Good Clinical Practice – ICH E6(R3)
Annex 2

Step 2

Step 2 document – to be released for comments

22 November 2024

Good Clinical Practice – ICH E6(R3) Annex 2

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Background: Good Clinical Practice – ICH E6(R3) Annex 2

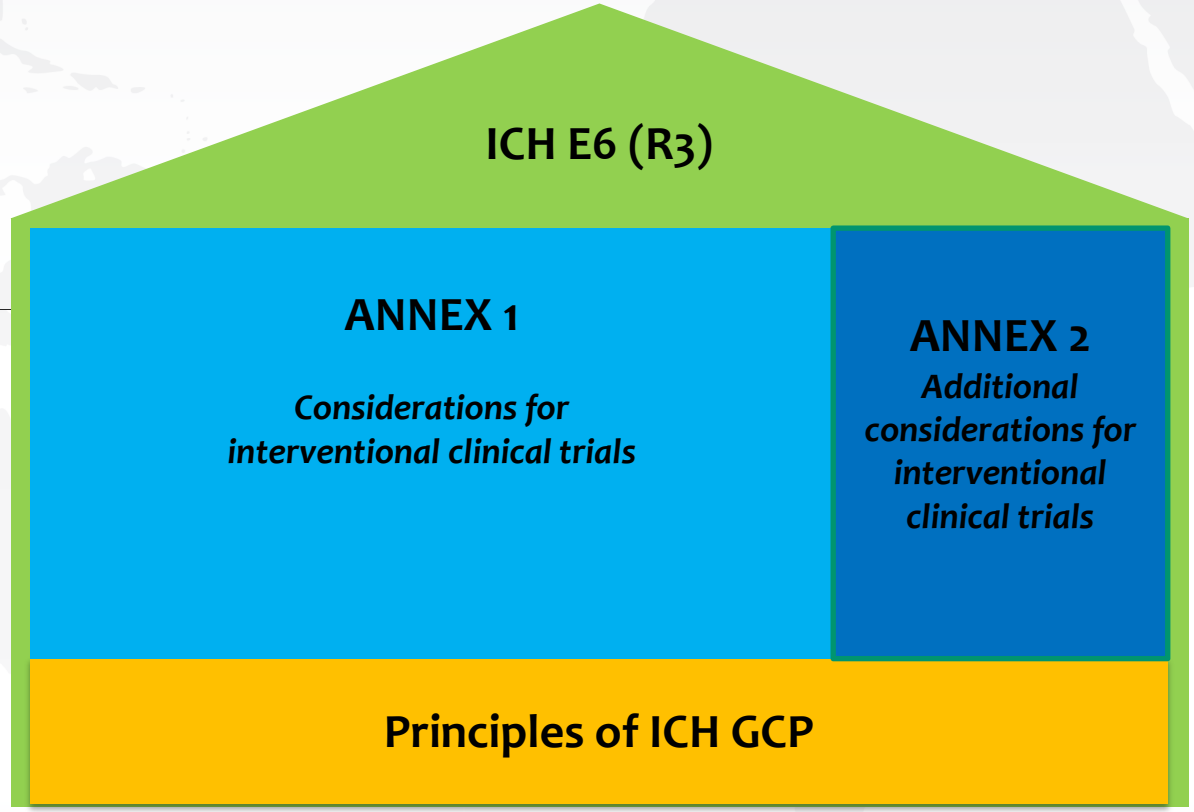
- Has been signed off as a *Step* 2 document (06 November 2024) to be issued by the ICH Regulatory Members for public consultation
- Was developed based on a Concept Paper (approved 28 April 2023) and a Business Plan (approved 18 November 2019)
- Is anticipated to be finalised as a *Step 3 Sign-off*/*Step 4* document to be implemented in the local regional regulatory system: Mid-2025

Background: Good Clinical Practice – ICH E6(R3) Annex 2

- Annex 2 is not intended to be comprehensive of all clinical trial design elements or data sources
- Should be read in conjunction with the ICH E6(R3) Principles and Annex 1 document
- Addresses the GCP considerations that arise from the increased use of a wider range of design elements and data sources. It has its foundations in the key concepts of quality-by-design, fitness for purpose and risk proportionality
- Annex 2 does not endorse specific design elements or data sources

Draft version of ICH E6(R3) Principles and Annex 1 was published on 19 May 2023, and Step 4 version expected to be available November/December 2024

OVERVIEW OF ICH E6(R3)



ICH E6(R3) Examples of Principles Supporting Proportionality

- Quality of a clinical trial is considered fitness for purpose
  - The quality and amount of the information generated in a clinical trial should be sufficient to support good decision-making
- Achieving fit-for-purpose clinical trial quality is rooted in the concept of quality by design and risk proportionality

Principle 8

- Clinical trials should be described in a clear, concise and operationally feasible protocol

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

Principle 6

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

ICH E6(R3) – Annex 2 Background

- Annex 2 provides considerations that focus on examples of trials that incorporate:

Decentralised Elements	**Trial-related activities conducted outside the investigator's location** • *E.g., trial visits conducted at participant's home / local healthcare centre / mobile medical units; or data acquisition performed remotely using digital health technologies (DHTs)*
Pragmatic Elements	**Those that integrate aspects of clinical practice into the design and conduct of the trial** • *E.g., simplified protocols with streamlined data collection*
Real World Data (RWD)	**Include the use of data relating to patient health status collected from a variety of sources outside of clinical trials** • *E.g., electronic health records (EHRs), registries, claims data*

ICH E6(R3) – Annex 2 Structure

- **Structure**

Introduction

1. 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 keeping with the Annex 1 Format

- **Emphasis on practical considerations for the use of various design elements and data sources.**

ICH E6(R3) – Annex 2
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 (e.g., decentralised or pragmatic elements).
  - Characteristics of the trial population and the appropriateness of the method and tools used to obtain informed consent should be considered.
  - Informed consent may be obtained remotely, where appropriate.
  - 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.

ICH E6(R3) – Annex 2 INVESTIGATOR (2)

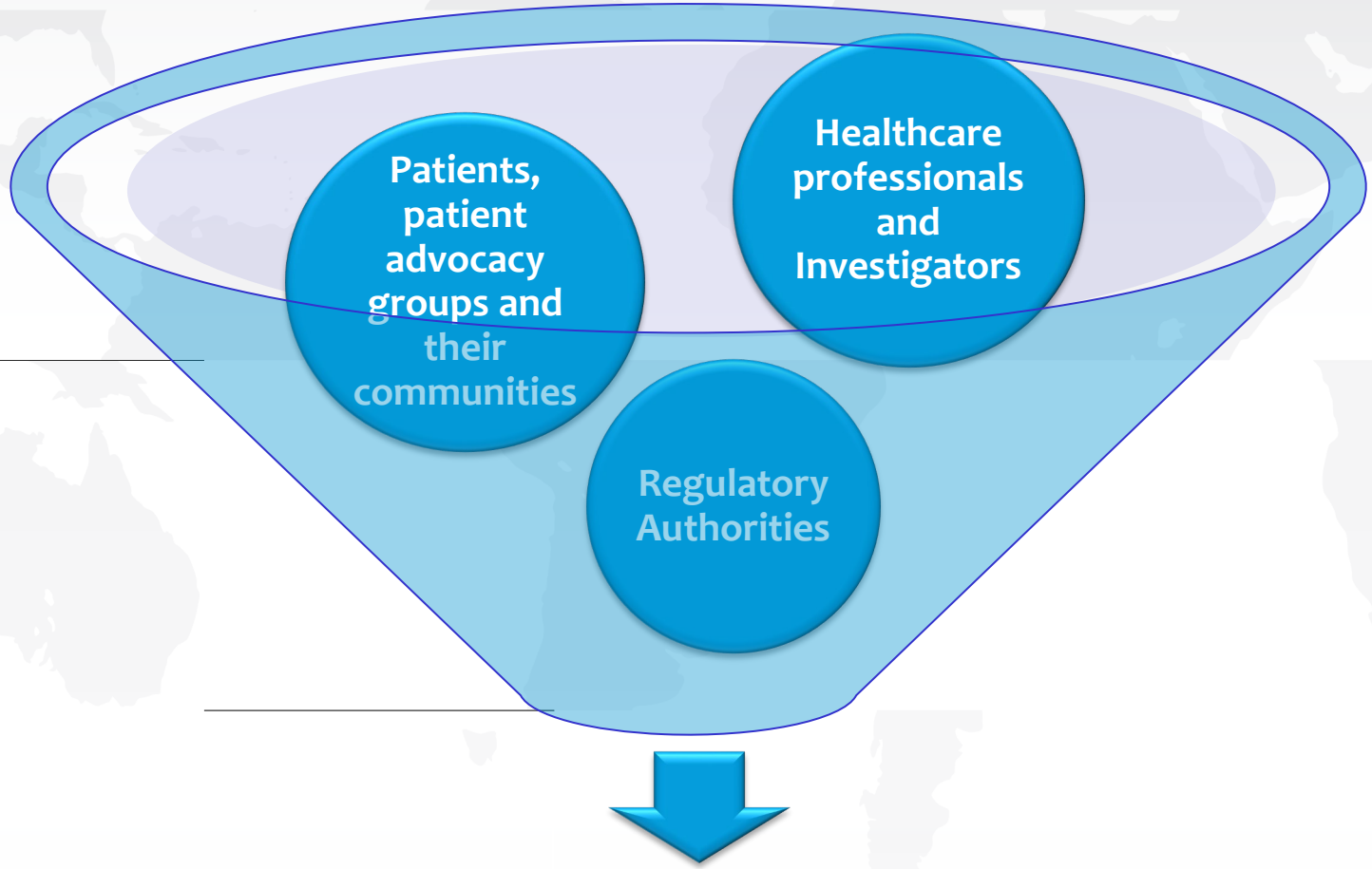
- **Investigational Product (IP) Management**
  - IP may be **dispensed or supplied** to participant or appropriate designee for administration at the **participant's location** by **appropriate parties**.
  - When **shipping IP to a participant**, consider the process for protecting the privacy, IP being received by the intended recipient.
  - The **level of investigator oversight** will depend on a number of factors (e.g., characteristics of the IP, route and complexity of administration, 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.
  - Approaches to IP management should be arranged and conducted in accordance with applicable regulatory requirements

ICH E6 (R3) – Annex 2
INVESTIGATOR (3)

- **Investigator Oversight**
  - **Healthcare professionals** may be involved in performing trial-related activities that are part of clinical practice. For such activities, delegation or appropriate arrangements should be in place.
  - **The level of investigator oversight** should depend on the nature of the activities and be proportionate to the importance of the data being collected and the risks to participant safety and data reliability.
- **Safety Assessment and Reporting**
  - Safety information may be coming from various sources (e.g., home nursing, 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**.

ICH E6(R3) – Annex 2
SPONSOR

- **Engagement and Communication**



For meaningful implementation of various operational approaches and data sources
(e.g., ensuring the suitability of DHTs, incorporating the routine workflow of healthcare professionals and identifying challenges and strategies for resolution)

ICH E6(R3) – Annex 2 SPONSOR (2)

- **Protocol and Trial Design**
  - Use of specific design elements and data sources, including rationale, fitness for purpose and feasibility
  - Impact of data variability from the use of different data sources or various practice settings should be considered in the trial design.
  - Flow of safety information from the variety of data sources and how this information will be provided to the investigator to help with decision making.
  - Modalities for informed consent process.

ICH E6(R3) – Annex 2 SPONSOR (3)

- **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.**

ICH E6(R3) – Annex 2 SPONSOR (4)

- **Data Considerations**
  - **RWD Considerations**
    - Apply **special considerations** to RWD sources **depending on the data collection** and **acquisition process** and if the **data are primary or secondary**, since the **sponsor may have different level of control over what and how the data elements are collected.**
    - Fitness for purpose of RWD;
    - 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 adequate measures should be implemented to sufficiently protect both data privacy and reliability of trial results.
  - **Remote Data Collection Considerations**
    - Special attention to be paid to data security vulnerabilities, including cybersecurity and data privacy.
    - Some of the RWD considerations mentioned previously may also apply to remote clinical trial data collection (e.g., DHTs including wearables).

ICH E6(R3) – Annex 2
SPONSOR (5)

- **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 and route of administration*
    - *Trial population*
    - *Knowledge about the safety profile of the IP*
    - *Need for in-person clinical observation post-IP administration and the need for emergency plans*
    - *Measures needed to protect blinding*
  - **Deploy systems and assist investigators** to establish the processes to ensure that the allocated IP was delivered to participants and administered appropriately.

ICH E6(R3) – Annex 2
SPONSOR (6)

- **Privacy and Confidentiality Considerations**
  - **Security safeguards,** including cybersecurity, are in place to **protect the privacy and confidentiality of personal information** of **participants.**
  - Access to the personal information should be limited to those authorised and appropriate informed consent should be provided by the participant**.**
  - **~~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 an appropriate level of oversight to protect **participants' rights, safety and well-being and to ensure the reliability of the results.**
  - **Quality control** and **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.

ICH E6(R3) – Annex 2
SPONSOR (7)

- **Safety Assessment and Reporting**
  - Safety information from clinical trials with decentralised and/or pragmatic elements should be
    - *Appropriately captured;*
    - *Made accessible to the investigator in a timely manner according to the protocol*
    - *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.

In Summary

- The intent of Annex 2 is to provide 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 while 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.

Thank You

- The ICH E6(R3) Expert Working Group would like to thank our academic stakeholder representatives for their time and thoughtful consideration of the draft guideline. They were invaluable in providing their expertise in the running of clinical trials.

Additional considerations

- Annex 2 applies as well as Annex 1 and the Principles
  - More 'thinking' does not mean more 'doing'
- Definitions are difficult
  - Within regions
  - Between regions
  - Harmonization is challenging accordingly
- The health system trials are implemented in, in different regions, are not the same
- There is not a unique mapping of these protocol elements and data sources onto the regulation defined "Low Risk Clinical Trial"

Any questions?

Further information

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