ICH E6 (R3)
Good Clinical Practice (GCP) Guideline

Annex 2
Additional Considerations for Interventional Clinical Trials
Overview of Step 2 draft

Innovation Office & Clinical Trials Branch
Health Products Regulation Group
Health Sciences Authority

Outline

- Background
- ICH E6 (R3) GCP guideline
  - Overview
  - Key timelines
  - Key considerations
- Draft Annex 2 of ICH E6 (R3) GCP guideline
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Background

- 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 Trials*

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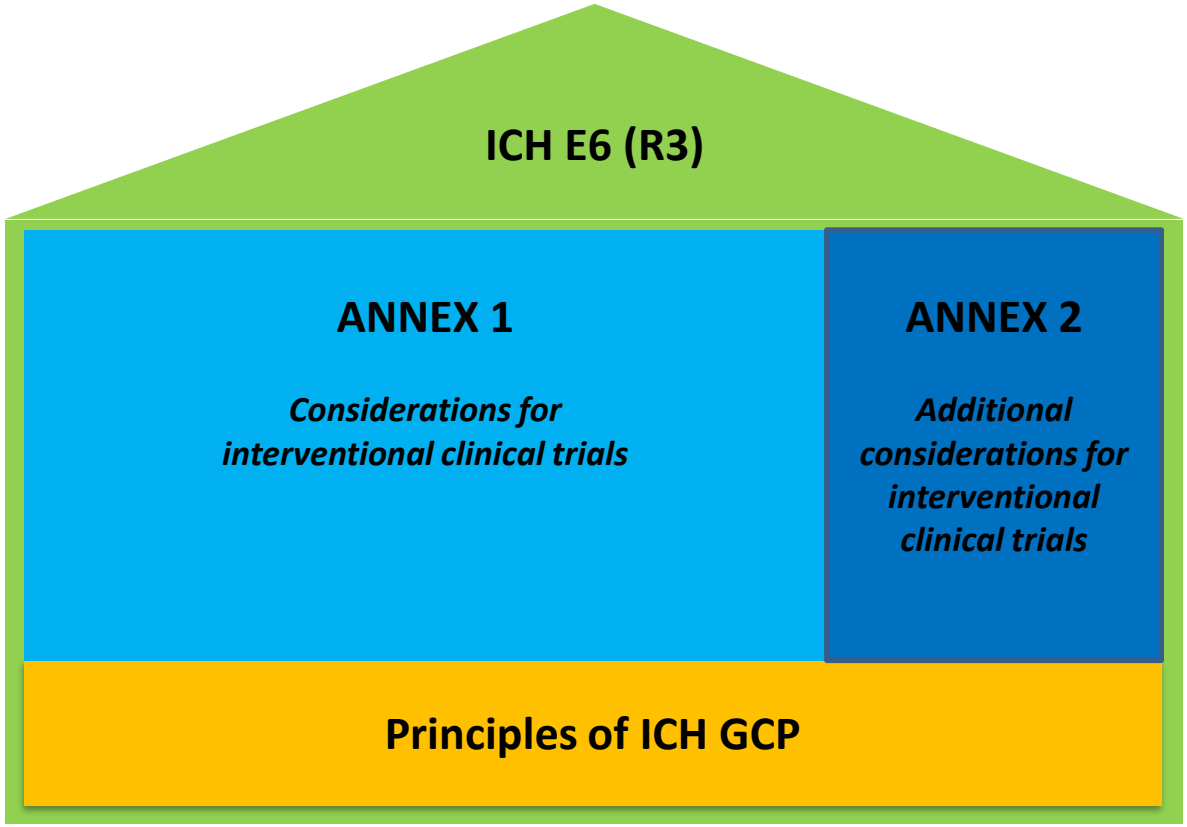
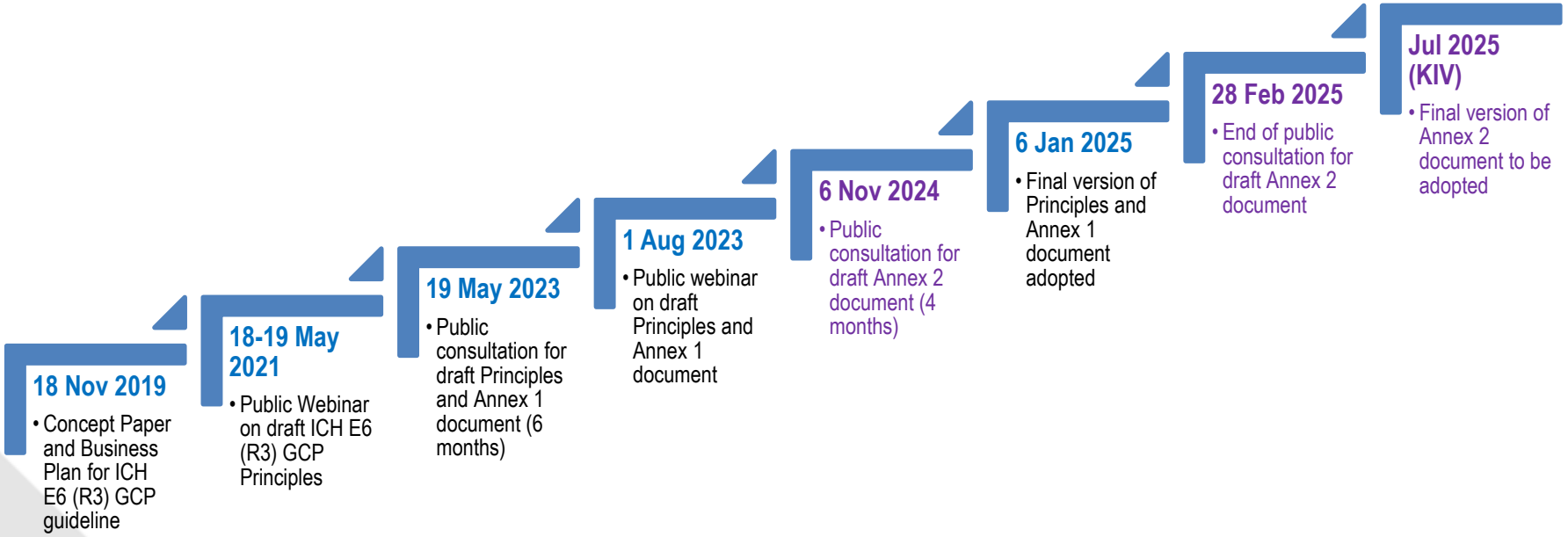
ICH E6 (R3) GCP guideline

Overview



ICH E6 (R3) GCP guideline

Key Timelines



ICH E6 (R3) GCP Guideline

Key Considerations

- **Fitness for purpose**
  - Quality is defined as fitness for purpose.
    - Fitness for purpose: Ability to meet the intended purpose.
  - The purpose of a clinical trial is to generate reliable information to answer the research question and support decision making while protecting trial participants.

- **Quality by Design (QbD)**
  - Ensures that the quality of a clinical trial is driven proactively by designing quality into the study protocol and processes.
  - Focuses on Critical to Quality factors (CtQ) of the clinical trial in order to maximise the likelihood of the trial meeting its objectives.
    - CtQ: 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.

- **Risk Proportionality**
  - Focuses on the risks inherent in the clinical trial and the importance of the information collected.
    - Risks include risks to:
      - Rights, safety and well-being of trial participants; and
      - Risks to the reliability of the trial results

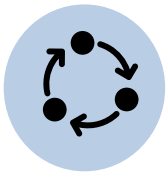
ICH E6(R3) Principle 6

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**.
- **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]

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.

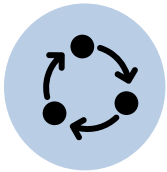


Trial processes should be **proportionate to the risks inherent in the trial** and the **importance of the information collected**.

- 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**.

ICH E6(R3) Principle 8

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

Clinical trials should generate reliable results.

- The **quality and amount of the information** generated in a clinical trial should **be 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** should be **fit for purpose, capture the data required by the protocol**, and **proportionate to the risks**.
- **Computerised systems** used in clinical trials should be **fit for purpose** and **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.
- Clinical trials should incorporate **efficient and robust processes for managing records (including data)** to help ensure that **record integrity and traceability** are **maintained** and that **personal information is protected**, thereby allowing the accurate reporting, interpretation and verification of the relevant clinical trial-related information.
- **Essential records** should be **retained securely** by sponsors and investigators, and should be **available upon request** to enable appropriate **evaluation of the trial conduct** in order to ensure the reliability of trial results.
- The **transparency of clinical trials** includes **timely registration on publicly accessible and recognised databases** and the **public posting of clinical trial results**. Communicating trial results to participants should be considered.

ICH E6 (R3) GCP Guideline

Key Considerations

Integrating the concepts of **quality by design**, **risk proportionality** and a **well-designed protocol** will ensure the **reliability of trial results**.

GCP Principles 6, 7 and 8

GCP Principle 9

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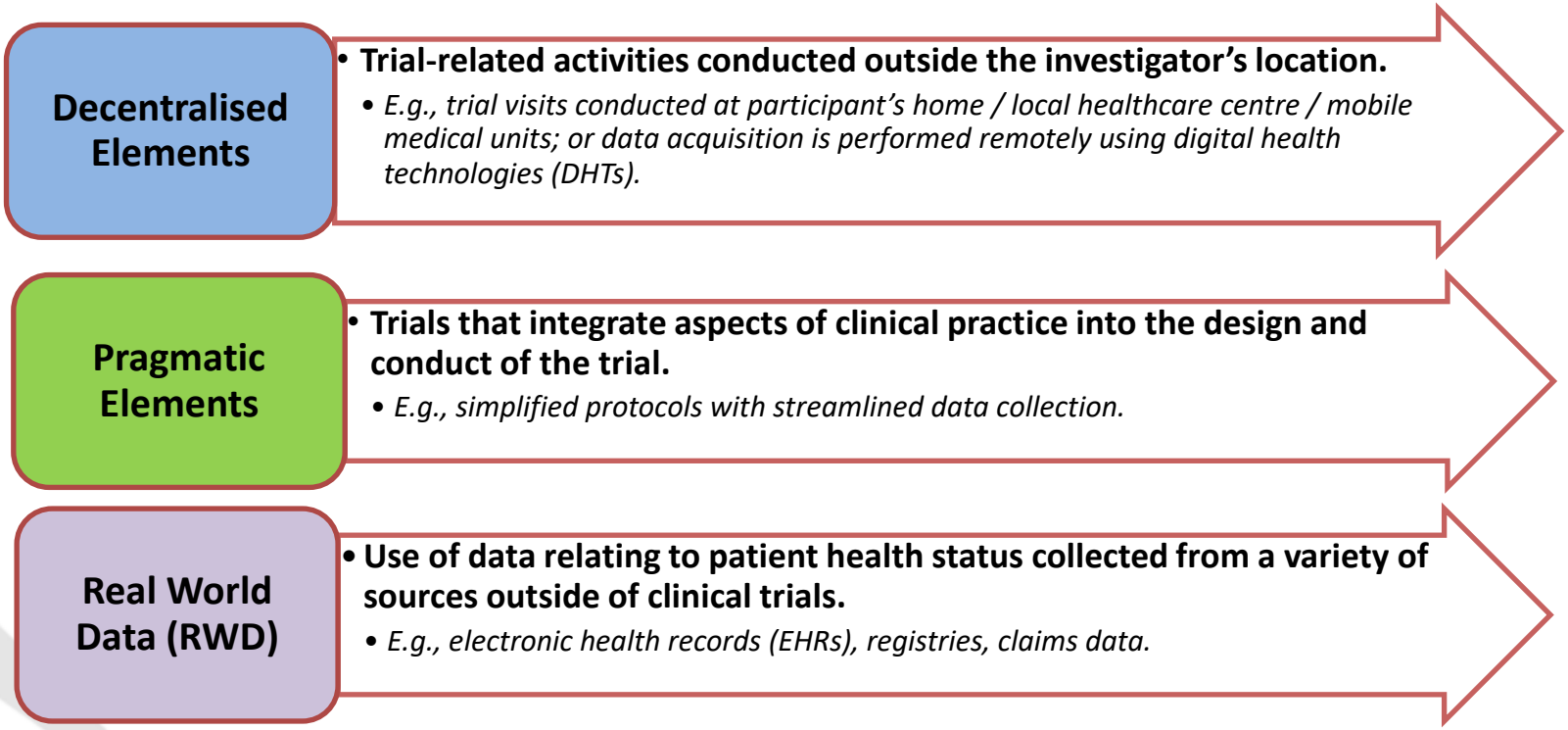
Draft Annex 2 of ICH E6 (R3) GCP guideline

Overview

- Provides additional GCP considerations, focusing on examples of trials that incorporate:



Draft Annex 2 of ICH E6 (R3) GCP guideline

Overview

- Not intended to be comprehensive of all clinical trial design elements or data sources.
- Should be read in conjunction with the Principles and Annex 1 document of ICH E6 (R3) GCP guideline.
- Has its foundations in the key concepts of the following:
  - Fitness for purpose
  - Quality by Design (QbD)
  - Risk proportionality
- Does not endorse any specific design elements or data sources

Draft Annex 2 of ICH E6 (R3) GCP guideline

Structure

Introduction

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

2. Investigator

- Communication with IRB/IEC
- Informed Consent Considerations
- Investigational Product Management
- Investigator Oversight
- Safety Assessment and Reporting

3. Sponsor

- Engagement and Communication
- Protocol and Trial Design
- Communication with IRB / IEC
- Consent or Permission Considerations for RWD
- Data Considerations
- Investigational Product Management
- Privacy and Confidentiality Considerations
- Sponsor Oversight
- Safety Assessment and Reporting

In line with Annex 1 format

Draft Annex 2 of ICH E6 (R3) GCP guideline

Institutional Review Board / Independent Ethics Committee

- Particular attention should be given to:
  - Privacy and confidentiality of trial participants
  - Security of the trial data

Draft Annex 2 of ICH E6 (R3) GCP Guideline

Investigator

- **Communication with IRB/IEC**
  - Provide information needed for the evaluation of the appropriateness of various operational approaches and data sources being used.

- **Informed Consent Considerations**
  - Informed consent materials and process should be tailored to reflect the design elements of the clinical trial (i.e., decentralised / pragmatic elements).
  - Remote consent may be considered, where appropriate.
    - Investigator should assure themselves of the identity of the participant / legal representative.
  - Characteristics of the trial population (e.g., lack of familiarity with electronic systems) and the appropriateness of the method / tools to obtain informed consent should be considered.
    - Options for paper-based approach or in-person consent process may be offered.
  - Informed consent materials should describe data to be collected, how the data may be used and who will have access to the trial participant's personal information.

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Investigator

- **Investigational Product (IP) Management**
  - IP may be dispensed or supplied to participant or appropriate designee for administration at the participant's location by appropriate parties.

  - When shipping IP to a participant, consider the process for:
    - Protecting the privacy of the participant;
    - Maintaining the confidentiality of the participant and their disease status;
    - IP is received by the intended recipient;
    - IP receipt, storage, handling, administration, return, destruction or alternative disposition and accountability;
    - Blinding is protected, where applicable; and/or
    - Availability of participant support tools (e.g., online tutorials, brochures, visual aids and technical support)

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Investigator

- **Investigational Product (IP) Management**
  - Investigator oversight:
    - IP receipt, use and return;
    - IP commencement, continuation, dosing and dose adjustments
  - The level of investigator oversight will depend on a number of factors. For e.g.:
    - Characteristics of the IP;
    - Route and complexity of administration; and/or
    - Level of existing knowledge about the IP's safety profile and marketing status
  - Certain documentation and processes already used in the institution/healthcare centre may be sufficient for IP management (i.e., dispensing and recording storage conditions).
  - Approaches to IP management should be arranged and conducted in accordance with applicable regulatory requirements.

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Investigator

- **Investigator Oversight**
  - Healthcare professionals may be involved in performing trial-related activities that are part of clinical practice.
    - Proportionate approach may be adopted for delegation and training.
      - ❑ Knowledge of protocol / IB / other trial-related document is <u>required</u> to perform a trial-related activity:
        - ✓ To be performed by delegated persons / parties who have been appropriately trained.
      - ❑ Knowledge of protocol / IB / other trial-related document is <u>not required</u> to perform a trial-related activity:
        - ✓ Appropriate arrangements (including plans to make the relevant information and records available to the investigator) and appropriate investigator oversight should be in place.
    - Level investigator oversight:
      - Depend on the nature of the activities;
      - Proportionate to the risks to participant safety and data reliability and the importance of the data being collected; and
      - Ensure that resulting records meet the protocol requirements, thereby ensuring reliable trial results, trial participant safety and appropriate decision-making.

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Investigator

- **Safety Assessment and Reporting**
  - Safety information may come from various sources. For e.g.:
    - Home visits
    - Remote trial visits
    - Use of DHTs
  - Investigator should review and assess information on the health status of participants across the sources of safety-related information.

Draft Annex 2 of ICH E6 (R3) GCP Guideline

Sponsor

- **Engagement and Communication**
  - Stakeholders
    - Patients
    - Patient advocacy groups and their communities
    - Healthcare professionals
    - Investigators
    - Regulatory Authorities

  - Ensures successful implementation of various operational approaches and data sources. For e.g.,
    - Protocol design
    - Training and support
    - Infrastructure
    - Incorporating into routine workflow
    - Challenges and strategies for resolution

Draft Annex 2 of ICH E6 (R3) GCP Guideline

Sponsor

- **Protocol and Trial Design**
  - Use of specific design approaches and data sources, including rationale, fitness for purpose and feasibility.
    - May be supplemented in a protocol-related document.
  - Impact of data variability from the use of different data sources / settings (e.g., sources with different timing of data collection) should be considered in the trial design.
  - Need for training and technical support for investigator, investigator site staff and participants.
  - Flow of safety information from the data sources (e.g., DHTs, in-person / remote visits) and how this information will be provided to the investigator to help with decision making (e.g., eligibility, treatment, continuing trial participation, care for the safety of the trial participant).
  - Modalities for informed consent process (e.g., in-person / remote consent).

Draft Annex 2 of ICH E6 (R3) GCP Guideline

Sponsor

- **Communication with IRB/IEC**
  - Provide information needed for the evaluation of the appropriateness of various operational approaches and data sources being used.

- **Consent or Permission Considerations for RWD**
  - In situations where RWD is used, appropriate consent or permission for the use of data should be obtained.

Draft Annex 2 of ICH E6 (R3) GCP Guideline

Sponsor

- **Data Considerations**
  - **RWD Considerations**
    - Apply special considerations to RWD sources depending on the data collection and acquisition process and if the data is primary / secondary, since the sponsor may have different level of control over what and how the data elements are collected.
      - Potential variability of data formats;
      - Lack of standardised timing of data collection and procedures;
      - Missing data or the occurrence of intercurrent events between clinical visits that may be difficult to capture or ascertain when using RWD;
      - The overall quality of data collected in clinical practice or registries;
      - De-identification methodologies used to protect the privacy and confidentiality of personal information of participants; and
      - Validation status of tools used for the acquisition of RWD

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Sponsor

- **Data Considerations**
  - **RWD Considerations (cont'd)**
    - Fitness for purpose of RWD
      - Reliability – includes accuracy, completeness and traceability
      - Relevance – includes availability of key data elements to answer the specific trial question with the specific method
    - Agreements with entities that own / control the RWD to allow access to source records for regulatory inspections
    - When data are linked, accurate matching to the individual should be assured and the adequate measures to sufficiently protect both data privacy and reliability of trial results.

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Sponsor

- **Data Considerations (cont'd)**
  - **Remote Data Collection Considerations**
    - Special attention to be paid to data security vulnerabilities, including cybersecurity and data privacy.
    - Some of the RWD considerations may also apply to remote clinical trial data collection (e.g., DHTs including wearables).

Draft Annex 2 of ICH E6 (R3) GCP Guideline

Sponsor

- **Investigational Product (IP) Management**
  - Various approaches to IP management should be assessed during protocol development, considering:
    - IP stability, including any specialised storage conditions;
    - IP preparation;
    - Route of Administration;
    - Trial population;
    - Knowledge about the safety profile of the IP;
    - Need for in-person clinical observation post-IP administration;
    - Measures needed to protect blinding; and/or
    - Need for emergency plans related to IP administration (e.g., rescue medication)
  - Arrange to send IP to the participants (Direct to Patient supply)
  - Deploy systems (e.g., interactive response technology DHTs) or assist investigators to establish the processes (e.g., home visits) to ensure that the allocated IP was delivered and administered appropriately to the participant.

Draft Annex 2 of ICH E6 (R3) GCP Guideline

Sponsor

- **Privacy and Confidentiality Considerations**
  - Security safeguards, including cybersecurity, are in place to protect the privacy and confidentiality of personal information of participants.
  - Appropriate consent should be obtained from the participants to provide their personal information to service providers to fulfil their activities.
  - Access should be limited to authorised personnel.
  - Personal information should be protected from inadvertent disclosure.
  - Address the risk of potential disclosure of personal information from a data breach when data from DHTs and/or RWD are used.

- **Sponsor Oversight**
  - Processes in place to provide appropriate level of oversight such that the participants' rights, safety and well-being are protected and the reliability of the results is ensured.
  - Quality control and quality assurance measures specifically customised to the clinical trial and its critical to quality factors and identified risks.
  - Appropriate oversight of service providers, including maintenance of their essential records.

Draft Annex 2 of ICH E6 (R3) GCP Guideline

Sponsor

- **Safety Assessment and Reporting**
  - Safety information from clinical trials with decentralised / pragmatic elements
    - Appropriately captured;
    - Made accessible to the investigator in a timely manner according to the protocol; and
    - Provided in an actionable manner to allow for medical decision making.
  - Approach to safety management, including any mitigating actions to safeguard participant safety, and to reporting, should be described in the protocol or protocol-related documents.

Draft Annex 2 of ICH E6 (R3) GCP Guideline

Public Consultation

- Please scan the QR code or go to the following URL to submit your feedback **by 28 Feb 2025**: https://www.hsa.gov.sg/therapeutic-products/international-collaboration/ich

Your feedback is important and contributes towards the finalisation of the ICH guidelines.

Please provide your comments using the template provided by ICH and email to HPRG_feedback@hsa.gov.sg with the subject title: **ICH <Guideline Code> Feedback**.

Draft ICH Guidelines	Status for consultation	Deadline for comments
Guideline Code: E6(R3) Annex 2 Guideline for Good Clinical Practice - Additional Considerations for Interventional Clinical Trials	Open	28 February 2025

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Summary

- The intent of Annex 2 is to provide additional GCP considerations in the context of clinical trials with various design elements and data sources to ensure they are fit for purpose.
- The appropriate and proportionate application of GCP will support these approaches whilst safeguarding participants' rights, safety and well-being, and helping to ensure the reliability of trial results.
- We welcome your comments on this draft guideline to highlight any considerations we have missed or clarify where the text is ambiguous.
  - **Public consultation period: 25 Nov 2024 to 28 Feb 2025**

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References

- ICH Reflection on GCP Renovation: Modernization of ICH E8 and Subsequent Renovation of ICH E6, 12 Jan 2017
- ICH E8 guideline on General Considerations for Clinical Trials
- ICH E6 (R3) Good Clinical Practice (GCP) guideline – Principles and Annex 1 document, final version, 6 Jan 2025
- ICH E6 (R3) Good Clinical Practice (GCP) guideline – Annex 2 document, Step 2 draft, 6 Nov 2024
- ICH E6 (R3) Annex 2 Step 2 presentation, 22 Nov 2024
- ICH E6 (R3) Annex 2 – Public Consultation for Singapore