THE ICH-GCP E6(R3) GUIDELINE: RETHINKING GCP

ARBEITSKREIS MEDIZINISCHER ETHIK-KOMMISSIONEN IN DER BUNDESREPUBLIK DEUTSCHLAND E.V. - 43. JAHRESTAGUNG

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AGENDA

- The make up of the Expert Working Group, writing E6(R3)
- The Principles and Annex 1 – specifically Ethics related
- Annex 2 - Main themes
- Considerations for Ethics Committees in this everchanging clinical trial landscape.

THE MAKE UP OF THE EXPERT WORKING GROUP WRITING ICH E6(R3)

Regulatory Members or Legislative or Administrative Authorities

- European Medicines Agency (EMA)
- Food and Drug Administration (FDA)
- Ministry of Health Labour and Welfare (MHLW)/Pharmaceuticals and Medicinal Devices Agency (PMDA)
- National Medical Products Administration (NMPA)
- Health Canada
- Brazilian Health Regulatory Agency (Anvisa)
- Health Sciences Authority (HSA)
- Therapeutic Goods Administration (TGA)
- CDSCO, India
- Taiwan Food and Drug Administration (TFDA)
- TITCK, Türkiye
- Roszdravnadzor

Standing Observers

- International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)
- World Health Organisation (WHO)

Academic Stakeholder Representatives

Industry Members

- European Federation of Pharmaceutical Industries and Ass ions (EFPIA)
- eutical and Research Manufacturers of erica (PhRMA)
- Japan Pharmaceutical Manufacturers Association (JPMA)
- International Generic and Biosimilar Medicines Association (IGBA)

International Organisation regulated or affected by ICH Guideline

- Pharmaceutical Inspectors Cooperation Scheme (PIC/S)

Good Clinical Practice – ICH E6(R3)

Step 4 document – to be implemented

23 January 2025

Good Clinical Practice – ICH E6(R3)

Legal Notice

ICH-E6(R3): Background to this Revision

E8 – integrating QbD into study design and conduct

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E6 – Applying the foundation of E8 to the conduct of clinical trials

Do not read E6(R3) in isolation

- **E6: Good Clinical Practice (GCP) – finalised in 1996**
  - Described the responsibilities of investigators and sponsors and expectations of interested parties in the conduct of clinical trials;
  - Covered aspects of monitoring, reporting, and archiving of clinical trials; and
  - Included sections for essential documents and investigator brochures
- **E6(R2) – finalised in 2016**
  - Included integrated addendum to encourage implementation of improved and more efficient approaches to GCP, while continuing to ensure human subject protection; and
  - Updated standards for electronic records.
- **E6(R3) – finalised in 2025**
  - Grounded in the foundational principle of Quality by Design (QbD)
  - Involves critical thinking
  - Utilises proportionate, risk-based approaches
  - Recognises that a one size does not fit all.

Initial Takeaways from Feedback and Comments on ICH E6(R2)

Concerns about the following:

- The clinical trial ecosystem is rapidly evolving and this was not reflected in the guideline.
- The academic community were concerned about a lack of proportionality.
- The R2 guidance was seen as a “one-size-fits-all” approach to clinical trials.
- The ability of clinical trials to meet all GCP requirements in different situations (e.g., during public health emergencies).
- GCP requirements were being applied where they were not applicable.

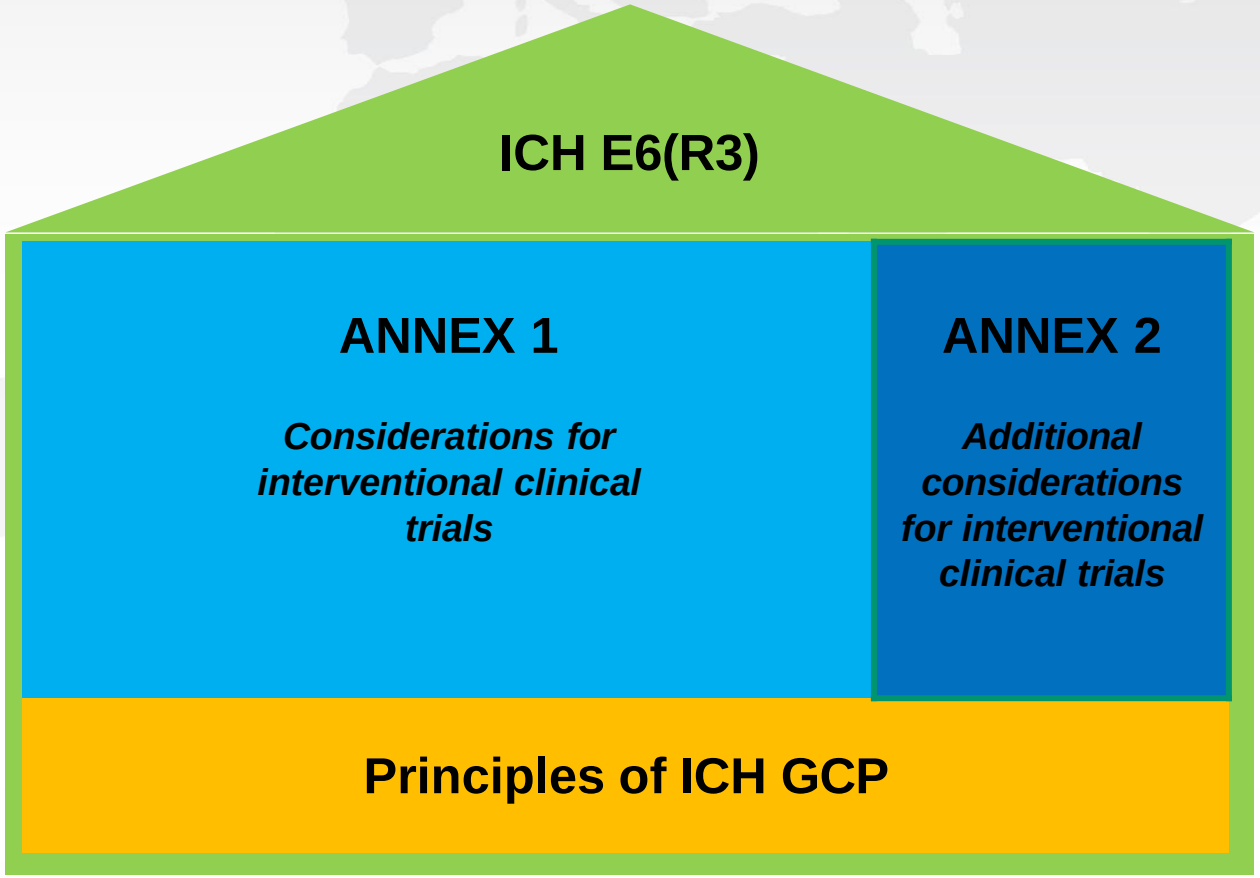
What is new about E6(R3) structure and content?

- New structure to provide clarity and better readability.
- Provide additional clarity on the scope.
- Included language to facilitate innovations in clinical trial design, technology and operational approaches.
- Set a foundation for practical/feasible expectations (through adoption of QbD and proportionate risk-based approaches) for responsibilities of sponsor and investigator in an evolving clinical trial ecosystem.

What is new about E6(R3) structure and content? (2)

- Encourage fit-for-purpose approaches.
  - Proportionality and risk-based approaches with a focus on the clinical trial's critical to quality factors (i.e., whose integrity is fundamental to safety of participants and the reliability of trial results);
  - Thoughtfulness in the design and conduct
- Incorporate learning from innovative clinical trial designs and lessons from public health emergencies/pandemics.
- Encourage transparency by clinical trial registration and result reporting.
- Provide additional language to enhance the informed consent process.

OVERVIEW OF ICH E6(R3)



Scope

- This guideline applies to interventional clinical trials of investigational products that are intended to be submitted to regulatory authorities. The Principles of GCP in this guideline may also be applicable to other interventional clinical trials of investigational products that are not intended to support marketing authorisation applications in accordance with local requirements.
- The Annexes provide the basis for the appropriate interpretation and application of the principles and should therefore be appropriately considered; however, various approaches to the provisions in the Annexes may be considered provided they are justified and achieve the intended purpose of the application of the principles.
- This guideline encourages a risk-based and proportionate approach to the conduct of a clinical trial.

Innovation, Efficiency & Engagement

- Encouraging the exploration of technology:
  - The principles are intended to support efficient approaches to trial design and conduct. For example, innovative digital health technologies, such as wearables and sensors may expand the possible approaches to trial conduct.
  - Such technologies can be incorporated into existing healthcare infrastructures and enable the use of a variety of relevant data sources in clinical trials.
  - The use of technology in the conduct of clinical trials should be adapted to fit the participant characteristics and the particular trial design.
- Encouraging engagement and inclusivity:
  - The use of innovative trial designs and technologies may enable the inclusion of a wider and more diverse population of participants and thereby broaden the applicability of trial outcomes.
  - The design and conduct of the clinical trial may be supported by obtaining the perspectives of interested parties, such as patients and their communities, patient advocacy groups and healthcare professionals. Their input can help to reduce unnecessary complexity, improve feasibility and increase the likelihood of meaningful trial outcomes.

PRINCIPLE 1 AND THE DECLARATION OF HELSINKI OCTOBER 2024

Principle 1, E6(R3)

1. **Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and applicable regulatory requirement(s). Clinical trials should be designed and conducted in ways that ensure the rights, safety and well-being of participants.**

Declaration of Helsinki

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human participants, including research using identifiable human material or data.

Both documents emphasise participant protection, inclusivity, and engagement.

Both address the ethical challenges of new technologies and diverse data sources.

Both highlight the evolving role and required expertise of ethics committees.

ICH E6(R3) Annex 1

Institutional Review Board/Independent Ethics Committee (IRB/IEC)

ICH E6(R3) Section	ICH E6(R2) Section
1.1 – Submission and Communication *In R3, added global language about reporting to IRB/IEC and regulatory authorities*	N/A
1.2 – Responsibilities	3.1
1.3 – Composition, Function and Operations	3.2
1.4 – Procedures	3.3
1.5 – Records	3.4

IRB/IEC

- Included global language about reporting to IRB/IEC and regulatory authorities.
- Updated to reflect digitisation and variable approaches to obtaining consent.
- Clarified the potential for participants to be compensated for costs incurred to participate in the trial.
- Clarified that the IRB/IEC should review the assent information, considering the age, maturity and psychological state of the minor, as well as applicable regulatory requirements.

Investigator - Informed Consent

- **Approaches to obtaining informed consent**
  - Varied approaches to the provision of information and the discussion about the trial can be used. This may include, for example, providing text in different formats, images and videos and other interactive methods.
  - The information should be as clear and concise as possible, use simple language and avoid unnecessary volume and complexity.
  - Informed consent is documented by means of a written (paper or electronic), signed and dated informed consent form.
  - Obtaining consent remotely may be considered when appropriate.
- **New information**
  - Considerations for re-consent, including stage of the clinical trial, whether the new information is relevant only to new / existing participants.
  - Revised informed consent materials require IRB/IEC approval in advance of use.
- **Enrolment of minors**
  - Where a minor is to be included as a participant, age-appropriate assent information should be provided and discussed with the minor as part of the consent process.
  - A process for consent should be considered if during the trial, the minor reaches the age of legal consent, in accordance with applicable regulatory requirements.

Step 2 Deck, Annex 2 Public consultation

Step 2

ICH E6(R3) – Annex 2 Background

- Annex 2 provides considerations that focus on examples of trials that incorporate:

Decentralised Elements

Trial-related activities conducted outside the investigator's location

- *E.g., trial visits conducted at participant's home / local healthcare centre / mobile medical units; or data acquisition performed remotely using digital health technologies (DHTs)*

Pragmatic Elements

Those that integrate aspects of clinical practice into the design and conduct of the trial

- *E.g., simplified protocols with streamlined data collection*

Real World Data (RWD)

Include the use of data relating to patient health status collected from a variety of sources outside of clinical trials

- *E.g., electronic health records (EHRs), registries, claims data*

WHAT DOES THIS MEAN FOR ETHICS COMMITTEES?

Ethics committees need to handle the increasing complexity, protocols of nearly 200 pages and Informed Consent of up to 40 pages, technology evolving and trial design evolving.

Do Ethics committees need to have persons with a knowledge of?

- data privacy,
- data security protection in the context of computerised systems,
- understanding of the use of RWD in clinical trials
- Applicability of digital health technologies in certain participant populations
- Assessment of the acceptability of such technologies to ensure populations not excluded.

FURTHER CONSIDERATIONS FOR ETHICS COMMITTEES

Reconsent:

- Who needs to be reconsented?
  - Dependent on what has changed
  - The status of the participant in the trial
  - The impact on that participant

Assent

- How do you determine whether an assent is appropriate for that age range?
- When can the new adult consent?

Decentralised Clinical Trial and Pragmatic Elements

- Have their own specific challenges
  - Technology
  - Linkage to other data sets, e.g., death data

Increasing Complexity

SUMMARY

ETHICS COMMITTEES ARE CRUCIAL TO INTERVENTIONAL CLINICAL TRIALS AS DESCRIBED IN E6(R3)

DE… PROF…ALS AND …RSONS …NG THEIR TIME

INCREASING COMPLEXITY, MAKES ROLE EVEN HARDER

HOW TO KEEP PACE WITH THE CHANGING CLINICAL TRIAL LANDSCAPE

Thank you for your commitment and time

THANK YOU

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