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Redline version compares Fourth edition to Third edition

ISO 14155

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 ... **vi**

Introduction ... **ix**

1 Scope ... **1**

2 Normative references ... **1**

3 Terms and definitions ... **1**

4 Summary of good clinical practice ~~(GCP)~~ principles ... **11**

5 Ethical considerations ... **12**
5.1 General ... 12
5.2 Improper influence or inducement ... 12
5.3 Compensation and additional health care ... 12
5.4 Registration in publicly accessible database ... 12
5.5 Responsibilities ... 12
5.6 Communication with the ethics committee ~~(EC)~~ ... 13
5.6.1 General ... 13
5.6.2 Initial EC submission ... 13
5.6.3 Information to be obtained from the EC ... 14
5.6.4 Continuing communication with the EC ... 14
5.6.5 Continuing information to be obtained from the EC ... 14
5.7 Vulnerable populations ... 15
5.8 Informed consent ... 15
5.8.1 General ... 15
5.8.2 Process of obtaining informed consent ... 15
5.8.3 Special circumstances for informed consent ... 16
5.8.4 Information to be provided to the subject ... 17
5.8.5 Informed consent signature ... 19
5.8.6 New information ... 19

6 Clinical investigation planning ... **19**
6.1 General ... 19
6.2 Risk management ... 20
6.2.1 General ... 20
6.2.2 ~~Investigational device including clinical procedure risks~~ Risks related to the use of the investigational device and their disclosure ... 20
6.2.3 Risks related to clinical procedures required by the CIP outside routine clinical practice ... 21
~~6.2.3~~6.2.4 ~~Clinical~~ Risks related to the clinical investigation process ... 21
6.3 Justification for the design of the clinical investigation ... 21
6.4 Clinical investigation plan ~~(CIP)~~ ... 22
6.5 Investigator's brochure ~~(IB)~~ ... 22
6.6 Case report forms ~~(CRFs)~~ ... 22
6.7 Monitoring plan ... 23
6.8 Investigation site selection ... 24
6.9 Agreement(s) ... 24
6.10 Labelling ... 24
6.11 Data monitoring committee ~~(DMC)~~ ... 24
6.12 Clinical events committee ... 25

7 Clinical investigation conduct ... **25**
7.1 General ... 25
7.2 Investigation site initiation ... 25
7.3 Investigation site monitoring ... 25
7.4 Adverse events and device deficiencies ... 26
7.4.1 Signals requiring immediate action ... 26
7.4.2 Adverse events ... 26

7.4.3 Device deficiencies ... 26
7.4.4 Risk assessment process for potentially unacceptable risks related to the use of the investigational device ... 27
7.4.5 Management of risks related to clinical procedures required by the CIP outside routine clinical practice ... 28
7.5 Clinical investigation documents and documentation ... 28
7.5.1 Amendments ... 28
7.5.2 Subject identification log ... 28
7.5.3 Source documents ... 28
7.6 Additional members of the investigation site team ... 28
7.7 Subject privacy and confidentiality of data ... 29
7.8 Document and data control ... 29
7.8.1 Traceability of documents and data ... 29
7.8.2 Recording of data ... 29
7.8.3 Electronic clinical data systems ... 30
7.9 Investigational device accountability ... 30
7.10 Accounting for subjects ... 31
7.11 Auditing ... 31

8 Suspension, termination and close-out of the clinical investigation ... 32
8.1 Completion of the clinical investigation ... 32
8.2 Suspension or premature termination of the clinical investigation ... 32
~~8.2.1 Procedure for suspension or premature termination~~ ... 32
8.2.1 General ... 32
8.2.2 Procedure for suspension ... 33
8.2.3 Procedure for premature termination ... 33
~~8.2.2~~ 8.2.4 Procedure for resuming the clinical investigation after ~~temporary~~ suspension ... 33
8.3 Routine close-out ... 34
8.4 Clinical investigation report ... 34
8.5 Risk assessment and conclusions ... 35
8.6 Document retention ... 35

9 Responsibilities of the sponsor ... 35
9.1 Clinical quality management ... 35
9.2 Clinical investigation planning and conduct ... 36
9.2.1 Selection and training of clinical personnel ... 36
9.2.2 Preparation of documents and materials ... 37
9.2.3 Conduct of clinical investigation ... 38
9.2.4 Monitoring ... 38
9.2.5 Safety evaluation and reporting ... 41
9.2.6 Clinical investigation close-out ... 41
9.3 Outsourcing of duties and functions ... 42
9.4 Communication with regulatory authorities ... 42

10 Responsibilities of the principal investigator ... 42
10.1 General ... 42
10.2 Qualification of the principal investigator ... 43
10.3 Qualification of investigation site ... 43
10.4 Communication with the EC ... 43
10.5 Informed consent process ... 44
10.6 Compliance with the CIP ... 44
10.7 Medical care of subjects ... 45
10.8 Safety reporting ... 45

Annex A (normative) **Clinical investigation plan ~~(CIP)~~ ... 46**
Annex B (normative) **Investigator's brochure ~~(IB)~~ ... 55**
Annex C (informative) **Case report forms ~~(CRFs)~~ ... 58**
Annex D (normative) **Clinical investigation report ... 60**

Annex E (informative) **Essential clinical investigation documents** **65**
Annex F (informative) **Adverse event categorization** **74**
Annex G (informative) **EC responsibilities** **78**
Annex H (informative) **Application of ISO 14971 ~~to~~ during clinical investigations** **82**
Annex I (informative) **Clinical development stages** **84**
Annex J (informative) **Clinical investigation audits** **89**
Annex K (informative) **Clinical investigation design considerations** **92**
Bibliography **94**

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~~document 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).

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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.~~, see www.iso.org/iso/foreword.html.

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~~fourth edition cancels and replaces the ~~second~~third edition (ISO 14155:~~2011~~2020), which has been technically revised. ~~The main changes to the previous edition are as follows:~~

The main changes are as follows:

— changed definition of clinical performance (3.12);

— clarified deviations from eligibility criteria not being permitted but subject to CIP amendment (see 5.6.4);

— clarified informed consent to be obtained where applicable from subject's legally designated representative (see 5.8.1);

— clarified subject must be given opportunity to discuss participation with others e.g. family members (see 5.8.2);

— clarified risk management by making clear distinction between risks related to the use of the device and risks related to the procedures required by the CIP which are not part of routine clinical practice (see 6.2.1);

— included required assessment of residual risks (see 6.2.2);

— corrected reference to risks related to the use of the investigational device (see 6.2.1, 7.4.4, 8.2, Annex F, Annex H and 3.2);

— added requirements (previously in Annex A) to 6.4;

— added requirement for data monitoring committee to confirm conditions for suspending or stopping the clinical investigation (see 6.11);

— included new section on clinical events committee (see 3.8, 6.12 and Clause A.14);

— clarified situations of reduced adverse events reporting requirements (see 7.4.2);

— included management of risks related to clinical procedures required by the CIP (see 7.4.5);

— clarified process of suspension or premature termination of the clinical investigation also in line with updated 7.4.4 and Figure H.1 (see 8.2);

— updated procedure section in CIP with methods and timing for assessing, recording and analysing variables and added requirement for calibration of equipment (see A.6.4);

— ~~inclusion of a summary section of GCP principles~~clarified requirements for non-inferiority margins and missing data (see Clause ~~4~~A.7);

— ~~reference to registration of the clinical investigation in a publicly accessible database (see 5.4);~~

— added requirement to justify absence of DMC involvement (see Clause A.14);

— added requirement for subject follow up and continued care to include those different from normal practice (see Clause A.16);

— ~~inclusion of clinical quality management (see 9.1);~~

— clarified aspects of local representative for better harmonisation with national regulatory requirements (see 9.2.1);

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

— included requirement for implant card (see 9.2.2);

— ~~inclusion of statistical considerations in Annex A;~~

— moved general requirements to 6.4 on objective and study design (see Clause A.5);

— ~~inclusion of guidance for ethics committees in Annex G;~~

— updated adverse events categorization clarifying terminology in Figure F.1;

— ~~reinforcement of risk management throughout the process of a clinical investigation (planning to consideration of results) including Annex H;~~

— updated Annex H in line with 6.2.1 and updated Figure H.1;

— ~~clarification of applicability of the requirements of this document to the different clinical development stages (see Annex I);~~

— included principles of estimands and their attributes (see 6.4, Clause A.5, Clause A.6, Clause A.7 and Annex K);

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

— included precautions (see Clause B.5), information on training on the use of investigational device (see Clause B.2), and in-silico tests (see Clause B.3).

— added an adverse event associated with a device deficiency – both Figure F.1 and Figure F.2 now apply.

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.

Introduction

For the purpose of this document, the use of the term compliance is applied when compliance to clinical investigation requirements and good clinical practice as per this document is required. In case of requirements outlined in regulatory documents or other standards the term ‘conformance with’ is applied.

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

1 Scope

This document ~~addresses~~specifies good clinical practice (GCP) 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 are intended to be followed as far as relevant, considering the nature of the clinical investigation (see Annex I).

This document specifies the general requirements intended to

— protect the rights, safety and well-being of human subjects, users or other persons,

— 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.~~

Other standards or national requirements can also apply to the investigational device(s) under consideration or the clinical investigation(s).

NOTE ~~2~~ For Software as a Medical Device (SaMD), where appropriate, 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~~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~~can consider whether either specific sections ~~and/~~or requirements of this document ~~could~~, or both, can 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~~terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obphttps://www.iso.org/obp

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

3.1
adverse device effect
ADE
adverse event (3.2) related to the use of an ~~investigational~~ *investigational medical device* (~~3.34~~3.30)

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~~3.34) 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~~) definition applies to *'comparator'* (3.13) if the comparator is a medical device.

3.2
adverse event
AE
untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including abnormal laboratory findings) in *subjects* (~~3.50~~3.51), users or other persons, whether or not related to the use of the *investigational medical device* (~~3.29~~3.30) and whether anticipated or unanticipated

Note 1 to entry: This definition includes events related to the use of the investigational medical device or the *comparator* (~~3.12~~3.13) and the clinical procedure(s) required by the *clinical investigation plan* (*CIP*) (3.10) that are outside to routine clinical practice but not related to the use of the device.

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

Note 2 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 examination of activities and documents related to a *clinical investigation* (~~3.0~~3.9) performed by (an) *independent* (~~3.26~~3.27) person(s), to determine whether these activities were conducted, and the data recorded, analysed and accurately reported, ~~according to the CIP~~ in compliance with the *clinical investigation plan* (*CIP*) (3.10), standard operating procedures, this document and in conformance with 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* (~~3.0~~3.9) are kept unaware of the treatment assignment(s)

Note 1 to entry: Single blinding usually refers to the *subject(s)* (~~3.50~~3.51) being unaware of the treatment assignment(s). Double blinding usually refers to the subject(s), *investigator(s)* (~~3.30~~3.31), 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~~3.23) is/are assessed without knowledge of whether an ~~investigational~~ *investigational medical device* (3.30) ~~medical device (3.29)~~ or *comparator* (~~3.12~~3.13) 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~~3.51) on which information to be reported to the *sponsor* (~~3.49~~3.50) is recorded, as required by the ~~CIP~~ *clinical investigation plan* (*CIP*) (3.10)

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 events committee
CEC
central events committee
clinical adjudication committee
CAC
endpoint adjudication committee
EAC
independent (3.27) committee of clinical experts that can be established by the *sponsor* (3.50) to ensure consistent event assessment across participating centres and mitigate inadequate reporting risks

~~**3.8**~~
3.9
clinical investigation
clinical trial
clinical study
systematic investigation in one or more human *subjects* (~~3.50~~3.51), undertaken to assess the *clinical performance* (~~3.11~~3.12), *effectiveness* (3.20) or safety of a *medical device* (~~3.34~~3.35)

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

~~**3.9**~~
3.10
clinical investigation plan
CIP
protocol
document that states the rationale, *objectives* (~~3.37~~3.38), design and pre-specified analysis, methodology, organization, *monitoring* (~~3.35~~3.36), conduct and record-keeping of the *clinical investigation* (~~3.8~~3.9)

Note 1 to entry: ~~For the purpose of this document "protocol" is synonymous with "CIP". However, protocol~~ As the term "protocol" has many different meanings, some not related to clinical investigation, and as these can differ from country to country~~. Therefore~~ , the term CIP is used in this document.

~~**3.10**~~
3.11
clinical investigation report
clinical study report
document describing the design, ~~execution~~ conduct, statistical analysis and results of a *clinical investigation* (~~3.8~~3.9)

~~**3.11**~~
3.12
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)~~

ability of a *medical device* (3.35), resulting from any direct or indirect medical effects which stem from its technical or functional characteristics, including diagnostic characteristics, to achieve its intended purpose as claimed by the manufacturer, thereby leading to a clinical benefit for *subject(s)* (3.51), when used as intended by the manufacturer

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

Note 2 to entry: Not all clinical investigations have clinical benefits to subjects e.g. healthy volunteers, clinical investigations only gathering data etc.

~~**3.12**~~
3.13
comparator
medical device (~~3.34~~3.35), therapy (e.g. active treatment, ~~normal~~ routine clinical practice), placebo, sham or no treatment, used in the *control group* (3.15) in a *clinical investigation* (~~3.8~~3.9)

~~**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~~3.50) to perform one or more of the sponsor's clinical investigation-related duties and functions

3.15
control group
group of *subjects* (~~3.50~~3.51) that receives the *comparator* (~~3.12~~3.13)

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

3.16
coordinating investigator
national investigator
global investigator
investigator (~~3.30~~3.31) who is appointed by the *sponsor* (~~3.49~~3.50) to assist in coordinating the work in a multicentre *clinical investigation* (~~3.8~~3.9)

~~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
data and safety monitoring board
DSMB
independent data monitoring committee
IDMC
data and safety monitoring committee
DSMC
independent (~~3.26~~3.27) committee that can be established by the *sponsor* (~~3.49~~3.50) to assess, at intervals, the progress of the *clinical investigation* (~~3.8~~3.9), the safety data or the critical *clinical performance* (~~3.11~~3.12) or *effectiveness* (3.20) *endpoints* (~~3.22~~3.23, 3.24) 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)", "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)~~*clinical investigation plan* (*CIP*) (3.10)

3.19
device deficiency
inadequacy ~~of a~~ in the ~~*medical device* (3.34) with respect to its~~ identity, quality, durability, reliability, usability, safety or performance of a *medical device* (3.35), including *malfunctions* (3.34), *use errors* (3.53) or inadequacy in the information supplied by the manufacturer including labelling

~~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 1 to entry: This definition includes device deficiencies related to the *investigational medical device* (~~3.29~~3.30) or the *comparator* (~~3.12~~3.13).

3.20
effectiveness
achievement of a clinically ~~significant~~ meaningful intended result in a defined portion of the target population when the *investigational medical device* (~~3.29~~3.30) is used within its intended uses and ~~according to~~ in compliance with its instructions for use, the *investigator's brochure* (~~3.31~~3.32) and the ~~*CIP* (3.9)~~*clinical investigation plan* (*CIP*) (3.10), as determined by documented scientific evidence

3.21
electronic clinical data system
hardware and software (including associated documents, such as a user manual) that creates, modifies, maintains, archives, retrieves or transmits in digital form information related to the conduct of a *clinical investigation* (3.9)

~~**3.21**~~
3.22
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~~ an ~~*computer*~~*electronic clinical data system* (~~3.13~~3.21)

EXAMPLE An electronic ~~CRF~~ case report form (CRF).

~~**3.22**~~
3.23
endpoint
<primary> principal indicator(s) used for providing the evidence for *clinical performance* (~~3.11~~3.12), *effectiveness* (3.20) or safety in a *clinical investigation* (~~3.8~~3.9)

~~**3.23**~~
3.24
endpoint
<secondary> indicator(s) used for assessing the secondary *objectives* (~~3.37~~3.38) of a *clinical investigation* (~~3.8~~3.9)