Good Clinical Practice – ICH E6(R3) Annex 2

Step 4 document – to be implemented

27 May 2026

ICH harmonisation for better health

Good Clinical Practice – ICH E6(R3) Annex 2

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ICH E6(R3) – Annex 2

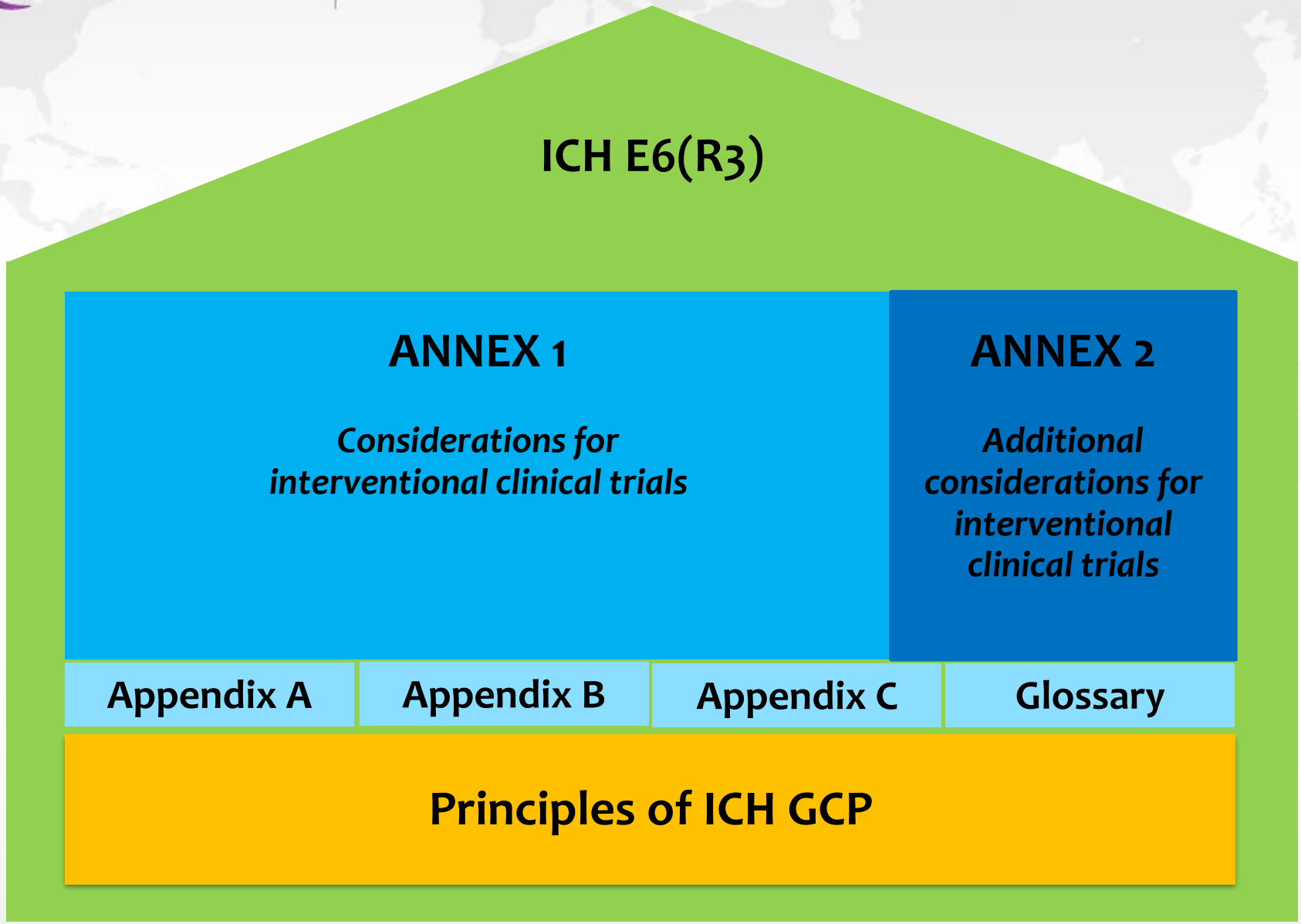
- This guideline reached Step 2 on 6 November 2024 and was issued by the ICH Regulatory Members for public consultation.
- The ICH E6 (R3) Expert Working Group reviewed public consultation comments and revised the document, as appropriate.
- This final document has been signed off as a Step 4 document (27 May 2026) to be implemented by the ICH Regulatory Members.
- This document was developed based on a Concept Paper (approved 28 April 2023) and a Business Plan (approved 18 November 2019).

ICH E6(R3) ANNEX 2 BACKGROUND

ICH E6(R3) – Annex 2

- Addresses additional GCP considerations that arise from various operational approaches, design elements and data sources, which are collectively referred to in this guideline as 'methodologies'.
- Has its foundations in the key concepts of quality-by-design, including fitness for purpose and risk proportionality.
- Does not endorse any specific operational approaches, design elements or data sources.
- Should be read in conjunction with the ICH E6(R3) Principles and Annex 1.

OVERVIEW OF ICH E6(R3)



ICH E6(R3) Guideline Structure

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

IV. ANNEX 2

Introduction

1. Institutional Review Board/Independent Ethics Committee (IRB/IEC)
2. Investigator
3. 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

Methodologies

- **Annex 2 provides considerations that focus on trials that incorporate:**
  - **Decentralised Elements**
  - **Pragmatic Elements**
  - **Real-World Data (RWD)**

Decentralised Elements

- Trial-related activities conducted outside the investigator’s location. For example, trial visits and/or protocol-related procedures conducted at the trial participant's home, local healthcare centres or mobile medical units.
    - Remote interactions, such as video calls or the use of digital health technologies (DHTs) to conduct visits, perform procedures and collect data.

Pragmatic Elements

- Those that integrate aspects of usual clinical practice into the design and conduct of the trial - *"Usual clinical practice" refers to the established day-to-day processes and procedures applied by healthcare professionals when caring for patients.*
  - *For example:*
    - *Protocols with trial processes and eligibility criteria that reflect usual clinical practice in that patient population and reflect the settings where usual care is provided, such as in hospitals, in healthcare centres and by primary physicians and/or local healthcare providers.*
    - *Streamlined data collection, for example, capturing only the minimum necessary data by aligning with usual clinical practice or capturing data only at the timing in routine care settings to minimise the complexity of trial conduct.*

Digital Health Technologies (DHTs)

- Broad term to reflect the wide range of technologies supporting healthcare used to collect, measure, or monitor health-related data from participants or patients. For example:
  - mobile applications
  - wearables
  - sensors

- Depending on the context, the term may refer to those technologies used specifically in trials or those used within broader healthcare settings.

- Where a DHT is used to acquire participant data for a clinical trial, it is considered a data acquisition tool as defined in the Glossary.

Real-World Data (RWD)

- RWD incorporated in interventional clinical trials refers to 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 databases).

Primary Data Collection vs Secondary Use of Data

In the context of clinical trials, data are often used in one of two ways as:

- **Primary Data Collection**
  - Involves gathering data prospectively in accordance with the trial protocol, typically through trial-specific procedures such as clinical assessments, laboratory tests or participant questionnaires.

- **Secondary Use of Data**
  - Refers to the use of data that were originally collected for purposes other than the clinical trial but are subsequently incorporated into that clinical trial.
    - When such data reflects patient experiences, outcomes or healthcare delivery outside a clinical trial setting, it is considered RWD.
      - These data can serve various roles in a trial, including but not limited to endpoint or outcome data or serving as an external control.
      - When such data are used in a trial, it is essential to ensure that the data are fit for their intended purpose in the clinical trial.

ICH E6(R3) Annex 2 – Section 1 IRB/IEC

IRB/IEC

- When incorporating decentralised elements, pragmatic elements and/or RWD, particular attention should be given to:
  - Ensure participants' rights, safety and well-being;
  - Protect their privacy and confidentiality; and
  - Secure their data.

- These methodologies may require additional considerations, for example, related to data protection.

ICH E6(R3) Annex 2 – Section 2 Investigator

2.1 Communication with IRB/IEC
2.2 Informed Consent Considerations
2.3 Investigational Product Management
2.4 Investigator Oversight
2.5 Safety Assessment and Reporting

Communication with IRB/IEC

- Provide the IRB/IEC with the information needed for the evaluation of the appropriateness of the methodologies being used.

Informed Consent Considerations

- The informed consent materials and process should be tailored to reflect the various operational approaches, design elements and data sources incorporated in the trial.
- Informed consent may be obtained remotely, where appropriate.
  - The investigator should assure themselves of the identity of the participant (or legally acceptable representative, where applicable).
- The characteristics of the trial population and the appropriateness of the method and tools used to obtain informed consent should be considered.
- The informed consent materials should also describe the:
  - Participant-related data to be collected;
  - Use of data in the trial; and/or
  - Parties who will have access to the participant's personal information (e.g., health records and home address).

Investigational Product Management

- Various investigational product management approaches (supply, storage, dispensing, administration, return, accountability, destruction/alternative disposition) may be utilised as appropriate.
- The investigational product may be dispensed/supplied to the participant or appropriate designee for administration at the participant's location (e.g., participant's home, local healthcare centre) by appropriate parties.
- All approaches should be arranged and conducted in accordance with applicable regulatory requirements.

Investigational Product Management (2)

- **Investigational Product Shipping: Roles and Responsibilities**
  - Investigator/institution may arrange to send the investigational product per sponsor instructions, where applicable, in accordance with applicable regulatory requirements.
  - Where permitted by applicable regulatory requirements, sponsor may arrange to send the investigational product to participant.
    - In such cases:
      - Investigator/institution retains responsibility for safe and appropriate investigational product use
      - Investigator should be aware of the arrangements for shipping made by the sponsor
      - Investigator remains informed of receipt, use, participant-reported issues, and resolution
      - Roles/responsibilities of sponsor and investigator should be clearly documented
      - Clear communication and predefined procedures required between sponsor, investigator, and any service provider, in accordance with applicable regulatory requirements

Investigational Product Management (3)

- **Investigational Product Shipping: Operational Considerations & Oversight**
  - When shipping investigational product to participants, in accordance with applicable regulatory requirements, the following needs to be considered:
    - Privacy/confidentiality (incl. disease status)
    - Investigational product being received by intended recipient
    - Receipt, storage, handling, administration, return, destruction/alternative disposition, accountability
    - Blinding protection (if applicable)
    - Availability of participant support tools
  - Institutional processes may be sufficient for investigational product management, depending on applicable regulatory requirements.
  - Investigator oversight level depends on e.g., trial design, investigational product characteristics, route/complexity of administration, and existing safety knowledge and marketing status.
    - Investigator oversight includes receipt, use, return (or alternative disposition), and commencement, continuation, dose and dose adjustments of the investigational product as specified in the trial protocol.

Investigator Oversight

- Maintain appropriate and proportionate oversight of trial-related activities to ensure the rights, safety and well-being of the trial participants; and the reliability of the trial data.

- Appropriate level of investigator oversight
  - Is context dependent (e.g., depending on trial characteristics, such as trial design, trial population, investigational product and data sources).
  - May range from direct supervision to less intensive oversight, whether in person or via remote communication methods (e.g., video, telephone or email), to only the review of essential records (including source records).

Only review of essential records | Less intensive oversight | Direct supervision

Investigator Oversight (2)

- The trial-related activities to be performed by healthcare professionals conducting these activities within usual clinical practice should be described in the protocol.
  - For trial-related activities that are part of usual clinical practice and do not require knowledge about the trial protocol, investigator's brochure or other trial-related documents:
    - Appropriate arrangements should be in place and should address plans for *making relevant information and records on the performed trial-related activities available to the investigator (e.g., defining how data are shared, how records are retained, how data privacy is maintained and what mechanisms are in place for ensuring data integrity)*

Investigator Oversight (3)

- For trial-related activities that are part of usual clinical practice and require knowledge about the trial protocol, investigator's brochure or other trial-related documents:
  - Delegated healthcare professionals who have been appropriately trained should perform these activities.

- **In any case, the level of investigator oversight should be proportionate to the criticality of the data to participant protection and the reliability of the trial results.**

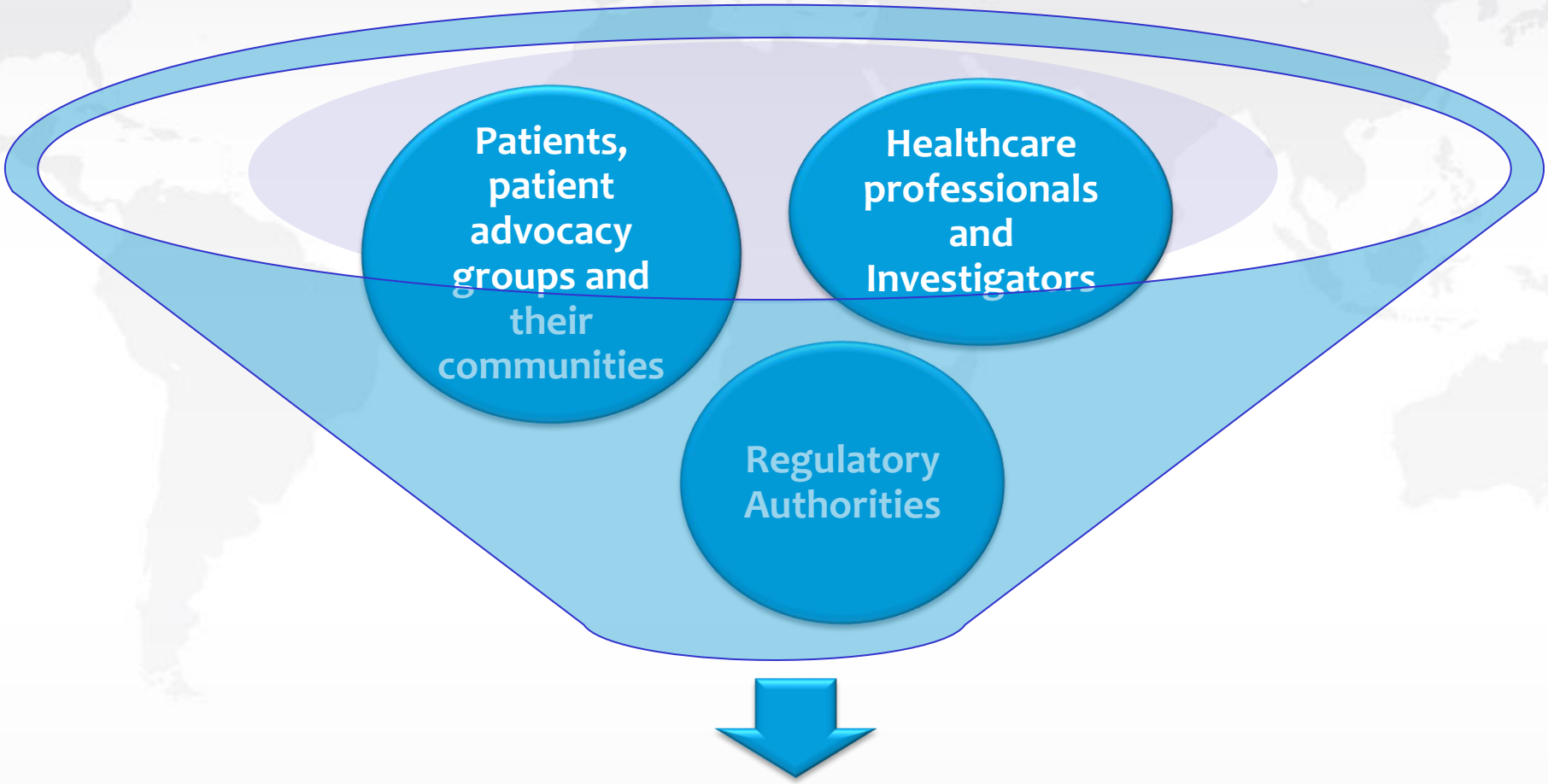
Safety Assessment and Reporting

- Safety information may be generated from various sources (e.g., home nursing, remote visits, use of DHTs)
  - The investigator should review and assess information on the health status of participants across the sources of safety-related information.
  - The safety information should be provided to the investigator in a manner that allows the investigator to make decisions on the care of the participant and ensures participant safety.

ICH E6(R3) Annex 2 – Section 3 SPONSOR

3.1 Engagement and Communication
3.2 Protocol and Trial Design
3.3 Communication with IRB / IEC
3.4 Access to and Use of RWD
3.5 Data Considerations
3.6 Investigational Product Management
3.7 Privacy and Confidentiality Considerations
3.8 Sponsor Oversight
3.9 Safety Assessment and Reporting

Engagement and Communication



Early involvement is valuable for meaningful implementation of various methodologies in clinical trials, which would be valuable in refining research questions; selecting meaningful interventions and outcomes; and shaping trial design, procedures and communication strategies.

Protocol and Trial Design

- Should adequately describe specific design elements, data sources and where appropriate, various operational approaches in the trial protocol, including the rationale and justification for the appropriateness of their use, fitness for purpose and feasibility.
- For clinical trials incorporating pragmatic elements,
  - Assess whether such approach is fit for purpose for use in the trial and complies with applicable regulatory requirements.
  - Ensure that the protocol clearly describes how, by whom, and under what circumstances these trial-related activities will be performed.
- Consider the impact of data variability from various data sources in the trial design; such impact should be discussed in the protocol or protocol-related documents (e.g., statistical analysis plan).

Protocol and Trial Design (2)

- Consider the methodologies used in the clinical trial when determining the need for appropriate training and technical support to be provided to the investigator, investigator site staff and participants.

- For safety information, describe the following in the protocol and where applicable, protocol-related documents:
  - How safety information will be collected from the variety of data sources;
  - How data and information suggesting a potential safety concern will be identified and made available to the investigator in a timely manner, and
  - What actions should be taken by the investigators in these instances.

- Describe the modalities for informed consent process in the protocol.

Communication with IRB/IEC

- Provide information needed for the evaluation of the appropriateness of the methodologies being used.

Access to and Use of RWD

- RWD used in a clinical trial should be managed in a manner that ensures participant protection and the reliability of trial results. This includes ensuring that:
  - The RWD are fit for purpose;
  - Appropriate access and oversight are in place; and
  - The use of RWD complies with applicable privacy and data protection requirements, including consent and permission.

Access to RWD

- Sponsors should have ability to access individual level data and data in source records (as necessary in accordance with applicable regulatory requirements), for example, to implement quality assurance and quality control activities:
  - **Individual-level data**
    - Datasets / listings capturing data for each individual, usually extracted from source records and structured for statistical analysis and reporting.
    - Pseudonymised for trial use (i.e., a *specific individual cannot be identified without collating the data with additional information)*
  - **Data in source records**
    - Data in original records, such as patient medical records, laboratory reports, imaging files and physician notes, from which individual-level data are derived.
    - Typically, not pseudonymised (i.e., *contains patient-identifying information and other information subject to data privacy and protection requirements)*
- Regulatory authorities may require access to individual-level data and data in source records for regulatory inspections.

Access to RWD (2)

- **If RWD used in a clinical trial are owned and controlled by entities other than the sponsor (e.g., healthcare institutions, registry holders, insurers):**
  - Sponsor should ensure appropriate arrangements are in place with these entities to enable access and use of the data for trial purposes, including access to data in source records by the sponsor in accordance with applicable regulatory requirements.
  - The arrangements should also allow regulatory authorities to access individual-level data and source records to support regulatory inspections.
  - These arrangements should include documented agreements that define how data will be shared and protected.

Access to RWD (3)

- Access to individual-level data and data in source records should be proportionate to the criticality of the data.
  - **For RWD use cases of higher criticality (e.g., when RWD are used to support key efficacy and safety endpoints)**
    - Simply assessing the fitness for purpose of the RWD source to be utilised may be insufficient.
    - Sponsors may need to for example, confirm whether a clinical event occurred, was assessed, or was documented. In such cases, sponsors should ensure access to source records to support their quality assurance and quality control activities.
    - Where such access is not feasible, sponsors should consult relevant regulatory authorities.
  - **For RWD use cases of lower criticality (e.g., for exploratory endpoints)**
    - It may be sufficient for sponsors to use system- and process-level assessments.
    - In this case, the protocol or protocol-related documents should describe the fitness for purpose of the RWD, including any relevant limitations and justification of the assessment approach.

Access to RWD (4)

- Regardless of which entity owns and/or controls or undertakes data processing steps, sponsors remain responsible for:
    - Maintaining oversight of these steps, including extraction, linkage and transformation; and
    - Implementing quality assurance and quality control measures to ensure data are of appropriate quality.

Consent and Permission Considerations for RWD

The sponsor should ensure that:

- Permission or approval is obtained from authorised entities (e.g., IRBs/IECs) or consent is provided by individuals whose health data or source records are used to obtain RWD (as applicable per regulatory requirements).

- The consent should describe use of and access to RWD and source records by:
  - Regulatory authorities
  - Sponsor representatives (where applicable)
  - IRBs/IECs (where applicable)

- Such consent does not imply involvement in an interventional trial-related activity.

- The records of consent/permissions should be retained and made available to regulatory authorities upon request.

Data Considerations

Should be read in conjunction with Annex 1, section 3.16.1 and section 4.

- **RWD Considerations**
  - Ensure fitness for purpose of RWD, which can be described by their:
    - Reliability – includes accuracy, completeness, provenance and traceability; and
    - Relevance - includes the availability of key data elements (e.g., exposure, outcomes, covariates) to answer the specific trial question with the specific method.
  - Attention should be paid to the variability in the data source, potential bias, generalisability and traceability of RWD.

Data Considerations (2)

- **RWD Considerations (2)**
  - Assess whether the RWD source is fit for purpose for the intended use of the trial.
    - Apply a risk-proportionate approach to the measures used to ensure appropriate data quality, integrity and governance for the RWD incorporated into the trial.
    - This approach should consider the importance of the data to the trial objectives and the potential impact of data limitations on trial results.
  - In selecting RWD sources:
    - Assess whether the data are appropriate to support the specific trial endpoints and objectives;
    - Weigh the potential benefits against limitations, taking into account the considerations provided in the guideline;
    - Reflect these considerations in trial planning, protocol design and oversight processes.

Data Considerations (3)

- **RWD Considerations**
  - When data are linked from multiple sources to support reliability, including completeness of RWD, ensure:
    - That data to be linked are pre-specified in the protocol and protocol-related documents, including how data inconsistencies between different sources will be resolved in a systematic and consistent manner;
    - That accurate matching to the individual is assured; and
    - Adequate measures to sufficiently protect both data privacy and the reliability of trial results.
  - Implement procedures that support adequate documentation, data linkage and quality control, while accounting for differences in how RWD are structured, collected and managed across various sources.

Data Considerations (4)

- **Remote Data Collection Considerations**
  - Remote data collection in clinical trials requires special attention to be paid to data security vulnerabilities, including cybersecurity and data privacy.
  - Some of the RWD considerations may also apply to remote data collection.

Investigational Product Management

- Assess approaches to investigational product management during protocol development, considering:
  - Investigational product stability, including any specialised storage conditions;
  - Investigational product preparation and route of administration;
  - Trial population;
  - Knowledge about the safety profile of the investigational product;
  - Need for in-person clinical observation post-investigational product administration and the need for emergency plans;
  - Measures needed to protect blinding, if applicable; and/or
  - Need for emergency plans related to investigational product administration (e.g., requirement for rescue medication)

Investigational Product Management (2)

- Sponsor may arrange to send investigational product to the participant (e.g., to the participant's home) in accordance with applicable regulatory requirements:
  - Investigational product shipment should be carried out in accordance with the protocol;
  - Investigational product shipment process may only be initiated after being authorised by the investigator; and
  - Trial participant privacy and confidentiality are taken into consideration.

- May deploy systems and assist investigators to establish the processes to ensure that the allocated investigational product was delivered to trial participants and administered appropriately.

Privacy and Confidentiality Considerations

- Security safeguards, including cybersecurity, should be in place to protect the privacy and confidentiality of personal information of participants.

- Participants' personal information:
  - May be required by service providers, for example, for investigational product shipment to participants or deployment of home nurses.
  - Access should be limited to those authorised and appropriate informed consent is required from the participants.
  - Risk of potential disclosure of personal information from a data breach (e.g., data from DHTs and/or RWD) should be considered.

Sponsor Oversight

- Sponsor oversight should ensure an appropriate level of oversight such that the participants' rights, safety and well-being are protected, and the reliability of the trial results is ensured. This includes:
  - Ensuring there are processes in place, including clear lines of communication.
  - Implementing quality control and assurance measures specifically customised to the clinical trial and its critical to quality factors and identified risks, with these measures being implemented in a risk-proportionate manner.
  - Ensuring appropriate oversight of service providers, including maintenance of their essential records.

Sponsor Oversight (2)

- When the sponsor arranges trial-related activities under the responsibility of the investigator, for example, home nursing.
  - The sponsor should ensure that service providers are suitable to conduct the trial-related activity.
  - Investigator:
    - Retains the ability to decide on the appropriateness of the proposed service provider; and
    - Maintains oversight of the trial-related activities.

Note: This requirement intends to cover trial-related activities under the responsibility of the investigator involving interaction (e.g., face to face, telephone, email) with the participants (such as home nursing). It is generally not intended to cover trial-related activities undertaken centrally by a sponsor arranged service provider that do not involve interaction with participants (such as biological sample analysis by a central laboratory).

Safety Assessment and Reporting

- **Safety information**
  - Management of safety information is essential to protect trial participants' safety through early detection and management of potential adverse drug reactions.
  - May be collected in various ways and from multiple sources in clinical trials with decentralised and/or pragmatic elements.
    - Appropriate processes and procedures should be in place to make the safety information accessible to the investigator in a timely manner, according to the protocol.
    - Safety information should be provided to the investigator in a manner that allows the investigator to make decisions on care of the participant and ensures their safety.

Safety Assessment and Reporting (2)

- Approach to safety management (including mitigating actions to safeguard participant safety) and reporting should:
  - Be described in the protocol or protocol-related documents (e.g., safety management plan).
  - Consider the methodologies used in the trial.

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ICH E6(R3) Annex 2 SUMMARY

Summary

- Annex 2 provides additional GCP considerations in the context of clinical trials with various operational approaches, design element and data sources, to ensure they are fit for purpose.

- Annex 2 provides considerations that focus on trials that incorporate decentralised elements, pragmatic elements and/or RWD.

- 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.

Thank You

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

Contact

- **For any questions, please contact the ICH Secretariat:**

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