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Understanding the New GCP: ICH E6(R3) - ICH E6 (R3) in Context: Addressing Gaps and Enhancing Global Clinical Practice

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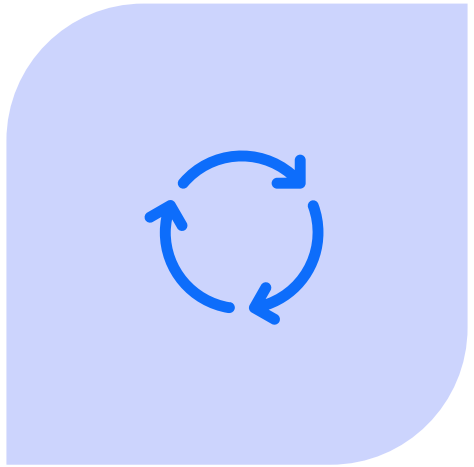
Outline

RENOVATION OF THE GUIDELINE



IMPLEMENTATION

What is Good Clinical Practice?

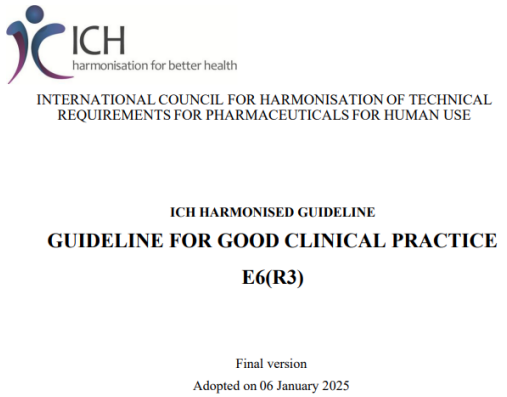
- **GCP is a standard** for the planning, initiating, performing, recording, oversight, evaluation, analysis and reporting of clinical trials **that provides assurance that the data and reported results are reliable** and that the **rights, safety and well-being of trial participants are protected**.
- **ICH E6 (R3)** is a **globally accepted standard** and **adherence is a requirement in Europe**
- **In effect since 1996**, revised in 2016 (R2), with a **full rewrite in 2025 (R3)**
- The **patient has always been at the forefront of this guideline**
  - The **rights, safety and well-being of the participants are the most important considerations** and should prevail over interests of science and society
  - **Informed consent is an integral feature** of the ethical conduct of a trial, and participants are **free to withdraw at any time**
  - High standards for the **qualifications of clinical staff conducting trials, sponsor oversight,** and **systems to ensure ongoing safety of participation in the trial**

Major concerns raised in relation to ICH E6 (R2)

- **One size fits all** approach
- **Over interpretation** and **rigid application** of the guideline (by regulators, industry, stakeholders)
- **Not flexible enough** to allow for new technologies, trial designs (including lower risk trials) and data sources
- Over focus on generation and retention of documentation and **unachievable perfect data**

ICH E6 (ICH GCP)

- Official ICH website: [ICH Official web site : ICH]
- [Microsoft PowerPoint - ICH_E6(R3)_Step 4_Presentation_2025_0123.pptx]


ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

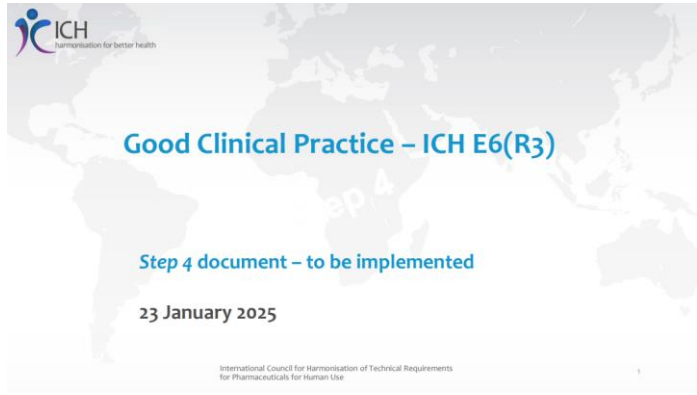
ICH HARMONISED GUIDELINE

GUIDELINE FOR GOOD CLINICAL PRACTICE

E6(R3)

Final version

Adopted on 06 January 2025



- EU: [ICH E6 (R3) Guideline on good clinical practice (GCP)_Step 5]

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SCIENCE MEDICINES HEALTH

23 January 2025
EMA/CHMP/ICH/135/1995
Committee for Human Medicinal Products

ICH E6 (R3) Guideline for good clinical practice (GCP)
Step 5

Transmission to CHMP	25 May 2023
Adoption by CHMP	25 May 2023
Release for public consultation	26 May 2023
Deadline for comments	26 September 2023
Final adoption by CHMP	12 December 2024
Date for coming into effect	23 July 2025

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Current state of ICH E6 (R3)

What happens next?

SOP_Approved_v13-0_2023_0512.pdf (ich.org)

2.1.6. Step 4: Adoption of an ICH Harmonised Guideline

- In Step 4 of the ICH process, the Regulatory Members of the Assembly adopt a harmonised Guideline in consultation with the MC.

2.1.7. Step 5: Implementation

- Once Step 4 is reached, the harmonised Guideline moves to the final step of the process and is implemented by each of the Regulatory Members in their respective regions. The harmonised Guideline is implemented according to the same national/regional procedures that apply to other regional, scientific or regulatory Guidelines and requirements, as for example, in the EU, Japan, USA, Canada, and Switzerland
- In the EU, six (6) months after final CHMP adoption, the ICH guideline will come into effect

In the EU, the current version, ICH E6(R2), remains in effect until 22 July 2025.
This gives stakeholders time to transition to the new version, while still adhering to the previous standards.

- EU: ICH E6 (R3) Guideline on good clinical practice (GCP)_Step 5

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Renovation

- Feedback from **investigators and sponsors expressed concerns** about **lack of flexibility of the guideline** and **not responding to technological advances**
- **Extensive engagement** with all parties involved in trials, including patients, was fundamental
- Guideline **focuses on what is most important** to **patient safety** and data reliability
  - Proportionality, risk-based approaches, good trial design and building quality in up front
  - Encouragement of engagement with patients and other interested parties
- Positioning the guideline for **novel technologies and trial types**
- New **data governance section**

Main changes

- Principles and Concepts
- Responsibilities and Oversight
- Informed Consent
- Data Governance
- Essential Records for the Conduct of a Clinical Trial

Main changes (continued)

New structure

Standalone section on principles	Annex 1 provides further detail (ethics committee/IRB, investigator, sponsor, data governance) Annex 2 on alternative trial types/data sources

Increased focus on proportionality and risk-based approaches and thoughtful trial design

New principle on proportionality/risk-based approaches	Dedicated annexes and appendices	Flexibilities throughout

More changes

- Dedicated data governance section (including computerised systems)
- Clarity on scope and application of guideline (e.g. not applicable to research not involving medicinal products)
- Media neutrality throughout the document
- Encouraging greater engagement with the community/stakeholders and transparency

Patient centricity

In addition to the fundamentals, the following has been added:

- Encouraging **greater transparency of trial results** and **community engagement**
- **Use of decentralised elements** (e.g. trial activities conducted in the home, investigational medicinal product delivery)
- **Meaningful and alternative methods of obtaining consent**
    - Conciseness of consent process
    - Potential for use of alternative methods where appropriate (e.g. use of electronic methods)
    - Balancing need to re-consent when new information becomes available with burden of process

Overarching concepts

- Quality by design
- Fit for purpose
- Critical to Quality Factors
- Proportionality – focus on what matters

Quality by design

- Prospective
- Identify and manage Critical to Quality Factors (including relevant risks) to the clinical trial
- ICH E6 (R3) builds on the quality by design principle, encourages critical thinking, utilises proportionate, risk-based approaches minimising unnecessary complexity and reducing burden on trial participants and Investigators
- The avoidance of unnecessary complexity and burden on trial participants and Investigators
    - Interconnected concepts

Investigator Oversight

- Investigator ~~Supervision~~
  - The term "supervision" has been replaced with "oversight". Oversight levels should be proportionate to the importance of the data and the risks to participant safety and data reliability.
  - For example, training requirements for delegated activities should be proportionate to the task complexity, taking into consideration routine medical care.
- Investigator oversight of contracted service providers
  - The Investigator retains ultimate responsibility for persons or service providers to which they delegate activities. The concept of proportionate Investigator oversight is determined by the delegated activity, the importance of the data collected and risks to trial participant safety and data reliability
  - When a service provider is contracted by the sponsor on behalf of the Investigator, for example a Home Nurse, the Investigator should have appropriate oversight of this person. The sponsor should provide sufficient information to allow the Investigator to evaluate the suitability of this person for undertaking this delegated task.

Investigator oversight (continued)

- **Investigational product management:** Investigators are responsible for oversight of investigational products, with adjusted procedures for products with limited safety data. Investigators should be able to perform unblinding in case of emergencies to protect participant safety.
- **Safety reporting:** Adverse events and/or abnormal test results should be reported to the sponsor according to the reporting requirements and within specified protocol timeframes. Unfavourable medical events before investigational product administration should be considered and reported as well, when required by the protocol.

Informed Consent

- Proportionate consent processes should remain relevant and appropriate throughout the trial, especially with new forms of clinical trials emerging.
- Avoidance of unnecessary complexity and greater clarity in the informed consent form is emphasised.
- Varied approaches in the informed consent process may be used; considerations should be made for re-consent based on trial stage and relevance.
    - Flexibility in consent options and clear, simple language are essential, as is ensuring participants can raise any questions during the whole process.

Sponsor oversight

- Focus on critical to quality factors (and their associated risks) throughout the course of a clinical trial
- Emphasis on not placing unnecessary burden on participants and Investigators
- Sponsors should ensure clear roles and responsibilities and that appropriate agreements are in place to document them where necessary.
- The focus in trial design is on clarity, defining the research question, and collecting only essential data, adhering to the principle of "quality by design.

Sponsor oversight (continued)

- Monitoring strategy should consider factors such as the trial purpose, design, blinding, safety profile, and endpoints that have the most potential to impact participant rights, safety and well-being in line with the risk proportionate approach for that investigational product in that participant population.
- Sponsors are responsible for ensuring data integrity, particularly around randomisation and blinding.
- Timely, clear documentation is stressed, including clinical trial reports and timely filing of essential records in the trial master file as its maintenance can support oversight activities.

Sponsors' risk-based approach

- Sponsors should provide clear and concise documentation of key decisions and their rationale, especially when deviating from established procedures.
- This ensures decisions are well-justified and understandable. Significant decisions, such as addressing omissions or non-compliance, should always be documented to explain actions taken.
- The goal is to create useful documentation that serves its purpose without becoming overly burdensome.

Implementation of risk-proportionate approach

- A proportionate approach is necessary, incorporating quality by design and defining critical data.
- It is important to assess whether each element in the trial design is necessary.
- Engaging stakeholders and designing practical, feasible trial protocols are essential to prevent overburdening both Investigators and participants.
- Assessing new information for re-consent is crucial, though it may only apply to new participants.

Data Governance

- Apply data integrity throughout the data life cycle
- Apply proportionate approaches towards computerised system responsibilities
- The sponsor should ensure that their computerised systems meet expectations in a risk-proportionate manner
- The new data governance section guides the responsible parties (i.e. Investigators and sponsors) in managing data integrity, covering e.g. data protection, computerised systems and essential elements like randomisation and blinding.

Data Governance (continued)

- **Electronic systems validation:** The responsibility for validating sponsor systems lies with the sponsor, not the Investigator. The Investigator's role is to use the systems as intended, report who needs access, and report any incidents, but not to validate the system itself.
- **Oversight of the Investigator on data integrity**: The expectation is not to have continuous signoffs for each eCRF page. Instead, the focus is on key milestones where the Investigator acknowledges the data and endorses its completeness and accuracy.
- **E-tools and patient's perspective**: From a patient perspective, using technologies in trials can provide valuable insights into symptoms and disease burden. However, it's crucial to consider the return on engagement for patients.
- **Timeline for clarifying data reported by trial participants or Investigators:** The guideline emphasises that corrections should be supported by source data recorded around the time of the event to avoid recall bias and manipulation of data.

Essential records

Updated guidance on what makes a record essential; and on the content and maintenance of such records

Essential records in clinical trials, according to the new guideline, are documents and data that ensure the evaluation of trial methods and verify compliance with regulatory standards. These records are necessary for reliable results, maintaining data integrity, and supporting informed decision-making throughout the trial

Appendix C of ICH E6 (R3) clarifies the types of essential records that should be maintained, including records related to safety, trial conduct and participant data

Essential records (continued)

The Essential Records Table in the guideline offers a useful tool to distinguish essential records according to their purpose and regulatory requirements.

The process of identifying, maintaining, and securing essential records is vital for clinical trials, supporting both the transparency of the trial and the reliability of its outcomes.

Transition/Implementation period

- Many concepts from E6 (R2) are already in place, and preparation for E6 (R3) can start
- It is crucial to apply change control activities and consider necessary adjustments.
- The transition/implementation should be fit-for-purpose and well-considered.
- A customised training approach, informed by existing clinical trial practices, is recommended.
- Performing a gap analysis to identify priority training needs—and addressing these needs promptly—is particularly important for sponsors implementing decentralised or pragmatic trial designs, or incorporating novel tools and technologies

ICH E6 (R3) Annex 2 (draft)

Provides additional considerations

Annex 2 should be read in conjunction with the ICH E6 (R3) Principles and Annex 1 document

Addresses the GCP considerations that arise from the increased use of a wider range of design elements and data sources and has its foundations in the key concepts of quality-by-design, fitness for purpose and risk proportionality

Decentralised elements, Real-world data, pragmatic elements

ICH E6(R3) Guideline for good clinical practice – Annex 2_Step 2b

The goal is to ensure the guideline remains fit-for-purpose and aligned with emerging trial designs that safeguard participant rights and enhance data reliability

expected completion: later in 2025.

More resources

Currently the ICH E6(R3) Expert Working Group is developing a series of training modules for the revised ICH E6 (R3) guideline.

The first modules are expected to be released later in 2025.

ACT EU Workshop (Feb 2025):

ACT EU workshop on ICH E6 R3 (principles and Annex 1) | European Medicines Agency (EMA)

- ACT EU workshop on ICH E6 R3 - DAY 1
- ACT EU workshop on ICH E6 R3 - DAY 2

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