



SLOVENSKI STANDARD
oSIST prEN ISO 14155:2018
01-september-2018

**Klinične raziskave medicinskih pripomočkov za ljudi - Dobre klinične prakse
(ISO/DIS 14155:2018)**

Clinical investigation of medical devices for human subjects - Good clinical practice
(ISO/DIS 14155:2018)

Klinische Prüfung von Medizinprodukten an Menschen - Gute klinische Praxis (ISO/DIS
14155:2018)

Investigation clinique des dispositifs médicaux pour sujets humains - Bonnes pratiques
cliniques (ISO/DIS 14155:2018)

Ta slovenski standard je istoveten z: prEN ISO 14155

ICS:

11.040.01	Medicinska oprema na splošno	Medical equipment in general
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oSIST prEN ISO 14155:2018	en
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DRAFT INTERNATIONAL STANDARD

ISO/DIS 14155

ISO/TC 194

Secretariat: DIN

Voting begins on:
2018-06-19Voting terminates on:
2018-09-11

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

Investigation clinique des dispositifs médicaux pour sujets humains — Bonnes pratiques cliniques

ICS: 11.100.20

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SIST EN ISO 14155:2020

<https://standards.iteh.ai/catalog/standards/sist/e948d5ad-2764-42b0-b6b0-e8255d9fb758/sist-en-iso-14155-2020>

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Reference number
ISO/DIS 14155:2018(E)

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Published in Switzerland

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ISO/DIS 14155:2018(E)

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).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation on 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 the following URL: www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 194, *Biological and clinical evaluation of medical devices*.

This third edition cancels and replaces the second edition (see ISO 14155:2011), which has been technically revised.

The main changes compared to the previous edition are as follows:

- inclusion of a summary section of GCP principles (see [Clause 4](#));
- reference to registration of the clinical investigation in a publicly accessible data base (see [5.4](#));
- inclusion of guidance with regards to clinical quality management (see [9.1](#));
- inclusion of risk-based monitoring (see [6.7](#));
- inclusion of guidance statistical considerations (see [Annex A](#));
- inclusion of guidance for ethics committees (see [Annex G](#));
- reinforcement of risk management throughout the process of a clinical investigation (planning to consideration of results) including [Annex H](#);
- clarification of applicability of the requirements of this standard to the different clinical development stages (see [Annex I](#));
- inclusion of guidance on clinical investigation audits (see [Annex J](#)).

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 pre-market clinical investigations carried out in human subjects to assess the clinical performance or effectiveness and safety of medical devices.

The principles set forth in this document also apply to post-market clinical investigations and should be followed as far as relevant, considering the nature of the clinical investigation and the requirements of national regulations (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 This standard can be used for regulatory purposes.

NOTE 2 Users of this International Standard will need to consider whether other standards and/or requirements also apply to the investigational device(s) under consideration.

NOTE 3 For Software as a Medical Device (SaMD), justifications for exemptions of this standard can consider the uniqueness of indirect contact between subjects and the SaMD. However it is required to demonstrate 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 (see Reference [5]).

This document does not apply to *in vitro* diagnostic medical devices.

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 standardisation at the following addresses:

- IEC Electropedia: available at <http://www.electropedia.org/>
- ISO Online browsing platform: available at <http://www.iso.org/obp>

ISO/DIS 14155:2018(E)**3.1
adverse device effect
ADE**

adverse event related to the use of an investigational medical device

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 of the investigational medical device.

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

**3.2
adverse event
AE**

untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device

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

Note 2 to entry: This definition includes events related to the procedures involved.

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

**3.3
audit**

systematic independent examination of activities and documents related to clinical investigation to determine whether these activities were conducted, and the data recorded, analysed and accurately reported, according to the CIP, standard operating procedures, this International Standard 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 are kept unaware of the treatment assignment(s)

Note 1 to entry: Single blinding usually refers to the subject(s) being unaware of the treatment assignment(s). Double blinding usually refers to the subject(s), investigator(s), 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) is/are assessed without knowledge of whether an investigational medical device or comparator has been used to treat a subject.

**3.6
case report forms
CRFs**

set of printed, optical or electronic documents for each subject on which information to be reported to the sponsor is recorded, as required by the CIP

**3.7
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

3.8**clinical investigation**

systematic investigation in one or more human subjects, undertaken to assess the clinical performance, effectiveness or safety of a medical device

Note 1 to entry: "Clinical trial" or "clinical study" are synonymous with "clinical investigation".

3.9**clinical investigation plan****CIP**

document that state(s) the rationale, objectives, design and pre-specified analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation

Note 1 to entry: The term "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 International Standard.

3.10**clinical investigation report**

document describing the design, execution, statistical analysis and results of a clinical investigation

3.11**clinical performance**

behaviour of a medical device and response of the subject(s) to that medical device in relation to its intended use, when correctly applied to appropriate subject(s)

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

3.12**comparator**

medical device, therapy (e.g. active treatment, standard of care), placebo or no treatment, used in the control group in a clinical investigation [EN ISO 14155:2020](https://standards.iteh.ai/catalog/standards/sist/e948d5ad-2764-42b0-b6b0-e8255d9fb758/sist-en-iso-14155-2020)

3.13**computer system**

includes hardware, software, and 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

3.14**contract research organisation****CRO**

person or organisation contracted by the sponsor to perform one or more of the sponsor's clinical investigation-related duties and functions

3.15**control group**

group of subjects that receives the comparator.

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

3.16**coordinating investigator**

investigator who is appointed by the sponsor to take responsibility to assist in coordinating the work in a multicentre clinical investigation

Note 1 to entry: "National investigator" or "global investigator" are synonymous with coordinating investigator.

ISO/DIS 14155:2018(E)**3.17****data monitoring committee****DMC**

independent committee that may be established by the sponsor to assess, at intervals, the progress of the clinical investigation, the safety data or the critical performance or effectiveness endpoints and to recommend the sponsor whether to continue, suspend, modify, or stop the clinical investigation

Note 1 to entry: Examples of DMCs are “data and safety monitoring board (DSMB)” or “data and safety monitoring committee (DSMC) or independent data monitoring committee (IDMC)”.

3.18**deviation**

instance(s) of failure to follow, intentionally or unintentionally, the requirements of the CIP

3.19**device deficiency**

inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance

Note 1 to entry: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.

Note 2 to entry: This definition includes device deficiencies related to the investigational medical device or the comparator.

3.20**effectiveness**

documented scientific evidence that the medical device produces clinically significant results in a defined portion of the target population when used within its intended uses and according to its instructions for use, the IB and the CIP

3.21**electronic record**

combination of text, graphics, data, audio, imaging, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system

Note 1 to entry: An electronic CRF is an example of an electronic record.

3.22**endpoint(s)**

<primary> principal indicator(s) used for providing the evidence for clinical performance, effectiveness or safety in a clinical investigation

3.23**endpoint(s)**

<secondary> indicator(s) used for assessing the secondary objectives of a clinical investigation

3.24**ethics committee****EC**

independent body whose responsibility it is to review clinical investigations in order to protect the rights, safety and well-being of human subjects participating in a clinical investigation

Note 1 to entry: For the purposes of this International Standard, “ethics committee” is synonymous with “research ethics committee”, “independent ethics committee” or “institutional review board”. The regulatory requirements pertaining to ethics committees or similar institutions vary by country or region.

3.25**hypothesis**

testable statement, derived from the objective of the clinical investigation to draw a conclusion about this objective, based on a pre-specified statistical test

Note 1 to entry: The primary hypothesis is formulated based on the pre-defined primary endpoint. and is usually used to calculate the sample size.

3.26**independent**

not involved in the conduct of a clinical investigation, except for their specifically assigned responsibilities, in order to avoid bias or a conflict of interest

3.27**informed consent**

process by which an individual voluntarily confirms willingness to participate in a particular clinical investigation, after having been informed of all aspects of the investigation that are relevant for the decision to participate

3.28**investigation site**

institution or site where the clinical investigation is carried out

Note 1 to entry: For the purpose of this International Standard, “investigation site” is synonymous with “investigation centre”.

3.29**investigational medical device**

medical device being assessed for clinical performance, effectiveness or safety in a clinical investigation

Note 1 to entry: This includes medical devices already on the market that are being evaluated for new intended uses, new populations, new materials or design changes. <https://standards.iteh.ai/catalog/standards/sist/e948d5ad-2764-42b0-b6b0-155:2020>

Note 2 to entry: This includes medical devices already on the market that are being evaluated within their intended use in a post market clinical investigation (interventional or non-interventional).

Note 3 to entry: In this International Standard, the terms “investigational medical device” and “investigational device” are used interchangeably.

3.30**investigator**

individual member of the investigation site team designated and supervised by the principal investigator at an investigation site to perform clinical investigation-related procedures or to make important clinical investigation-related and medical treatment decisions

Note 1 to entry: An individual member of the investigation site team can also be called “sub-investigator” or “co-investigator”.

3.31**investigator's brochure****IB**

compilation of the current clinical and non-clinical information on the investigational medical device(s), relevant to the clinical investigation

3.32**legally designated representative**

individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical investigation

Note 1 to entry: “Legally authorized representative” or “legally acceptable representative” are other terminologies used under national regulations for “legally designated representative”.

ISO/DIS 14155:2018(E)**3.33****malfunction**

failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP, or IB

3.34**medical device**

instrument, apparatus, implement, machine, appliance, implant, reagent for *in vitro* use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific purpose(s) of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease;
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury;
- investigation, replacement, modification, or support of the anatomy or of a physiological process;
- supporting or sustaining life;
- control of conception;
- disinfection of medical devices;
- providing information by means of *in vitro* examination of specimens derived from the human body;

and does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means

Note 1 to entry: products which may be considered to be medical devices in some jurisdictions but not in others include:

- disinfection substances;
- aids for persons with disabilities;
- devices incorporating animal and/or human tissues;
- devices for *in vitro* fertilization or assisted reproduction technologies.

[SOURCE: ISO 13485:2016, 3.11]

3.35**monitoring**

act of overseeing the progress of a clinical investigation and to ensure that it is conducted, recorded, and reported in accordance with the CIP, written procedures, this International Standard, and the applicable regulatory requirements

3.36**multicentre investigation**

clinical investigation that is conducted according to a single CIP and takes place at two or more investigation sites

3.37**objective**

main purpose for conducting the clinical investigation

3.38**point of enrolment**

time at which, following recruitment and before any clinical investigation-related procedures are undertaken, a subject signs and dates the informed consent form

3.39**principal investigator**

qualified person responsible for conducting the clinical investigation at an investigation site

Note 1 to entry: If a clinical investigation is conducted by a team of individuals at an investigation site, the principal investigator is responsible for leading the team.

Note 2 to entry: Whether this is the responsibility of an individual or an institution can depend on national regulations.

3.40**quality assurance**

planned and systematic actions that are established to ensure that the clinical investigation is performed, and the data are generated, documented (recorded), and reported in compliance with this standard and the applicable regulatory requirement(s)

3.41**quality control**

operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the clinical investigation-related activities have been fulfilled

3.42**randomisation**

process of assigning subjects to the investigational medical device or control groups using an established recognized statistical method using an element of chance to determine the unforeseeable assignment in order to reduce bias

3.43**recruitment**

active efforts to identify subjects who can be suitable for enrolment into the clinical investigation

3.44**serious adverse device effect****SADE**

adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event

3.45**serious adverse event****SAE**

adverse event that led to any of the following

- a) death,
- b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:
 - 1) a life-threatening illness or injury, or
 - 2) a permanent impairment of a body structure or a body function including chronic diseases, or
 - 3) in-patient or prolonged hospitalisation, or
 - 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- c) foetal distress, foetal death or a congenital abnormality or birth defect including physical or mental impairment

Note 1 to entry: Planned hospitalisation for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.