SLOVENSKI STANDARD
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Klinične raziskave medicinskih pripomočkov za ljudi - Dobre klinične prakse (ISO/DIS 14155:2024)

Clinical investigation of medical devices for human subjects - Good clinical practice (ISO/DIS 14155:2024)

Klinische Prüfung von Medizinprodukten an Menschen - Gute klinische Praxis (ISO/DIS 14155:2024)

Investigation clinique des dispositifs médicaux pour sujets humains - Bonne pratique clinique (ISO/DIS 14155:2024)

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 194, *Biological and clinical evaluation of medical devices*, in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 206, *Biological and clinical evaluation of medical devices*, in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This fourth edition cancels and replaces the third edition (ISO 14155:2020), which has been technically revised. The main changes to the previous edition are as follows:

— Change in definition of clinical performance (3.12);

— Clarification about deviations from eligibility criteria not being permitted but subject to CIP amendment (see 5.6.4);

— Clarified informed consent to be obtained where applicable from subject's legally designated representative (see 5.8.1);

— Clarified subject must be given opportunity to discuss participation with others e.g. family members (see 5.8.2);

— Clarification on risk management clear distinction between risks related to the use of the device and risks related to the procedures required by the CIP which are not part of normal clinical practice (see 6.2.1);

— Inclusion of required assessment of residual risks including quantified estimation (see 6.2.2);

— Correction of reference to risks related to the use of the investigational device (see 6.2.1, 7.4.4, 8.2 Annex F, Annex H and 3.2);

— Added normative requirements (previously in Annex A) to 6.4;

— Added requirement for data monitoring committee to confirm conditions for suspending or stopping the clinical investigation (see 6.11);

— Inclusion of new section on clinical events committee (see 3.7, 6.12 and A.14);

— Clarify situations of reduced adverse events reporting requirements (see 7.4.2);

— Inclusion of management of risks related to clinical procedures required by the CIP (see 7.4.5);

— Clarified process of suspension or premature termination of the clinical investigation also in line with updated sections 7.4.4 and Figure H.1 (see 8.2);

— Update of procedure section in CIP with methods and timing for assessing, recording and analysing variables and added requirement for calibration of equipment (see A.6.4);

— Clarified requirements for non-inferiority margins and missing data (see A.7);

— Added requirement to justify absence of DMC involvement (see A.14);

— Added requirement for subject follow up and continued care to include those different from normal practice (see A.16);

— Clarification on local representative for better harmonisation with national regulatory requirements (see 9.2.1);

— Include requirement for implant card (see 9.2.2);

— Moved general requirements to clause 6.4 on objective and study design (see A.5);

— Updated adverse events categorization clarifying terminology in updated flowchart F1 (see Annex F);

— Clarification in Annex H in line with 6.2.1 and updated flowchart (see Annex H);

— Inclusion of estimands and their attributes (see, 6.4, A.5, A.6, A.7, new Annex K);

— Inclusion of precautions (see Clause B.5), information on training on the use of investigational device (see B.2), and in-silico tests (see B.3).

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Clinical investigation of medical devices for human subjects — Good clinical practice

1 Scope

This document addresses good clinical practice for the design, conduct, recording and reporting of clinical investigations carried out in human subjects to assess the clinical performance or effectiveness and safety of medical devices.

For post-market clinical investigations, the principles set forth in this document are intended to be followed as far as relevant, considering the nature of the clinical investigation (see Annex I).

This document specifies general requirements intended to:

— protect the rights, safety and well-being of human subjects,

— ensure the scientific conduct of the clinical investigation and the credibility of the clinical investigation results,

— define the responsibilities of the sponsor and principal investigator, and

— assist sponsors, investigators, ethics committees, regulatory authorities and other bodies involved in the conformity assessment of medical devices.

NOTE 1 Users of this document need to consider whether other standards and/or national requirements also apply to the investigational device(s) under consideration or the clinical investigation. If differences in requirements exist, the most stringent apply.

NOTE 2 For Software as a Medical Device (SaMD) demonstration of the analytical validity (the SaMD's output is accurate for a given input), and where appropriate, the scientific validity (the SaMD's output is associated to the intended clinical condition/physiological state), and clinical performance (the SaMD's output yields a clinically meaningful association to the target use) of the SaMD, the requirements of this document apply as far as relevant (see Reference [5]). Justifications for exemptions from this document can consider the uniqueness of indirect contact between subjects and the SaMD.This document does not apply to *in vitro* diagnostic medical devices. However, there can be situations, dependent on the device and national or regional requirements, where users of this document might consider whether specific sections and/or requirements of this document could be applicable.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 14971, *Medical devices — Application of risk management to medical devices*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1
adverse device effect
ADE
adverse event (3.2) related to the use of an *investigational medical device* (3.30)

Note 1 to entry: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any *malfunction* (3.34) of the investigational medical device.

Note 2 to entry: This definition includes any event resulting from *use error* (3.53) or from intentional misuse of the investigational medical device.

Note 3 to entry: This includes *'comparator'* (3.13) if the comparator is a medical device.

3.2
adverse event
AE
untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including abnormal laboratory findings) in *subjects* (3.51), users or other persons, whether or not related to the *investigational medical device* (3.30) and whether anticipated or unanticipated

Note 1 to entry: This definition includes events related to the investigational medical device or the *comparator* (3.13).

Note 2 to entry: This definition includes events related to the use of the investigational medical device and the clinical procedure(s) required by the CIP that are additional to normal clinical practice.

Note 3 to entry: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

3.3
audit
systematic examination of activities and documents related to a *clinical investigation* (3.9) performed by (an) *independent* (3.27) person(s), to determine whether these activities were conducted, and the data recorded, analysed and accurately reported, according to the CIP, standard operating procedures, this document and applicable regulatory requirements

3.4
audit trail
documentation that allows reconstruction of the course of events

3.5
blinding
masking
procedure in which one or more parties to the *clinical investigation* (3.9) are kept unaware of the treatment assignment(s)

Note 1 to entry: Single blinding usually refers to the *subject(s)* (3.51) being unaware of the treatment assignment(s). Double blinding usually refers to the subject(s), *investigator(s)* (3.31), monitor and, in some cases, centralized assessors being unaware of the treatment assignment(s).

Note 2 to entry: A clinical investigation is termed 'observer blind', if at least the *primary endpoint(s)* (3.23) is/are assessed without knowledge of whether an *investigational medical device* (3.30) or *comparator* (3.13) has been used to treat a subject.

3.6
case report form
CRF
set of printed, optical or electronic documents for each *subject* (3.51) on which information to be reported to the *sponsor* (3.50) is recorded, as required by the CIP

3.7
Clinical events committee
CEC
independent committee of clinical experts that can be established by the sponsor to ensure consistent event assessment across participating centres and mitigate inadequate reporting risks

Note 1 to entry: For the purpose of this document, "central events committee", ''clinical adjudication committee (CAC)'', ''endpoint adjudication committee (EAC)'' are synonymous with CEC.

3.8
certified copy
copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information including data that describe the context, content, and structure, as the original

3.9
clinical investigation
systematic investigation in one or more human *subjects* (3.51), undertaken to assess the *clinical performance* (3.12), *effectiveness* (3.21) or safety of a *medical device* (3.35)

Note 1 to entry: For the purpose of this document, "clinical trial" or "clinical study" are synonymous with "clinical investigation".

3.10
clinical investigation plan
CIP
document that states the rationale, *objectives* (3.38), design and pre-specified analysis, methodology, organization, *monitoring* (3.36), conduct and record-keeping of the *clinical investigation* (3.9)

Note 1 to entry: For the purpose of this document "protocol" is synonymous with "CIP". However, protocol has many different meanings, some not related to clinical investigation, and these can differ from country to country. Therefore, the term CIP is used in this document.

3.11
clinical investigation report
document describing the design, conduct, statistical analysis and results of a *clinical investigation* (3.9)

3.12
clinical performance

ability of a *medical device* (3.35), resulting from any direct or indirect medical effects which stem from its technical or functional characteristics, including diagnostic characteristics, to achieve its intended purpose as claimed by the manufacturer, thereby leading to a clinical benefit for *subject(s)* (3.51), when used as intended by the manufacturer

Note 1 to entry: Clinical performance can be defined under national regulations.

3.13
comparator
medical device (3.35), therapy (e.g. active treatment, normal clinical practice), placebo or no treatment, used in the *control group* (3.16) in a *clinical investigation* (3.9)

3.14
computer system
hardware and software (including associated documents, e.g. user manual) that creates, modifies, maintains, archives, retrieves, or transmits in digital form information related to the conduct of a *clinical investigation* (3.9)

3.15
contract research organization
CRO
person or organization contracted by the *sponsor* (3.50) to perform one or more of the sponsor's clinical investigation-related duties and functions

3.16
control group
group of *subjects* (3.51) that receives the *comparator* (3.13)

Note 1 to entry: A control group may be concurrent or historical, or subjects may serve as their own control.

3.17
coordinating investigator
investigator (3.31) who is appointed by the *sponsor* (3.50) to assist in coordinating the work in a multicentre *clinical investigation* (3.9)

Note 1 to entry: For the purpose of this document, “national investigator” or “global investigator” are synonymous with “coordinating investigator”.

3.18
data monitoring committee
DMC
independent (3.27) committee that can be established by the *sponsor* (3.50) to assess, at intervals, the progress of the *clinical investigation* (3.9), the safety data or the critical *clinical performance* (3.12) or *effectiveness* (3.21) *endpoints* (3.23, 3.24) and to recommend to the sponsor whether to continue, suspend, modify, or stop the clinical investigation

Note 1 to entry: For the purpose of this document, “data and safety monitoring board (DSMB)”, “data and safety monitoring committee (DSMC)" or "independent data monitoring committee (IDMC)” are synonymous with DMC.

3.19
deviation
instance of failure to follow, intentionally or unintentionally, the requirements of the *CIP* (3.10)

3.20
device deficiency
inadequacy in the identity, quality, durability, reliability, usability, safety or performance of a *medical device* (3.35), including *malfunctions* (3.34), *use errors* (3.53), or inadequacy in the information supplied by the manufacturer including labelling

Note 1 to entry: This definition includes device deficiencies related to the *investigational medical device* (3.30) or the *comparator* (3.13).

3.21
effectiveness
achievement of a clinically meaningful intended result in a defined portion of the target population when the *investigational medical device* (3.30) is used within its intended uses and according to its instructions for use, the *investigator’s brochure* (3.32) and the *CIP* (3.10), as determined by documented scientific evidence

3.22
electronic record
combination of text, graphics, data, audio, imaging, or other information in digital form that is created, modified, maintained, archived, retrieved, or distributed by a *computer system* (3.14)

EXAMPLE An electronic CRF.

3.23
endpoint
<primary> principal indicator(s) used for providing the evidence for *clinical performance* (3.12), *effectiveness* (3.21) or safety in a *clinical investigation* (3.9)

3.24
endpoint
<secondary> indicator(s) used for assessing the secondary *objectives* (3.38) of a *clinical investigation* (3.9)