Investigator: Main changes

Flexibility

Risk-based

Proportionality

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Agenda

- Overview of main changes for the Investigator.
- Changes from the draft to the final.
- Take home message.

Revised Structure

E6(R3) Guideline

E6(R3) Principles and Annex 1 replacing E6(R2)

- **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
- **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**

ANNEX 2 – *under public consultation from November 2024 to March 2025*

Federal Institute for Drugs and Medical Devices

ICH E6 (R3) Annex 1 *Investigator*

ICH E6 (R3) Section	ICH E6 (R2) Section
2.1 – Qualifications and Training	4.1
2.2 – Resources	4.2
2.3 – Responsibilities	4.1, 4.2
2.4 – Communication with IRB/IEC	4.4, 4.10
2.5 – Compliance with Protocol	4.1
2.6 – Premature Termination or Suspension of a Trial	4.12
2.7 – Participant Medical Care and Safety Reporting	4.3, 4.11
2.8 – Informed Consent of Trial Participants	4.8
2.9 – End of participation in a clinical trial	4.3
2.10 – Investigational Product Management	4.6
2.11 – Randomisation Procedures and Unblinding	4.7
2.12 – Records	4.9
2.13 – Reports	4.13

Investigator - Informed Consent

- **Approaches to obtaining informed consent**
  - Varied approaches to the provision of information and the discussion about the trial can be used. This may include, for example, providing text in different formats, images and videos and other interactive methods.
  - The information should be as clear and concise as possible, use simple language and avoid unnecessary volume and complexity.
  - Informed consent is documented by means of a written (paper or electronic), signed and dated informed consent form.
  - Obtaining consent remotely may be considered when appropriate.
- **New information**
  - Considerations for re-consent, including stage of the clinical trial, whether the new information is relevant only to new / existing participants.
  - Revised informed consent materials require IRB/IEC approval in advance of use.
- **Enrolment of minors**
  - Where a minor is to be included as a participant, age-appropriate assent information should be provided and discussed with the minor as part of the consent process.
  - A process for consent should be considered if during the trial, the minor reaches the age of legal consent, in accordance with applicable regulatory requirements.

Investigator (2)

- **Qualifications and training**
  - Clarified expectations on evidence for qualifications: allow flexibility about documentation.
  - Clarified overall training requirements for trial staff: trial-related training to persons assisting in the clinical trial should correspond to what is necessary to enable them to fulfil their delegated trial-related activities that go beyond their usual training and experience.
- **Medical Care**
  - Clarified that other appropriately qualified health professionals may be involved in medical care of trial participants in line with their normal activities and in accordance with local regulatory requirements.
- **Safety Reporting**
  - Included language about the reporting of unfavourable medical events occurring in participants before IP administration (e.g., during screening) to the sponsor, if required by the protocol.

Investigator (3)

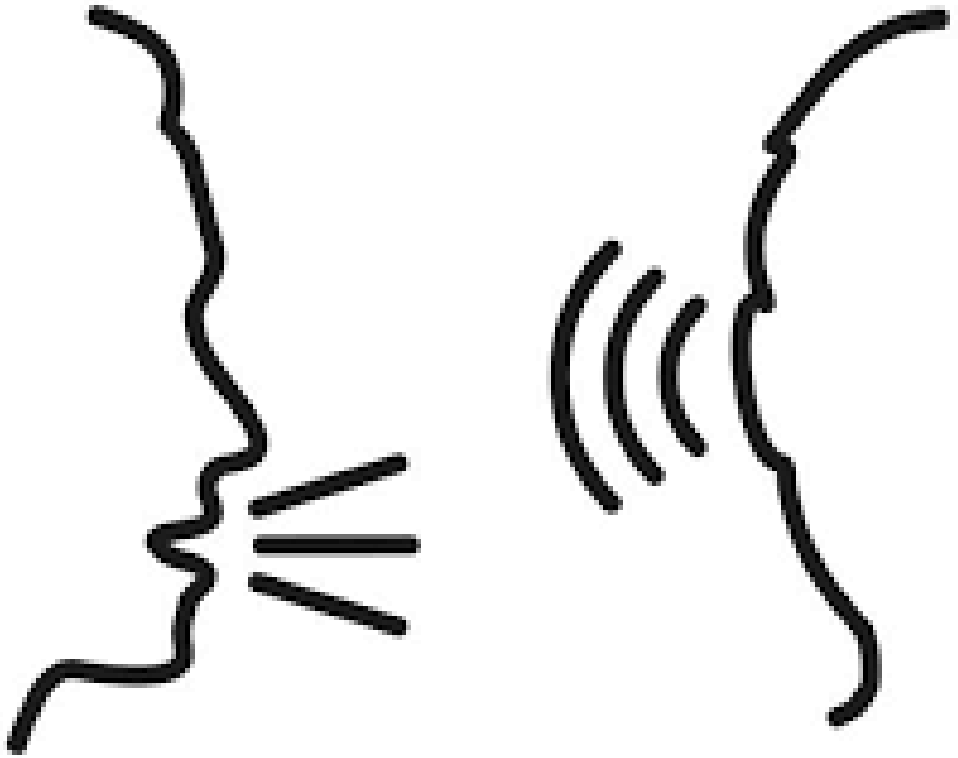
- **Responsibilities**
  - Clarified the expectations between the sponsor and investigator regarding service providers.
  - Confirmed that the investigator retains the ultimate responsibility for the persons or parties undertaking the activities delegated.
  - Clarified that the level of investigator oversight of the delegated activities should depend on the nature of the delegated activities and be proportionate to the importance of the data being collected and the risks to trial participant safety and data reliability.
  - Clarified the requirements for delegation documentation.

- **Considerations for participants who did not reach the routine end of the trial**
  - Clarified that appropriate follow up per protocol and/or other protocol-related documents is required.
  - Included language about the potential for instructions to avoid loss of already collected data, in accordance with regulatory requirements.

Investigator (4)

- **Computerised systems**
  - Clarified the investigator's responsibility for computerised systems.
- **Data and source records**
  - Clarified expectations regarding identification and maintenance of source records and timely data access and review.
- **Investigational product (IP) management**
  - Clarified that the sponsor may facilitate aspects of IP management.
  - Clarified that the level of investigator oversight will depend on a number of factors including:
    - Characteristics of the IP;
    - Route and complexity of administration;
    - Level of existing knowledge about the IP's safety; and
    - Marketing status of the IP.
  - Clarified that for authorised medicinal products, alternative approaches to IP documentation may be considered, in accordance with applicable regulatory requirements.
  - Included language that the investigators should be prepared and capable from the start of the trial to perform unblinding without undue delay and hindrance in the case of an emergency, to protect participant safety.

Changes from the draft to the final



Investigator’s site

E6R2

Trial Site

The location(s) where trial-related activities are actually conducted

E6R3 caucus

Investigators site

The location(s) at or from where trial-related activities are conducted under the investigator’s/institution’s supervision

E6R3 Step 4

Investigator Site

The location(s) where trial-related activities are conducted and/or coordinated under the investigator’s/institution’s oversight.

Investigator Oversight + proportionality of oversight

E6R2

The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site

E6R3 caucus

The investigator retains the ultimate responsibility and maintains appropriate supervision of the persons or parties undertaking the activities delegated to ensure the rights, safety and well-being of the trial participants and data reliability.

E6R3 Step 4

The investigator retains the ultimate responsibility and should maintain appropriate oversight of the persons or parties undertaking the activities delegated to ensure the rights, safety and well-being of the trial participants and the reliability of data.

The level of investigator oversight of the delegated activities should depend on the nature of the delegated activities and be proportionate to the importance of the data being collected and the risks to trial participant safety and data reliability.

IMP management – sponsor may facilitate

E6R3 caucus

Responsibility for investigational product(s) accountability rests with the investigator/institution. The sponsor may facilitate this process.

E6R3 Step 4

Responsibility for investigational product(s) management, including accountability, handling, dispensing, administration and return, rests with the investigator/institution. The sponsor may facilitate aspects of investigational product management (e.g., by providing forms and technical solutions, such as computerised systems, and arranging distribution of investigational product to trial participants).

Essential documents responsible - addition

E6R3 Step 4

- 2.12.12 …. The investigator/institution should take measures to ensure **availability, accessibility and readability** and **to prevent unauthorised access** and accidental or premature destruction of these records.
- 2.12.13 The investigator/institution should keep the sponsor informed of the name of the person responsible for maintaining the essential records during the retention period; for example, when the investigator site closes or an investigator leaves the site.

Take Home Message for Investigators

Proportionality

- Trial related training to fulfil trial activities beyond usual training
- Oversight to be proportionate to the importance of the data being collected and the risks to trial participant safety and data reliability
- Delegation may not be necessary if within routine clinical care

Flexibility

- Decentralized trials

Thank you!