



Editorial

ISO 14155 is an asset for every professional working in the medical device industry. With the new update to this standard, we see improved harmonisation and a clearer

guidance to medical device manufacturers who are amidst transition to the newly implemented Medical Device Regulation (MDR). This article, by Diana Nogueira, helps introduce the essential updates done to

ISO 14155 from its previous version and how it may facilitate manufacturers to implement the requirements for clinical investigations for medical devices.

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Good Clinical Practice applied to medical devices: The new ISO 14155:2020

After many years of preparation, the International Organization for Standardisation (ISO) published the ISO 14155:2020 (3rd version) in July 2020, which replaces the second version from 2011. Analogous 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), the utmost purpose of ISO 14155 is to protect the rights, safety and well-being of human subjects in clinical research.

Essential updates

The main changes in comparison to the previous version are:

- Inclusion of a summary section of GCP principles (aligned with ICH E6)
- Reference to registration of clinical investigations in a publicly accessible database (aligned with DoH)
- Inclusion of clinical quality management
- Inclusion of risk-based monitoring
- Inclusion of statistical considerations in Annex A (Clinical Investigation Plan, or CIP)
- Inclusion of guidance for ethics committees (ECs) in Annex G (EC responsibilities)
- Reinforcement of risk management throughout the process of a clinical investigation, including Annex H (application of ISO 14971 to clinical investigations and interaction between ISO 14971 and ISO 14155)
- Clarification of applicability of requirements

to different clinical development stages in Annex I

- Inclusion of guidance on clinical investigation audits in Annex J.

GCP principles

The GCP principles summarised in ISO 14155 are aligned with the DoH and ICH E6, as follows:

1. Clinical investigations shall be conducted in accordance with the ethical principles that have their origin in the DoH, and that are consistent with this document.
2. Before a clinical investigation is initiated, foreseeable risks and inconveniences shall be weighed against the anticipated benefit for the individual subject and society. A clinical investigation shall be initiated and continued only if the anticipated benefits outweigh the risks.
3. The rights, safety, and well-being of human subjects are the most important considerations and prevail over interests of science and society.
4. The available non-clinical and clinical information on the investigational device shall be adequate to support the proposed clinical investigation.
5. Clinical investigations shall be scientifically sound and described in a clearly detailed CIP.
6. A clinical investigation shall be conducted in compliance with the CIP that has received prior EC approval/favourable opinion and, where applicable, approval/non-objection of

regulatory authorities.

7. The medical care given to, and medical decisions made on behalf of subjects shall always be the responsibility of a qualified healthcare professional.
8. Each individual involved in designing, conducting, recording, and reporting a clinical investigation shall be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given informed consent shall be obtained from every subject prior to the participation in the clinical investigation.
10. All clinical investigation-related information shall be recorded, handled, and securely stored in a way that allows its accurate reporting, interpretation, monitoring, auditing, and verification.
11. The confidentiality of records that could identify subjects shall be protected, respecting the privacy and confidentiality rules.
12. Investigational devices shall be designed, manufactured, handled, and stored in accordance with the essential principles. They shall be used in accordance with the approved CIP, the investigator's brochure (IB) and manufacturer's instructions for use (IFU).
13. Systems with procedures that ensure the quality of every aspect of the clinical investigation shall be implemented.

Clinical quality management

The inclusion of clinical quality management is a new requirement that obliges the use of quality management principles in alignment with ISO 13485:2016. This is to ensure that the clinical investigation is designed, conducted, monitored,

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and that the data generated is documented, evaluated, and reported in accordance with regulatory requirements and in compliance with the ISO 14155, the CIP and other applicable standards. The sponsor shall document the implementation of these clinical quality procedures in writing.

Risk-based monitoring

Another new aspect of ISO 14155 is a risk-based approach to study monitoring. Results of the device risk assessment shall be used to develop a risk-based monitoring plan, in which the extent and nature of the monitoring shall be based on the objective, design, complexity, size, critical data points, and endpoints of the clinical investigation and the degree of deviation from normal clinical practice. In particular, the sponsor shall ensure that unanticipated adverse device effects are identified and investigated rapidly, so that additional risk control measures can be implemented where necessary.

The application of ISO 14971:2019 to clinical investigations is described in detail in Annex H of ISO 14155. The risk management process associated with a clinical investigation allows the hazards and hazardous situations associated with the investigational device to be identified. The associated risks are first identified and estimated (risk analysis), then evaluated (benefit-risk analysis), followed by a reduction of these risks to an acceptable level where necessary (risk control). The effectiveness of risk control is

evaluated throughout the product's lifecycle and during clinical investigations. As soon as the risks are no longer acceptable, any clinical investigation should be terminated. Information on acceptable and 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.

Types of clinical investigations

Annex I of ISO 14155 provides a general indication of the possible types of clinical investigations. It is categorised based on different clinical development stages (pilot, pivotal or post-market stage) and in relation to the regulatory status (pre-market or post-market stage) including exploratory, confirmatory or observational studies (registry or post-market

clinical follow-up studies), interventional or non-interventional studies. This overview is helpful in face of the expected increase in rate of clinical investigations brought about by the European Medical Device Regulation (MDR) 2017/745. According to this regulation, clinical investigations should be conducted in line with international guidelines, such as ISO 14155 on good clinical practice and the DoH.

Overall considerations

Altogether, the new ISO 14155 underpins the importance of risk management in all phases of product development, including clinical investigations, and the beneficial interplay with other ISO guidance documents (i.e ISO 13485 and ISO 14971). Adherence to ISO 14155:2020 is important for complying with ethical aspects in clinical research and human rights. In addition, it contributes to the generation of high-quality clinical data, regulatory compliance and acceptance of study conduct, and outcomes across countries.

Conflicts of interest

The author declares no conflicts of interest.

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