# Overview of ICH E6 R3 renovation

## ICH E6 R3 workshop

## 19 February 2025

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# Disclaimer

I have no conflict of interest to disclose of relevance to this presentation.

Any views expressed in this presentation are mine and should not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency, one of its committees or working parties or the ICH E6 Expert Working Group (EWG).

- History of ICH E6
- Reasons for change
- Development of R3
- Overview of main changes
- Focusing on main structure, introduction and principles

# History of ICH E6

**E6 - 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**;
- Included sections for **essential documents** and **investigator brochures**

**E6 (R2) - 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) - 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**.

# Reasons for change

Inputs from stakeholders indicated a **need for change**

- Including Clinical Trials Transformation Initiative survey, articles (incl. open letter to ICH and EMA) and regional stakeholder engagement

Concerns about:

- **Rapidly evolving clinical trial ecosystem** not reflected by R2
- Academic community were concerned about a **lack of proportionality**
- R2 guidance was seen as  a **“one-size-fits-all” approach**
- **Ability of clinical trials to meet all GCP requirements** in different situations (e.g. during public health emergencies)
- GCP **applied when not applicable**

# Development of ICH E6 R3

- **Major rewrite** responding to need for change
- **Stakeholder engagement essential**
  - Expert working group (EWG) comprised of global industry and regulator representatives
  - **Engaged extensively with academic stakeholders** throughout the process
  - Various international and regional workshops (including workshop at EMA in July 2023)
  - **Over 7,000 comments received** during public consultation on principles and annex 1
- Increased transparency during development
  - **Draft principles published in April 2021** along with public web conference in May 2021

# Overview of main changes (1)

**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 (e.g. media neutrality in documents).

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.

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**

# Overview of main changes (2)

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**.

New **data governance section** (applicable to investigators and sponsors)

Greater **proportionality added to essential records** appendix

# New structure

Principles are in the core part of the guideline – **focus should be on their fulfilment**

**E6(R3) Guideline**

E6(R3) Principles and Annex 1 replacing E6(R2)

**I. INTRODUCTION**

**II. PRINCIPLES OF ICH GCP**

**III.ANNEX 1**

1. Institutional Review Board/Independent Ethics Committee (IRB/IEC)
2. Investigator
3. Sponsor
4. Data Governance – Investigator and Sponsor **(new)**

**APPENDICES**

Appendix A. Investigator's Brochure
Appendix B. Clinical Trial Protocol and Protocol Amendment(s)
Appendix C. Essential Records for the Conduct of a Clinical Trial

**GLOSSARY**

**ANNEX 2** – *under public consultation from November 2024 to March 2025*

# Introduction – 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.

# Introduction - Principles and interplay with annexes

The **principles are intended to apply across clinical trial types** and settings and to remain relevant as technological and methodological advances occur.

The **principles outlined in this guideline may be satisfied using differing approaches and should be applied to fit the intended purpose of the clinical trial**.

**Annex 1**, including its Appendices, is intended to **provide information on how the Principles can be appropriately applied** to clinical trials.

# Other aspects

Guideline should be **read in conjunction with other ICH guidelines** (e.g. E2 (safety), E3 (CSR) E8 (general considerations for CTs) and E9 (statistical considerations)

**Focus on fit for purpose clinical trial quality** (Quality by Design (QbD) and proportionate, risk-based approaches)

- Builds on key concepts in ICH E8 (R1) General Considerations for Clinical Studies
- Acknowledgement that clinical trials vary widely in scale, complexity and cost.
- Careful evaluation of critical to quality factors involved in each trial and risks associated with the priorities

Encourages **exploration of new technologies/trial designs** and **community engagement**

# Principles

- Additional clarification and streamlining of principles – **11 principles in R3**
- New dedicated principles for **risk proportionality** and **roles and responsibilities**

| ICH E6 (R3) PRINCIPLE | TOPIC | ICH E6 (R2) PRINCIPLE |
|---|---|---|
| 1 | Ethical Principles | 2.1, 2.2, 2.3, 2.7, 2.11 |
| 2 | Informed Consent | 2.9 |
| 3 | IRB/IEC Review | 2.6 |
| 4 | Science | 2.4, 2.5 |
| 5 | Qualified Individuals | 2.8 |
| 6 | Quality | 2.13 |
| **7** | **Risk Proportionality** | **N/A** |
| 8 | Protocol | 2.5 |
| 9 | Reliable Results | 2.10 |
| **10** | **Roles and Responsibilities** | **N/A** |
| 11 | Investigational Products | 2.12 |

# New principles for R3

Principle 7: Proportionality, risk-based

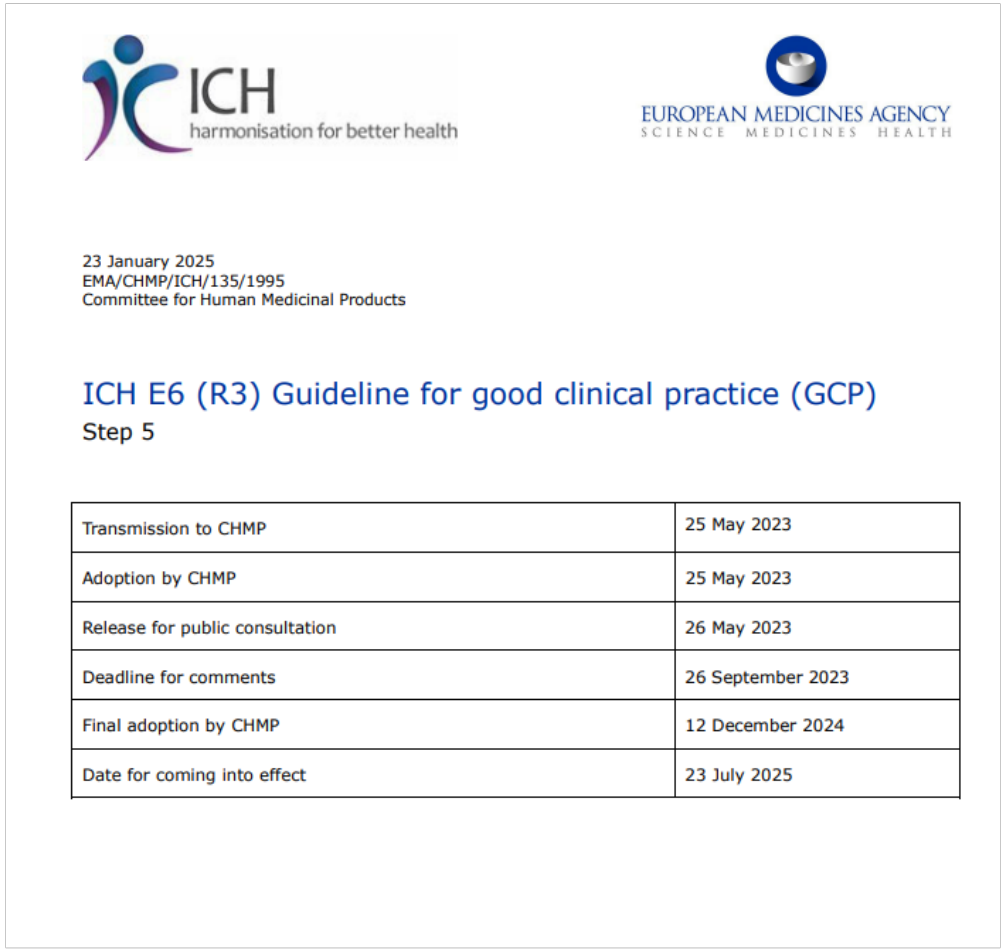
- Focus on **participant's safety and reliability of results**.
- Focus on the **risks associated with trial participation**.
- Focus on **risks beyond those associated with usual medical care** for clinical trials involving patients.
- The **sponsor should not place unnecessary burden on investigators**

Principle 10: Roles and responsibilities

- **Clarification of transfer of activities** by the Sponsor and delegation by the Investigator.
- **Maintenance of appropriate oversight**.

# Implementation

- In EU, guideline comes into effect on **23 July 2025**
- Sponsors, investigators and service providers/CROs should consider how they will implement the guideline in practice
  - Noteworthy that many fundamental concepts in R2 remain in R3
  - Activities to take account of the update, e.g. training of staff may be implemented in a customised, fit for purpose approach



ICH harmonisation for better health

EUROPEAN MEDICINES AGENCY
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 |

# Summary

- **Major rewrite of R2**, responding to technological advances in clinical trials and stakeholder feedback
- **New structure** with a focus on principles, **dedicated data governance section** and new **annex 2**
- **Two new principles**, focusing on proportionality/risk-based approaches and clarifying roles and responsibilities
- All provisions looked at **ensure future proof and strip out unnecessary burden**
- Important to **read guideline in conjunction with other ICH guidelines** (in particular E8)
- Implementation date in EU **23 July 2025**

# Thank you

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