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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

<b>Foreword</b>	<b>vi</b>
<b>1 Scope</b>	<b>1</b>
<b>2 Normative references</b>	<b>1</b>
<b>3 Terms and definitions</b>	<b>1</b>
<b>4 Summary of good clinical practice (GCP) principles</b>	<b>9</b>
<b>5 Ethical considerations</b>	<b>10</b>
5.1 General	10
5.2 Improper influence or inducement	10
5.3 Compensation and additional health care	10
5.4 Registration in publicly accessible database	10
5.5 Responsibilities	11
5.6 Communication with the ethics committee (EC)	11
5.6.1 General	11
5.6.2 Initial EC submission	11
5.6.3 Information to be obtained from the EC	11
5.6.4 Continuing communication with the EC	12
5.6.5 Continuing information to be obtained from the EC	12
5.7 Vulnerable populations	12
5.8 Informed consent	13
5.8.1 General	13
5.8.2 Process of obtaining informed consent	13
5.8.3 Special circumstances for informed consent	13
5.8.4 Information to be provided to the subject	15
5.8.5 Informed consent signature	17
5.8.6 New information	17
<b>6 Clinical investigation planning</b>	<b>17</b>
6.1 General	17
6.2 Risk management	17
6.2.1 General	17
6.2.2 Investigational device including clinical procedure risks and their disclosure	18
6.2.3 Clinical investigation process	18
6.3 Justification for the design of the clinical investigation	18
6.4 Clinical investigation plan (CIP)	19
6.5 Investigator's brochure (IB)	19
6.6 Case report forms (CRFs)	19
6.7 Monitoring plan	20
6.8 Investigation site selection	21
6.9 Agreement(s)	21
6.10 Labelling	21
6.11 Data monitoring committee (DMC)	21
<b>7 Clinical investigation conduct</b>	<b>22</b>
7.1 General	22
7.2 Investigation site initiation	22
7.3 Investigation site monitoring	22
7.4 Adverse events and device deficiencies	22
7.4.1 Signals requiring immediate action	22
7.4.2 Adverse events	22
7.4.3 Device deficiencies	23
7.4.4 Risk assessment process for potentially unacceptable risks	23
7.5 Clinical investigation documents and documentation	24
7.5.1 Amendments	24
7.5.2 Subject identification log	24

7.5.3	Source documents .....	24
7.6	Additional members of the investigation site team .....	24
7.7	Subject privacy and confidentiality of data .....	24
7.8	Document and data control .....	25
7.8.1	Traceability of documents and data .....	25
7.8.2	Recording of data .....	25
7.8.3	Electronic clinical data systems .....	26
7.9	Investigational device accountability .....	26
7.10	Accounting for subjects .....	27
7.11	Auditing .....	27
<b>8</b>	<b>Suspension, termination, and close-out of the clinical investigation .....</b>	<b>28</b>
8.1	Completion of the clinical investigation .....	28
8.2	Suspension or premature termination of the clinical investigation .....	28
8.2.1	Procedure for suspension or premature termination .....	28
8.2.2	Procedure for resuming the clinical investigation after temporary suspension .....	29
8.3	Routine close-out .....	29
8.4	Clinical investigation report .....	29
8.5	Risk assessment and conclusions .....	30
8.6	Document retention .....	30
<b>9</b>	<b>Responsibilities of the sponsor .....</b>	<b>30</b>
9.1	Clinical quality management .....	30
9.2	Clinical investigation planning and conduct .....	31
9.2.1	Selection and training of clinical personnel .....	31
9.2.2	Preparation of documents and materials .....	32
9.2.3	Conduct of clinical investigation .....	32
9.2.4	Monitoring .....	33
9.2.5	Safety evaluation and reporting .....	36
9.2.6	Clinical investigation close-out .....	36
9.3	Outsourcing of duties and functions .....	37
9.4	Communication with regulatory authorities .....	37
<b>10</b>	<b>Responsibilities of the principal investigator .....</b>	<b>37</b>
10.1	General .....	37
10.2	Qualification of the principal investigator .....	38
10.3	Qualification of investigation site .....	38
10.4	Communication with the EC .....	38
10.5	Informed consent process .....	39
10.6	Compliance with the CIP .....	39
10.7	Medical care of subjects .....	40
10.8	Safety reporting .....	40
	<b>Annex A (normative) Clinical investigation plan (CIP) .....</b>	<b>41</b>
	<b>Annex B (normative) Investigator's brochure (IB) .....</b>	<b>50</b>
	<b>Annex C (informative) Case report forms (CRFs) .....</b>	<b>53</b>
	<b>Annex D (normative) Clinical investigation report .....</b>	<b>55</b>
	<b>Annex E (informative) Essential clinical investigation documents .....</b>	<b>60</b>
	<b>Annex F (informative) Adverse event categorization .....</b>	<b>67</b>
	<b>Annex G (informative) EC responsibilities .....</b>	<b>69</b>
	<b>Annex H (informative) Application of ISO 14971 to clinical investigations .....</b>	<b>73</b>
	<b>Annex I (informative) Clinical development stages .....</b>	<b>74</b>
	<b>Annex J (informative) Clinical investigation audits .....</b>	<b>79</b>
	<b>Annex ZA (informative) Relationship between this European Standard and the essential requirements of Directive 93/42/EEC [OJ L 169] aimed to be covered .....</b>	<b>82</b>

<b>Annex ZB (informative) Relationship between this European Standard and the essential requirements of Directive 90/385/EEC [OJ L 189] aimed to be covered</b> .....	<b>84</b>
<b>Annex ZC (informative) Relationship between this European standard and Article 62 and Annex XV of Regulation (EU) 2017/745 aimed to be covered</b> .....	<b>86</b>
<b>Bibliography</b> .....	<b>91</b>

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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](http://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](http://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](http://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](http://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,