

Good Clinical Practices – ICH E6 (R3) – Summary of Changes

This document provides additional details on the new elements and changes introduced in Revision 3 of the International Council for Harmonisation (ICH) Good Clinical Practices (GCP).

Click [here](#) to consult the full version of the Good Clinical Practices guideline.

1. GCP PRINCIPLES

The 13 principles of ICH E6 (R2) have been reorganized into **11 more detailed principles**.

P1 Rights, Safety, and Well-Being of Participants

Includes content encouraging the **representative selection of participants** and an added point allowing a **broader range of healthcare professionals** to be responsible for medical care and decisions.

P2 Informed Consent

Includes the requirement for **consent** to be “**clear and concise**”, and a reference to consent for **minors** and consent in **emergency situations**.

P3 Review by the Ethics Committee

Confirms the need for **periodic review** by the ethics committee.

P4 Scientific Soundness and Adaptability

Emphasizes that trials must “reflect current scientific knowledge,” implying the need for **periodic review of that knowledge** to determine whether modifications are required.

P5 Qualified Personnel

Expands the range of examples of qualified personnel needed for trials. needed for trials.

P6 Building Quality into Trials

Emphasizes the concepts of “**fit for purpose**” and “**critical to quality**,” as well as the need to implement **strategies to prevent, detect, and address serious non-compliance**.

P7 Proportionate Trial Conduct

Clarifies that trial-related risks are **those that exceed the risks of standard care**. Requires sponsors to avoid **imposing unnecessary burden** on participants and investigators.

P8 Clear and Feasible Protocols

Specifies that **scientific objectives** must be explicitly stated and that **study plans** must be operationally feasible.

P9 Reliable Results

Requires systems that are fit for purpose, including **data traceability**. Encourages **transparency in trials**, including timely **registration and reporting of results**.

P10 Roles and Responsibilities

Covers delegation, oversight, clarity of roles and responsibilities, and appropriate documentation.

P11 GMP Standards

Relates to the **manufacture of investigational products**. Includes information on quality preservation, labelling, and shipping.

2. SIGNIFICANT CHANGES INTRODUCED IN GCP REVISION 3

a. For Ethics

- Confirmation that reviews by **an ethics committee and a regulatory authority may be combined**. (1.1)
- Requirement to review consent documents for **trials involving minors**. (1.2.2.b)
- Confirmation that IRBs/IECs must receive an alternative document (e.g., a product information summary) **when an Investigator's Brochure is not required**. (1.2.2.c)
- Confirmation that **reasonable reimbursement to participants** (e.g., travel/lodging expenses) is not coercive. (1.2.8)
- Expanded definition of **a non-scientific member**, now defined as any individual not belonging to the medical sciences. (1.3.1.b)
- Requirement to ensure that certain participant populations are **not unnecessarily excluded**.

b. For Investigators

Responsibilities

- Clarification that investigators retain the final decision regarding the suitability of a **service provider** (sub-contractor) engaged by the sponsor to support the trial. (2.3.1)
- Confirmation that **training** (e.g., GCP) for individuals participating in the trial must be appropriate for the delegated activities that **go beyond their usual training and experience**. (2.3.2)
- **Removal** of the requirement to include **individuals performing activities as part of clinical practice** in the delegation log. (2.3.3)

Medical Care and Safety Reporting for Participants

- Confirmation that **healthcare professionals other than physicians and dentists** may assume overall responsibility for trial-related medical care and decisions. (2.7.1)
- Clarification that **adverse medical events occurring before administration of the investigational product (IP)** must be reported to the sponsor. (2.7.2.a)

Informed Consent

- Confirmation of the need to **establish participant identity**. (2.8.1.e)
- Confirmation that consent is an iterative process and must be updated when new information becomes available. (2.8.2)
- Confirmation that **electronic methods** may be used to obtain consent. (2.8.7)
- **Flexibility to adapt consent elements**, allowing specific items to be included in the participant information sheet when appropriate. Three consent elements (m, n, and v) have been added. (2.8.10)
- Clarification regarding consent from **minor** participants. (2.8.12)

End of Trial Participation

- Suggestion to include in the protocol instructions **to prevent loss of already collected data when participants withdraw**, in order to avoid bias. (2.9.1)
- Recommendation concerning **participant withdrawal**, requiring investigators to explore ways to address issues and encourage participants (without undue influence) **to reconsider withdrawal**. (2.9.2)
- Emphasis on trial transparency, encouraging investigators to **inform participants of trial results and the treatment received**, when applicable. (2.9.3)

Investigational Product (IP) Management and Unblinding

- Clarification that the level of oversight of **delegated IP management will depend on the characteristics of the IP**. (2.10.3)
- Support for additional **approaches to IP management** and accountability in authorized trials. (2.10.4)
- Confirmation that **IPs may be shipped to participants** and administered by investigator-site personnel, participants themselves, caregivers, or healthcare professionals. (2.10.8)

Randomization

- Emphasis that **unblinding systems must be in place at the start of the trial** to ensure readiness in case unblinding becomes necessary. (2.11)

Records

Additional requirements for the investigator/institution are included in section 4.

Increased emphasis on site **computer systems**, including:

- Requirement to inform the sponsor **when system access needs to be revoked**. (2.12.10.b)
- Requirement for **traceability of participant-facing devices** and appropriate training for their use. (2.12.10.d)

Additional requirements for investigators:

- **Define source records and data entry methods** prior to trial initiation. (2.12.2)
- Perform **timely reviews of all relevant data**, including data from external sources that impact eligibility, treatment, or participant safety. (2.12.3)
- **Identify a person responsible for retaining essential records** during the retention period and communicate their name to the sponsor. (2.12.13)

c. For Sponsors

Trial Design and Conduct

- Requirement to integrate **quality by design** by identifying **critical-to-quality factors** and implementing proactive risk management. (3.1.2, expanded in 3.10)
- Encouragement to **involve stakeholders** (patients, healthcare professionals) during trial planning. (3.1.3)
- Requirement to **minimize unnecessary burden** on participants and investigators. (3.1.4)

Sponsor Resources

- Confirmation that the sponsor has **sufficient resources** to conduct the trial appropriately. (3.2)

Research Protocol

- Mandatory inclusion of **critical-to-quality factors**. (Annex B.12.1)
- Encouragement to ensure **clarity** and **simplicity**.

Agreements

- Roles, responsibilities, and activities must be clearly defined and documented. When activities are transferred or delegated to service providers, the responsibility for trial conduct remains with the sponsor or the investigator, respectively.
- Confirmation that **service providers** must agree to report incidents that impact participant safety and data reliability. (3.6.6)
- Clarification that **service providers' quality management processes** must be fit for purpose but do not necessarily need to be designed to comply with GCP. (3.6.10)
- Confirmation that a trial may have **multiple sponsors** and that documented agreements outlining their respective responsibilities must be in place. (3.6.11)

Sponsor Oversight

- Requirement for trial-specific criteria to **classify deviations as significant** (3.9.3) and to ensure their oversight. (3.9.5)
- Confirmation that **issues arising during a trial must be reported and followed up in a timely manner**. (3.9.6)
- Consideration of establishing **endpoint adjudication committees**, which should generally be blinded. (3.9.8)

Monitoring

- General alignment with **quality principles** (proportionality, focus on critical-to-quality factors, and risk-adapted approaches). (3.11.4.3)
- Reference to the **independence of monitoring**. (3.11.4)
- Additional clarification that **centralized monitoring** may be used as the sole monitoring approach. (3.11.4.2.b)
- Requirement that **monitoring reports** include findings requiring escalation, as well as actions and resolutions. (3.11.4.6.c)

Safety Monitoring and Reporting

- Clarification that **the sponsor must aggregate relevant safety information**, when applicable, and include adverse medical events occurring before administration of the investigational product. (3.13.1)
- Emphasis on assessing **expectedness** and introduction of the term “reference safety information.” (3.13.2.c)
- Replacement of the 7/15-day deadline for notifying **SUSARs** to investigators/IRBs/IECs (ICH E2A) with the requirement to notify SUSARs within a timeline “reflecting the urgency of the required action.” (3.13.2.d)
- Confirmation that alternative approaches for **notifying safety information to regulatory authorities, ethics committees, and investigators are permitted**, including selective safety reporting in late-stage trials. (3.13.2.f)

Investigational Product

- Confirmation that **sponsors may facilitate IP management**, for example by organizing distribution. (2.10.1)
- Confirmation that **risk-based approaches for shipping and distributing** investigational products are acceptable. (3.15.3.a)
- Removal of the requirement for sponsors to **retain samples of authorized, unmodified investigational products**. (3.15.3.c.vi)

Data and Records

- A detailed section outlines expectations for **data processing and data management**, including:
 - A new list of 24 expectations for data processing, such as:

- Pre-specification of the data to be collected and the method of collection. (3.16.1.c)
 - Clear description of the data flow—e.g., through data flow diagrams. (3.16.1.c)
 - Validation of data acquisition tools before required use. (3.16.1.d)
 - Training of investigators on the use of computerized systems. (3.16.1.n)
 - Data validation by investigators at predetermined stages. (3.16.1.o)
 - Documentation of data-management steps prior to analysis. (3.16.1.p)
 - Processes for reporting incidents with significant impact (e.g., security breaches). (3.16.1.w)
- Clarification of expectations when **computerized systems** are deployed by sponsors and sites, including system **validation**. (3.16.1)
- Clarification of expectations for **statistical programming and data analysis**. (3.16.2)
- Confirmation that **the retention period for sponsor-specific essential documents** is now aligned with applicable regulatory requirements. (3.16.3.a)
- Requirement to report **any transfer of ownership of essential documents**. (3.16.3.c)
- Recognition of the **coordinating investigator as a signatory of the clinical study report**. (3.17.2.b)
- Expectations for **trial transparency**, including registration, communication of trial results to investigators, and—when blinded trials are involved—providing information on the treatment received by their participants. (3.17.2.c)

3. OVERVIEW OF OTHER SECTIONS

Section 4: Data Governance

- New section providing comprehensive guidance on data integrity, traceability, and security, as well as on computerized systems, addressing both systems deployed by investigators and those deployed by sponsors.

Annex A: Investigator’s Brochure

- New heading describing reference safety information, its purpose, and its content. (A.1.2)

Annex B: Protocol/Protocol Amendments

Overall structure remains unchanged but now includes:

- Reference to a broader range of trial designs, such as adaptive trials and umbrella trials. (B.4.2)
- Mandatory inclusion of critical-to-quality factors. (B.12.1)

Annex C: Essential Documents

- **Removal of a specific retention period** for essential documents held by the investigator/institution. (C.1.3)
- Requirement, where applicable, to include **contact details for authors, reviewers, and approvers** in essential documents. (C.2.1)
- Expanded content on **digital data requirements**, including clarification on the party responsible for retaining original documents and a new framework for determining whether trial documents are essential. (C.3)
- Inclusion of an example table.

4. GLOSSARY

New terms: Assent, Data Acquisition Tool (DAT), Data Integrity, Metadata, Monitoring Plan, Reference Safety Information (RSI), Service Provider (sub-contractor), Signature.

Deleted terms: Coordinating Committee, Documentation, Investigator/Institution, Notice (in relation to IRBs/IECs), Original Medical Record, Standard Operating Procedures, Well-being (of trial subjects).

Original Term in ICH E6 (R2)	Modified Term in ICH E6 (R3)
Contract	Agreement
Unexpected Adverse Drug Reaction	Suspected Unexpected Serious Adverse Reaction (SUSAR)
Essential Documents	Essential Records
Trial Site	Investigator Site
Source Data / Source Documents	Source Records
Subject / Trial Subject	Trial Participant
Subject Identification Code	Trial Participant Identification Code
Vulnerable Subjects	Vulnerable Participants