INTERNATIONAL STANDARD

ISO 14155

Second edition
2011-02-01

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

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

Reference number
ISO 14155:2011(E)

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Published in Switzerland

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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.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

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.

ISO 14155 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*.

This second edition cancels and replaces the first edition of ISO 14155-1:2003 and the first edition of ISO 14155-2:2003, which have been technically revised.

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

1 Scope

This International Standard 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 of medical devices for regulatory purposes.

The principles set forth in this International Standard also apply to all other clinical investigations and should be followed as far as possible, considering the nature of the clinical investigation and the requirements of national regulations.

This International Standard 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 Standards developed by ISO/TC 194 are intended to be applied to medical devices. Users of this International Standard will need to consider whether other standards and/or requirements also apply to the investigational device(s) under consideration.

2 Normative references

The following referenced documents are indispensable for the application 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.

3.1
adverse device effect
ADE
adverse event related to the use of an investigational medical device

NOTE 1 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 This definition includes any event resulting from use error or from intentional misuse of the investigational 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, users or other persons, whether or not related to the investigational medical device

NOTE 1 This definition includes events related to the investigational medical device or the comparator.

NOTE 2 This definition includes events related to the procedures involved.

NOTE 3 For users or other persons, this definition is restricted to events related to 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
blinding/masking
procedure in which one or more parties to the clinical investigation are kept unaware of the treatment assignment(s)

NOTE 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).

3.5
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

3.6
clinical investigation
systematic investigation in one or more human subjects, undertaken to assess the safety or performance of a medical device

NOTE "Clinical trial" or "clinical study" are synonymous with "clinical investigation".

3.7
clinical investigation plan
CIP
document that state(s) the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation

NOTE 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.

3.8
clinical investigation report
document describing the design, execution, statistical analysis and results of a clinical investigation

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

3.10
comparator
medical device, therapy (e.g. active control), placebo or no treatment, used in the reference group in a clinical investigation

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

3.12
coordinating investigator
investigator who is appointed by the sponsor to coordinate work in a multicentre clinical investigation

3.13
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 endpoints and to recommend the sponsor whether to continue, suspend, modify, or stop the clinical investigation

NOTE Examples of DMCs are “data safety monitoring board (DSMB)” or “data safety monitoring committee (DSMC)”.

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

3.15
device deficiency
inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance

NOTE Device deficiencies include malfunctions, use errors, and inadequate labelling.

3.16
endpoint(s)
⟨primary⟩ principal indicator(s) used for assessing the primary hypothesis of a clinical investigation

3.17
endpoint(s)
⟨secondary⟩ indicator(s) used for assessing the secondary hypotheses of a clinical investigation

3.18
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 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.

3.19
hypothesis
testable statement, resulting from the objective, regarding the investigational medical device safety or performance that is used to design the clinical investigation and that can be accepted or rejected based on results of the clinical investigation and statistical calculations

NOTE The primary hypothesis is the determinant of the investigational medical device safety or performance parameters and is usually used to calculate the sample size. Secondary hypotheses concerning other points of interest can also be evaluated.

3.20
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

3.21
informed consent process
process by which an individual is provided information and is asked to voluntarily participate in a clinical investigation

NOTE Informed consent is documented by means of a written, signed and dated informed consent form.

3.22
investigation site
institution or site where the clinical investigation is carried out

NOTE For the purpose of this International Standard, “investigation site” is synonymous with “investigation centre”.

3.23
investigational medical device
medical device being assessed for safety or performance in a clinical investigation

NOTE 1 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 In this International Standard, the terms “investigational medical device” and “investigational device” are used interchangeably.

3.24
investigator
individual member of the investigation site team designated and supervised by the principal investigator at an investigation site to perform critical clinical-investigation-related procedures or to make important clinical-investigation-related decisions

NOTE An individual member of the investigation site team can also be called “sub-investigator” or “co-investigator”.

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

3.26
legally authorized 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

3.27
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

3.28
medical device
any instrument, apparatus, implement, machine, appliance, implant, software, material, or other similar or related article

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

   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

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

NOTE The term “medical device” is usually defined by national regulations. For the purposes of this International Standard, this definition does not list “*in vitro* diagnostic medical devices” (see ISO 13485:2003, definition 3.7[1]).

3.29
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

3.30
multicentre investigation
clinical investigation that is conducted according to a single CIP and takes place at two or more investigation sites

3.31
objective
main purpose for conducting the clinical investigation

3.32
point of enrolment
time at which, following recruitment, a subject signs and dates the informed consent form

3.33
principal investigator
qualified person responsible for conducting the clinical investigation at an investigation site

NOTE 1 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 Whether this is the responsibility of an individual or an institution can depend on national regulations.

3.34
randomization
process of assigning subjects to the investigational medical device or comparator groups using an established recognized statistical methodology to determine the assignment in order to reduce bias

3.35
recruitment
active efforts to identify subjects who may be suitable for enrolment into the clinical investigation

3.36
serious adverse device effect
SADE
adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event

3.37
serious adverse event
SAE
adverse event that

a) led to death,

b) led to serious deterioration in the health of the subject, that either resulted in

   1) a life-threatening illness or injury, or

   2) a permanent impairment of a body structure or a body function, or

   3) in-patient or prolonged hospitalization, 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) led to foetal distress, foetal death or a congenital abnormality or birth defect

NOTE Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

3.38
source data
all information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation

3.39
source document
printed, optical or electronic document containing source data

EXAMPLES Hospital records, laboratory notes, device accountability records, photographic negatives, radiographs, records kept at the investigation site, at the laboratories and at the medico-technical departments involved in the clinical investigation.

3.40
sponsor
individual or organization taking responsibility and liability for the initiation or implementation of a clinical investigation

NOTE When an investigator initiates, implements and takes full responsibility for the clinical investigation, the investigator also assumes the role of the sponsor and is identified as the sponsor-investigator.

3.41
subject
individual who participates in a clinical investigation

NOTE A subject can be either a healthy volunteer or a patient.

3.42
unanticipated serious adverse device effect
USADE
serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report

NOTE Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

3.43
use error
act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user

NOTE 1 Use error includes slips, lapses, and mistakes.

NOTE 2 An unexpected physiological response of the subject does not in itself constitute a use error.

[ISO 14971:2007, definition 2.27]

3.44
vulnerable subject
individual whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate

EXAMPLE Individuals with lack of or loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving informed consent. Other vulnerable subjects include, for example, members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the sponsor, members of the armed forces, and persons kept in detention.

4 Ethical considerations

4.1 General

Clinical investigations shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (see Reference [8]). These principles protect the rights, safety and well-being of human subjects, which are the most important considerations and shall prevail over interests of science and society. These principles shall be understood, observed, and applied at every step in the clinical investigation.

4.2 Improper influence or inducement

The sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the clinical investigation.

All investigators shall avoid improper influence on or inducement of the subject, sponsor, monitor, other investigator(s) or other parties participating in or contributing to the clinical investigation.

4.3 Compensation and additional health care

Compensating subjects for costs resulting from participation in the clinical investigation (e.g. transportation) may be appropriate if allowed by national regulations, but the compensation shall not be so large as to unduly encourage the subjects to participate.

Arrangements for additional health care for subjects who suffer from an adverse event as a result of participating in the clinical investigation shall be made and documented.

NOTE Such arrangements can be subject to national regulations.

4.4 Responsibilities

All parties involved in the conduct of the clinical investigation shall share the responsibility for its ethical conduct in accordance with their respective roles in the clinical investigation.

4.5 Communication with the ethics committee (EC)

4.5.1 General

If national or regional EC requirements are less strict than the requirements of this International Standard, the sponsor shall apply the requirements of this International Standard to the greatest extent possible, irrespective of any lesser requirements, and shall record such efforts.

4.5.2 Initial EC submission

As a minimum, the following information and any amendments shall be provided to the EC:

a) CIP;

b) IB or equivalent documentation;

c) informed consent form and any other written information to be provided to subjects;

d) procedures for recruiting subjects and advertising materials, if any;

e) a copy of the curriculum vitae (CV) of the principal investigator(s) for which the EC has oversight.

The following documents might also need to be provided to the EC depending on the clinical investigation design and national or regional requirements:

f) sample or draft CRFs, including other data collection tools, as required by the CIP;

g) documents related to payments and compensation available to subjects;

h) proposed compensation to the institution or principal investigator;

i) documentation related to any conflict of interest, including financial, on the part of an investigator;

j) evidence of the clinical investigation insurance.

4.5.3 Information to be obtained from the EC

Prior to commencing the clinical investigation, the sponsor shall obtain documentation of the EC's approval/favourable opinion identifying the documents and amendments on which the opinion was based.

NOTE The sponsor can request the EC opinion voting list for the clinical investigation to document that members of the investigation site team were not part of the voting.

4.5.4 Continuing communication with the EC

The following information shall be provided to the EC, if required by national regulations, the CIP or the EC, whichever is more stringent:

a) serious adverse events;

b) requests for deviations, and reports of deviations, if the deviation affects subject's rights, safety and well-being, or the scientific integrity of the clinical investigation;

   Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the EC. Such deviations shall be documented and reported to the sponsor and the EC as soon as possible.

c) progress reports, including safety summary and deviations;

d) amendments to any documents already approved by the EC;

   NOTE For non-substantial changes [e.g. minor logistical or administrative changes, change of monitor(s), telephone numbers, renewal of insurance] not affecting the rights, safety and well-being of human subjects or not related to the clinical investigation objectives or endpoints, a simple notification to the EC and, where appropriate, regulatory authorities can be sufficient.

e) if applicable, notifications of suspensions or premature termination;

f) if applicable, justification and request for resuming the clinical investigation after a suspension;

g) clinical investigation report or its summary.

4.5.5 Continuing information to be obtained from the EC

As a minimum, during the clinical investigation, the following information shall be obtained in writing from the EC prior to implementation:

a) approval/favourable opinion of amendments, as stated in 4.5.4 d);

b) approval of the request for deviations that can affect the subject's rights, safety and well-being or the scientific integrity of the clinical investigation, as stated in 4.5.4 b);

c) approval for resumption of a suspended clinical investigation, as stated in 4.5.4 f), if applicable.

4.6 Vulnerable populations

Clinical investigations shall be conducted in vulnerable populations only when they cannot be carried out in non-vulnerable populations and shall follow the additional EC procedures where applicable. These clinical investigations shall be designed specifically to address health problems that occur in the vulnerable population, and offer the possibility of direct health-related benefit to the vulnerable population.