INTERNATIONAL STANDARD

ISO 14155

Redline version
compares Fourth editon to
Third edition

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

Investigation clinique des dispositifs médicaux pour sujets humains — Bonne pratique clinique

Reference number
ISO 14155:redline:2020(E)

IMPORTANT

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Text example 1 — Text has been added (in green)

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1.x ... — If there are changes in a clause/subclause, the corresponding clause/subclause number is highlighted in yellow in the Table of contents

IMPORTANT

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Foreword

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~~International Standards are~~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 ~~rules given in~~editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

~~The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.~~

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).

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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 the following URL: www.iso.org/iso/foreword.html.

~~ISO 14155~~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 ~~second~~third edition cancels and replaces the ~~first edition of~~second edition (ISO 14155~~:2003~~:2011 ~~and the first edition of ISO 14155-2:2003~~), which ~~have~~has been technically revised. The main changes 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 database (see 5.4);

— inclusion of clinical quality management (see 9.1);

— inclusion of risk-based monitoring (see 6.7);

— inclusion of statistical considerations in Annex A;

— inclusion of guidance for ethics committees in 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 document to the different clinical development stages (see Annex I);

— inclusion of guidance on clinical investigation audits (see Annex J).

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

~~The~~For post-market clinical investigations, the principles set forth in this ~~International Standard also apply to all other clinical investigations and should~~document are intended to be followed as far as ~~possible~~relevant, considering the nature of the clinical investigation (see Annex I~~and the requirements of national regulations~~).

This ~~International Standard~~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.

~~It does not apply to *in vitro* diagnostic medical devices.~~

NOTE 1 ~~Standards developed by ISO/TC 194 are intended to be applied to medical devices. Users of this International Standard will~~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 [4]). 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 ~~referenced~~ documents are ~~indispensable for the application of~~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~~:2007~~, *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 http://www.iso.org/obp

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

3.1
adverse device effect
ADE
~~adverse event~~ *adverse event* (3.2) related to the use of an investigational ~~medical device~~*medical device* (3.34)

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~~*malfunction* (3.33) of the investigational medical device.

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

Note 3 to entry: This includes '*comparator*' (3.12) if the comparator is a medical device.

3.2
adverse event
AE
~~any~~ untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in ~~subjects~~*subjects* (3.50), users or other persons, whether or not related to the ~~investigational medical device~~*investigational medical device* (3.29) and whether anticipated or unanticipated

Note 1 to entry: This definition includes events related to the investigational medical device or the ~~comparator~~*comparator* (3.12).

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 or comparators.

3.3
audit
systematic ~~independent~~ examination of activities and documents related to ~~clinical investigation~~a *clinical investigation* (3.8) performed by (an) *independent* (3.26) 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 ~~International Standard~~document and applicable regulatory requirements

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

~~3.4~~3.5
blinding~~/masking~~
masking
procedure in which one or more parties to the ~~clinical investigation~~ *clinical investigation* (3.8) are kept unaware of the treatment assignment(s)

Note 1 to entry: Single blinding usually refers to the ~~subject(s)~~*subject(s)* (3.50) being unaware of the treatment assignment(s). Double blinding usually refers to the subject(s), ~~investigator(s)~~*investigator(s)* (3.30), 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)* (3.22) is/are assessed without knowledge of whether an investigational medical device (3.29) or *comparator* (3.12) has been used to treat a subject.

~~3.5~~3.6
case report ~~forms~~form
~~CRFs~~CRF
set of printed, optical or electronic documents for each ~~subject~~*subject* (3.50) on which information to be reported to the ~~sponsor~~*sponsor* (3.49) 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

~~3.6~~3.8
clinical investigation
systematic investigation in one or more human ~~subjects~~*subjects* (3.50), undertaken to assess the ~~safety~~ *clinical performance* (3.11), *effectiveness* (3.20) or ~~performance~~safety of a ~~medical device~~*medical device* (3.34)

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

~~3.7~~3.9
clinical investigation plan
CIP
document that ~~state(s)~~states the rationale, ~~objectives~~*objectives* (3.37), design and ~~proposed~~pre-specified analysis, methodology, ~~monitoring~~organization, *monitoring* (3.35), conduct and record-keeping of the ~~clinical investigation~~*clinical investigation* (3.8)

Note 1 to entry: ~~The term~~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 ~~International Standard~~document.

~~3.8~~3.10
clinical investigation report
document describing the design, execution, statistical analysis and results of a ~~clinical investigation~~*clinical investigation* (3.8)

~~3.9~~3.11
clinical performance
behaviour of a ~~medical device or~~ *medical device* (3.34) and response of the ~~subject(s)~~*subject(s)* (3.50) to that medical device in relation to its intended use, when correctly applied to appropriate subject(s)

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

~~3.10~~3.12
comparator
~~medical device~~*medical device* (3.34), therapy (e.g. active ~~control~~treatment, normal clinical practice), placebo or no treatment, used in the ~~reference group~~ *control group* (3.15) in a ~~clinical investigation~~*clinical investigation* (3.8)

3.13
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* (3.8)

~~3.11~~3.14
contract research organization
CRO
person or organization contracted by the ~~sponsor~~*sponsor* (3.49) to perform one or more of the sponsor's clinical investigation-related duties and functions

3.15
control group
group of *subjects* (3.50) that receives the *comparator* (3.12)

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

~~3.12~~3.16
coordinating investigator
~~investigator~~*investigator* (3.30) who is appointed by the ~~sponsor~~*sponsor* (3.49) to ~~coordinate~~assist in coordinating the work in a multicentre ~~clinical investigation~~*clinical investigation* (3.8)

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

~~3.13~~3.17
data monitoring committee
DMC
~~independent~~*independent* (3.26) committee that can be established by the ~~sponsor~~*sponsor* (3.49) to assess, at intervals, the progress of the ~~clinical investigation~~*clinical investigation* (3.8), the safety data or the critical ~~performance endpoints~~*clinical performance* (3.11) or *effectiveness* (3.20)*endpoints* (3.22) and to recommend to the sponsor whether to continue, suspend, modify, or stop the clinical investigation

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

~~3.14~~3.18
deviation
instance~~(s)~~ of failure to follow, intentionally or unintentionally, the requirements of the ~~CIP~~*CIP* (3.9)

~~3.15~~3.19
device deficiency
inadequacy of a ~~medical device~~ *medical device* (3.34) with respect to its identity, quality, durability, reliability, usability, safety or performance

Note 1 to entry: Device deficiencies include ~~malfunctions~~*malfunctions* (3.33), ~~use errors~~*use errors* (3.53), and ~~inadequate~~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* (3.29) or the *comparator* (3.12).

3.20
effectiveness
achievement of a clinically significant intended result in a defined portion of the target population when the *investigational medical device* (3.29) is used within its intended uses and according to its instructions for use, the *investigator's brochure* (3.31) and the *CIP* (3.9), as determined by documented scientific evidence

3.21
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* (3.13)

EXAMPLE An electronic CRF.

~~3.16~~3.22
endpoint~~(s)~~
~~(primary)~~ <primary> principal indicator(s) used for ~~assessing the primary hypothesis of~~providing the evidence for *clinical performance* (3.11), *effectiveness* (3.20)~~a clinical investigation~~ or safety in a *clinical investigation* (3.8)

~~3.17~~3.23
endpoint~~(s)~~
~~(secondary)~~ <secondary> indicator(s) used for assessing the secondary ~~hypotheses~~*objectives* (3.37) of a ~~clinical investigation~~*clinical investigation* (3.8)

~~3.18~~3.24
ethics committee
EC
~~independent~~*independent* (3.26) body whose responsibility it is to review ~~clinical investigations~~ *clinical investigations* (3.8) in order to protect the rights, safety, and well-being of human ~~subjects~~*subjects* (3.50) participating in a clinical investigation

Note 1 to entry: For the purposes of this ~~International Standard~~document, "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.

~~3.19~~3.25
hypothesis
testable statement, ~~resulting~~derived from the ~~objective, regarding~~*objective* (3.37) ~~the investigational medical device safety or performance that is used~~of the *clinical investigation* (3.8) to ~~design the clinical investigation and that can be accepted or rejected based on results of the clinical investigation and statistical calculations~~draw a conclusion about this objective, based on a pre-specified statistical test

Note 1 to entry: The primary hypothesis is ~~the determinant of the investigational medical device safety or performance parameters~~formulated based on the pre-defined *primary endpoint* (3.22) and is usually used to calculate the sample size. ~~Secondary hypotheses concerning other points of interest can also be evaluated.~~

~~3.20~~3.26
independent
not involved in the development of the investigational device or the conduct of a ~~clinical investigation~~*clinical investigation* (3.8), except for their specifically assigned responsibilities, in order to avoid bias or a conflict of interest

~~3.21~~3.27
informed consent ~~process~~
process by which an individual ~~is provided information and is asked to voluntarily~~ voluntarily confirms willingness to participate in a ~~clinical~~particular *clinical investigation* (3.8)~~investigation~~, after having been informed of all aspects of the investigation that are relevant to the decision to participate

~~Note 1 to entry: Informed consent is documented by means of a written, signed and dated informed consent form.~~

~~3.22~~3.28
investigation site
institution or site where the ~~clinical investigation~~ *clinical investigation* (3.8) is carried out

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

~~3.23~~3.29
investigational medical device
~~medical device~~ *medical device* (3.34) being assessed for ~~safety~~ *clinical performance* (3.11), *effectiveness* (3.20), or ~~performance~~safety in a ~~clinical investigation~~*clinical investigation* (3.8)

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.

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~~For the purpose of this document, the terms "investigational medical device" and "investigational device" are used interchangeably.

~~3.24~~3.30
investigator
individual member of the ~~investigation site~~ *investigation site* (3.28) team designated and supervised by the ~~principal investigator~~ *principal investigator* (3.39) at an investigation site to perform ~~critical~~ 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".

~~3.25~~3.31
investigator's brochure
IB
compilation of the current clinical and non-clinical information on the ~~investigational medical device(s)~~*investigational medical device(s)* (3.29), relevant to the ~~clinical investigation~~*clinical investigation* (3.8)

~~3.26~~3.32
legally ~~authorized~~designated representative
individual ~~or~~, judicial, or other body authorized under applicable law to consent, on behalf of a prospective ~~subject~~*subject* (3.50), to the subject's participation in the ~~clinical investigation~~*clinical investigation* (3.8)

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

~~3.27~~3.33
malfunction
failure of an ~~investigational medical device~~ *investigational medical device* (3.29) to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP, or IB

~~3.28~~3.34
medical device
~~any~~ 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* (3.35), treatment or alleviation of disease;

— diagnosis, monitoring, treatment, alleviation of or compensation for an injury;

~~a)~~ — ~~intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of~~investigation, replacement, modification, or support of the anatomy or of a physiological process;

~~1) diagnosis, prevention, monitoring, treatment or alleviation of disease,~~

~~2) diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury,~~

~~3) investigation, replacement, modification, or support of the anatomy or of a physiological process,~~

~~4) supporting or sustaining life,~~

~~5) control of conception,~~

~~6) disinfection of medical devices, and~~

