Principles of ICH E6 (R3) GCP Guideline

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Sumitra Sachidanandan
Regulatory Consultant
Innovation Office & Clinical Trials Branch
Health Products Regulation Group
Health Sciences Authority, Singapore

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BACKGROUND OF ICH E6 GCP GUIDELINE

What is GCP?

An international **ethical**, **scientific** and **quality** standard for the design, conduct, recording and reporting of clinical trials that involve human participants.

Why it matters?

Compliance with GCP provides assurance:

- Rights, safety and well-being of participants are protected
- Clinical trial results are reliable

Who is responsible?

Shared responsibility to collectively achieve compliance to the standard:

- *IRBs*
- *Investigators*
- *Sponsors (including institutions)*

EVOLUTION OF ICH E6 GCP GUIDELINE

Revision 1: 1996

- Described responsibilities and expectations of stakeholders in the conduct of clinical trials.

Revision 2: 2016

- Integrated addendum to encourage implementation of improved and more efficient approaches to GCP.

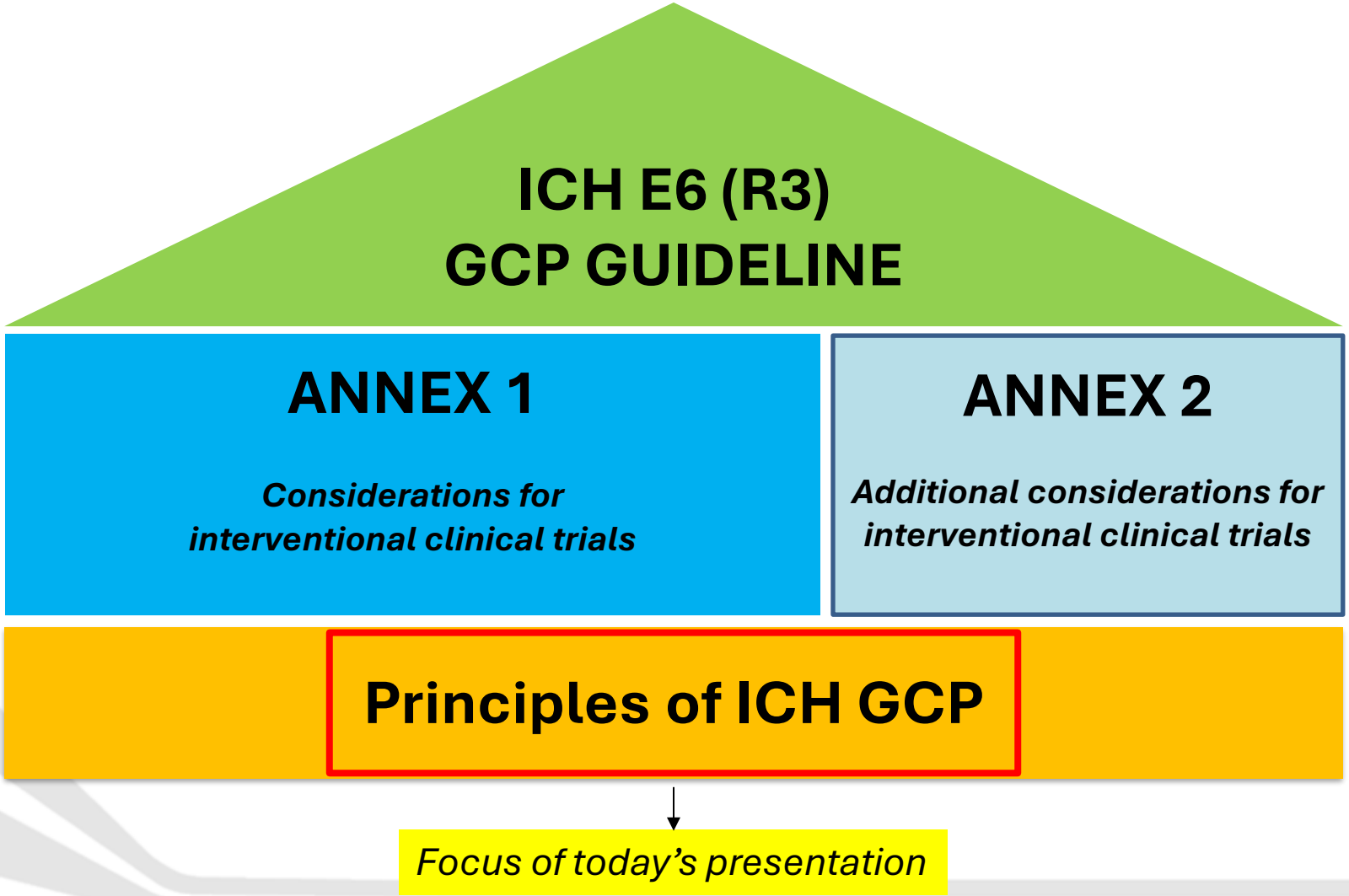
Revision 3: 2025

- Following the ICH Reflection Paper on GCP Renovation in Jan 2017,
  - There was a need to modernise ICH guidelines relating to clinical trial design, planning, management and conduct.
  - The scope of the proposed renovation included revising the ICH E6 and E8 guidelines.

NB:
- *ICH E6: Guideline for Good Clinical Practice*
- *ICH E8: Guideline on General Considerations for Clinical Studies*

ICH E6 (R3) GCP GUIDELINE

OVERVIEW



SCOPE

Applies to **interventional clinical trials** of **investigational products** that are intended to be **submitted to Regulatory Authorities**.

Principles of GCP may be applicable for **other interventional clinical trials of investigational products** that are **not intended** to **support marketing authorisation applications,** in accordance with local requirements.

Annexes provide a basis for interpretation and application of GCP principles.

FITNESS FOR PURPOSE

- **Quality of a clinical trial is defined as fitness for purpose.**
  - ✓ Meets the trial's objectives
  - ✓ Provides confidence in the trial's results
  - ✓ Supports good decision making
  - ✓ Whilst protecting the rights, safety and well-being of participants.

QUALITY BY DESIGN (QbD)

- **QbD involves proactively building quality into the design of the clinical trial in order to maximise the likelihood of the trial meeting its objectives.**

- A prospective and multidisciplinary approach that focuses on:
  - ✓ Gathering inputs from interested parties
    - Healthcare professionals
    - Patient Advocacy Groups
    - Patients
  - ✓ Identifying Critical to Quality (CTQ) factors
  - ✓ Identifying, prioritising and controlling the important risks to the CTQ factors

CRITICAL TO QUALITY (CTQ) FACTORS

- **Attributes of a clinical trial that are fundamental to:**
  - ✓ Protection of **rights, safety and well-being of participants;**
  - ✓ **Reliability and interpretability of the trial results;** and
  - ✓ **Decisions made based on those results**
- **Applies to data, processes and systems**
  - ➢ Focus on important critical data, processes and systems!
- **Identified for each clinical trial**

CRITICAL TO QUALITY (CTQ) FACTORS

- **Examples of CTQ factors for IITs:**

Data	Processes	Systems
• Primary endpoints • Secondary endpoints • Adverse Events • Data integrity • Privacy and Confidentiality	• Informed Consent • Eligibility assessment • Decentralised elements • IP management • Safety assessment and reporting • Data Collection and Handling	• Interactive Response Technology (IRT) • eCRF

PROPORTIONATE, RISK-BASED APPROACH

- **Proportionate**
  - ✓ **Tailoring level of oversight, resources, and controls to risks inherent in the trial and the importance of information collected**

- **Risk-based approach**
  - ✓ Proactively identifying, evaluating and managing risks that could affect the:
    - ✓ **Rights, safety and well-being of trial participants;**
    - ✓ **Reliability of trial results**

QUALITY MANAGEMENT (QM)

- **Design and implementation of efficient trial protocols, including tools and procedures for trial conduct,** in order to ensure the:
  - ✓ Rights, safety and well-being of participants
  - ✓ Reliability of trial results

RISK-BASED QUALITY MANAGEMENT (RBQM)

- The sponsor should adopt a **proportionate and risk-based approach to quality management,** which involves:
  - ✓ incorporating quality into the design of the clinical trial **(i.e., quality by design);** and
  - ✓ identifying those factors that are likely to have a meaningful impact on participants' rights, safety and well-being and the reliability of the results **(i.e., CTQ factors)**

PRINCIPLES OF ICH E6 (R3) GCP

ICH E6 (R3) PRINCIPLE	TOPIC	ICH E6 (R2) Section
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

ICH E6(R3) PRINCIPLE 1
Ethical Principles

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.

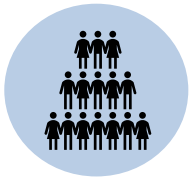
The rights, safety and well-being of participants are the **most important considerations** and **should prevail over interests of science and society.**

The safety of the participants should be **reviewed in a timely manner** as new safety information becomes available, which could **impact participant safety, their willingness to continue trial participation or trial conduct.**

Foreseeable **risks and inconveniences** should be **weighed against the anticipated benefits** for the individual participants and society.
A trial should be **initiated and continued** only if the **anticipated benefits justify the known and anticipated risks.**

ICH E6(R3) PRINCIPLE 1
Ethical Principles (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.



When designing a clinical trial,

- The **scientific goal and purpose** should be **carefully considered** so as not to unnecessarily exclude particular participant populations.
- The participant **selection process** should be **representative** of the population groups that the **investigational product is intended** to **benefit**, once authorised, to allow for generalising the results across the broader population.
- **Certain trials** (e.g., **early phase, proof of concept trials, bioequivalence studies) may not** require such a **heterogenous population.**

ICH E6(R3) PRINCIPLE 1
Ethical Principles (2)

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.

A qualified physician or, when appropriate, a **qualified dentist** (or other qualified healthcare professionals in accordance with local regulatory requirements) should have the **overall responsibility** for the **trial-related medical care given to, and medical decisions made on behalf** of participants; however, the **practical interactions and the delivery of medical care and decisions** can be carried out by **appropriately qualified healthcare professionals** in accordance with applicable regulatory requirements.

Information that **could identify participants** must be **kept confidential** in accordance with applicable privacy and data protection requirements.

ICH E6(R3) PRINCIPLE 2
Informed Consent (1)

Informed consent is an integral feature of the ethical conduct of a trial. Clinical trial participation should be voluntary and based on a consent process that ensures participants (or their legally acceptable representatives, where applicable) are well-informed.

Freely given informed consent should be **obtained and documented** from every participant **prior to clinical trial participation.**

<u>For potential participants unable to provide informed consent</u>,

- Their **Legally Acceptable Representative**, acting in the **participants' best interest,** should **provide consent** prior to clinical trial participation.
- These **potential participants should be informed** about the trial in a manner that facilitates their understanding.

<u>In the event that a minor is a participant</u>,

- **Assent should be collected from that minor**, as appropriate, and in accordance with local regulatory requirements.

ICH E6(R3) PRINCIPLE 2
Informed Consent (2)

Informed consent is an integral feature of the ethical conduct of a trial. Clinical trial participation should be voluntary and based on a consent process that ensures participants (or their legally acceptable representatives, where applicable) are well-informed.

- The **process and information provided** should enable potential participants to:
  - **evaluate the benefits, risks and burden of participating in the trial;** and
  - make an **informed decision** on whether or not to participate in the trial.

- The information provided should be **clear and concise to facilitate understanding** by the participants or their Legally Acceptable Representatives.

ICH E6(R3) PRINCIPLE 2
Informed Consent (3)

Informed consent is an integral feature of the ethical conduct of a trial. Clinical trial participation should be voluntary and based on a consent process that ensures participants (or their legally acceptable representatives, where applicable) are well-informed.

- The **informed consent process** should take into consideration **relevant aspects of the trial**:
  - Characteristics of participants;
  - Trial design;
  - Anticipated benefits and risks of medical interventions;
  - Setting and context in which the trial will be conducted; and
  - Use of technology to inform and obtain informed consent.

- In **emergency situations**,
  - Consent should be obtained from the **participant or their Legally Acceptable Representative** as soon as possible; and
  - The processes **approved by the IRB / IEC.**

ICH E6(R3) PRINCIPLE 3
IRB / IEC Review

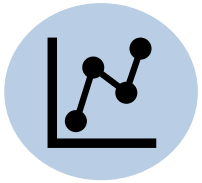
Clinical trials should be subject to an independent review by an IRB/IEC.

A trial should be conducted in compliance with the protocol approved by IRB/IEC.

Periodic review of the trial by the IRB/IEC should also be conducted in accordance with applicable regulatory requirements.

ICH E6(R3) PRINCIPLE 4
Science

Clinical trials should be scientifically sound for their intended purpose and based on adequate and current scientific knowledge and approaches.



The **available nonclinical and clinical information on an investigational product(s)** should be adequate to support the proposed clinical trial.

Clinical trials should reflect the state of knowledge and experience with the Investigational Product (IP).
Including, if applicable, the condition to be treated / diagnosed / prevented, the current understanding of the underlying biological mechanism, and the population for which the IP is intended.

Periodic review of current scientific knowledge and approaches to **determine whether modifications** to the trial are needed, since new or unanticipated information may arise once the trial has begun.

ICH E6(R3) PRINCIPLE 5
Qualified Individuals

Clinical trials should be designed and conducted by qualified individuals.

- Individuals with **different expertise and training** may be needed **across all phases of a clinical trial,**
  - E.g., physicians, nurses, pharmacists, scientists, ethicists, technology experts, trial coordinators, monitors, auditors and biostatisticians.

- Individuals involved in a trial should be **qualified by education, training and experience to perform their respective task(s)**.

ICH E6(R3) PRINCIPLE 6
Quality

Quality should be built into the scientific and operational design and conduct of clinical trials.

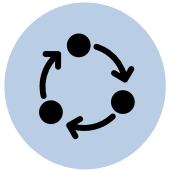
- **Quality of a clinical trial** is considered as **fitness for purpose**.

- **Factors critical to the quality** of the trial should be **identified prospectively.**
  - These factors are **attributes of a trial** that are **fundamental** to the **protection of participants,** the **reliability and interpretability of the trial results** and the **decisions made based on those trial results**.
  - It is important to **identify critical to quality factors prospectively**.

- **Strategies** should be implemented to **avoid, detect, address and prevent recurrence of serious noncompliance** with GCP, the trial protocol and applicable regulatory requirements.

ICH E6(R3) PRINCIPLE 7 [NEW]
Risk Proportionality (1)

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.**

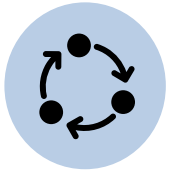
The focus should be on the risks associated with trial participation.

- For clinical trials involving patients, the focus should be on **risks that go beyond** those associated with **usual medical care.**
- The **risks relating to investigational products that have a marketing authorisation** when used in the clinical trial context **may differ from the usual care of patients** and should be taken into consideration.

ICH E6(R3) PRINCIPLE 7 [NEW]
Risk Proportionality (2)

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.

- **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;**
  - **avoid unnecessary complexity, procedures and data collection;** and
  - **support key trial objectives**.

- **Sponsor** should not place **unnecessary burden** on **participants and investigators.**

ICH E6(R3) PRINCIPLE 8
Protocol

Clinical trials should be described in a clear, concise, scientifically sound and operationally feasible protocol.

A **well-designed trial protocol** is fundamental to the **protection of participants** and for the **generation of reliable results**.

The **scientific objectives of any trial** should **be clear** and **explicitly stated in the protocol**.

The clinical trial protocol and the **plans or documents for the protocol execution** should be **clear, concise and operationally feasible.**

ICH E6(R3) PRINCIPLE 9
Reliable Results (1)

Clinical trials should generate reliable results.

- **Quality and amount of information generated**
  - **Fit for purpose;** and
  - **Sufficient to provide confidence** in the **trial's results** and **support good decision making.**

- **Systems and processes that aid in data capture, management and analyses**
  - **Fit for purpose;**
  - **Capture the data required by the protocol**; and
  - Implemented in a way that is **proportionate to the risks to participants** and the **importance of acquired data.**

- **Computerised systems**
  - **Fit for purpose** (e.g., through risk-based validation, if appropriate);
  - **Factors critical to their quality** should be addressed in their **design or adaptation for clinical trial purposes** to ensure the **integrity of relevant trial data.**

ICH E6(R3) PRINCIPLE 9 Reliable Results (2)

Clinical trials should generate reliable results.

- **Efficient and robust processes for managing records (including data)**
  - Maintain **record integrity and traceability**, and **protect personal information.**
    - Thereby allowing the **accurate reporting, interpretation** and **verification of trial information**.

- **Essential records**
  - **Retained securely** by sponsors and investigators for the **required period** in accordance with applicable regulatory requirements;
  - **Available upon request** by regulatory authorities, monitors, auditors and IRBs/IECs to enable **appropriate evaluation of the trial conduct** in order to ensure **the reliability of trial results**.

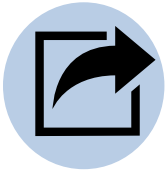
ICH E6(R3) PRINCIPLE 9 Reliable Results (3)

Clinical trials should generate reliable results.

- **Transparency of clinical trials**
  - Includes **timely registration on publicly accessible and recognised databases**, and **public posting of clinical trial results**.
  - **Communicating trial results to participants** should be considered.
    - Such communication should be **objective and non-promotional**.

ICH E6(R3) PRINCIPLE 10 [NEW] Roles and Responsibilities

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.

ICH E6(R3) PRINCIPLE 11
Investigational Products (IP)

IPs used in a clinical trial should be manufactured in accordance with applicable Good Manufacturing Practice (GMP) standards and be managed in accordance with the product specifications and the trial protocol.

Investigational products should be **manufactured in accordance with applicable GMP standards**.

IP should be **used** in accordance with the **protocol and relevant trial documents.**

IP labelling should **follow applicable regulatory requirements.**

Measures should be in place to ensure that the **IP provided to participants retains its quality**.

IP manufacturing, handling and labelling should be undertaken in a manner that **aligns with treatment assignment and maintains blinding,** where applicable.

Appropriate processes should be implemented for the **handling, shipping, storage, dispensing, returning and destroying or alternatively disposing of the IP.**

SUMMARY

- **ICH E6 (R3) GCP guideline:**
  - Applies to interventional clinical trials of investigational products that are intended to be submitted to Regulatory Authorities.
  - Principles of GCP may be applicable for other interventional clinical trials of investigational products that are not intended to support marketing authorisation applications, in accordance with local requirements.

- **Important to apply the key concepts throughout the ICH E6 (R3) GCP guideline:**
  - Fitness for Purpose
  - Quality by Design (QbD)
  - Proportionate, risk-based approach
  - Risk-based Quality Management (RBQM)

REFERENCES

- ICH E6 (R3) – Guideline for Good Clinical Practice, 6 Jan 2025
- ICH E8 (R1) Guideline on General Considerations for Clinical Studies, 6 Oct 2021
- ICH training library

Thank You!

We welcome your queries!

HSA_CT@hsa.gov.sg