ICH-GCP Update: Konsequenzen

„SCIENCE FROM THE HEART OF EUROPE“

ABCSG AUSTRIAN BREAST & COLORECTAL CANCER STUDY GROUP

ICH-GCP: Guidance für klinische Studien

Wir alle arbeiten nach Prinzipien der **Good Clinical Practice der International Conference on Harmonization (ICH)**

- ICH-Leitlinie E6 zur guten klinischen Praxis (GCP) bietet einen einheitlichen Standard, um ethische Prinzipien zu verankern und die gegenseitige Anerkennung von Daten aus klinischen Prüfungen in den Ländern durch die zuständigen Überwachungsbehörden zu erleichtern.
- **Seit 23. Juli 2025 gibt es eine neue Version (Revision 3),** die sowohl an Zentren als auch bei anderem Personal geschult werden sollte, das an klinischen Studien mitarbeitet.
- Nicht alle Abschnitte und Änderungen sind relevant für onkologische Studien bzw. ABCSG-Studien, dieser **Überblick fokussiert auf einige der wichtigsten Neuerungen v. a. aus Sicht der Zentren und PIs.**

ICH-GCP Revision 3 – Key Changes

The main changes between ICH GCP E6 Revision 2 and Revision 3 revolve around

- a more **risk-based approach**,
- increased **focus on data integrity,**
- enhanced emphasis on **electronic systems,**
- and a **broader scope for trial designs**.

R3 emphasizes **risk-based monitoring** and data integrity, while R2 focused on general principles and data management. R3 also introduces **more flexible trial designs**, including decentralized trials and adaptive designs, and incorporates learning from public health emergencies (e.g. COVID-19 pandemic).

ICH-GCP Revision 3 – Key Changes

Risk-Based Approach:

- R3 shifts towards a risk-based approach throughout the trial process, focusing on identifying, assessing, and managing risks to ensure participant safety and data integrity. R2 had a less explicit focus on risk management.

Data Integrity:

- R3 places a strong emphasis on data integrity, **requiring investigators to ensure the integrity of data under their responsibility and defining source records, methods of data capture, and data locations at the site.** R2's focus on data integrity was more general.

ICH-GCP Revision 3 – Key Changes

Electronic Systems:

- R3 provides more guidance on the use of **electronic systems, including digital health technologies and electronic sources,** and addresses the use of electronic systems for data acquisition and storage. R2's guidance on electronic systems was less comprehensive.

→ Stichwort: Electronic Medical Records (EMR-Dokumente müssen an Zentren aufliegen)

Trial Designs:

- R3 recognizes the increasing use of decentralized clinical trial designs, including adaptive designs and incorporating learning from public health emergencies. R2's focus on trial designs was more limited.

ICH-GCP Revision 3 – Key Changes

Focus on Participants:

- R3 incorporates a more explicit focus on study participants, considering their perspective in trial design and conduct.

Principles:

- R3 expands the principles of ICH GCP to include new ones like **risk proportionality**, clear roles and responsibilities, and the use of investigational products.

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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

E6(R3)
Document History

Code	History	Date
E6	Approval by the Steering Committee under *Step 2* and release for public consultation.	27 April 1995
E6	Approval by the Steering Committee under *Step 4* and recommended for adoption to the three ICH regulatory bodies.	1 May 1996
E6(R1)	Approval by the Steering Committee of Post-*Step 4* editorial corrections.	10 June 1996
E6(R2)	Adoption by the Regulatory Members of the ICH Assembly under *Step 4*. Integrated Addendum to ICH E6(R1) document. Changes are integrated directly into the following sections of the parental Guideline: Introduction, 1.63, 1.64, 1.65, 2.10, 2.13, 4.2.5, 4.2.6, 4.9.0, 5.0, 5.0.1, 5.0.2, 5.0.3, 5.0.4, 5.0.5, 5.0.6, 5.0.7, 5.2.2, 5.5.3 (a), 5.5.3 (b), 5.5.3 (h), 5.18.3, 5.18.6 (e), 5.18.7, 5.20.1, 8.1	9 November 2016
E6(R3)	Endorsement by the Members of the ICH Assembly under *Step 2* and release for public consultation.	19 May 2023
E6(R3)	Endorsement by the Regulatory Members of the ICH Assembly under *Step 4*.	06 January 2025
E6(R3)	Error Correction: Typographical corrections to references in; Section 1.2.5 and 3.16.4	24 October 2025

ICH-E6(R3): Background to this Revision

E8 – integrating QbD into study design and conduct

↕

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.

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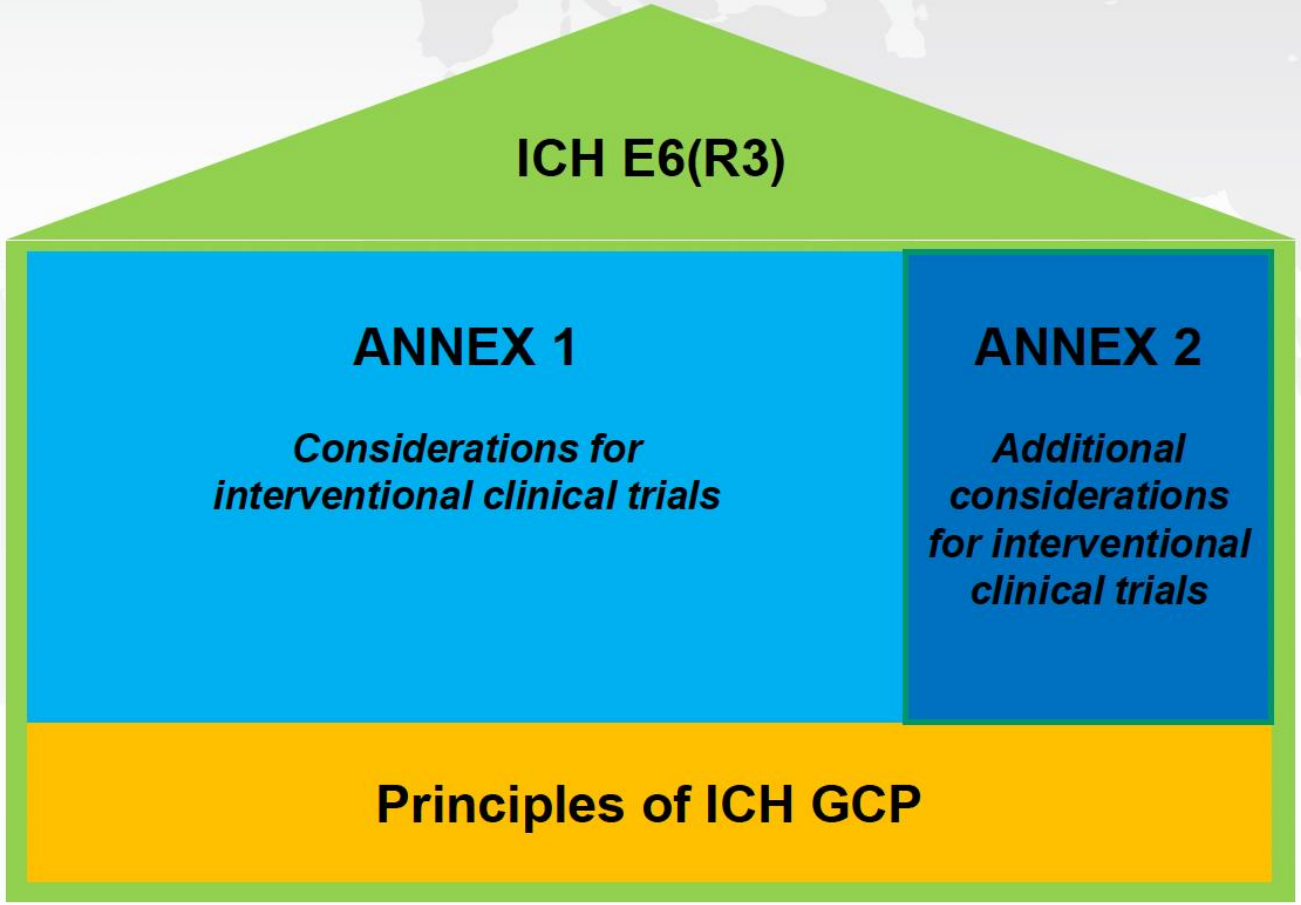
OVERVIEW OF ICH E6(R3)



Revised Structure

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
- **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*

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Summary of Changes

Substantial Changes

- **Principles of GCP**
- **Annex 1**
  - Investigator
  - Sponsor
  - Data Governance – Investigator and Sponsor **(New)**
- **Appendix C**
  - Essential Records for the Conduct of a Clinical Trial
- **Glossary**

Other Changes

- **Annex 1**
  - Institutional Review Board/Independent Ethics Committee (IRB/IEC)
- **Appendices A & B**
  - Investigator's Brochure
  - Clinical Trial Protocol and Protocol Amendments

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ICH E6(R3) Principle

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

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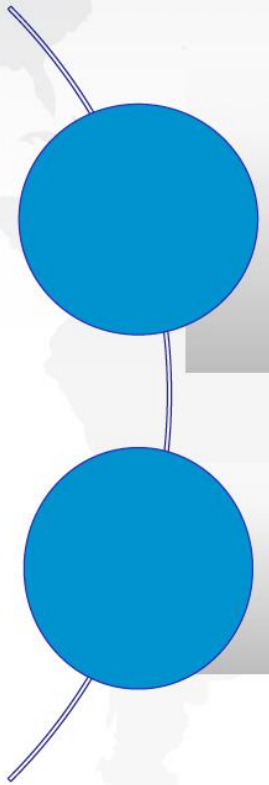
ICH E6(R3) Principles - New



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.

Roles and Responsibilities

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

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ICH E6(R3) Principle 7

Clinical trial processes, measures and approaches should be implemented in a way that is proportionate to the risks to participants and to the importance of the data collected and that avoids unnecessary burden on participants and investigators.

Trial processes should be proportionate to the risks inherent in the trial and the importance of the information collected.

- Risks to rights, safety and well-being of participants; and
- Risks to the reliability of trial results.

The focus should be on the risks associated with trial participation.

Risks to critical to quality factors should be managed proactively and adjusted when new or unanticipated issues arise once the trial has begun.

Trial processes should be operationally feasible and avoid unnecessary complexity, procedures and data collection.

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ICH E6(R3) Principle 10

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

The sponsor may transfer or the investigator may delegate their tasks, duties or functions, but they retain overall responsibility for their respective activities.

Agreements should clearly define the roles, activities and responsibilities for the clinical trial and be documented appropriately. Where activities have been transferred or delegated to service providers, the responsibility for the conduct of the trial resides with the sponsor or investigator, respectively.

The sponsor or investigator should maintain appropriate oversight of the aforementioned activities.

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ICH E6(R3) Principles - Revised

Ethical Principles

- Making sure not to unnecessarily exclude particular participant populations.

Informed Consent

- Taking into consideration relevant aspects of the trial.

IRB/IEC Review

- Periodic review according to applicable regulatory requirements.

Science

- Periodic review of scientific knowledge and approaches to determine whether modifications to the trial are needed.

Qualified Individuals

- Individuals with different expertise and training may be needed across all phases of a clinical trial.

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ICH E6(R3) Principles – Revised (2)

Quality

- The quality and amount of the information generated should support good decision making.

Protocol

- A well-designed trial protocol is fundamental to the protection of participants and for the generation of reliable results.
- The protocol and other documents (e.g., statistical analysis plan, data management plan) for trial execution should be clear, concise and operationally feasible.

Reliable Results

- Trial processes should support the key trial objectives.
- Clinical trials should incorporate efficient and well-controlled processes for managing records through appropriate management of data integrity.
- The transparency of clinical trials should involve registration on publicly accessible databases and the public posting of clinical trial results.

Investigational Product

- Investigational products should be carefully managed to align with treatment assignment and maintain blinding, where applicable.
- The investigational product provided to the trial participant should retain its quality.

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ICH E6(R3) Annex 1 *Glossary*

New Glossary Terms

- Assent
- Computerised Systems Validation
- Data Acquisition Tool
- Data Integrity
- Metadata
- Reference Safety Information
- Service Provider
- Signature

Revised Glossary Terms

- Adverse Events and Adverse Reaction-related definitions
- Essential Records
- IRB/IEC
- Investigator
- Investigator Site
- Source Records
- Sponsor
- Trial Participant
- And Others…

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Updating The Glossary (examples)

- Added terms that support advances in an evolving clinical trial ecosystem.
  - Data Acquisition Tool (DAT): A paper or electronic tool designed to collect data and associated metadata from a data originator in a clinical trial according to the protocol and to report the data to the sponsor.
  - Service provider: A person or organisation (commercial, academic or other) providing a service used during the conduct of a clinical trial to either the sponsor or the investigator to fulfil one or more of their trial-related activities.
- Provided more clarity on Adverse Events and Adverse Reactions.
- Updated some definitions (e.g., investigator site) to adapt for clinical trial operations in decentralised settings.
- Adapted definitions as needed to implement the media-neutral approach consistently.
- Revised subjects to participants.
- Removed confusing language and terms (e.g., non-therapeutic trials).

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In Summary

- Various approaches to clinical trial design and conduct have the potential to streamline drug development and increase the convenience of clinical trials for participants.
- The intent of the revised guideline is to facilitate innovations in clinical trial design and conduct, while at the same time provide guidance to help ensure participant safety and that the clinical trial produces reliable results.
- Training materials are planned to be developed (with use-cases) that clarify or provide supplementary explanation to the application of the GCP guideline.

ICH-GCP Revision 3 – Trainings

- **Aktuelle GCP-Trainings gemäß Revision 3** werden von den meisten Sponsoren bereits für laufende und startende klinische Studien eingefordert
- Schulungen liegen prinzipiell in der Verantwortung der Zentren
- **Hinweis:** für alle Zentren, die an der **ABCSG 42 / PALLAS** Studie teilnehmen, gibt es die Möglichkeit, das ICH-GCP Revision 3 Online-Modul zu absolvieren (www.pallasportal.com)

34. JAHRESTAGUNG DER ABCSG
7.- 8. NOV. 2025

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