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

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

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Contents

Page

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 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.

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

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 third edition cancels and replaces the second edition (ISO 14155:2011), which 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 guidance with regards to clinical quality management (see 9.1);

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

— inclusion of guidance 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 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 can 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 http://www.iso.org/obp

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

3.1
adverse device effect
ADE
adverse event (3.2) related to the use of an investigational *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* (3.33) 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*' (3.12) if the comparator is a medical device.

3.2
adverse event
AE
untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in *subjects* (3.50), users or other persons, whether or not related to the *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* (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.

3.3
audit
systematic examination of activities and documents related to 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 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* (3.8) are kept unaware of the treatment assignment(s)

Note 1 to entry: Single blinding usually refers to the *subject(s)* (3.50) being unaware of the treatment assignment(s). Double blinding usually refers to the subject(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.

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

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

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

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

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.

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

3.11
clinical performance
behaviour of a *medical device* (3.34) and response of the *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.

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

3.14
contract research organization
CRO
person or organization contracted by the *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.

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

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

3.17
data monitoring committee
DMC
independent (3.26) committee that can be established by the *sponsor* (3.49) to assess, at intervals, the progress of the *clinical investigation* (3.8), the safety data or the critical *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: 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.

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

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

Note 1 to entry: Device deficiencies include *malfunctions* (3.33), *use errors* (3.53), 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* (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.

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

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

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

Note 1 to entry: For the purposes of this 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.

3.25
hypothesis
testable statement, derived from the *objective* (3.37) of the *clinical investigation* (3.8) 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* (3.22) and is usually used to calculate the sample size.

3.26
independent
not involved in the development of the investigational device or the conduct of a *clinical investigation* (3.8), 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* (3.8), after having been informed of all aspects of the investigation that are relevant to the decision to participate

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

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

3.29
investigational medical device
medical device (3.34) being assessed for *clinical performance* (3.11), *effectiveness* (3.20), or safety in a *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: For the purpose of this document, the terms "investigational medical device" and "investigational device" are used interchangeably.

3.30
investigator
individual member of the *investigation site* (3.28) team designated and supervised by the *principal investigator* (3.39) 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)* (3.29), relevant to the *clinical investigation* (3.8)

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

3.33
malfunction
failure of an *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

3.34
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* (3.35), 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* (3.8) to ensure that it is conducted, recorded, and reported in accordance with the CIP, written procedures, this document, and the applicable regulatory requirements

Note 1 to entry: Centralized monitoring is a remote evaluation of accumulated data and compliance to provide additional monitoring capabilities that can complement or reduce the extent and frequency of on-site monitoring.

3.36
multicentre investigation
clinical investigation (3.8) that is conducted according to a single CIP and takes place at two or more *investigation sites* (3.28)

3.37
objective
main purpose for conducting the *clinical investigation* (3.8)

3.38
point of enrolment
time at which, following *recruitment* (3.43) and before any clinical investigation-related procedures are undertaken, a *subject* (3.50) signs and dates the *informed consent* (3.27) form

3.39
principal investigator
qualified person responsible for conducting the *clinical investigation* (3.8) at an *investigation site* (3.28)

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* (3.8) is performed, and the data are generated, documented (recorded), and reported in compliance with this document and the applicable regulatory requirement(s)

3.41
quality control
operational techniques and activities undertaken within the *quality assurance* (3.40) system to verify that the requirements for quality of the clinical investigation-related activities have been fulfilled

3.42
randomization
process of assigning *subjects* (3.50) to the *investigational medical device* (3.29) or *control groups* (3.15) 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* (3.50) who can be suitable for enrolment into the *clinical investigation* (3.8)

3.44
serious adverse device effect
SADE
adverse device effect (3.1) that has resulted in any of the consequences characteristic of a *serious adverse event* (3.45)

3.45
serious adverse event
SAE
adverse event (3.2) that led to any of the following

a) death,