R3): Guideline for Good Clinical Practice - Draft Summary

Jeanine Pitts (jpitts@pharmateksol.com), Kirsten Johnson (kjohnson@pharmateksol.com)
Pharmatek Solutions, pharmateksol.com

Purpose

To develop a responsive GCP guideline

To provide Felxibility

- Acknowledge the diversity of trial designs, data sources, and the different contents in which trials can be conducted.
- Highlight that GCP principles can be satisfied in a variety of ways.

Approach

A rewrite and reorganization of ICH-E6(R2)

- Principles document and Annexes
- Align with ICH-E8 as appropriate
- Bridge identified gaps within E6 and between E6 and relevant ICH guidances.

Clear and concise scope

- Expectations should be fit for purpose

Focus on key concepts

- Quality by design and Risk-based approach
- Proportionality
- Critical to quality factors

Overall

Takes an adaptive approach toward technological innovations and computer systems.

Stresses the need for Risk-based approaches, critical to quality factors, and quality by design.

Risk Mitigation Proportionality

Heightened Responsibility for Patient Communication and Consent

Section II. Principles of ICH GCP Changes

Section 1: Safety and well-being of participants

Incorporate most of the R2 principles with minimal changes, but also include new principles which make the section overall more comprehensive: Implementing Quality into the trial design and generation of reliable results are the most significant changes. The principles cover the importance of innovative trial designs. Risk evaluations. Periodic review of information. Sections 6, 7, and 9 are new.

Section 3: Clinical and Trial Review

Periodic review by the IRB/IEC should also be conducted in accordance with applicable regulatory requirements.

Section 4: Scientifically Sound

There should be periodic review of current scientific knowledge and approaches to determine whether modifications to the trial are needed, since new or unanticipated information may arise once the trial has begun.

NEW!

Section 6: Quality of Design and Conduct.

- Quality of a clinical trial is considered in this guideline as fit for purpose.
- Factors critical to the quality of the trial should be identified.
- Strategies should be implemented to avoid, detect and address serious noncompliance with GCP, the trial protocol and applicable regulatory requirements to prevent recurrence.

NEW!

Section 7: Proportionate Processes, Measures, and Approaches

- Trial processes should be proportionate to the risks inherent in the trial and the importance of the information collected.
- Focus on the risks to participants beyond those associated with standard medical care.
- Risks to critical quality factors should be managed prospectively and adjusted when new issues arise.

NEW!

Section 9: Reliable Results.

- The quality and amount of the information generated in a clinical trial should be sufficient to provide confidence in the trial's results and support good decision making.
- Systems and processes that aid in data capture, management, and analyses, and that ensure quality of information should be fit for purpose, capture data required, and be implemented in a way that is proportionate to the risks to participants and the importance of acquired data.
- Trial processes should be operationally feasible and avoid unnecessary complexity, procedures, and data collection. Trial processes should support the key trial objectives.
- Computerized systems should be fit for purpose, and factors critical to their quality should be addressed in their design or adaptation for clinical trial purposes.
- Incorporate efficient and well-controlled processes for managing records through appropriate management of data integrity, traceability, and protection of personal information.
- Records should be retained securely by sponsors and investigators for the required period of time and available to regulatory authorities upon request to enable reconstruction of the trial conduct and results in order to ensure the reliability of trial results.
- Transparency of clinical trials in drug development includes registration on publicly accessible and recognized databases and the public posting of clinical trial results.

Section 10:

Roles and responsibilities in clinical trials should be clear and documented appropriately.

Section 11:

Investigational products should be manufactured in accordance with applicable GMP standards and be stored, shipped, handled, and disposed of in accordance with the product specifications and the trial protocol.

Section III. Annex 1 Changes

Section 1. IRB/IEC

Updated. IRB: innovative methods of collection of consent and data such as electronic ICFs, removed text on non-therapeutic trials.

Section 2. Investigator

Updated. Significant additions, deletions, and restructuring.

2.1 Qualifications and Training

Investigator is responsible for service providers provided by sponsor (i.e., home health nurses).

Training proportionate to responsibilities of staff, recording the delegation of staff may not be necessary, restrictions eased on medical care decisions, required to inform primary care if participant agrees to inform.

2.8 Informed Consent

Informed consent - new information (i.e., protocol amendments requiring new ICFs to be signed) clearly identified in the revised consent.

Remote consent.

Varied approaches to the IC process (videos, images, other interactive methods).

Notification of participants on how data will be handled, including premature withdrawal.

2.9 End of participation in a trial

New text on informing participants of trial outcomes.

Update to types of withdrawals.

Follow up measures to avoid data loss.

2.10 Investigational Product Management

New references to DCT (decentralized trials).

2.11 Randomization Procedures and Unblinding

Added requirement that unblinding processes in an emergency are not subject to delays or hindrance.

2.12 Records

Investigators should ensure the integrity of the data under their responsibility; this is different from R2 which states "maintain adequate and accurate source records."

Avoid unnecessary transcription steps.

Timely access and review of data by PI.

Investigator/institution systems should be assessed to ensure:

- Attributable access.
- Traceability of ePRO equipment provided to participants.
- Incidents in the use and operation of systems are reported to the sponsor and IRB/IEC.

Control of essential records generated before, during, and after the trial.

Notify sponsor of closure of site or investigator departure and determine where records will be stored.

Section 3. Sponsor

3.1 Trial Design

Input from a wide variety of stakeholders (healthcare professionals and patients).

Quality incorporated into design of trial; identification of factors critical to the quality of the trial.

Ensure trial is operationally feasible and avoids unnecessary complexity.

Data acquisition tools are fit for purpose, clear, concise, and consistent.

NEW!

3.6 Agreements

Service providers should report incidents to the sponsor that may have an impact on safety or trial results.

Sponsors must notify investigators of service providers under their responsibility.

Obtain agreement from service provider to conduct trial in accordance with protocol and GCP.

Agreements should be documented prior to initiating activities.

Service provider should implement appropriate quality management.

NEW!

3.8 Communication with IRB/IEC and Regulatory Authorities

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NEW!

3.9 Sponsor Oversight

New Section on sponsor oversight directs sponsor to ensure oversight measures are fit for purpose to the trial complexity and risks, and that escalation and follow up on issues is performed appropriately and in a timely manner.

Important protocol deviations should be defined according to trial-specific criteria, and any trial decisions should be assessed for impact and risks related to those decisions managed.

3.10 Quality Management

Risk identification has been updated to reflect the use of critical to quality factors, and removed the system and trial level segregation, however, risk evaluation remains the same.

Risk control has been revised; the main change being the removal of the phrase "quality tolerance limits".

3.11 Quality Assurance and Quality Control

Audits should be proportionate to the risks associated with the trial. Audits should assess that processes in place are effective as well as compliant. The auditor no longer needs to be independent from the systems, just the clinical trial.

NEW!

3.11.4 Monitoring

Monitoring section contains new sections on "investigator site monitoring" and "centralized monitoring".

New requirements for monitoring.

Emphasizes that monitoring cannot be performed by those involved in the clinical conduct of the trial.

Frequency of site monitoring activities based on risks and frequency modified using knowledge gained.

Secure, remote, direct read-only access to source records.

Selection of data for verification based on data analytics, adjusted based on data quality, and critical data identified in the monitoring plan.

Actions to secure compliance are appropriate and proportionate to the non-compliance.

3.13 Safety Assessment

New text stating IB forms the basis of the safety assessment, this should contain the Reference Safety Information (RSI).

Expedited reporting of SUSAR cases is for the awareness of Reg Authorities; IRB and investigators may be subject to different expectations (based on urgency and the use of aggregate information).

3.15.2 Mfg. Packaging, Labeling and Coding of IP

New wording allowing sponsor to supply IP directly to trial participants.

Instructions should be available for trial participants and IP delivered in time to ensure no interruption in treatment.

3.16.1 Data Handling

Heightened focus on good data:

- Focus on reliability of results (as opposed to data).
- Expanded requirements on data handling and computerized systems.
- Investigator access to data.
- Sponsor not having exclusive control of the data.
- Sponsor should ensure data are of sufficient quality to generate reliable results.
- Investigators instructed on the use of computerized systems.
- Investigator required to endorse data at predetermined milestones and access restrictions to data acquisition tools may be required.
- Expansion of sponsor responsibilities for computerized systems.

NEW!

Section 4. Data Governance

New section provides guidance to both sponsors and investigators on appropriate management on data integrity, including:

- Maintaining the integrity of the blind.
- Procedures in place to cover the full data lifecycle.
- Computerized systems.
- Technical support.
- User management.
- Audit trails.
- Data capture, transfer, exchange, migration.
- Security.
- Training.

References:

Fisher, A. (2023, May 26). ICH E6 (R3) Good Clinical Practice. MHRA Inspectorate.

https://mhrainspectorate.blog.gov.uk/2023/05/26/ich-e6-r3-good-clinical-practice/

International Council for Harmonization 2023, May 19) Guideline Good Clinical Practice (GCP) E6(R3) Draft