Application of ISO 14971 to Clinical Investigations. Interaction with ISO 14155:2020

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Overview of the ISO 14155:2020

- Similarly to the International Conference on Harmonisation (ICH) Guideline E6 (R2) for Good Clinical Practice (GCP), ISO 14155 regulates the design, conduct, recording and reporting of clinical investigations carried out in human subjects to assess the clinical performance and safety of medical devices.
- In alignment with the Declaration of Helsinki (DoH), ISO 14155 aims to protect the rights, safety and well-being of human subjects in clinical research.
- The ISO 14155:2020 is the third edition of this standard
- The ISO 14155 standard provides the general specifications and requirements for clinical investigations to:
  - ✓ Protect the rights, safety, and well-being of human subjects;
  - ✓ Ensure scientific conduct of the clinical investigation and credibility of the clinical investigation results;
  - ✓ Define the responsibilities of the sponsor and principal investigator;
  - ✓ Assist sponsors, investigators, ethics committees, regulatory authorities, and other bodies involved in the conformity assessment of medical devices.

Contents of the ISO

Scope Section 1	Summary of GCP Principles Section 4	Ethical considerations Section 5	Clinical Investigation planning Section 6
Clinical Investigation conduct Section 7	Suspension, Termination and Close-out of the Clinical Investigation Section 8	Responsibilities of the Sponsor Section 9	Responsibilities of the Investigator Section 10
Annex A: Clinical Investigation Plan - CIP (normative)	Annex B: Investigator's Brochure – IB (normative)	Annex C: Case Report Forms – CRFs (informative)	Annex D: Clinical Investigation Report- CIR (normative)
Annex E: Essential Clinical Investigation Documents (informative)	Annex F : Adverse event categorization (informative)	Annex G : Responsibilities of the Ethics Committee - EC (informative)	**Annex H : Application of ISO 14971 to Clinical Investigations (informative)**
Annex I : Clinical Development stages (informative)		**Annex ZA: Relationship between the Standard and the Essential Requirement of Directive 93/42/EEC aimed to be covered (informative)**	**Annex ZB: Relationship between the Standard and the Essential Requirement of Directive 90/385/EEC aimed to be covered (informative)**

Major updates in ISO 14155:2020

- strong emphasis on the role of clinical evidence, as per EU-MDR
- application of ISO 14971 risk management principles across clinical investigations
- improved guidance on clinical study design & introduction of clinical quality management

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Overview of differences with ISO 14155:2011 and References to Risk Management

Differences compared to ISO 14155:2011	
Inclusion of a summary section of GCP principles	Clause 4
Reference to registration of the clinical investigation in a publicly accessible database	Section 5.4
Inclusion of clinical quality management	Section 9.1
Inclusion of risk-based monitoring	Section 6.7
Inclusion of statistical considerations for the description and justification of the Clinical Investigation Plan (CIP)	Annex A – A7: Statistical design & analysis
Inclusion of Guidance for ethics committees	Annex G
Reinforcement of risk management throughout the process of a clinical investigation (planning to consideration of results including Annex H)	**Section 6.2** **Section 7.4.4** **Section 8.5** **Annex B – part B5** **Annex H**
Clarification of applicability of the requirements of this document to the different clinical development stages	Annex I
Inclusion of guidance on clinical investigation audits	Annex J

7.4.4 – Clinical Investigation Conduct
Risk assessment for potentially unacceptable risks

- ❑ Risk identification
- ❑ Risk monitoring against established risk acceptability thresholds
- ❑ Risk assessment in compliance with ISO 14971 resulting in
  - ✓ no further actions required
  - ✓ corrective actions are required
- ❑ If corrective actions cannot be applied, the clinical investigation shall be terminated

8.5 – Suspension, termination and close out of the clinical investigation
Conclusion of the risk assessment

- ❑ A formal review of risk information should be carried out upon completion of the clinical investigation and fed into the risk analysis and clinical evaluation with an update of the benefit-risk conclusions in both documents

Annex B – Investigator's Brochure
B5: Risk management of the investigational device

- ❑ Summary of the benefit-risk analysis including identification of residual risks and identification of contraindications and warnings for the investigational device.

Section 6.2 – Clinical Investigation Planning

- ❑ Risks associated with the investigational device and its related clinical procedure shall be estimated in accordance with ISO 14971 prior to design and conduct of clinical investigation
- ❑ A summary of benefit-risk analysis shall be disclosed
- ❑ The residual risk shall be disclosed in the IB and IFU
- ❑ The CIP shall include all anticipated adverse device effects AND a rationale for the related benefit-risk ratio
- ❑ Training on the investigational device should be provided when required by the risk management report
- ❑ Risk management shall be applied to both planning and conduct of clinical investigations
- ❑ Clinical risks related to clinical procedures, including follow-up procedures required by the CIP other than those related to the investigational device, shall be identified from a literature review
- ❑ Risk control shall be considered at both the clinical quality management system level and clinical investigation planning & conduct

Annex H : Application of ISO 14971 to Clinical Investigations

- ❑ The risk management process associated with a clinical investigation of a medical device allows the identification of hazards and hazardous situations related to the investigational device.
- ❑ The process follows the typical steps of a risk management program:
- ❑ Estimation of associated risks – risk analysis
- ❑ Evaluation of associated risks – benefit-risk analysis
- ❑ Reduction of risk to an acceptable level ≠ EU-MDR (risk reduction as far as possible)
- ❑ Evaluation of risk control throughout the lifetime of the medical device
- ❑ Clinical data provided by the clinical investigation feeds into the clinical valuation of the overall residual risk acceptability

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Annex H : Application of ISO 14971 to Clinical Investigations

- Enhanced presentation of risk management principles in accordance with ISO 14971 for all phases of clinical investigations and improved guidance for the design of clinical investigations allowing identification of hazards and hazardous situations associated with the investigational device.

- Annex H contains a flowchart that outlines the process to be followed after identification of any event suggesting that the investigational device and/or a procedure could represent a safety concern.

- The 2011 version only referred to ISO 14971 with regard to "investigational device risks" and to the facilitation of risk-benefit assessments in order to meet the requirements for the design of clinical investigations ⇒ ⇒ ⇒ The 2020 version adds "clinical risk management" to the list of the sponsor's responsibilities and introduces the concept of clinical quality management processes.

- Steps of the process:
  - The associated risks are identified
    - ✓ estimated (risk analysis) and
    - ✓ evaluated (benefit-risk analysis)
  - Risks are reduced to an acceptable level where necessary (risk control).
  - The effectiveness of risk control is evaluated throughout the product's lifecycle including during clinical investigations.
  - As soon as the risks are no longer acceptable, any clinical investigation should be terminated.
  - Information on acceptable, anticipated risks should be part of the CIP, IB, IFU and Informed Consent Forms.
  - Risks should be monitored against risk acceptability thresholds throughout the clinical investigation.
  - In case an unanticipated safety concern is identified, a thorough risk assessment should be conducted to determine risk acceptability.

- The same principles must also be applied to the investigation of any serious adverse event, device deficiency or other occurrence that could have an impact on the safety of participating subjects.

ISO 14971 - Reasonably foreseeable misuse

- "Use of a product or system in a way not intended by the manufacturer, but which can result from readily predictable human behavior."

- "Readily predictable human behaviour includes the behaviour of all types of users, e.g. lay and professional users."

- "Reasonably foreseeable misuse can be intentional or unintentional."

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Application of ISO 14971 to the management of potential safety concerns in a Clinical Investigation

Adapted from figure H.1, Annex H, ISO 14155:2020