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Introduction

This draft standard is based on national and international discussions. Your comments on this draft are invited and will assist in the preparation of the consequent standard.

For international standards, comments will be reviewed by the relevant UK national committee before sending the consensus UK vote and comments to the international committee, which will then decide appropriate action. If the international standard is approved, it is usual for the text to be published as a British Standard.

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Template for comments and secretariat observations

Date: xx/xx/20xx	Document: ISO/DIS xxxx
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1	2	(3)	4	5	(6)	7
MB	Clause No./ Subclause No./Annex (e.g. 3.1)	Paragraph/ Figure/Table/Note	Type of comment	Comment (justification for change) by the MB	Proposed change by the MB	Secretariat observations on each comment submitted
	3.1	Definition 1	ed	Definition is ambiguous and needs clarifying.	Amend to read '...so that the mains connector to which no connection...'	
	6.4	Paragraph 2	te	The use of the UV photometer as an alternative cannot be supported as serious problems have been encountered in its use in the UK.	Delete reference to UV photometer.	



DRAFT International Standard

ISO/DIS 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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ISO/TC 194

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This document is circulated as received from the committee secretariat.

ISO/CEN PARALLEL PROCESSING

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Contents

Page

Foreword	vi
1 Scope	1
2 Normative references	1
3 Terms and definitions	1
4 Summary of good clinical practice (GCP) principles	9
5 Ethical considerations	10
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	10
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	11
5.6.5 Continuing information to be obtained from the EC	12
5.7 Vulnerable populations	12
5.8 Informed consent	12
5.8.1 General	12
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	14
5.8.5 Informed consent signature	16
5.8.6 New information	17
6 Clinical investigation planning	17
6.1 General	17
6.2 Risk management	17
6.2.1 General	17
6.2.2 Risks related to the use of the investigational device and their disclosure	17
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
6.12 Clinical events committee (CEC)	21
7 Clinical investigation conduct	22
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	23
7.4.3 Device deficiencies	23
7.4.4 Risk assessment process for potentially unacceptable risks related to the use of the investigational device	23
7.4.5 Management of risks related to clinical procedures required by the CIP	24
7.5 Clinical investigation documents and documentation	24

7.5.1	Amendments	24
7.5.2	Subject identification log	25
7.5.3	Source documents	25
7.6	Additional members of the investigation site team	25
7.7	Subject privacy and confidentiality of data	25
7.8	Document and data control	25
7.8.1	Traceability of documents and data	25
7.8.2	Recording of data	26
7.8.3	Electronic clinical data systems	26
7.9	Investigational device accountability	27
7.10	Accounting for subjects	27
7.11	Auditing	27
8	Suspension, termination, and close-out of the clinical investigation	28
8.1	Completion of the clinical investigation	28
8.2	Suspension or premature termination of the clinical investigation	28
8.2.1	General	28
8.2.2	Suspension	29
8.2.3	Procedure for premature termination	29
8.2.4	Procedure for resuming the clinical investigation after suspension	29
8.3	Routine close-out	30
8.4	Clinical investigation report	30
8.5	Risk assessment and conclusions	31
8.6	Document retention	31
9	Responsibilities of the sponsor	31
9.1	Clinical quality management	31
9.2	Clinical investigation planning and conduct	32
9.2.1	Selection and training of clinical personnel	32
9.2.2	Preparation of documents and materials	33
9.2.3	Conduct of clinical investigation	33
9.2.4	Monitoring	34
9.2.5	Safety evaluation and reporting	36
9.2.6	Clinical investigation close-out	37
9.3	Outsourcing of duties and functions	37
9.4	Communication with regulatory authorities	38
10	Responsibilities of the principal investigator	38
10.1	General	38
10.2	Qualification of the principal investigator	38
10.3	Qualification of investigation site	39
10.4	Communication with the EC	39
10.5	Informed consent process	39
10.6	Compliance with the CIP	39
10.7	Medical care of subjects	40
10.8	Safety reporting	41
	Annex A (normative) Clinical investigation plan (CIP)	42
	Annex B (normative) Investigator's brochure (IB)	50
	Annex C (informative) Case report forms (CRFs)	53
	Annex D (normative) Clinical investigation report	55
	Annex E (informative) Essential clinical investigation documents	60
	Annex F (informative) Adverse event categorization	67
	Annex G (informative) EC responsibilities	69
	Annex H (informative) Application of ISO 14971 during clinical investigations	73
	Annex I (informative) Clinical development stages	74
	Annex J (informative) Clinical investigation audits	79

Annex K (informative) Clinical investigation design considerations.....	82
Annex ZA (informative) Relationship between this European standard and the requirements of Regulation (EU) 2017/745 aimed to be covered.....	84
Bibliography.....	91

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).

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

- Change in definition of clinical performance ([3.12](#));
- Clarification about 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](#));
- Clarification on risk management 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 normal clinical practice (see [6.2.1](#));
- Inclusion of required assessment of residual risks including quantified estimation (see [6.2.2](#));
- Correction of 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 normative 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](#));
- Inclusion of new section on clinical events committee (see [3.7](#), [6.12](#) and [A.14](#));

- Clarify situations of reduced adverse events reporting requirements (see [7.4.2](#));
- Inclusion of 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 [sections 7.4.4](#) and [Figure H.1](#) (see [8.2](#));
- Update of 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](#));
- Clarified requirements for non-inferiority margins and missing data (see [A.7](#));
- Added requirement to justify absence of DMC involvement (see [A.14](#));
- Added requirement for subject follow up and continued care to include those different from normal practice (see [A.16](#));
- Clarification on local representative for better harmonisation with national regulatory requirements (see [9.2.1](#));
- Include requirement for implant card (see [9.2.2](#));
- Moved general requirements to [clause 6.4](#) on objective and study design (see [A.5](#));
- Updated adverse events categorization clarifying terminology in updated flowchart F1 (see [Annex F](#));
- Clarification in [Annex H](#) in line with [6.2.1](#) and updated flowchart (see [Annex H](#));
- Inclusion of estimands and their attributes (see, [6.4](#), [A.5](#), [A.6](#), [A.7](#), new [Annex K](#));
- Inclusion of precautions (see [Clause B.5](#)), information on training on the use of investigational device (see [B.2](#)), and in-silico tests (see [B.3](#)).

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 are intended to 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 <https://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 medical device* (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* (3.34) 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*’ (3.13) 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* (3.51), users or other persons, whether or not related to the *investigational medical device* (3.30) and whether anticipated or unanticipated

Note 1 to entry: This definition includes events related to the investigational medical device or the *comparator* (3.13).

Note 2 to entry: This definition includes events related to the use of the investigational medical device and the clinical procedure(s) required by the CIP that are additional to normal clinical practice.

Note 3 to entry: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

3.3 audit

systematic examination of activities and documents related to a *clinical investigation* (3.9) performed by (an) *independent* (3.27) 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* (3.9) are kept unaware of the treatment assignment(s)

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

3.7**Clinical events committee****CEC**

independent committee of clinical experts that can be established by the sponsor to ensure consistent event assessment across participating centres and mitigate inadequate reporting risks

Note 1 to entry: For the purpose of this document, “central events committee”, “clinical adjudication committee (CAC)”, “endpoint adjudication committee (EAC)” are synonymous with CEC.

3.8**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

3.9**clinical investigation**

systematic investigation in one or more human *subjects* (3.51), undertaken to assess the *clinical performance* (3.12), *effectiveness* (3.21) or safety of a *medical device* (3.35)

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

3.10**clinical investigation plan****CIP**

document that states the rationale, *objectives* (3.38), design and pre-specified analysis, methodology, organization, *monitoring* (3.36), conduct and record-keeping of the *clinical investigation* (3.9)

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.

3.11**clinical investigation report**

document describing the design, conduct, statistical analysis and results of a *clinical investigation* (3.9)

3.12**clinical performance**

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.

3.13**comparator**

medical device (3.35), therapy (e.g. active treatment, normal clinical practice), placebo or no treatment, used in the *control group* (3.16) in a *clinical investigation* (3.9)

3.14**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* (3.9)

3.15**contract research organization****CRO**

person or organization contracted by the *sponsor* (3.50) to perform one or more of the sponsor's clinical investigation-related duties and functions

3.16**control group**

group of *subjects* (3.51) that receives the *comparator* (3.13)

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

3.17**coordinating investigator**

investigator (3.31) who is appointed by the *sponsor* (3.50) to assist in coordinating the work in a multicentre *clinical investigation* (3.9)

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

3.18**data monitoring committee****DMC**

independent (3.27) committee that can be established by the *sponsor* (3.50) to assess, at intervals, the progress of the *clinical investigation* (3.9), the safety data or the critical *clinical performance* (3.12) or *effectiveness* (3.21) *endpoints* (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.

3.19**deviation**

instance of failure to follow, intentionally or unintentionally, the requirements of the *CIP* (3.10)

3.20**device deficiency**

inadequacy in the 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: This definition includes device deficiencies related to the *investigational medical device* (3.30) or the *comparator* (3.13).

3.21**effectiveness**

achievement of a clinically meaningful intended result in a defined portion of the target population when the *investigational medical device* (3.30) is used within its intended uses and according to its instructions for use, the *investigator’s brochure* (3.32) and the *CIP* (3.10), as determined by documented scientific evidence

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 *computer system* (3.14)

EXAMPLE An electronic CRF.

3.23**endpoint**

<primary> principal indicator(s) used for providing the evidence for *clinical performance* (3.12), *effectiveness* (3.21) or safety in a *clinical investigation* (3.9)

3.24**endpoint**

<secondary> indicator(s) used for assessing the secondary *objectives* (3.38) of a *clinical investigation* (3.9)

3.25**ethics committee****EC**

independent (3.27) body whose responsibility it is to review *clinical investigations* (3.9) in order to protect the rights, safety, and well-being of human *subjects* (3.51) participating in a *clinical investigation* (3.9)

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.

3.26**hypothesis**

testable statement, derived from the *objective* (3.38) of the *clinical investigation* (3.9) 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* (3.23) and is usually used to calculate the sample size.

3.27**independent**

not involved in the development of the investigational device or the conduct of a *clinical investigation* (3.9), except for their specifically assigned responsibilities, in order to avoid bias or a conflict of interest

3.28**informed consent**

process by which an individual voluntarily confirms willingness to participate in a particular *clinical investigation* (3.9), after having been informed of all aspects of the investigation that are relevant to the decision to participate

3.29**investigation site**

institution or site where the *clinical investigation* (3.9) is carried out

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

3.30**investigational medical device**

medical device (3.35) being assessed for safety, *clinical performance* (3.12) or *effectiveness* (3.21) in a *clinical investigation* (3.9)

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.

3.31**investigator**

individual member of the *investigation site* (3.29) team designated and supervised by the *principal investigator* (3.40) 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”.

3.32**investigator's brochure****IB**

compilation of the current clinical and non-clinical information on the *investigational medical device(s)* (3.30), relevant to the *clinical investigation* (3.9)

3.33**legally designated representative**

individual, judicial, or other body authorized under applicable law to consent, on behalf of a prospective *subject* (3.51), to the subject's participation in the *clinical investigation* (3.9)

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

3.34**malfunction**

failure of an *investigational medical device* (3.30) to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP, or IB

3.35**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* (3.36), 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]

3.36**monitoring**

act of overseeing the progress of a *clinical investigation* (3.9) 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.

3.37**multicentre investigation**

clinical investigation (3.9) that is conducted according to a single CIP and takes place at two or more *investigation sites* (3.29)

3.38

objective

main purpose for conducting the *clinical investigation* (3.9)

3.39

point of enrolment

time at which, following *recruitment* (3.44) and before any clinical investigation-related procedures are undertaken, a *subject* (3.51) signs and dates the *informed consent* (3.28) form

3.40

principal investigator

qualified person responsible for conducting the *clinical investigation* (3.9) at an *investigation site* (3.29)

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.

3.41

quality assurance

planned and systematic actions that are established to ensure that the *clinical investigation* (3.9) is performed, and the data are generated, documented (recorded), and reported in compliance with this document and the applicable regulatory requirement(s)

3.42

quality control

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

3.43

randomization

process of assigning *subjects* (3.52) to the *investigational medical device* (3.30) or *control groups* (3.16) using an established recognized statistical method based on an element of chance to determine the unforeseeable assignment in order to reduce bias

3.44

recruitment

active efforts to identify *subjects* (3.51) who can be suitable for enrolment into the *clinical investigation* (3.9)

3.45

serious adverse device effect

SADE

adverse device effect (3.1) that has resulted in any of the consequences characteristic of a *serious adverse event* (3.46)

3.46

serious adverse event

SAE

adverse event (3.2) that led to any of the following:

- a) death,
- b) serious deterioration in the health of the *subject* (3.51), users, or other persons as defined by one or more of the following:
 - 1) a life-threatening illness or injury, or
 - 2) a permanent impairment of a body structure or a body function including chronic disease, 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) foetal distress, foetal death, or a congenital abnormality, or birth defect including physical or mental impairment.

Note 1 to entry: Planned hospitalization for a pre-existing condition, or a procedure required by the *CIP* (3.10), without serious deterioration in health, is not considered a serious adverse event.

3.47

serious health threat

signal from any adverse event or *device deficiency* (3.20) that indicates an imminent risk of death or a serious deterioration in the health in *subjects* (3.51), users or other persons, and that requires prompt remedial action for other subjects, users or other persons

Note 1 to entry: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

3.48

source data

all information in original records, certified copies of original records of clinical findings, observations, or other activities in a *clinical investigation* (3.9), necessary for the reconstruction and evaluation of the clinical investigation

Note 1 to entry: This includes source data initially recorded in an electronic format.

3.49

source document

original or *certified copy* (3.8) of printed, optical or electronic document containing *source data* (3.48)

EXAMPLE Hospital records, laboratory notes, device accountability records, photographic negatives, radiographs, records kept at the *investigation site* (3.29), at the laboratories and at the medico-technical departments involved in the *clinical investigation* (3.9).

3.50

sponsor

individual, company, institution or organization taking responsibility and liability for the initiation and management of a *clinical investigation* (3.9), and arranging the financial setup

Note 1 to entry: When an *investigator* (3.31) 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.

3.51

subject

individual who is or becomes a participant in a *clinical investigation* (3.9), either as a recipient of the *investigational medical device* (3.30) or a *comparator* (3.13)

Note 1 to entry: This includes healthy volunteers.

3.52

unanticipated serious adverse device effect

USADE

serious adverse device effect (3.45) which by its nature, incidence, severity or outcome has not been identified in the current risk assessment

Note 1 to entry: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

3.53

use error

user action or lack of user action while using the *medical device* (3.35) that leads to a different result than that intended by the manufacturer or expected by the user

Note 1 to entry: Use error includes the inability of the user to complete a task.

Note 2 to entry: Use errors can result from a mismatch between the characteristics of the user, user interface, task or use environment.

Note 3 to entry: Users might be aware or unaware that a use error has occurred.

Note 4 to entry: An unexpected physiological response of the patient is not by itself considered a use error.

Note 5 to entry: A malfunction of a medical device that causes an unexpected result is not considered a use error.

[SOURCE: ISO 14971:2019, 3.30]

3.54

validation

confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled

3.55

verification

confirmation by examination and provision of objective evidence that specified requirements have been fulfilled

3.56

vulnerable subject

individuals who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response

4 Summary of good clinical practice (GCP) principles

- a) Clinical investigations shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (see Reference [8]), and that are consistent with this document.
- b) Before a clinical investigation is initiated, foreseeable risks and inconveniences shall be weighed against the anticipated benefit for the individual subject and society. A clinical investigation shall be initiated and continued only if the anticipated benefits justify the risk.
- c) The rights, safety, and well-being of human subjects are the most important considerations and shall prevail over interests of science and society.
- d) The available non-clinical and clinical information on the investigational device shall be adequate to support the proposed clinical investigation.
- e) Clinical investigations shall be scientifically sound and described in a clearly detailed CIP.
- f) A clinical investigation shall be conducted in compliance with the CIP that has received prior ethics committee approval/favourable opinion and, where applicable, approval/non-objection of regulatory authorities.
- g) The medical care given to, and medical decisions made on behalf of subjects shall always be the responsibility of a qualified healthcare professional.
- h) Individuals involved in designing, conducting, recording, and reporting a clinical investigation shall be qualified by education, training, and experience to perform his or her respective task(s).

- i) Freely given informed consent shall be obtained from every subject prior to the participation in the clinical investigation.

NOTE 1 Some exceptions can exist (see [5.8.3](#)).

- j) All clinical investigation related information shall be recorded, handled, and securely stored in a way that allows its accurate reporting, interpretation, monitoring, auditing, and verification.
- k) The confidentiality of records that could identify subjects shall be protected, respecting the privacy and confidentiality rules.
- l) Investigational devices shall be designed, manufactured, handled, and stored in accordance with the essential principles (see Reference [\[8\]](#)). They shall be used in accordance with the approved CIP, the IB and manufacturer's instructions for use.

NOTE 2 Essential principles can be further outlined in national regulations.

- m) Systems with procedures that ensure the quality of every aspect of the clinical investigation shall be implemented.

5 Ethical considerations

5.1 General

The principles outlined in [Clause 4](#) shall be understood, observed, and applied at every step in the clinical investigation.

5.2 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.

5.3 Compensation and additional health care

Compensating subjects for costs resulting from participation in the clinical investigation (e.g. transportation) can be appropriate, but the compensation shall not be so large as to unduly encourage the subjects to participate or affect the subject's ability to withdraw prematurely from the clinical investigation.

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 compensation and arrangements can be subject to national regulations.

5.4 Registration in publicly accessible database

In accordance with the Declaration of Helsinki, a description of the clinical investigation shall be registered in a publicly accessible database before the start of recruitment activities and the content shall be updated throughout the conduct of the clinical investigation and the results entered at completion of the clinical investigation.

NOTE National regulations can apply concerning the timing of registration or updating of the contents.

5.5 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.

5.6 Communication with the ethics committee (EC)

5.6.1 General

If national or regional EC requirements are less strict than the requirements of this document, the sponsor shall apply the requirements of this document to the greatest extent possible, irrespective of any lesser requirements, and shall record such efforts (see [Annex G](#)).

5.6.2 Initial EC submission

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

- a) the CIP;
- b) the IB or equivalent documentation;
- c) the informed consent form and any other written information to be provided to subjects;
- d) the 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:

- a) the sample or draft CRFs, including other data collection tools, as required by the CIP;
- b) the documents related to payments and compensation available to subjects;
- c) the clinical investigation agreement and proposed compensation to the investigation site or principal investigator;

NOTE Local requirements can apply to the possibility of submitting a draft version of the agreement.

- d) the documentation related to any conflict of interest, including financial, on the part of an investigator;
- e) the evidence of the clinical investigation insurance;
- f) the letter of the sponsor confirming outsourcing of duties and functions;
- g) a copy of the CV of other members of the investigation site team.

5.6.3 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 persons with conflict of interest or potential bias (e.g. members of the investigation site team) were not part of the voting.

5.6.4 Continuing communication with the EC

The following information shall be provided to the EC if required by 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; requests for deviations from eligibility criteria are not permitted, such changes require an amendment to the CIP (see [5.6.4 e](#));

- c) deviations from the CIP to protect the rights, safety and well-being of human subjects under emergency circumstances 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;
- d) progress reports, including safety summary and deviations;
- e) amendments to any documents already approved by the EC;

NOTE 1 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.

- f) if applicable, notifications of suspensions or premature termination;
- g) if applicable, justification and request for resuming the clinical investigation after a suspension;
- h) clinical investigation report or its summary;
- i) if applicable, a copy of the CV of additional members of the investigation site team.

NOTE 2 In addition to the EC and CIP requirements, national regulations can apply to any or all of the above.

5.6.5 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 [5.6.4 e\)](#);
- 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 [5.6.4 b\)](#);
- c) approval for resumption of a suspended clinical investigation, as stated in [5.6.4 g\)](#), if applicable.

5.7 Vulnerable populations

Clinical investigations shall not be conducted in vulnerable populations unless they cannot be carried out in non-vulnerable populations and shall follow the additional EC procedures where applicable.

NOTE 1 National regulations can also dictate additional procedures for clinical investigations on vulnerable populations.

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 and shall not be conducted when there is no potential for therapeutic benefit.

NOTE 2 These conditions might not apply to healthy volunteers.

5.8 Informed consent

5.8.1 General

Informed consent shall be obtained in writing from the subject or where applicable, the subject's legally designated representative and the process shall be documented before any procedure specific to the clinical investigation is applied to the subject, except when special circumstances described in [5.8.3.4](#) apply.

NOTE Dated signatures can be electronic.

The informed consent form consists of an information form (see [5.8.4](#)) and an informed consent signature form (see [5.8.5](#)). These two forms can either be combined in one document or separated into two documents.

5.8.2 Process of obtaining informed consent

The principal investigator or his/her authorized designee shall comply with the general process for obtaining informed consent as documented in the CIP including the following:

- a) explain all aspects of the clinical investigation that are relevant to the subject's decision to participate throughout the clinical investigation;
- b) avoid any coercion or undue improper influence on, or inducement of, the subject to participate;
- c) not waive or appear to waive the subject's legal rights;
- d) use lay-person, non-technical language that is understandable to the subject;
- e) provide ample time for the subject to read and understand the informed consent form and to if desired, discuss with others e.g. family members to consider participation in the clinical investigation;
- f) ensure personally dated signatures of the subject and the principal investigator or an authorized designee responsible for conducting the informed consent process;
- g) provide the subject with a copy of the signed and dated informed consent form and any other written information;
- h) ensure documentation of the process in the subject's source documents and maintain the investigation site's signed informed consents with the essential documents;
- i) show how informed consent is obtained and recorded in special circumstances (see [5.8.3](#)) where the subject is unable to provide it him- or herself;
- j) ensure important new information is provided to new and existing subjects throughout the clinical investigation, which may relate to the subject's willingness to continue participation in the clinical investigation.

The above requirements shall also apply with respect to informed consent obtained from a subject's legally designated representative.

NOTE The qualification of a principal investigator's authorized designee can be subject to national regulation.

5.8.3 Special circumstances for informed consent

5.8.3.1 General

The provisions given in [5.8.3.2](#) to [5.8.3.4](#) are subject to national regulations.

5.8.3.2 Subject needing legally designated representatives

Informed consent may be given by the legally designated representative only if a subject is unable to make the decision to participate in a clinical investigation (e.g., infant, child, or juvenile, seriously ill or unconscious subject, or subject with a mental or intellectual disability). In such cases, the subject shall also be informed about the clinical investigation within his/her ability to understand.

5.8.3.3 Subject unable to read or write

Informed consent shall be obtained through a supervised oral process if a subject or legally designated representative is unable to read or write. An independent and impartial witness shall be present throughout the process. The written informed consent form and any other information shall be read aloud and explained to the prospective subject or his/her legally designated representative. Whenever possible, either the subject or his/her legally designated representative shall sign and personally date the informed consent form. The witness shall sign and personally date the informed consent form attesting that the information was accurately explained, and that informed consent was freely given.

5.8.3.4 Emergency treatments

For clinical investigations involving emergency treatments, when prior informed consent of the subject is not possible because of the subject's medical condition, the informed consent of the subject's legally designated representative, if present, shall be requested.

When it is not possible to obtain prior informed consent from the subject, and the subject's legally designated representative is not available, the subject may still be enrolled if a specific process has been described in the CIP as given in [clause A.13 b](#)).

Arrangements shall be made to inform the subject or legally designated representative, as soon as possible,

- a) about the subject's inclusion in the clinical investigation, and
- b) about all aspects of the clinical investigation.

The subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows or from the legally designated representative as soon as the person is available.

The principal investigator may enrol a subject without obtaining the informed consent of the subject or his/her legally designated representative only when the following conditions are fulfilled:

- a) the prospective subject fulfils the emergency conditions and is obviously in a life-threatening situation;
- b) no sufficient clinical benefits are anticipated from the currently available treatment;
- c) there is a fair possibility that the life-threatening risk to the prospective subject can be avoided if the subject receives the treatment as specified in the CIP;
- d) anticipated risks are outweighed by the potential benefits of participation in the clinical investigation;
- e) the legally designated representative cannot be promptly reached and informed.

NOTE Requirements for conducting clinical investigations in emergency situations can be subject to national regulations.

5.8.4 Information to be provided to the subject

All information pertinent to the clinical investigation, including at least the following, shall be provided in writing and in native, non-technical language that is understandable to the subject (or the subject's legally designated representative).

NOTE 1 Additional elements can be required by national regulations.

- a) Description and purpose:
 - 1) statement that the clinical investigation involves research;
 - 2) purpose of the clinical investigation;
 - 3) anticipated duration of the clinical investigation, and extent of the involvement and responsibilities of each subject during the clinical investigation;
 - 4) description of the investigational device and comparator, if any;
 - 5) description of all procedures involving the subject;
 - 6) description concerning possible future use of samples collected from the subject or health-related data concerning the subject obtained during the clinical investigation, if applicable;
 - 7) aspects of the clinical investigation that are experimental, if applicable;
 - 8) description of the clinical investigation, including a mention of any comparison groups and the method of assignment to each group;

- 9) number of subjects expected to participate in the clinical investigation.
 - b) Potential benefits:
 - 1) description of benefits for the subject that can reasonably be expected (if there is no direct therapeutic benefit anticipated, this shall be noted);
 - 2) description of potential benefits for research or public health.
 - c) Risks and inconveniences for the subject and, when applicable, for an embryo, foetus, or nursing infant:
 - 1) description of anticipated adverse device effects;
 - 2) description of risks associated with the clinical procedures required by the CIP different to local standard practice;
 - 3) statement that unanticipated risks can occur;
 - 4) description of inconveniences.
 - d) Alternative procedure(s):
 - 1) information on established alternative treatments or procedures that can be available to the subject, and their potential benefits and risks.
 - e) Confidentiality:
 - 1) statement confirming that subject participation is confidential;
 - 2) statement confirming that records including samples identifying the subject will be kept confidential;
 - 3) statement confirming that the subject acknowledges that regulatory authorities, EC representatives and sponsor's representatives involved in the clinical investigation will have direct access to medical records;
 - 4) statement indicating that clinical investigation results may be published without disclosing the subject's identity;
 - 5) statement that the subject agrees to have personal data transported outside of the geographic region.
- NOTE 2 National requirements regarding personal data protection can apply to 2) and 5).
- f) Compensation:
 - 1) information about provisions for compensation available in the event of injury arising from participation in the clinical investigation;
 - 2) information about additional health care for subjects who suffer from an adverse event as a result of participating in the clinical investigation;
 - 3) information on financial compensation for participation, if applicable.
 - g) Anticipated expenses, if any, to be borne by the subject for participating in the clinical investigation.
 - h) Information on the role of sponsor's representative (e.g., monitor, product specialist, field engineer) in the clinical investigation.
 - i) Contact persons:
 - 1) whom to contact regarding questions about the clinical investigation;
 - 2) whom to contact in the event of injury;

- 3) whom to contact regarding questions about subject's rights.
- j) Statement declaring that new findings or the reasons for any amendment to the CIP that affect the subject's continued participation shall be made available to the subject.
- k) Statement indicating that, only upon subject's approval, the subject's personal physician will be informed of the subject's participation in the clinical investigation.
- l) If relevant for the clinical investigation, statement indicating upon subject's approval, that in case subject is not reachable for follow-up that:
 - 1) a person identified by the subject is informed of the possibility to be contacted by the principal investigator regarding how to reach the subject and the subject's health status;
 - 2) the civil register may be contacted by the principal investigator to inquire about the subject's whereabouts.

NOTE 3 National requirements regarding personal data protection can apply to some or all of the above.

- m) Statement indicating that a description of the clinical investigation has or shall be registered in a publicly accessible database (see [5.4](#)).

NOTE 4 Certain national regulations can apply regarding disclosure of the identification/registration number to the subject.

- n) Termination:
 - 1) circumstances under which the subject's participation can be terminated by the principal investigator, if applicable;
 - 2) circumstances under which the sponsor can suspend or prematurely terminate the clinical investigation.

5.8.5 Informed consent signature

The informed consent signature form shall contain the following:

- a) the voluntary agreement to participate in the clinical investigation and follow the investigator's instructions;
- b) a statement declaring that refusal of participation incurs no penalty for the subject and no loss of benefits to which the subject is otherwise entitled;
- c) a statement declaring that discontinuation/withdrawal and thereby revoking the informed consent at any time incurs no penalty for the subject;
- d) a statement with regard to the possible consequences of withdrawal;
- e) an acknowledgement of the information provided and confirmation that all the subject's questions were answered, that the subject acknowledges the information provided during the informed consent process and that (s)he had ample time to consider participation;
- f) a statement confirming that the subject or his/her legally designated representative agrees to the use of the subject's relevant personal data for the purpose of the clinical investigation;
- g) a statement confirming that the subject or his/her legally designated representative agrees that sponsor's representatives, regulatory authorities and EC representatives will be granted direct access to the subject's medical records;
- h) a statement whereby the subject provides the name of a person to be contacted by the principal investigator in case the subject cannot be reached for follow-up.

NOTE National requirements regarding personal data protection can apply.

5.8.6 New information

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form. If relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing.

6 Clinical investigation planning

6.1 General

All parties participating in the design and conduct of the clinical investigation shall be qualified by education, training, or experience to perform their tasks and this shall be documented appropriately (see [9.2.1](#)).

The sponsor shall have access to medical expertise relevant to the clinical investigation.

NOTE Medical expertise is provided by a person qualified by education, training, and experience, who is readily available to advise on the clinical investigation, and related medical questions or problems. If necessary, outside consultant(s) can be available for this purpose.

6.2 Risk management

6.2.1 General

The decision to embark upon or continue a clinical investigation of an investigational medical device requires that the residual risk(s) related to its use, as identified in the risk analysis, as well as risk(s) to the subject associated with the clinical procedure(s) required by the CIP that are additional to normal clinical practice (see [clause I.6](#)) be balanced against the anticipated benefits to the subjects.

NOTE 1 'the use of the investigational medical device' includes risks of the device/technology itself and its use-procedure(s) as per instructions for use.

NOTE 2 'the clinical procedure(s)' required by the CIP may include additional follow up procedures outside normal clinical practice. Normal clinical practice may be different from one region to another.

Risk management activities shall be performed throughout the clinical investigation.

For the investigational device including any applicable clinical procedure related to its use (see [6.2.2](#)), the sponsor shall predefine or establish risk acceptability thresholds and trigger a risk assessment to determine whether actions are needed as soon as thresholds are reached or exceeded (see [Annex H](#)).

NOTE 3 Risk acceptability thresholds related to the use of the investigational device are normally derived from the expected incidence of harm. In a clinical investigation such a harm is considered to be an adverse device effect.

Risk based approach shall be applied to both the planning and the conduct of clinical investigations, in order to ensure the reliability of the clinical data generated, the safety of subjects and the reliability of the clinical data generated (see [6.2.3](#)). This risk management differs from the principles outlined in [Annex H](#) and ISO 14971.

6.2.2 Risks related to the use of the investigational device and their disclosure

Residual risks, associated with the use of the investigational device shall be evaluated, proportionate to the clinical investigation sample size/population, in accordance with ISO 14971 prior to design and conduct of a clinical investigation (see [Annex H](#)). This risk evaluation shall include or refer to an objective review of published and unpublished medical and scientific data. The residual risk evaluation should be relevant to the targeted indication(s) and population(s) under investigation.

NOTE 1 It is acknowledged that the observed occurrence rate of adverse device effects can differ between a clinical investigation and rates in the general population, due to reporting rates, specifics of the patient population, indications and sample size of the clinical investigation.

A summary of the benefit-risk evaluation shall be disclosed in the relevant clinical investigation documents. The residual risk, including the characterization of their nature (hazards), incidence (occurrence), severity and outcome (harms) shall be disclosed in the IB (see [clause B.5](#)) and the instructions for use. The level of detail necessary shall be determined by the sponsor and managed in the interest of subject safety.

The CIP shall include all anticipated adverse device effects and a rationale for overall evaluation of residual risks in relation to the benefits (see [clause A.4](#)). All anticipated adverse device effects shall be disclosed in the informed consent form (see [5.8.4](#)).

NOTE 2 The level of disclosure may be dependent on ethics committees or regulatory reviews.

The information concerning risk and benefits shall be aligned between the different documents i.e., IB, IFU, CIP and informed consent form.

Where the defined risk mitigation measures, identified residual risks or management of the risks require training on the investigational device, consideration should be made by the sponsor about the extent of the training (e.g., animal model, cadaver training, support to users throughout the clinical investigation).

6.2.3 Clinical investigation process

The sponsor shall identify, assess and control risks associated with clinical investigation processes to ensure the ethical and scientific conduct of the clinical investigation and the credibility of the clinical investigation results.

Risks related to the clinical procedures required by the CIP other than those related to the medical device, shall be identified from the literature review. Their disclosure in the CIP and if applicable, the informed consent, shall also be determined by the sponsor and managed in the interest of subject safety.

Risk control measures should be considered at both the clinical quality management system level (e.g., standard operating procedures, computerized systems, personnel) and clinical investigation planning and conduct (e.g. clinical investigation design, data collection, informed consent process, monitoring).

6.3 Justification for the design of the clinical investigation

The justification for the design of the clinical investigation shall be based on the evaluation of pre-clinical data and the results of a clinical evaluation including existing clinical data on the device under investigation (see References [\[7\]](#) and [\[10\]](#)) and shall be aligned with the results of the risk assessment.

The clinical evaluation includes an assessment and analysis of applicable data concerning clinical performance, effectiveness or safety of the investigational device or similar devices or therapies. The evaluation shall be relevant to the intended purpose and the proposed method of use of the investigational device or similar devices or therapies. This is a scientific activity that shall be done according to scientific standards (see References [\[7\]](#) and [\[10\]](#)).

The results of the clinical evaluation and the risk assessment shall be used to determine the required clinical development stages (see [Annex I](#)) and justify the optimal design of the clinical investigation. They shall also help identify relevant endpoints and confounding factors to be taken into consideration and serve to justify the choice of control group(s) and if applicable, comparator(s), the use of randomization or blinding, and other methods to minimize bias.

The clinical investigation shall be designed to evaluate whether the investigational device is suitable for the purpose(s) and the population(s) for which it is intended. It shall be designed in such a way as to ensure that the results obtained have clinical relevance and scientific validity and address the clinical investigation objectives, in particular the benefit-risk profile of the investigational device.

Several factors are important when designing any medical device clinical investigation, including general considerations of sources of bias and bias minimization, as well as specific considerations related to clinical investigation objectives, subject selection, subject endpoint(s), stratification, investigation site selection, and choice of comparator (see [clause A.6](#) and [clause A.7](#)).

The clinical investigation should be designed to allow confirmation of the benefit-risk analysis of the investigational device as outlined in the risk management report.

NOTE 1 The need to conduct a clinical investigation to meet regulatory requirements can be determined by the applicable national regulations.

NOTE 2 The requirements for clinical evaluation can be the subject of national regulations (see References [6] and [9]).

NOTE 3 Further informative reading can be found in References [10], [11], and [15].

6.4 Clinical investigation plan (CIP)

The CIP shall include the information specified in [Annex A](#).

The CIP shall clearly outline the objectives of the clinical investigation which should primarily relate to safety, performance or effectiveness for a given intended use of the investigational device.

The proposed design shall be adequately justified based on scientific and ethical principles. The objective(s) and clinical development stage of the investigational device determine whether an exploratory, confirmatory or observational design is appropriate to ascertain that the objectives of the clinical investigation can be reached.

The objective(s) shall relate to the hypotheses (where applicable) and corresponding endpoints relevant to the target population.

The objectives of the clinical investigation shall translate directly into the pre-specification and operationalisation of the primary endpoint(s).

NOTE Where applicable, objectives may be translated into one or more estimand(s), requiring interdisciplinary scientific input for defining intercurrent events and of setting the analysis strategies (see [Annex K](#)).

The CIP and all subsequent amendments to the CIP are prepared by the sponsor in consultation with the biostatistician when relevant, agreed upon between the sponsor and the coordinating investigator and accepted by all principal investigators, and are recorded with a justification for each amendment.

6.5 Investigator's brochure (IB)

The purpose of the IB is to provide the principal investigator and the investigation site team with sufficient safety and performance data from pre-clinical investigations or clinical investigations to justify human exposure to the investigational device specified in the CIP. The IB shall be updated throughout the course of the clinical investigation as significant new information becomes available (e.g., a significant change in risk). In case of an investigational device design change that can occur during the course of the clinical investigation, the IB shall be updated and provide a justification for the change including an update of the risk management section of the IB, if required.

The principal investigator(s) shall acknowledge the receipt of the IB and all subsequent amendments in writing and shall keep all its information confidential.

The IB shall include the information specified in [Annex B](#).

6.6 Case report forms (CRFs)

The CRFs shall be developed to capture the data for each enrolled subject as required by the CIP. The CRFs shall include information on the condition of each subject upon enrolment, and during the course of the clinical investigation, exposure to the investigational device and any other therapies (see [Annex C](#)).

CRFs completion guidelines can also be developed to provide instructions to the investigation site team for accurate completion, correction and signature of CRFs along with expectations on handling clinical investigation deviations and unknown or missing data, thus reducing the need of sponsor data queries.

A procedure shall be in place to ensure, that when it is necessary to amend the CIP, the sponsor shall review the CRFs to determine if an amendment of these documents is also necessary.

6.7 Monitoring plan

The sponsor shall determine the extent and nature of monitoring appropriate for the clinical investigation based on the risk assessment (see 6.2). The extent and nature of the monitoring, including the strategy for source data verification versus centralized data review (evaluation without visiting the investigation site), subject protection and timely reporting, shall be based on the objective, design, complexity, size, critical data points and endpoints of the clinical investigation and the degree of variation from normal clinical practice – risk-based monitoring.

NOTE 1 Monitoring methods can differ between countries and arrangements for source data verification are subject to national or regional regulations regarding personal data protection.

NOTE 2 Activities of centralized monitoring can include, but are not limited to, examining data quality, remote contact with the investigation site, EC renewals, adverse event review, DMC review, and investigational device accountability.

In general, there is a need for on-site monitoring throughout the clinical investigation. Centralized monitoring can be performed in addition to complement on-site monitoring. In exceptional circumstances, the sponsor can determine that centralized monitoring in conjunction with procedures such as investigator's documented training, meetings, and extensive written guidance or telephone communication, can ensure appropriate conduct of the clinical investigation. In such circumstances, the sponsor shall provide a justification for omitting the source data verification. In addition, the sponsor shall ensure that the processes and expectations for site record keeping, data entry, reporting are well-defined and ensure timely access to clinical data and supporting documentation.

The sponsor shall ensure, through oversight of the clinical investigation and timely adverse event reporting, that unanticipated adverse device effects are identified and investigated rapidly so that, where necessary, additional risk control measures can be implemented (see 7.4.4).

Results of the risk assessment shall be used to develop a risk-based monitoring plan and a supporting rationale. The monitoring plan shall describe:

- a) the risks associated with the clinical investigation (see 6.2.3) and adequate information on relevant risk control measures;
- b) the processes that need to be monitored including data that is required to be verified in source documents;
- c) the monitoring methods (on-site, a combination of on-site and where justified, centralized monitoring, as appropriate);
- d) the responsibilities;
- e) the procedures and requirements for the investigation's oversight;
- f) the methods for documenting and communicating monitoring results;
- g) the methods for obtaining compliance;
- h) the process for escalation in case of continuous or egregious non-compliance;
- i) those aspects of the clinical investigation which need special attention because if performed incorrectly or inadequately, would compromise the protection of human subjects or the integrity of the data;
- j) the special requirements regarding personal data protection.

The monitoring plan shall be tailored according to the stage of clinical development and the type of clinical investigation (see Reference [12] and [13]).

6.8 Investigation site selection

The sponsor shall identify criteria necessary for the successful conduct of the clinical investigation prior to start of the site qualification process, including the facilities required at the clinical investigation site, principal investigator's qualification and the type of environment (e.g., hospital versus home-based).

The investigation site's facilities should be similar to the facilities required for the intended use of the investigational device(s), although additional equipment and capabilities may be needed at investigation sites during the clinical investigation to ensure that the necessary safety precautions are available.

Prior to the initiation of the clinical investigation, the qualifications of the principal investigator(s) and adequacy of the investigation site(s) shall be verified and documented in an investigation site selection report. The rationale for selecting an investigation site shall be documented.

NOTE Investigation site selection rationale can be based on prior experience of the sponsor with the principal investigator or the investigation site.

6.9 Agreement(s)

There shall be an agreement between the sponsor and the principal investigator(s)/investigation site(s) and any other relevant parties (e.g., investigators, CRO(s), and core laboratories), which defines the responsibilities of each party in the clinical investigation. All agreements shall be recorded in writing, signed, and dated by all parties involved.

The agreement shall identify instances where, by participating in a clinical investigation, the parties share regulatory responsibilities with the sponsor.

6.10 Labelling

The investigational device, the instructions for use, or the packaging shall indicate that the investigational device is exclusively for use in a clinical investigation, unless this is not required (see clause J.7).

NOTE See ISO 15223-1 and national or regional regulations for further information on labelling.

6.11 Data monitoring committee (DMC)

The sponsor shall consider establishing a DMC prior to starting the clinical investigation.

The decision to establish a DMC shall be guided by the risk assessment, taking into account both the risks associated with the use of the investigational device and the risks associated with subject's participation in the clinical investigation.

The primary function of the DMC shall be described in the CIP.

The sponsor or DMC shall establish a Charter to document the following but not limited to:

- a) the responsibilities and scope of activities of the DMC;
- b) the frequency, format, and documentation of meetings;
- c) arrangements for handling emergency situations;
- d) confirm conditions for suspending or stopping the clinical investigation, if relevant for safety management (see [clause A.16 a](#))).

NOTE For further information on establishment of a DMC and contents of the Charter, see Reference [\[18\]](#).

6.12 Clinical events committee (CEC)

The sponsor shall consider establishing a CEC prior to starting the clinical investigation.