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

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

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see the following URL: www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 194, *Biological and clinical evaluation of medical devices*, in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 206, *Biological and clinical evaluation of medical devices*, in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

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

— inclusion of a summary section of GCP principles (see Clause 4);

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

— inclusion of clinical quality management (see 9.1);

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

— inclusion of statistical considerations in Annex A;

— inclusion of guidance for ethics committees in Annex G;

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

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

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

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

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

1 Scope

This document addresses good clinical practice for the design, conduct, recording and reporting of clinical investigations carried out in human subjects to assess the clinical performance or effectiveness and safety of medical devices.

For post-market clinical investigations, the principles set forth in this document 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 [4]). Justifications for exemptions from this document can consider the uniqueness of indirect contact between subjects and the SaMD.

This document does not apply to *in vitro* diagnostic medical devices. However, there can be situations, dependent on the device and national or regional requirements, where users of this document might consider whether specific sections and/or requirements of this document could be applicable.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 14971, *Medical devices — Application of risk management to medical devices*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

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

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

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

Note 1 to entry: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any *malfunction* (3.33) of the investigational medical device.

Note 2 to entry: This definition includes any event resulting from *use error* (3.53) or from intentional misuse of the investigational medical device.

Note 3 to entry: This includes '*comparator*' (3.12) if the comparator is a medical device.

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

Note 1 to entry: This definition includes events related to the investigational medical device or the *comparator* (3.12).

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

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

3.3
audit
systematic examination of activities and documents related to a *clinical investigation* (3.8) performed by (an) *independent* (3.26) person(s), to determine whether these activities were conducted, and the data recorded, analysed and accurately reported, according to the CIP, standard operating procedures, this document and applicable regulatory requirements

3.4
audit trail
documentation that allows reconstruction of the course of events

3.5
blinding
masking
procedure in which one or more parties to the *clinical investigation* (3.8) are kept unaware of the treatment assignment(s)

Note 1 to entry: Single blinding usually refers to the *subject(s)* (3.50) being unaware of the treatment assignment(s). Double blinding usually refers to the subject(s), *investigator(s)* (3.30), monitor and, in some cases, centralized assessors being unaware of the treatment assignment(s).

Note 2 to entry: A clinical investigation is termed 'observer blind', if at least the *primary endpoint(s)* (3.22) is/are assessed without knowledge of whether an investigational medical device (3.29) or *comparator* (3.12) has been used to treat a subject.

3.6
case report form
CRF
set of printed, optical or electronic documents for each *subject* (3.50) on which information to be reported to the *sponsor* (3.49) is recorded, as required by the CIP

3.7
certified copy
copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information including data that describe the context, content, and structure, as the original

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

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

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

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

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

3.11
clinical performance
behaviour of a *medical device* (3.34) and response of the *subject(s)* (3.50) to that medical device in relation to its intended use, when correctly applied to appropriate subject(s)

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

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

3.13
computer system
hardware and software (including associated documents, e.g. user manual) that creates, modifies, maintains, archives, retrieves, or transmits in digital form information related to the conduct of a *clinical investigation* (3.8)

3.14
contract research organization
CRO
person or organization contracted by the *sponsor* (3.49) to perform one or more of the sponsor's clinical investigation-related duties and functions

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

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

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

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

3.17
data monitoring committee
DMC
independent (3.26) committee that can be established by the *sponsor* (3.49) to assess, at intervals, the progress of the *clinical investigation* (3.8), the safety data or the critical *clinical performance* (3.11) or *effectiveness* (3.20) *endpoints* (3.22) and to recommend to the sponsor whether to continue, suspend, modify, or stop the clinical investigation

Note 1 to entry: For the purpose of this document, "data and safety monitoring board (DSMB)", "data and safety monitoring committee (DSMC)" or "independent data monitoring committee (IDMC)" are synonymous with DMC.

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

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

Note 1 to entry: Device deficiencies include *malfunctions* (3.33), *use errors* (3.53), and inadequacy in the information supplied by the manufacturer including labelling.

Note 2 to entry: This definition includes device deficiencies related to the *investigational medical device* (3.29) or the *comparator* (3.12).

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

3.21
electronic record
combination of text, graphics, data, audio, imaging, or other information in digital form that is created, modified, maintained, archived, retrieved, or distributed by a *computer system* (3.13)

EXAMPLE An electronic CRF.

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

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

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

Note 1 to entry: For the purposes of this document, "ethics committee" is synonymous with "research ethics committee", "independent ethics committee" or "institutional review board". The regulatory requirements pertaining to ethics committees or similar institutions vary by country or region.

3.25
hypothesis
testable statement, derived from the *objective* (3.37) of the *clinical investigation* (3.8) to draw a conclusion about this objective, based on a pre-specified statistical test

Note 1 to entry: The primary hypothesis is formulated based on the pre-defined *primary endpoint* (3.22) and is usually used to calculate the sample size.

3.26
independent
not involved in the development of the investigational device or the conduct of a *clinical investigation* (3.8), except for their specifically assigned responsibilities, in order to avoid bias or a conflict of interest

3.27
informed consent
process by which an individual voluntarily confirms willingness to participate in a particular *clinical investigation* (3.8), after having been informed of all aspects of the investigation that are relevant to the decision to participate

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

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

3.29
investigational medical device
medical device (3.34) being assessed for *clinical performance* (3.11), *effectiveness* (3.20), or safety in a *clinical investigation* (3.8)

Note 1 to entry: This includes medical devices already on the market that are being evaluated for new intended uses, new populations, new materials or design changes.

Note 2 to entry: This includes medical devices already on the market that are being evaluated within their intended use in a post-market clinical investigation (interventional or non-interventional).

Note 3 to entry: For the purpose of this document, the terms "investigational medical device" and "investigational device" are used interchangeably.

3.30
investigator
individual member of the *investigation site* (3.28) team designated and supervised by the *principal investigator* (3.39) at an investigation site to perform clinical investigation-related procedures or to make important clinical investigation-related and medical treatment decisions

Note 1 to entry: An individual member of the investigation site team can also be called "sub-investigator" or "co-investigator".

3.31
investigator's brochure
IB
compilation of the current clinical and non-clinical information on the *investigational medical device(s)* (3.29), relevant to the *clinical investigation* (3.8)

3.32
legally designated representative
individual, judicial, or other body authorized under applicable law to consent, on behalf of a prospective *subject* (3.50), to the subject's participation in the *clinical investigation* (3.8)

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

3.33
malfunction
failure of an *investigational medical device* (3.29) to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP, or IB

3.34
medical device
instrument, apparatus, implement, machine, appliance, implant, reagent for *in vitro* use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific purpose(s) of:

— diagnosis, prevention, *monitoring* (3.35), treatment or alleviation of disease;

— diagnosis, monitoring, treatment, alleviation of or compensation for an injury;

— investigation, replacement, modification, or support of the anatomy or of a physiological process;

— supporting or sustaining life;

— control of conception;

— disinfection of medical devices;

— providing information by means of *in vitro* examination of specimens derived from the human body;

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

Note 1 to entry: Products which may be considered to be medical devices in some jurisdictions but not in others include:

— disinfection substances;

— aids for persons with disabilities;

— devices incorporating animal and/or human tissues;

— devices for *in vitro* fertilization or assisted reproduction technologies.

[SOURCE: ISO 13485:2016, 3.11]

3.35
monitoring
act of overseeing the progress of a *clinical investigation* (3.8) to ensure that it is conducted, recorded, and reported in accordance with the CIP, written procedures, this document, and the applicable regulatory requirements

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

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

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

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

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

Note 1 to entry: If a clinical investigation is conducted by a team of individuals at an investigation site, the principal investigator is responsible for leading the team.

Note 2 to entry: Whether this is the responsibility of an individual or an institution can depend on national regulations.

3.40
quality assurance
planned and systematic actions that are established to ensure that the *clinical investigation* (3.8) is performed, and the data are generated, documented (recorded), and reported in compliance with this document and the applicable regulatory requirement(s)

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

3.42
randomization
process of assigning *subjects* (3.50) to the *investigational medical device* (3.29) or *control groups* (3.15) using an established recognized statistical method using an element of chance to determine the unforeseeable assignment in order to reduce bias

3.43
recruitment
active efforts to identify *subjects* (3.50) who can be suitable for enrolment into the *clinical investigation* (3.8)

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

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

a) death,

b) serious deterioration in the health of the *subject* (3.50), 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 diseases, 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, 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 (3.9), without serious deterioration in health, is not considered a serious adverse event.

3.46
serious health threat
signal from any adverse event or *device deficiency* (3.19) that indicates an imminent risk of death or a serious deterioration in the health in *subjects* (3.50), 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.

3.47
source data
all information in original records, certified copies of original records of clinical findings, observations, or other activities in a *clinical investigation* (3.8), necessary for the reconstruction and evaluation of the clinical investigation

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

3.48
source document
original or *certified copy* (3.7) of printed, optical or electronic document containing *source data* (3.47)

EXAMPLE Hospital records, laboratory notes, device accountability records, photographic negatives, radiographs, records kept at the *investigation site* (3.28), at the laboratories and at the medico-technical departments involved in the *clinical investigation* (3.8).

3.49
sponsor
individual, company, institution or organization taking responsibility and liability for the initiation and management of a *clinical investigation* (3.8), and arranging the financial setup

Note 1 to entry: When an *investigator* (3.30) 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.

3.50
subject
individual who is or becomes a participant in a *clinical investigation* (3.8), either as a recipient of the investigational device or a *comparator* (3.12)

Note 1 to entry: This includes healthy volunteers.

3.51
unanticipated serious adverse device effect
USADE
serious adverse device effect (3.44) 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.

3.52
use error
user action or lack of user action while using the *medical device* (3.34) 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]

3.53
validation
confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled

3.54
verification
confirmation by examination and provision of objective evidence that specified requirements have been fulfilled

3.55
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 [7]), 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 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) Each individual 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 [7]). 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:

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

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

h) 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.

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

j) the evidence of the clinical investigation insurance;

k) the letter of the sponsor confirming outsourcing of duties and functions.

l) 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;

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 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 native 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 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 and 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 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:

c) the prospective subject fulfils the emergency conditions and is obviously in a life-threatening situation;

d) no sufficient clinical benefits are anticipated from the currently available treatment;

e) 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;

f) anticipated risks are outweighed by the potential benefits of participation in the clinical investigation;

g) 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, 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 others.

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), as identified in the risk analysis, as well as risk(s) to the subject associated with the clinical procedure including follow-up procedures required by the CIP be balanced against the anticipated benefits to the subjects.

Risk management activities shall be performed throughout the clinical investigation (see Figure H.1).

For both the investigational device including clinical procedure (see 6.2.2) and clinical investigation process (see 6.2.3), 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).

6.2.2 Investigational device including clinical procedure risks and their disclosure

Risks associated with the investigational device and its related clinical procedure shall be estimated in accordance with ISO 14971 prior to design and conduct of a clinical investigation (see Annex H). The risk assessment shall include or refer to an objective review of published and available unpublished medical and scientific data.

A summary of the benefit-risk analysis 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 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 the related benefit-risk ratio (see A.4).

All anticipated adverse device effects shall be disclosed in the informed consent form (see 5.8.4).

Where the risk management report's conclusions 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

Risk management principles shall be applied to both the planning and the conduct of clinical investigations, in order to ensure the reliability of the clinical data generated and the safety of subjects.

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.

Clinical risks related to the clinical procedures, including follow-up 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).

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 (see References [6] and [9]) and shall be aligned with the results of the risk assessment.

The clinical evaluation includes an assessment and analysis of clinical 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 with rigour and objectivity according to scientific standards (see References [6] and [9]).

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 comparative clinical investigation designs (see A.6 and 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 [5] and [8]).

NOTE 3 Further informative reading can be found in References [9], [10], and [13].

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

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 or 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 entering, 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 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 deviation 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 [11]).

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 I.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.

NOTE For further information on establishment of a DMC and contents of the Charter, see Reference [16].

7 Clinical investigation conduct

7.1 General

The clinical investigation shall be conducted in accordance with the CIP.

The clinical investigation shall not commence until written approval/favourable opinion from the EC and, if required, the relevant regulatory authority of the countries where the clinical investigation is taking place has been received.

The sponsor shall ensure ongoing risk management throughout the clinical investigation taking into consideration all aspects related to the investigational device, clinical procedures required by the CIP, and the investigation process (see 6.2 and 7.4.4).

7.2 Investigation site initiation

An initiation visit for each participating investigation site or, alternatively, an investigator meeting shall be conducted and documented by the sponsor or monitor at the beginning of the clinical investigation (see 9.2.4.4). A log shall be initiated identifying names, initials, signatures, functions, and designated authorisations for the principal investigator and members of the investigation site team.

NOTE Depending on the type and complexity of the clinical investigation, and its associated risks, site initiation can be performed by a telephone call or other communication, as specified in the risk-based monitoring plan.

7.3 Investigation site monitoring

The conduct of the clinical investigation shall be monitored according to the monitoring plan (see 6.7 and 9.2.4).

The results of all monitoring activities (on-site [see 9.2.4.7] and centralized) shall be documented.

7.4 Adverse events and device deficiencies

7.4.1 Signals requiring immediate action

Signals from adverse events or device deficiencies that might indicate a serious health threat can be detected by either the sponsor or principal investigator but are evaluated by the sponsor.

Any occurrence of a serious health threat can require a specific reporting process according to regulatory requirements as specified in 9.2.5.

7.4.2 Adverse events

All adverse events and any new information concerning these events shall be documented in a timely manner throughout the clinical investigation and shall be reported as specified in 9.2.5 and 10.8 (for adverse event categorization, see Annex F).

NOTE 1 This includes adverse events identified in the CIP as critical to the evaluation of the results of the clinical investigation.

NOTE 2 Adverse events associated with users or other persons can be documented separate from adverse events associated with the subject, taking into account the data privacy regulations (see 7.7).

NOTE 3 Certain national regulations can apply to reporting of adverse events during post-market clinical investigations.

All adverse events shall be reported in an interim or final report of the clinical investigation.

7.4.3 Device deficiencies

All device deficiencies of an investigational device shall be documented throughout the clinical investigation and managed by the sponsor in accordance with written procedures for the control of a non-conforming product. The sponsor shall take, where applicable, appropriate corrective and preventive actions to protect the safety of subjects, users, and other persons. Device deficiencies of the comparator, if applicable, shall be documented.

The sponsor shall arrange for the safe return of the investigational device that is related to the device deficiency (see 7.9).

Device deficiencies that did not lead to an adverse event but could have led to a serious adverse device effect

a) if either suitable action had not been taken,

b) if intervention had not been made, or

c) if circumstances had been less fortunate,

shall be reported as specified in 9.2.5 and 10.8. Where applicable, the analysis of used or explanted investigational devices shall be included as supportive information.

7.4.4 Risk assessment process for potentially unacceptable risks

Risks arising during the course of a clinical investigation shall be managed as follows (see Figure H.1).

a) Any person identifying an event or information that could have an impact on subjects', users' or other persons' safety, has an obligation to inform the principal investigator and the sponsor of their concerns.

b) Risks are monitored against established risk acceptability thresholds.

c) When circumstances of concern have been recognized, a preliminary risk analysis shall be performed by the sponsor in consultation with the principal investigator and, if appropriate, other advisors. The preliminary risk analysis can lead to the following outcomes.

    1) The new information is adequately reflected in the existing risk assessment and the individual and overall residual risks to subjects, users, or other persons remain acceptable. The sponsor shall ensure that a rationale for this is recorded in the clinical investigation documentation.

    2) Where possible, unacceptable risk or serious health threat has been identified, the sponsor shall suspend the clinical investigation immediately and the preliminary risk analysis shall

be documented and notified to the interested parties as required in 8.2.1, while further investigation is conducted.

d) Where a preliminary risk analysis has resulted in the recognition of the possibility of an unacceptable risk, the sponsor shall make appropriate arrangements for a comprehensive risk assessment in compliance with ISO 14971. Where appropriate, a DMC or expert advisors should provide input into or conduct the risk assessment (see 8.2.1).

e) The comprehensive risk assessment can lead to the following outcomes.

   1) The new information is adequately reflected in the existing risk assessment and individual and overall residual risks to subjects, users or other persons remain acceptable. The sponsor shall ensure that a rationale for this is recorded in the clinical investigation documentation and necessary activities are performed before resuming the clinical investigation (see 8.2.2).

   2) Corrective actions can be applied, including the following options:

      i) if the corrective actions do not affect the validity of the clinical investigation, the sponsor shall revise the benefit-risk analysis to justify continuation of the clinical investigation; perform necessary activities before resuming the clinical investigation (see 8.2.2); see Figure H.1 for impact on clinical investigation documents;

      ii) if the corrective actions affect the validity of the clinical investigation, the clinical investigation shall be terminated.

   3) If corrective actions cannot be applied, the clinical investigation shall be terminated.

7.5 Clinical investigation documents and documentation

7.5.1 Amendments

The IB, CIP, CRFs, informed consent form and other subject information, or other clinical investigation documents such as instructions for use shall be amended as needed throughout the clinical investigation in accordance with written procedures for the control of documents and document changes.

Documentation of changes shall include a description of the changes, justification of the changes and their potential impact on the performance, effectiveness, safety or other endpoints, and identification of the affected documents.

Proposed amendments to the CIP shall be reviewed and approved by the same parties as specified in 6.4, unless specifically designated otherwise. The amendments to the CIP and the subject's informed consent form shall be notified to, or approved by, the EC and regulatory authorities, if required (see 5.6.4). The version number and date of amendments shall be documented.

If the amendment impacts the integrity of the clinical investigation, the data collected before and after the amendment shall be analysed statistically to assess the effect of the amendment on performance, effectiveness or safety analysis. This analysis shall be included in the clinical investigation report.

7.5.2 Subject identification log

Each investigation site shall maintain a log of all the subjects enrolled in the clinical investigation, assigning an identification code linked to their names, alternative subject identification or contact information.

NOTE Depending on the clinical investigation design, a log can be maintained at the investigation site that identifies everyone who has been pre-screened for potential enrolment in the clinical investigation.

7.5.3 Source documents

Source documents shall be created and maintained by the investigation site team throughout the clinical investigation. The type and location of these source documents shall be documented.

7.6 Additional members of the investigation site team

New members of the investigation site team may be added from time to time at new or existing sites. New personnel should only start their assignment after receiving adequate training in the clinical investigation requirements and this training shall be documented. The names, initials, signatures, functions, and designated authorisations of new personnel shall be documented.

NOTE EC approval of new members of the investigation site team can be required before commencement of their responsibilities, in addition to internal site documentation of these responsibilities and new member training.

7.7 Subject privacy and confidentiality of data

Confidentiality of data shall be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access.

The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data.

The principal investigator or investigation site shall provide direct access to source data during and after the clinical investigation for monitoring, audits, EC review and regulatory authority inspections. As required, the principal investigator or investigation site shall obtain permission for direct access to source documents from the subject, hospital administration and regulatory authorities before starting the clinical investigation.

7.8 Document and data control

7.8.1 Traceability of documents and data

All documents and data shall be produced and maintained in a way that ensures reliability, integrity, control and traceability. All documents, and subsequent versions, related to a clinical investigation shall be identifiable, traceable and appropriately stored to provide a complete history of the clinical investigation. Where relevant, the accuracy of translations shall be guaranteed and documented.

The investigator shall ensure the accuracy, attribution, completeness, legibility and timeliness of the data reported to the sponsor on the CRFs and in all required reports. All copies of the retained original source documents shall be certified, as indicated by a dated signature by a member of the investigation site team unless generated through a validated process. Special requirements should be applied to the capture, review and retention of electronic source data, to ensure reliability, quality, integrity and traceability (see Reference [12]).

If assignment to a treatment group is blinded/masked in any way, it shall be safeguarded throughout the clinical investigation, including data entry and processing. Written procedures for decoding blinded/masked clinical investigations shall be followed.

7.8.2 Recording of data

The data reported on the CRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. The CIP shall specify which data can be recorded directly in the CRFs.

NOTE 1 The acceptance of direct entry of source data in the CRF can be subject to a hospital's specific documentation requirements.

NOTE 2 Data that can be directly recorded in the CRFs can also be documented in the monitoring plan.

The CRFs shall be signed and dated by the principal investigator or his/her authorized designee(s). Any change or correction to data reported on a CRF shall be dated, initialled and explained if necessary, and shall not obscure the original entry (i.e. an audit trail shall be maintained); this applies to both written and electronic changes or corrections.

The sponsor shall:

a) provide guidance to the principal investigators or his/her authorized designee on making such corrections; the sponsor shall have written procedures to ensure that changes or corrections in CRFs are documented, are necessary, are legible and traceable, and are endorsed by the principal investigator or his/her authorized designee; records of the changes and corrections shall be maintained,

b) ensure that it is possible to compare the original data and observations with the processed data, if data are transformed during processing;

c) use an unambiguous subject identification code that allows identification of all the data reported for each subject. The link between the code and each subject shall be retained by the principal investigator in a secure location.

7.8.3 Electronic clinical data systems

Validation of electronic clinical data systems is necessary in order to evaluate the authenticity, accuracy, reliability, and consistent intended performance of the data system from design until decommissioning of the system or transition to a new system.

These requirements are applicable to any electronic records as defined in 3.21, including electronic CRFs, electronic systems used for entering and processing data from paper CRFs received from sites and other electronic systems required in the clinical investigation.

When electronic clinical databases or electronic clinical data systems are used, written procedures shall be implemented to

a) describe system validation and functionality testing, data collection and handling, system maintenance, system security measures, change control, data backup, recovery, contingency planning, and decommissioning,

b) establish and document requirements for the electronic clinical data system to receive and process data,

c) verify and validate that the requirements for the electronic clinical data system can be consistently met,

d) ensure attributability, completeness, reliability, consistency, and logic of the data entered,

e) ensure accuracy of reports,

f) ensure that data changes are documented and that there is no deletion of entered data, i.e. maintain an audit trail, data trail and edit trail,

NOTE National regulations on data protection can require deletion.

g) maintain a security system that prevents unauthorized access to the data, both internally and externally,

h) maintain a list of individuals who have access to the electronic data system as well as the dates of access, privileges granted to each user and removal of access,

i) ensure the accuracy and completeness of the data reported to the sponsor in the CRFs by implementing a signature by the principal investigator or authorized designee,

j) maintain adequate backup, retention and retrievability of the data,

k) train users on the use of the system, and

l) safeguard the blinding, if any (e.g. maintain blinding during data entry, and processing).

7.9 Investigational device accountability

Access to investigational devices shall be controlled and the investigational devices shall be used only in the clinical investigation and according to the CIP.

The sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigation sites until return or disposal. The sponsor shall have instructions in place and make packaging materials available, if applicable, for the safe return or disposal of investigational devices, including potentially hazardous devices. The principal investigator or an authorized designee shall keep records documenting the following:

a) name(s) of person(s) who received, used, returned, or disposed of the device;

b) the date of receipt, identification, and quantity of each investigational device (batch number/serial number or unique code);

c) the expiry date, if applicable;

d) the date or dates of use;

e) subject identification;

f) date on which the investigational device was returned/explanted from subject, if applicable;

g) the date of return of unused, expired, or malfunctioning investigational devices, if applicable;

h) the date and documentation of disposal of the investigational devices as per instructions of the sponsor, if applicable.

Written procedures shall be established for the entire process of device accountability.

7.10 Accounting for subjects

All subjects enrolled in the clinical investigation (including those withdrawn from the clinical investigation or lost to follow-up) shall be accounted for and documented.

If a subject discontinues participation in the clinical investigation, the reason(s) shall be recorded. The investigator can use existing data and ask for the subject's permission to collect follow-up data about his/her status/condition including information about device clinical performance, effectiveness or safety. If permission is obtained, the relevant data shall be included in the clinical investigation report.

NOTE The collection of follow-up data from discontinued subjects can be subject to national regulations.

7.11 Auditing

Audits of the clinical investigation may be conducted to evaluate compliance with the CIP, written procedures, this document and the applicable regulatory requirements (see Annex J). These audits may cover all involved parties, systems, processes, and facilities, and are independent of, and separate from quality control functions or routine monitoring.

An audit can be used

a) as a routine part of the sponsor's quality assurance,

b) to assess the effectiveness of the monitoring activity,

c) whenever there are serious or repeated CIP deviations or suspicion of fraud,

d) to bring an investigation site into "inspection readiness" (i.e. to prepare the investigation site for a potential regulatory inspection),

e) when requested or suggested by a regulatory authority.

The auditors shall be qualified by training and experience to conduct audits and shall be independent of the clinical investigation.

The auditing of clinical investigation systems and processes shall be conducted in accordance with written procedures or specific plan on what to audit, how to audit, the frequency of audits, and the form and content of audit reports and audit certificates.

The audit plan or procedures for a clinical investigation audit shall be guided by the importance of the clinical investigation, the number of subjects in the clinical investigation, the type and complexity of the clinical investigation, the level of risk to the subjects and any identified problem(s).

The audit results shall be documented and communicated to relevant parties. If applicable, an audit certificate shall be kept in the sponsor files.

8 Suspension, termination, and close-out of the clinical investigation

8.1 Completion of the clinical investigation

The completion of a clinical investigation shall be deemed to coincide with the last visit of the last subject and when follow-up is complete for the clinical investigation, whether the clinical investigation concluded according to the pre-specified clinical investigation plan or was terminated prematurely, unless another point in time for such end is set out in the clinical investigation plan.

NOTE Completion of a clinical investigation can also be referred to as the end of a clinical investigation.

8.2 Suspension or premature termination of the clinical investigation

8.2.1 Procedure for suspension or premature termination

The sponsor may suspend or prematurely terminate either a clinical investigation at an individual investigation site or the entire clinical investigation for significant and documented reasons, such as when recommended by the DMC.

A principal investigator, EC, or regulatory authority may suspend or prematurely terminate participation in a clinical investigation at the investigation sites for which they are responsible.

If suspicion of an unacceptable risk, including serious health threat to subjects, arises during the clinical investigation, or when so instructed by the EC or regulatory authorities, the sponsor shall suspend the clinical investigation while the risk is assessed. The sponsor shall terminate the clinical investigation if an unacceptable risk which cannot be controlled is confirmed (see 7.4.4 and Figure H.1).

The sponsor shall consider terminating or suspending the participation of a particular investigation site or investigator in the clinical investigation if monitoring or auditing identifies serious or repeated deviations on the part of an investigator.

If suspension or premature termination occurs, the terminating party shall justify its decision in writing and promptly inform the other parties with whom they are in direct communication.

NOTE 1 The usual lines of communication are sponsor <-> principal investigator or sponsor <-> EC and sponsor <-> regulatory authority.

The principal investigator and sponsor shall keep each other informed of any communication received from either the EC or the regulatory authority.

If, for any reason, the sponsor suspends or prematurely terminates the investigation at an individual investigation site, the sponsor shall inform the responsible regulatory authority as appropriate and ensure that the EC is notified, either by the principal investigator or by the sponsor. If the suspension or premature termination was in the interest of safety (see 7.4.4 and Figure H.1) the sponsor shall inform all other principal investigators.

If suspension or premature termination occurs,

a) the sponsor shall remain responsible for providing resources to fulfil the obligations for following up the subjects enrolled in the clinical investigation, and

b) the principal investigator or authorized designee shall promptly inform the enrolled subjects at his/her investigation site, if appropriate.

NOTE 2 The method and the timing of this communication depends on the circumstances, the perceived risks, and national regulations.

All activities listed in 8.3 shall also be conducted.

8.2.2 Procedure for resuming the clinical investigation after temporary suspension

When the sponsor concludes an analysis of the reason(s) for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, the sponsor shall inform the principal investigators, the ECs, and, where appropriate, the regulatory authority of the rationale and provide them with the relevant data supporting this decision.

NOTE The usual lines of communication are sponsor <-> principal investigator or sponsor <-> EC and sponsor <-> regulatory authority.

Concurrence shall be obtained from the ECs and, where appropriate, regulatory authorities before the clinical investigation resumes.

If subjects have been informed of the suspension, the principal investigator, or authorized designee shall inform them of the reasons for resumption.

8.3 Routine close-out

Routine close-out activities shall be conducted to ensure that the principal investigator's records are complete, all documents needed for the sponsor's files are retrieved, remaining clinical investigation materials are disposed of, previously identified issues have been resolved, and all parties are notified.

a) Completing the records includes ensuring that

   1) all essential documents are complete and up to date,

   2) all CRFs are completed,

   3) all outstanding queries are resolved,

   4) the current status of all ongoing adverse events is documented,

   5) arrangements are made for archiving and record retention, and

   6) documenting disposition of any:

      i) investigational devices;

      ii) remaining samples (e.g. blood or tissue);

iii) other clinical investigation materials.

b) Notification includes:

1) notification to EC;

2) notification to regulatory authorities, if required;

NOTE Certain national regulations can also require this to be done within specific timelines.

3) notification of clinical investigation completion in publicly accessible database (see 5.4).

8.4 Clinical investigation report

After close-out of the clinical investigation, a report of the clinical investigation shall be completed, even if the clinical investigation was terminated prematurely. The clinical investigation report shall include the information specified in Annex D.

NOTE 1 National regulations can apply to the requirements of the clinical investigation report completion and reporting.

a) The clinical investigation report shall be in written form.

b) The clinical investigation report shall include identification of the device(s), a description of the methodology and design of the clinical investigation, any deviations from the CIP, data analysis together with any statistics, and a critical appraisal of the results compared to the objectives of the clinical investigation.

c) The results reported in the clinical investigation report shall be derived from data reported on the CRFs and other applicable data capture methods in a repeatable and traceable manner. Records shall be kept demonstrating this.

d) The clinical investigation report shall take into account the data from each investigation site and for all subjects. No subject shall be identifiable either from the clinical investigation report or the published results.

e) The clinical investigation report shall be made available to the coordinating investigator where applicable, and all principal investigators for review and comment. The sponsor shall maintain records confirming that the clinical investigation report has been provided for review. If a reviewer does not agree with all or part of the clinical investigation report, his/her comments shall be recorded and communicated to the other principal investigators.

f) The sponsor and coordinating investigator shall be asked to provide their signatures, indicating their agreement with the content of the clinical investigation report. If no coordinating investigator is appointed, the signature of the principal investigator(s) shall be obtained.

g) The clinical investigation report shall be provided to the EC(s) and regulatory authorities.

h) The results of the clinical investigation shall be entered in a publicly accessible database where the clinical investigation was registered (see 5.4) and published whether positive, inconclusive or negative, to help guide future research, device development and medical treatment.

NOTE 2 Further guidance on the content of the clinical investigation report is given in Annex D.

8.5 Risk assessment and conclusions

A formal review of risk information should be carried out upon completion of the clinical investigation (see D.8) and fed into the risk analysis and clinical evaluation with an update of the benefit-risk conclusions in both documents.

8.6 Document retention

The sponsor and principal investigator shall maintain the clinical investigation documents. They shall take measures to prevent accidental or premature destruction of these documents. The principal investigator or sponsor may transfer custody of records to another person/party and document the transfer at the investigation site or at the sponsor's facility.

NOTE A list of essential clinical investigation documents to be maintained in sponsor and investigation site files is given in Annex E.

Clinical investigation documents, including but not limited to CIP, IB, CRF and clinical investigation report(s) should be incorporated into the device technical documentation under the quality management system of the manufacturer. For sponsor-investigator initiated clinical investigations, this should be applied to the extent possible.

9 Responsibilities of the sponsor

9.1 Clinical quality management

Quality management principles shall apply to the processes of the clinical investigation to ensure that the clinical investigation is designed, conducted, and monitored, and that data are generated, documented, recorded, evaluated, and reported in compliance with this document, the CIP, any subsequent amendment(s), and any other applicable standards and in accordance with regulatory requirements. The sponsor shall

a) implement and maintain written clinical quality procedures,

b) maintain records to document the compliance of all parties involved in the clinical investigation,

c) ensure that the auditing requirements of 7.11 are met, if applicable, and

d) justify and document significant exceptions to the requirements of this document (see Annex I for examples of exemptions).

Clinical quality procedures can be integrated in the applicable sections of the sponsor's overall quality system.

NOTE For further information, see ISO 13485 or equivalent regulatory requirements.

9.2 Clinical investigation planning and conduct

9.2.1 Selection and training of clinical personnel

Prior to commencement of the clinical investigation, the sponsor shall

a) define, establish, and allocate all the roles and responsibilities related to the clinical investigation in one or more written agreements, as defined in 6.9,

b) select a local representative if the sponsor is not resident in the country (countries) in which the clinical investigation is to be carried out, who acts as the sponsor fulfilling responsibilities of the sponsor in that country (those countries),

NOTE National or regional regulations can apply to the requirements of local representative selection.

c) select appropriately qualified principal investigators, as outlined in 6.8 and 10.2,

d) select a coordinating investigator, if appropriate, as in the case of a multicentre investigation,

e) receive disclosures of conflict of interest from principal investigators and investigators,

f) ensure the members of the investigation site team and their designated authorization(s) are identified in a log with details, as defined in 7.2,

g) designate or appoint one or more monitors, who are independent from the investigation site(s), or otherwise assume the responsibilities of the monitor(s),

h) ensure documentation and verification of training, experience, and scientific or clinical knowledge for all the relevant parties involved in order to adequately conduct the clinical investigation, including training, on

   1) the use of the investigational device(s) and where relevant the comparator,

   2) device accountability procedures (see 7.9),

   3) IB,

   4) CIP,

   5) CRFs,

   6) the written informed consent form and process as well as other written information provided to subjects, and

   7) sponsor's written procedures, this document and applicable regulatory requirements;

i) ensure that, in multicentre investigations, all investigators and all other parties involved are given instructions on uniformly assessing and documenting clinical and laboratory findings,

j) ensure that any clinical investigation-related activities involving potential contact with subjects and sponsor representative(s) at the investigation site(s) are described in the CIP and the informed consent form, and that these activities occur in such a way that they do not bias the data integrity,

   NOTE Individuals such as monitors, field engineers, or product specialists, who provide technical expertise in the implementation of the clinical investigation, are examples of sponsor representatives.

k) consider the need for a DMC and, if appropriate, establish the committee.

9.2.2 Preparation of documents and materials

Prior to commencement of the clinical investigation, the sponsor shall

a) prepare the documents, as described in Clauses 5, 6, and 7, and ensure they are approved by the relevant persons by dated signature; if required, copies shall be provided to all parties involved, and dated signatures obtained as appropriate,

b) ensure the accuracy of the translation, where relevant,

c) ensure that a supply of investigational devices, as characterized in 7.9, is available in a timely manner for the clinical investigation; investigational devices shall not be made available to the principal investigator until all requirements to start the clinical investigation are met,

d) establish a procedure assuring device accountability, which enables the immediate identification and where necessary, the recall of devices used in the clinical investigation,

e) provide insurance covering the cost of treatment of subjects in the event of clinical investigation-related injuries, if applicable,

   NOTE Certain national or local regulations can apply.

f) document any financial arrangements between the principal investigator or the investigation site and the sponsor,

g) submit any required application(s) to begin the clinical investigation in a given country to the appropriate regulatory authority (authorities) for review, acceptance or permission,

h) ensure that EC's approval/favourable opinion is obtained and documented, and that appropriate provisions are made to meet any conditions imposed by the EC,

i) ensure that any modification(s) required by the EC or regulatory authority are made and documented by the principal investigator and have gained the approval/favourable opinion of the EC or regulatory authority,

j) register the information of the clinical investigation in a publicly accessible database prior to recruitment of the first subject (see 5.4).

9.2.3 Conduct of clinical investigation

The sponsor shall be responsible for

a) accountability of investigational devices throughout the clinical investigation,

b) documenting correspondence with all parties involved in the clinical investigation, including ECs and regulatory authorities,

c) ensuring that the clinical investigation is appropriately monitored by determining the extent and nature of monitoring, including the strategy for source data verification, based on considerations such as the objective, design, complexity, size, critical data points and endpoints of the clinical investigation,

d) ensuring that risk management activities are performed and documented (see 6.2 and 7.1),

e) reviewing the monitoring report(s) and following up any action(s) required in the monitoring report(s) (see 9.2.4.7),

f) taking prompt action to secure compliance with all clinical investigation requirements,

g) performing and documenting root cause analysis and implementation of appropriate corrective and preventive action if noncompliance significantly affects or has the potential to significantly affect subject protection or reliability of clinical investigation results,

h) submitting progress reports after the data integrity is confirmed, including safety summary and deviations, when requested, to all reviewing ECs and the regulatory authorities.

9.2.4 Monitoring

9.2.4.1 General

Monitoring shall be conducted according to the monitoring plan (see 6.7).

The purpose of clinical investigation monitoring is to verify that

a) the rights, safety, and well-being of the human subjects are protected,

b) the reported data are accurate, complete, and verifiable from source documents, and

c) the conduct of the clinical investigation complies with the approved CIP, subsequent amendment(s), this document, and the applicable regulatory requirement(s) and applicable requirements of the EC.

9.2.4.2 Qualifications of the monitor

Monitors shall be

a) qualified in the field of this document through training and experience as well as scientific or clinical knowledge,

b) knowledgeable on the use of the investigational device(s) and relevant requirements, CIP, and informed consent process (see 5.8),

c) trained on the sponsor's clinical quality management procedures relevant to monitoring activities as well as any special procedures for monitoring a specific clinical investigation.

Training shall be documented in the sponsor's files.

9.2.4.3 Assessment of the investigation site

The monitor shall assess each investigation site to verify that the principal investigator has

a) adequate qualifications,

b) adequate resources, including facilities, laboratories, equipment, and a qualified investigation site team,

c) access to an adequate number of subjects.

9.2.4.4 Initiation of the investigation site

The monitor shall initiate each investigation site in accordance with the monitoring plan to ensure that the principal investigator and investigation site team

a) have received and understood the requirements and contents of

   1) the CIP,

   2) the IB,

   3) the informed consent form,

   4) the CRFs,

   5) the instructions for use,

   6) any written clinical investigation agreements, as appropriate,

b) have access to an adequate number of investigational devices,

c) have been trained in the use of the investigational device,

d) are familiar with the responsibilities of the principal investigator, as described in Clause 10.

9.2.4.5 Routine monitoring visits

The monitor shall perform routine monitoring activities to verify that

a) compliance with the CIP, any subsequent amendment(s), this document and regulatory requirements is maintained; deviations shall be discussed with the principal investigator(s) or authorized designee, documented and reported to the sponsor,

b) only authorized members of the investigation site team, as described in 9.2.1 f), are participating in the clinical investigation,

c) the investigational device and, where applicable, the comparator are used according to the CIP, IB or instructions for use and that, where modifications are required to the device, its method of use, or the CIP, these are reported to the sponsor,

d) investigation site resources, including laboratories, equipment and the investigation site team, remain adequate throughout the duration of the clinical investigation,

e) the principal investigator continues to have access to an adequate number of subjects and investigational devices,

f) signed and dated informed consent forms have been obtained from each subject or their legally designated representative before any clinical investigation-related procedures are undertaken,

g) source documents including the documentation of type and location, and other clinical investigation records are accurate, complete, up to date, stored, and maintained appropriately,

h) CRFs and queries are complete, recorded in a timely manner, and consistent with source documents, and are consistent with the requirements in the CIP,

i) appropriate corrections, additions or deletions are made to the CRFs, dated, explained if necessary and initialled by the principal investigator or by his/her authorized designee; the monitor shall not make corrections, additions, or deletions to the CRFs,

j) visits that the subjects fail to make, tests not conducted, or examinations not performed, as well as subjects withdrawn (including reason if available) are appropriately reported on the CRFs,

k) all adverse events and device deficiencies are reported to the sponsor, and all serious adverse events and device deficiencies that could have led to a serious adverse device effect are reported to the sponsor without unjustified delay,

l) serious adverse events and device deficiencies that could have led to a serious adverse device effect are reported to the EC and the regulatory authority, as required,

m) deviations (see 5.6.4 b)) are reported to the EC and can also be reported to the regulatory authority,

NOTE National regulations can also apply.

n) the storage and investigational device accountability are correct, and the traceability process is being followed and documented in the investigator’s files,

o) all required reports, notifications, applications, submissions and correspondence are maintained in the investigator's files and are accurate, complete, timely, legible, dated and identify the clinical investigation,

p) maintenance and calibration of the equipment relevant to the assessment of the clinical investigation is appropriately performed and documented, where applicable,

q) current laboratory normal values, laboratory certifications, accreditations, or other validations are present in the investigator's file, if required,

r) subject withdrawal has been documented; the monitor shall discuss this with the principal investigator or his/her authorized designee,

s) subject non-compliance with the requirements stated in the informed consent has been documented; the monitor shall discuss this with the principal investigator or his/her authorized designee,

t) the principal investigator and investigation site team are informed and knowledgeable of all relevant document updates concerning the clinical investigation,

u) any corrective and preventive actions, as needed, have been implemented and are effective.

9.2.4.6 Close-out activities

The monitor shall perform close-out activities as described in Clause 8.

9.2.4.7 Monitoring reports

Results of monitoring activities should be documented in sufficient detail to allow verification of compliance with the monitoring plan (see 6.7).

All monitoring activities shall be documented and reported to the sponsor [see also 9.2.3 c)] and shall include

a) the date, investigation site identification, name of the monitor and name of the principal investigator or other individuals contacted,

b) a summary of what the monitor reviewed and his/her observation(s) regarding the completion of previous action items, significant findings, facts, deviations, conclusions, and recommended actions to be taken to secure compliance.

A copy of the monitoring report or a summary of key findings shall be shared with the principal investigator in writing.

NOTE The above requirements can also apply to clinical investigation-related communication(s) depending on sponsor procedures or national regulations.

9.2.5 Safety evaluation and reporting

The sponsor is responsible for the classification of adverse events and ongoing safety evaluation of the clinical investigation and shall

a) review the investigator's assessment of all adverse events and determine and document in writing their seriousness and relationship to the investigational device and procedures required by the CIP; in case of disagreement between the sponsor and the principal investigator(s), the sponsor shall communicate both opinions to concerned parties, as defined in c), d), and e) given below,

   NOTE 1 Classification of adverse events and safety evaluation can be performed by an independent Clinical Events Committee (CEC) to mitigate the potential for bias and financial conflict.

b) review all device deficiencies and determine and document in writing whether they could have led to a serious adverse device effect; in case of disagreement between the sponsor and the principal investigator(s), the sponsor shall communicate both opinions to concerned parties, as defined in c), d), and e) given below,

c) report or ensure the reporting, to the EC by the principal investigator(s), of all serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by the CIP or by the EC,

   NOTE 2 Certain national regulations can also apply.

d) report to regulatory authorities, within the required time period, all serious adverse events and device deficiencies that could have led to a serious adverse device effect, including serious health threat, if required by the CIP,

   NOTE 3 Certain national regulations can also apply.

e) report all relevant safety information to the DMC, if established, according to written procedures,

f) in the case of a multicentre clinical investigation, inform all principal investigators in writing of all the serious adverse events at all investigation sites that have been reported to the sponsor, and ensure that they are reported to their EC, if required by the CIP or by the EC, whichever is more stringent; this information shall be sent to all the principal investigators within a time frame established based on the perceived risk as defined in the risk assessment (analysis and evaluation),

NOTE 4 Certain national regulations can also apply.

g) ensure that the EC and the regulatory authorities are informed of significant new information about the clinical investigation,

h) in case of serious adverse device effects and device deficiencies that could have led to serious adverse device effects, determine whether the risk analysis needs to be updated and assess whether corrective or preventive action is required.

9.2.6 Clinical investigation close-out

The sponsor shall

a) ensure all clinical investigation close-out activities are properly conducted as described in Clause 8,

b) perform a statistical analysis of the data,

c) produce a clinical investigation report and submit it for review, as described in 8.4,

d) ensure that the clinical investigation report, whether for a completed or prematurely terminated clinical investigation, is provided to the EC, participating investigators and regulatory authorities,

NOTE National regulations can also apply.

e) update publicly accessible database with clinical investigation results, if applicable (see 5.4).

9.3 Outsourcing of duties and functions

The sponsor may transfer any or all of the duties and functions related to the clinical investigation, including monitoring, to an external organization (such as a CRO or individual contractor), but the ultimate responsibility for the quality and integrity of the clinical investigation conduct shall reside with the sponsor. The sponsor shall ensure oversight of any clinical investigation-related duties and functions.

The outsourcing of duties or functions to external organizations, including subcontractors of the sponsor's CRO(s), shall be addressed by the sponsor in accordance with written procedures for the control of suppliers. The sponsor shall specify in writing any clinical investigation-related duty or function assumed by the external organization, retaining any clinical investigation-related duties and functions not specifically transferred to, and assumed by, the external organization. Records of transfer of duties and functions shall be maintained.

The sponsor shall be responsible for verifying the existence of and adherence to written procedures at the external organization.

All requirements in this document applying to a sponsor shall also apply to the external organization inasmuch as this organization assumes the clinical investigation-related duties and functions of the sponsor.

9.4 Communication with regulatory authorities

The sponsor shall, if required,

a) notify or obtain approval/non-objection from regulatory authorities in the country where the clinical investigation is conducted,

b) notify or obtain approval/non-objection from regulatory authorities in the country where the clinical investigation is conducted on any amendments of documents already reviewed by these authorities before these amendments are applied,

c) report on the progress and status of the clinical investigation,

d) perform safety reporting as specified in 9.2.5,

e) report any occurrence of withdrawing the investigational devices from the investigation site for reasons related to safety of the subject or investigational device clinical performance.

10 Responsibilities of the principal investigator

10.1 General

The role of the principal investigator is to implement, oversee the management of the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety, and well-being of the subjects involved in the clinical investigation.

The principal investigator is responsible for ensuring adequate training and qualification of the investigation site team and for maintaining oversight of their activities. The principal investigator may delegate tasks to qualified members of the investigation site team but retains responsibility for the clinical investigation (see also 7.6). This also applies when activities are outsourced to an external organization by the principal investigator in which case he/she shall implement procedures to ensure the integrity of all tasks performed and any data generated by this external organization.

10.2 Qualification of the principal investigator

The principal investigator shall

a) be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation in accordance with this document; evidence of such qualifications of the principal investigator shall be provided to the sponsor through up-to-date CVs or other relevant documentation,

NOTE National regulations can also apply.

b) be experienced in the field of application and trained in the use of the investigational device under consideration,

c) disclose potential conflicts of interest, including financial, that can interfere with the conduct of the clinical investigation or interpretation of results, and

d) be knowledgeable with the method of obtaining informed consent.

10.3 Qualification of investigation site

The principal investigator shall be able to demonstrate that the proposed investigation site

a) has the required number of eligible subjects needed within the agreed recruitment period,

b) has an investigation site team that is: qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation in accordance with this document; evidence of such qualifications for members of the investigation site team shall be documented through up-to-date CVs or other relevant documentation,

NOTE National regulations can also apply.

c) has adequate facilities.

10.4 Communication with the EC

The principal investigator shall

a) provide the sponsor with copies of any clinical investigation-related communications between the principal investigator and the EC,

b) comply with the requirements described in 5.6,

c) obtain the written and dated approval/favourable opinion of the EC for the clinical investigation, and ensure that regulatory authority approval is provided by the sponsor and communicated to the EC where required, before recruiting subjects and implementing all subsequent amendments, if required,

d) perform safety reporting as specified in 10.8 (for adverse event categorization, see Annex F),

e) promptly report any deviations from the CIP that affect the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation, including those which occur under emergency circumstances, if required by the EC or the CIP,

NOTE National regulations can also apply.

f) notify suspension, premature termination, or routine close-out of the clinical investigation as described in Clause 8.

In particular circumstances, the communication with the EC can be performed by the sponsor, partly or in full, in which case the sponsor shall keep the principal investigator informed.

10.5 Informed consent process

The principal investigator shall

a) comply with the requirements specified in 5.8,

b) ensure compliance with ethical principles for the process of obtaining informed consent, and

c) ensure and document appropriate training if an authorized designee is appointed to conduct the informed consent process.

NOTE Regulatory requirements can apply.

10.6 Compliance with the CIP

The principal investigator shall

a) indicate his/her acceptance of the CIP in writing,

b) conduct the clinical investigation in compliance with the CIP,

c) create and maintain source documents throughout the clinical investigation and make them available as requested during monitoring visits or audits as well as maintain documentation of the type and location of these source documents,

d) ensure that the investigational device is used solely by authorized users as specified in 7.2, and in accordance with the CIP and instructions for use,

e) propose to the sponsor any appropriate modification(s) of the CIP or investigational device or of the use of the investigational device,

f) refrain from implementing any modifications to the CIP without agreement from the sponsor, EC and regulatory authorities, if required,

g) document and explain any deviation from the approved CIP that occurred during the course of the clinical investigation,

h) ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation,

i) ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable,

j) ensure the accuracy, completeness, legibility and timeliness of the data reported to the sponsor in the CRFs and in all required reports,

k) maintain the device accountability records,

l) comply with the procedure for the safe return of investigational devices including potentially hazardous devices, and in case of reported device deficiencies, collaborate with the sponsor to provide the necessary information allowing an accurate analysis where appropriate,

m) allow and support the sponsor to perform monitoring and auditing activities,

n) be accessible to the monitor and respond to questions during monitoring visits,

o) determine the cause and implement appropriate corrective and preventive actions to address significant noncompliance,

p) allow and support regulatory authorities and the EC when performing auditing activities,

q) ensure that all clinical investigation-related records are retained as specified in 8.3,

r) sign the clinical investigation report, as specified in 8.4.

10.7 Medical care of subjects

The principal investigator shall

a) provide adequate medical care to a subject during and after a subject's participation in a clinical investigation in the case of adverse events, as described in the informed consent,

b) inform the subject of the nature and possible cause of any adverse events experienced,

c) provide the subject with the necessary instructions on proper use, handling, storage and return of the investigational device, when it is used or operated by the subject,

d) inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that can be required,

e) provide the subject with well-defined procedures for possible emergency situations related to the clinical investigation, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed,

f) ensure that clinical records are clearly marked to indicate that the subject is enrolled in a particular clinical investigation,

g) if appropriate, provide subjects enrolled in the clinical investigation with some means of showing their participation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided),

h) inform, with the subject's approval the subject's personal physician about the subject's participation in the clinical investigation,

NOTE National regulations can apply.

i) make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from the clinical investigation while fully respecting the subject's rights.

10.8 Safety reporting

The principal investigator shall

a) record every adverse event and observed device deficiency, together with an assessment (adverse event categorization, see Annex F),

b) report to the sponsor, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect; this information shall be promptly followed by detailed written reports, as specified in the CIP,

c) report to the EC serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by the CIP or by the EC,

NOTE 1 National regulations can also apply.

d) report to regulatory authorities serious adverse events and device deficiencies that could have led to a serious adverse device effect,

NOTE 2 National regulations can apply.

e) supply the sponsor, upon sponsor's request, with any additional information related to the safety reporting of a particular event.

Annex A
(normative)

Clinical investigation plan (CIP)

A.1 General

A.1.1 Introduction

This annex specifies the content of a CIP. If the required information is written in other documentation, for example the IB, such documentation shall be referenced in the CIP and shall be made available on request.

The content of a CIP and any subsequent amendments shall include all the topics listed in this annex, together with a justification for each topic if this is not self-explanatory.

NOTE Some requirements might not be applicable for exploratory and observational clinical investigations (see I.7).

A.1.2 Identification of the clinical investigation plan

a) Title of the clinical investigation.

b) Reference number identifying the specific clinical investigation, if any.

c) Version or date of the CIP.

d) Summary of the revision history in the case of amendments.

e) Version/issue number and reference number, if any, with the page number and the total number of pages on each page of the CIP.

f) Abbreviations and acronyms.

A.1.3 Sponsor

Name and address of the sponsor of the clinical investigation and information about funding source.

Certain national or regional regulations can require that if the sponsor is not resident in the country (countries) in which the clinical investigation is to be carried out, the name and address of a local representative who acts as the sponsor fulfilling responsibilities of the sponsor in that country (those countries) are provided.

A.1.4 Principal investigator, coordinating investigator and investigation site(s)

a) Name, address, contact details and professional position of

   1) principal investigator(s),

   2) coordinating investigator, if appointed.

b) Name and address of the investigation site(s) in which the clinical investigation will be conducted.

c) Name(s) and address(es) of external organizations (such as core laboratories, CROs, consultants or other contractors) involved in the clinical investigation.

The different roles, responsibilities and qualifications of investigators shall be specified.

The sponsor shall maintain an updated list of principal investigators and investigation sites. This list can be kept separately from the CIP. The definitive list shall be provided with the clinical investigation report (see Annex D).

A.1.5 Overall synopsis of the clinical investigation

A summary or overview of the clinical investigation shall include all the relevant information regarding the clinical investigation design such as inclusion/exclusion criteria, number of subjects, duration of the clinical investigation, follow-up, objective(s) and endpoint(s).

NOTE It can be useful to include a flow chart showing the key stages of the clinical investigation or any other information that can be of value for the conduct of the clinical investigation.

A.2 Identification and description of the investigational device

a) Summary description of the investigational device.

b) Details concerning the manufacturer of the investigational device.

c) Name or number of the model/type, including software version and accessories, if any, to permit full identification.

d) Description as to how traceability shall be achieved during and after the clinical investigation, for example, by assignment of lot numbers, batch numbers, or serial numbers.

e) Intended purpose of the investigational device in the proposed clinical investigation.

f) The populations and indications for which the investigational device is intended.

g) Description of the investigational device, including any materials, that will be in contact with tissues or body fluids. This shall include details of any medicinal substances, human or animal tissues or their derivatives, or other biologically active substances and reference to compliance with applicable national regulations.

h) Summary of the necessary training and experience needed to use the investigational device based on risk assessment.

i) Description of the specific medical or surgical procedures involved in the use of the investigational device.

j) References to the IB and IFU.

The above information shall also be provided as far as available for the comparator, if applicable.

A.3 Justification for the design of the clinical investigation

Justification for the design of the clinical investigation, which shall be based on the conclusions of the clinical evaluation, as specified in 6.3, and shall comprise

a) an evaluation of the results of the relevant pre-clinical testing/assessment and prior clinical investigations, if applicable carried out to justify the use of the investigational device in human subjects,

b) an evaluation of clinical data that are relevant to the proposed clinical investigation,

c) a description of the clinical development stage (see Annex I), if appropriate.

A.4 Benefits and risks of the investigational device, clinical procedure, and clinical investigation

a) Anticipated clinical benefits.

b) Anticipated adverse device effects (see 6.2.2).

c) Risks associated with participation in the clinical investigation (see 6.2.3).

d) Possible interactions with concomitant medical treatments as considered under the risk analysis.

e) Steps that will be taken to control or mitigate the risks.

f) Rationale for benefit-risk ratio.

A.5 Objectives and hypotheses of the clinical investigation

a) The purpose of the clinical investigation, claims for clinical performance, effectiveness or safety of the investigational device that are to be verified.

b) Objectives, primary and secondary, described as 'superiority', 'non-inferiority', or 'equivalence', if applicable.

c) Scientific justification and clinical relevance for effect sizes, non-inferiority margins or equivalence limits, where applicable.

d) Primary and secondary hypotheses, if applicable.

e) Risks and anticipated adverse device effects that are to be assessed.

The objective(s) shall serve the purpose of the clinical investigation and 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). Claims shall be linked to eligibility criteria for subject and users.

A.6 Design of the clinical investigation

A.6.1 General

a) Description of the design type of clinical investigation to be performed (e.g. randomized, blinded or open-label, parallel groups or crossover, multicentre, international) the control group, (e.g. comparative claim and reversible treatment of a chronic state) and the comparator with rationale and justification for the choice.

   Absence of control(s) shall be justified.

b) Description of the measures to be taken to minimize or avoid bias, such as randomization, concealment of allocation, blinding/masking, and management of potential confounding factors.

c) Primary and secondary endpoints, with rationale for their selection and measurement. If applicable, composite endpoints, with rationale for their selection and measurement.

   The primary endpoint shall be appropriate for the investigational device and should be clinically relevant.

   NOTE Composite endpoint is a pre-specified combination of more than one endpoint and can be used cautiously by including only components that have relatively equal clinical importance, frequency, and anticipated response to the presumed mechanism of action.

d) Methods and timing for assessing, recording, and analysing variables.

e) Equipment to be used for assessing the clinical investigation variables and arrangements for monitoring maintenance and calibration.

f) Any procedures for the replacement of subjects (generally, not applicable to randomized clinical investigations).

g) Investigation sites: number, location, and, if appropriate, differences in investigation site environment.

h) Definition of completion of the clinical investigation (see 8.1).

A.6.2 Investigational device(s) and comparator(s)

a) Description of the exposure to the investigational device(s) or comparator(s), if used.

b) List of any other medical device or medication to be used during the clinical investigation if not already specified in the instructions for use.

c) Number of investigational devices to be used, together with a justification.

A.6.3 Subjects

a) Inclusion criteria for subject selection.

b) Exclusion criteria for subject selection.

c) Criteria and procedures for subject withdrawal or lost to follow-up

   1) when and how to withdraw a subject from the clinical investigation or stop the use of the investigational device,

   2) documentation of efforts to be made to trace subjects that are lost to follow-up and possible reasons,

   3) whether and how subjects are to be replaced.

d) Point of enrolment.

e) Point of randomization, if applicable.

f) Total expected duration of the clinical investigation.

g) Expected duration of each subject's participation.

h) Number of subjects required to be included in the clinical investigation, and where needed, anticipated distribution of enrolment among the participating investigation sites.

i) Estimated time needed to select this number (i.e. enrolment period).

j) Relationship of investigation population to target population.

k) Information on vulnerable, pregnant, and breastfeeding population, if applicable.

A.6.4 Procedures

a) Description of all the clinical investigation-related procedures that subjects undergo during the clinical investigation including any deviation from normal clinical practice.

b) Description of those activities performed by sponsor representatives (excluding monitoring).

c) Any known or foreseeable factors that can compromise the outcome of the clinical investigation or the interpretation of results.

EXAMPLE Factors include subject baseline characteristics, concomitant medication, the use of other medical devices, and subject-related factors such as age, gender, or lifestyle.

d) The methods for addressing these factors in the clinical investigation, for example, by subject selection, clinical investigation design, such as stratified randomization, or by statistical analysis shall be described.

e) The follow-up period during the clinical investigation shall permit the demonstration of clinical performance, effectiveness or safety over a period of time sufficient to represent a realistic test of the investigational device and allow any risks associated with adverse device effects to be identified and assessed.

f) Address what specific medical care is appropriate to be provided for the subjects after the clinical investigation has been completed, if applicable.

g) Address recommended follow-up for the subjects after the clinical investigation has been completed.

h) Address the final disposition or potential future use of samples obtained from subjects, if applicable.

A.6.5 Monitoring plan

General outline of the monitoring plan to be followed, including access to source data and the extent of source data verification planned.

It is possible to provide a detailed plan for monitoring arrangements separately from the CIP.

A.7 Statistical design and analysis

With reference to A.5 and A.6, the description of and justification for statistical design and analysis of the clinical investigation shall cover the following.

a) Analysis population (e.g. intention-to-treat, per-protocol, as-treated) and procedures that take into account all the data.

b) Descriptive statistics of baseline data, treatments, safety data and where applicable, primary and secondary endpoints.

c) Analytical procedures including measures of precision such as confidence intervals, if applicable.

d) The significance level and the power of primary endpoint(s) and the overall statistical testing strategy, if applicable.

   If a hypothesis is tested, a significance level alpha 0,05 (two-sided) and 0,025 (one-sided) and powers between 0,8 and 1 minus alpha need no justification. Depending on the characteristics of the investigational medical device or the clinical investigation, higher or lower levels of significance can be used. Examples of justifications include but are not limited to: product standards, scientific reasons or discussion with regulatory authorities.

e) Sample size calculation and justification taking into account:

   1) all relevant clinical data on outcome variable and effect size, if applicable;

   2) assumptions of expected outcomes across treatment groups, if applicable;

   3) adjustments due to any pre-planned interim analyses, if applicable;

   4) detectable effect size and non-inferiority margin, which shall be smaller than the detectable effect size and justified with reference to the effect of the comparator, if applicable;

   5) randomization allocation ratio (e.g. 1:1, 1:2), if applicable;

6) expected drop-out rate, such as withdrawal, lost to follow-up, death (unless death is an endpoint).

All the statistical parameters and methods used to calculate sample size or the non-inferiority margin shall be clearly provided.

For exploratory and observational clinical investigations (see Annex I), in which the sample size is not required to be derived by calculation, the scientific rationale for the chosen sample size shall be provided.

f) The rationale for the number of procedures to be performed by a single user as part of the learning curve and how these data are to be analysed, if applicable.

g) Pass/fail criteria to be applied to the results of the clinical investigation.

h) The provision for an interim analysis, criteria for the termination of the clinical investigation on statistical grounds, where applicable.

i) Management of bias and, when randomization, matching, or blinding are applied, plan for assessment of success thereof.

j) Management of potential confounding factors (e.g. adjustment, stratification, or stratified randomization).

k) Description of procedures for multiplicity control and adjustment of error probabilities, if applicable.

l) The specification of subgroups for analysis, if applicable, or if response to treatment is expected to be different in these groups.

m) Management, justification, and documentation of missing, unused or spurious data, including drop-outs.

n) Exploratory analysis and sensitivity analysis (e.g. to explore robustness of results of primary and secondary analysis with respect to different methods used for handling missing data), if applicable.

o) Procedures for reporting any deviation(s) from the original statistical analysis plan.

p) For multicentre clinical investigations, a strategy for handling the potential imbalance of the numbers of subjects across investigation sites.

q) A strategy for pooling data, if applicable.

Further or more specific information can be found in standards for different types of medical devices or in national regulations or guidance documents (see References [9], [10], [13]).

A.8 Data management

a) Methods (e.g. CRF) for data entry and collection.

b) Procedures used for CRF tracking, data review, database cleaning, and issuing and resolving data queries. Specifically, timely, and reliable processes for recording data and rectifying errors and omissions, medical coding uniformity, and reconciliation, if applicable, are necessary to ensure delivery of a quality database and the achievement of the clinical investigation objectives through the implementation of the planned analysis.

c) Procedures for verification, validation, and securing of electronic clinical data systems, if applicable.

d) Procedures to maintain and protect subject privacy.

e) Methods for database locking at the start of the analysis and storage upon completion of the clinical investigation.

f) Procedures for data retention.

g) Specified retention period.

h) Other aspects of clinical quality assurance, as appropriate.

A.9 Amendments to the CIP

Description of the procedures to amend the CIP.

A.10 Deviations from clinical investigation plan

a) Statement specifying that the investigator is not allowed to deviate from the CIP, except as specified in 5.6.4 c).

b) Procedures for recording, reporting, and analysing CIP deviations.

c) Notification requirements and time frames.

d) Corrective and preventive actions and principal investigator disqualification criteria.

A.11 Device accountability

a) Description of the procedures for the accountability of investigational devices as specified in 7.9;

b) Procedures and particular materials and instructions for the safe return of investigational devices, including those that are potentially hazardous.

A.12 Statements of compliance

a) Statement specifying that the clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (see Reference [7]).

b) Statement specifying compliance with this document and any regional or national regulations, as appropriate.

c) Statement specifying that the clinical investigation shall not begin until the required approval/favourable opinion from the EC and regulatory authority have been obtained, if appropriate.

d) Statement specifying that any additional requirements imposed by the EC or regulatory authority shall be followed, if appropriate.

e) Statement specifying the type of insurance that shall be provided for subjects, if appropriate.

f) Statement addressing the financing of the clinical investigation including a description of the agreement between the sponsor and investigation site(s), and where applicable with the investigator(s) if not addressed in a separate agreement.

A.13 Informed consent process

a) Description of the general process for obtaining informed consent, including the process for providing subjects with new information and process for incentives for subjects, as needed.

b) Description of the informed consent process in circumstances where the subject is unable to give it; in the case of emergency treatment, the items specified in 5.8.3.4 shall be included.

A.14 Adverse events, adverse device effects, and device deficiencies

a) Definitions of adverse events and adverse device effects.

b) Definition of device deficiencies.

c) Definitions of serious adverse events including serious health threat and serious adverse device effects and, where appropriate, unanticipated serious adverse device effects.

d) List of non-reportable adverse events, if applicable, including rationale.

e) Time period in which the principal investigator shall report all adverse events and device deficiencies to the sponsor and, where appropriate, to ECs and the regulatory authority.

f) Details of the process for reporting adverse events (date of the adverse event, treatment, resolution, assessment of both the seriousness and the relationship to the investigational device and the related procedure).

g) Details of the process for reporting device deficiencies.

h) List of foreseeable adverse events and anticipated adverse device effects, together with their likely incidence, mitigation, or treatment.

i) Emergency contact details for reporting serious adverse events and serious adverse device effects.

j) Information regarding the DMC, if established.

A.15 Vulnerable population (if applicable)

a) Description of the vulnerable population to be included in the clinical investigation.

b) Description of the screening process to identify and protect the vulnerable population.

c) Description of the specific informed consent process.

d) Description of the EC's specific responsibility.

e) Description of what medical care, if any, will be provided for subjects after the clinical investigation has been completed.

A.16 Suspension or premature termination of the clinical investigation

a) Criteria and arrangements for suspension or premature termination of the whole clinical investigation or of the clinical investigation in one or more investigation sites.

b) Criteria for access to and breaking the blinding/masking code in the case of suspension or premature termination of the clinical investigation, if the clinical investigation involves a blinding/masking technique.

c) Requirements for subject follow-up and continued care.

A.17 Publication policy

a) Statement that the clinical investigation will be registered in a publicly accessible database (see 5.4).

b) Statement indicating that the results of the clinical investigation will be made publicly available.

c) Statement indicating the conditions and timeframes under which the results of the clinical investigation will be offered for publication including the role of the sponsor and criteria for authorship.

A.18 Bibliography

List of bibliographic references pertaining to the clinical investigation.

Annex B
(normative)

Investigator's brochure (IB)

B.1 General

B.1.1 Introduction

If the required information of the IB is provided in other documentation (e.g. the CIP or instructions for use); such documents shall be referenced in the IB and shall be made available upon request.

The content of the IB shall contain, as a minimum, all topics listed in this annex.

NOTE Not all requirement elements might be relevant for post-market clinical investigations or information can be described in other product documentation (see I.7).

The information shall be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased benefit-risk analysis of the appropriateness of the proposed clinical investigation. For this reason, a medically qualified person shall generally participate in the editing of an IB, but the contents of the IB shall be approved by the disciplines that generated the described data.

B.1.2 Identification of the IB

a) Name of the investigational device.

b) Document reference number, if any.

c) Version or date of the IB.

d) Confidentiality statement, if appropriate.

e) Summary of the revision history in the case of amendments, if appropriate.

f) Version/issue number and reference number, if any, with the page number and the total number of pages on each page of the IB.

g) Table of contents.

B.1.3 Sponsor/manufacturer

Name and address of the sponsor of the clinical investigation and manufacturer of the investigational device, if different from the sponsor.

B.2 Investigational device information

a) Summary of the literature and evaluation supporting the rationale for the design and intended use of the investigational device.

b) Statement concerning the regulatory classification of the investigational device, if relevant.

c) General description of the investigational device and its components, including any materials used, and details on those that will be in contact with tissues or body fluids. This shall include details of

any medicinal substances, human, or animal tissues or their derivatives, or other biologically active substances and reference to compliance with applicable national regulations.

d) Summary of relevant manufacturing processes and related validation processes, to demonstrate that the investigational devices are manufactured and verified under a controlled process according to the applicable regulations.

e) Description of the mechanism of action of the investigational device, along with supporting scientific literature.

f) Manufacturer's instructions for installation, maintenance of hygienic conditions and use of the investigational device, including any necessary storage and handling requirements, preparation for use and any intended re-use (e.g. sterilization), any pre-use safety or performance checks and any precautions to be taken after use (e.g. disposal), if relevant.

g) Sample of the label, for example sticker or copy, and instructions for use or reference to, and information on any training required.

h) Description of the intended clinical performance.

B.3 Preclinical testing

Summary of the preclinical testing that has been performed on the investigational device, together with an evaluation of the results of such testing, justifying its use in human subjects.

The summary shall include or, where applicable, refer to the results of

a) design calculations,

b) *in vitro* tests,

c) mechanical and electrical safety tests,

d) reliability tests,

e) validation of software relating to the function of the device,

f) any performance tests,

g) *ex vivo* tests,

h) *in vivo* animal test,

i) evaluation of biological safety,

j) validation of procedures for cleaning, disinfection, or sterilization.

NOTE 1 Guidance on the biological evaluation of medical devices is given in ISO 10993-1.

NOTE 2 For animal tests, include specifications of species, number of animals per group, devices used, and duration of exposure.

B.4 Existing clinical data

a) Summary of relevant previous clinical experience with the investigational device and with medical devices that have similar characteristics, including such characteristics that relate to other indications for use of the investigational device.

b) Analysis of adverse device effects and any history of modification or recall.

B.5 Risk management of the investigational device

a) Summary of the benefit-risk analysis including identification of residual risks.

b) Contra-indications and warnings for the investigational device.

B.6 Regulatory and other references

a) List of international standards, if any, complied with in full or in part.

b) Statement of conformity with national regulations, where appropriate.

c) List of references, if relevant.

Annex C
(informative)

Case report forms (CRFs)

C.1 General

CRFs are established to implement the CIP, to facilitate subject observation and to record subject and investigational device data during the clinical investigation according to the CIP. They can exist as printed, optical, or electronic documents and can be organized into a separate section for each subject. The CRFs should reflect the CIP and take account of the nature of the investigational device.

C.2 Content and format

C.2.1 Overall considerations

The CRFs can be organized such that they reflect all the data from a single procedure or a single visit or other grouping that makes clinical or chronological sense.

The format of CRFs should be such as to minimize errors that can be made by those who enter data and those who transcribe the data into other systems.

The data categories and format listed in this annex can be considered when designing CRFs.

C.2.2 Cover page/login screen

a) Name of sponsor or sponsor logo.

b) CIP version and date (if required).

c) Version number of CRFs.

d) Name of clinical investigation or reference number (if applicable).

C.2.3 Header or footer/e-CRF identifier

a) Name of the clinical investigation or reference number.

b) Version number of CRFs.

c) Investigation site/principal investigator identification number.

d) Subject identification number and additional identification such as date of birth or initials.

NOTE Certain national regulations can apply.

e) CRF number or date of visit or visit number.

f) Page/screen number of CRF and total number of pages/screens (e.g. “page *x* of *xx*”).

To avoid repeat entries, it is possible to pre-print or pre-programme some of the elements above.

C.2.4 Types of CRF

The following is a suggested list of CRFs that can be developed to support a clinical investigation. This is not an exhaustive list and is intended to be used as a guideline.

a) Screening.

b) Documentation of subject's informed consent.

c) Inclusion/exclusion.

d) Baseline visit:

   1) demographics;

   2) medical diagnosis;

   3) relevant previous medications or procedures;

   4) date of enrolment;

   5) other characteristics.

e) Intervention(s) or treatment(s).

f) Follow-up visit(s).

g) Clinical investigation procedure(s).

h) Adverse event(s).

i) Device deficiencies.

j) Concomitant illness(es)/medication(s)/treatment(s).

k) Unscheduled visit(s).

l) Subject diary.

m) Subject withdrawal or lost to follow-up.

n) Form signifying the completion of the clinical investigation for a given subject, signed by the principal investigator or his/her authorized designee.

o) CIP deviation(s).

C.3 Procedural issues

A system should be established to enable cross-referencing of CRFs and CIP versions.

Supplemental CRFs may be developed for collecting additional data at individual investigation sites in multicentre investigations.

Annex D
(normative)

Clinical investigation report

D.1 General

This annex specifies the contents of the clinical investigation report that describes the design, conduct, statistical analysis, and results of a clinical investigation.

The format given in this annex may also be used in interim, progress or annual reports, if such reports are required, however some sections might only apply to the final report.

D.2 Cover page

The title page shall contain the following:

a) title of the clinical investigation;

b) if not clear from the title, a single sentence describing the design, comparison, period, usage method, and subject population;

c) identification of the investigational devices, including names and models, as relevant for complete identification;

d) name and contact details of sponsor or sponsor's representative;

e) CIP identification;

f) publicly accessible database registration number;

g) name and department of coordinating investigator and names of other relevant parties (e.g. experts, biostatistician, laboratory personnel);

h) statement indicating whether the clinical investigation was performed in accordance with this document or any other applicable guidelines and applicable regulations;

i) date of report;

j) author(s) of report.

D.3 Table of contents

The table of contents shall include the following:

a) the page number or locating information of each section, including summary tables, figures, and graphs;

b) a list of appendices and their location.

D.4 Summary

The summary shall contain the following:

a) the title of the clinical investigation;

b) an introduction;

c) the purpose of the clinical investigation;

d) the description of the clinical investigation population;

e) the clinical investigation method used;

f) the results of the clinical investigation;

g) the conclusion;

h) the date of the clinical investigation initiation;

i) the completion date of the clinical investigation or, if the clinical investigation is discontinued, the date of premature termination.

D.5 Introduction

The introduction shall contain a brief statement placing the clinical investigation in the context of the development of the investigational device and relating the critical features of the clinical investigation (e.g. objectives and hypotheses, target population, treatment and follow-up duration) to that development.

Any guidelines that were followed in the development of the CIP or any other agreements/meetings between the sponsor and regulatory authorities that are relevant to the particular clinical investigation should be identified or described.

D.6 Investigational device and methods

D.6.1 Investigational device description

The description of the investigational device shall contain the following:

a) a description of the investigational device;

b) the intended use of the investigational device(s);

c) previous intended uses or indications for use, if relevant;

d) any changes to the investigational device during the clinical investigation or any changes from the IB, including

   1) raw materials,

   2) software,

   3) components,

   4) shelf-life,

   5) storage conditions,

   6) instructions for use, and

   7) other changes.

D.6.2 Clinical investigation plan (CIP)

A summary of the CIP, including any subsequent amendment(s) with a rationale for each amendment, shall be provided. The summary shall include a brief description of the following:

a) the clinical investigation objectives;

b) the clinical investigation design including

   1) the type of clinical investigation,

   2) the clinical investigation endpoints, and

   3) the control group;

c) the ethical considerations;

d) the data quality assurance;

e) the subject population for the clinical investigation, with the

   1) inclusion/exclusion criteria, and

   2) sample size;

f) the treatment and treatment allocation schedule;

g) any concomitant medications/treatments;

h) the duration of follow-up;

i) the statistical design, analysis, and justifications including

   1) the clinical investigation hypothesis or pass/fail criteria,

   2) a sample size calculation,

   3) statistical analysis methods,

   4) interim analyses, if applicable.

D.7 Results

The results section shall include the following:

a) the clinical investigation initiation date;

b) the clinical investigation completion/suspension date;

c) the disposition of subjects; numbers screened, randomized and received therapy;

d) the disposition of investigational devices;

e) the subject demographics and other relevant baseline characteristics;

f) CIP compliance;

g) an analysis with rationale and justifications, which includes

   1) all clinical performance, effectiveness or safety analyses provided for in the CIP,

      NOTE These include results for the components of composite endpoints, when used.

2) a summary of all adverse events and adverse device effects, including a discussion of the severity, treatment needed, resolution, and relevant principal investigator's judgment concerning the causal relationship with the investigational devices or procedure,

3) a table compiling all observed device deficiencies that could have led to a serious adverse device effect, and any corrective actions taken during the clinical investigation, if any,

4) any needed subgroup analyses for special populations (i.e. gender, racial/cultural/ethnic subgroups), as appropriate,

5) an accountability of all subjects with a description of how missing data or deviation(s) were dealt with in the analysis, including subjects

   i) not passing screening tests,

   ii) lost to follow-up, and

   iii) withdrawn or discontinued from the clinical investigation and the reason.

6) clear distinctions between primary analyses, other pre-specified analyses, and additional analyses,

h) listings of deaths and reasons for deaths.

D.8 Discussion and overall conclusions

The conclusions shall be based on the intended use and target population of the investigational device and shall include the following:

a) the clinical performance, effectiveness, or safety results and any other endpoints;

b) an assessment of benefits and risks;

c) a discussion of the clinical relevance and importance of the results in the light of other existing data;

d) any specific benefits or special precautions required for individual subjects or groups considered to be at risk;

e) any implications for the conduct of future clinical investigations;

f) any limitations of the clinical investigation including but not limited to:

   1) selection, retention, and compliance of subjects,

   2) selection, retention, adherence (to CIP, instructions for use and the requirements of this document) of investigation sites and users, and investigation site environment type(s),

   3) bias introduced by missing observations, by confounders and by 1) and 2) above.

Requirements in f) also apply to the control group(s).

D.9 Abbreviated terms and definitions

A list of abbreviated terms and definitions of specialized or unusual terms shall be provided.

D.10 Ethics

The ethics section shall include the following:

a) confirmation that the CIP and any amendments to it were reviewed by the EC (if required);

b) list of all ECs consulted (can be given in an annex; see D.13);

c) confirmation that the clinical investigation was conducted in accordance with the ethical principles in the Declaration of Helsinki;

d) statement that informed consent was obtained and when it was obtained.

D.11 Investigators and administrative structure of clinical investigation

The overview of the administrative structure shall include the following:

a) a brief description of the organization of the clinical investigation;

b) a list of investigators, including their affiliations (can be given in an annex; see D.13);

c) the names and addresses of any external organizations (such as core laboratories, CROs, consultants or other contractors) that contributed to the clinical investigation (can be given in an annex; see D.13);

d) the names and addresses of the sponsor(s) or sponsors' representative(s).

D.12 Signature page

The signatures of the sponsor and coordinating investigator(s), indicating their agreement with the contents of the report, shall be provided. If no coordinating investigator is appointed, then the signature of the principal investigators shall be obtained. The signature pages may be separate from the clinical investigation report itself.

D.13 Annexes to the report

There can be annexes to the report which contain the following:

a) the CIP, including amendments;

b) the instructions for use;

c) the list of principal investigators and their affiliated investigation sites, including a summary of their qualifications or a copy of their CVs;

d) the list of names and addresses of any external organizations (such as core laboratories, CROs, consultants or other contractors) that contributed to the clinical investigation;

e) the list of monitors;

f) the list of ECs;

g) the tabulation of all relevant data sets, including

   1) CIP deviations that can have affected the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation,

   2) all adverse events, adverse device effects and device deficiencies, and

   3) withdrawals and discontinuations,

h) the audit certificate, if applicable.

Annex E
(informative)

Essential clinical investigation documents

National regulatory authorities may require a list of the documents given in Tables E.1, E.2 and E.3, which should be maintained in the investigation site and sponsor files. The information below may differ among clinical investigations.

The sponsor and principal investigator/investigation site should maintain a record of the location(s) of their respective essential documents. The storage system (irrespective of the media used) should provide for document identification, version history, search, and retrieval.

Depending on the activities being carried out, individual clinical investigations may require additional documents not specifically mentioned in the essential document list. The sponsor or principal investigator/investigation site should include these as part of the essential clinical investigation documents file.

Table E.1 — Essential clinical investigation documents prior to clinical investigation

No.	Title of document	Purpose or comment	Site files	Sponsor files	Reference in this document
E.1.1	IB	Describes the investigational device, including instructions for device use.	X	X	6.5 Annex B
E.1.2	CIP	Describes the clinical investigation design and procedures.	X	X	6.4 Annex A
E.1.3	Sample of labelling attached to investigational device	Confirms appropriate labelling (includes packaging labels and instructions for use).	X	X	6.10
E.1.4	Principal investigator's CV: current, signed, and dated	Identifies the principal investigator. The site has CVs for principal investigators at that site; the sponsor has CVs for principal investigators from all investigation sites.	X	X	5.6.2 e) 10.2 a) D.13 c)
E.1.5	CV of members of the investigation site team: current, signed and dated	Identifies the members of the investigation site team. The site has CVs for members of investigation site team at that site.	X	X	5.6.2 l) 10.3 b)
E.1.6	CV or other qualification documentation of individuals other than those cited in E.1.4 and E.1.5, who materially contribute to the clinical investigation	Documents qualification of all other parties involved in clinical investigation.	—	X	6.1 9.2.1 9.2.4.3
E.1.7	Log of principal investigator and members of investigation site team at each investigation site	Documents the attribution of responsibilities, with signature, title, and responsibilities in the clinical investigation.	X	X	7.2 9.2.1 f) 9.2.4.5 b)

[a] Regulations might not require this in the investigation site file.

Table E.1 *(continued)*

No.	Title of document	Purpose or comment	Site files	Sponsor files	Reference in this document
E.1.8	List of investigation sites	Evidences who is conducting the clinical investigation, with names and addresses.	—	X	A.1.4
E.1.9	EC notification, correspondence and opinion/approval	Gives evidence that a qualified, independent EC has reviewed the clinical investigation.	X	X	5.6.3 7.1 9.2.2 h) 10.4 c)
E.1.10	EC voting list for the clinical investigation	Provides evidence that the investigator is not part of the voters (dependent on regulatory requirements).	X	X	5.6.3
E.1.11	Regulatory authority notification, correspondence and approval (where required)	Verifies information provided to regulatory authorities. Confirms notification or approval.	X[a]	X	7.1 9.2.2 g) 9.4
E.1.12	Signed agreement between principal investigator(s)/ investigation site(s) and sponsor	Demonstrates understanding of each party's respective responsibilities.	X	X	6.9 9.2.1 a)
E.1.13	Signed agreements between sponsors and external organizations, e.g. CRO, core laboratories	Demonstrates understanding of each party's responsibilities.	—	X	6.9 9.2.1 a)
E.1.14	Financial agreements, if separate from agreements on responsibilities	Provides evidence of financial arrangements between investigator/investigation site and sponsor (can be kept separate from other site files).	X	X	9.2.2 f)
E.1.15	Insurance certificates, if applicable	Gives evidence that compensation to subject(s) for clinical investigation-related injuries will be available.	X	X	5.3 5.6.2 j) 9.2.2 e)
E.1.16	Shipping records for investigational devices	Verifies physical possession of devices.	X	X	7.9 9.2.2 c) 9.2.3 a) 9.2.4.5 n) 10.6 k)
E.1.17	Shipping records for clinical investigation-related documents and materials	Verifies physical shipment of documents and materials.	X	X	9.2.2 a) 9.2.4.4 b)
E.1.18	Sample of approved informed consent forms, information for the subjects and advertisements, including translations	Gives evidence of the content of the informed consent forms and of the information provided to the subject during the clinical investigation.	X	X	5.6.2 c), d) 5.8.4 7.8.1 9.2.2 b)
E.1.19	Randomization list for randomized clinical investigations	Verifies that randomization has been followed. Depending on the design of the clinical investigation, the list might not be available at the investigation site for blinded/masked clinical investigations.	X	X	7.8.1

[a] Regulations might not require this in the investigation site file.

Table E.1 *(continued)*

No.	Title of document	Purpose or comment	Site files	Sponsor files	Reference in this document
E.1.20	Decoding procedures for blinded/masked clinical investigations, where applicable	Might not take place on the investigation site depending on clinical investigation design.	X	X	7.8.1 A.6.1 b) A.16 b) 10.7 e)
E.1.21	Investigation site selection report	Verifies that qualifications of investigator and investigation site have been reviewed.	—	X	6.8 9.2.1 c) 9.2.4.3 9.2.4.7
E.1.22	Clinical investigation initiation monitoring report	Verifies that investigator and investigation site team have been trained to device use and CIP compliance.	—	X	7.2 9.2.4.4 9.2.4.7
E.1.23	Identification of type and location of source documents	Identifies all types of source document relevant to the clinical investigation and where they are located to enable access for review and inspection and ensure all site files are identified.	X	—	7.5.3 10.6 c)
E.1.24	Follow-up letter further to clinical investigation initiation monitoring; correspondence with the investigation site	Identifies any findings and actions to the investigation site.	X	X	9.2.4.7
E.1.25	CRF	Blank set to evidence the content of data being collected.	X	X	6.6 Annex C
E.1.26	Adverse events forms	Documents all adverse events as required by this document. Forms may or may not be part of the CRFs.	X	X	6.6 7.4.2 Annex C
E.1.27	Device deficiency forms	Document all device deficiencies. Forms may or may not be part of the CRFs.	X	X	6.6 7.4.3 Annex C
E.1.28	Names/contact information of monitor(s)	Document the person who has ensured continuing compliance of the clinical investigation.	X	X	6.1 9.2.1 a) 9.2.1 g) D.13 e)
E.1.29	Training records	Provides evidence that investigator(s) have been trained in the use of the investigational device and all relevant aspects of the clinical investigation.	X	X	9.2.1 h)
E.1.30	Normal value(s)/range(s) for clinical laboratory test, if relevant to the clinical investigation	Documents normal values.	X	X	9.2.4.5 q)
E.1.31	Confirmation of adequacy of equipment, if relevant to the clinical investigation	Documents equipment maintenance and calibration.	X	X	9.2.4.5 p) 10.6 i)
E.1.32	— Certification, accreditation or established quality control or external quality assessment or	Documents the competence and responsibilities of the facility to perform the required test(s) and support the reliability of results.			

[a] Regulations might not require this in the investigation site file.

Table E.1 *(continued)*

No.	Title of document	Purpose or comment	Site files	Sponsor files	Reference in this document
	— Other validation of the laboratory, if relevant to the clinical investigation or — Identification and qualification of the laboratory director, if relevant to the clinical investigation		X	X	6.1 9.2.1 9.2.4.5 q)
E.1.33	Disclosures of conflicts of interest	Documentation of conflicts of interest, e.g. financial.	X	X	5.6.2 d) 9.2.1 e) 10.2 c)
E.1.34	Agreements between principal investigator and external organizations (e.g. site management organization)	Demonstrates understanding of each party's responsibilities.	X	—	10.1

[a] Regulations might not require this in the investigation site file.

Table E.2 — Essential clinical investigation documents during clinical investigation

No.	Title of document	Purpose or comment	Site files	Sponsor files	Reference in this document
E.2.1	IB amendments, if any	Documents changes to the IB.	X	X	7.5.1
E.2.2	CIP amendments, if any	Describes changes to the clinical investigation design.	X	X	7.5.1
E.2.3	Sample of amendments to informed consent form		X	X	7.5.1
E.2.4	EC approval/favourable opinion of any amendments		X	X	5.6.4 e) 5.6.5 a) 7.5.1 9.2.3 b) 9.2.4.5 o) 10.4 c)
E.2.5	Notices or approvals to regulatory authorities of any amendments, where required	Verifies information provided to authorities. Confirms notification or approval. Regulations might not require this in the investigation site file and, if required, it may be either a copy or original depending on the regulatory requirements.	X	X	7.1 7.5.1 9.4 b)
E.2.6	CV of new principal investigators	Identifies the principal investigators; the investigation site has CVs for principal investigators at that site; sponsor has CVs for principal investigators from all investigation sites.	X	X	5.6.2 e) 10.2 a) D.13 c)

Table E.2 *(continued)*

No.	Title of document	Purpose or comment	Site files	Sponsor files	Reference in this document
E.2.7	CV of new members of the investigation site team: current, signed and dated	Identifies the new members of the investigation site team. The investigation site has CVs for members of investigation site team at that investigation site.	X	X	5.6.4 j) 10.3 b)
E.2.8	Shipping records and investigational device accountability records		X	X	7.9 9.2.2 c), 9.2.3 a) 9.2.4.5 n) 10.6 k)
E.2.9	Shipping records for clinical investigation-related document materials		X	X	9.2.2 a) 9.2.4.4 a)
E.2.10	Monitoring visit reports	Provides summary of key findings to the principal investigator.	(X)	X	9.2.3 e) 9.2.4.7
E.2.11	Correspondence related to the clinical investigation, including emails, letters, meeting notes, and phone reports		X	X	9.2.3 b) 9.2.4.5 o) 10.6 h)
E.2.12	Updated log of the principal investigator and members of the investigation site team at each investigation site, including signature, title, and responsibilities in the clinical investigation	Documents attribution of responsibilities.	X	X	7.2 9.2.1 f) 9.2.4.5 b)
E.2.13	Signed, dated, and fully executed informed consent forms	Verifies that informed consent has been given.	X	—	5.8.1 9.2.4.5 f) 10.5
E.2.14	Source documents		X	—	7.5.3 7.8.2 10.6 c) 10.7 f)
E.2.15	Updates of documentation on type and location of source documents	Identifies all types of source document relevant to the clinical investigation and where they are located to enable access for review and inspection and ensure all site files are identified.	X	—	7.5.3 9.2.4.5 g) 10.6 c)
E.2.16	CRFs, fully executed	Evidences what data were collected and that their authenticity has been verified by principal investigator.	X	X	7.3 7.8.1 7.8.2 9.2.4.5 h), i), j) 10.6 j)
E.2.17	Reports of adverse events, adverse device effects, and device deficiencies	Documents the occurrence and resolution of adverse events and adverse device effects.	X	X	7.4 9.2.4.5 k),l) 9.2.5 10.8 D.13 g)
E.2.18	CRFs corrections	Gives evidence of any changes, additions, or corrections made to CRFs after data were initially recorded.	X	X	7.8.2 9.2.4.5 i) 10.6 j)

Table E.2 *(continued)*

No.	Title of document	Purpose or comment	Site files	Sponsor files	Reference in this document
E.2.19	Reports of adverse events or device deficiencies by sponsor to regulatory authorities or by the principal investigator, where applicable	Filing in investigation site files only where national regulations require notification by the principal investigator.	X	X	7.4 9.2.4.5 l) 9.2.5 d) 9.4 10.8 d)
E.2.20	Reports of adverse events by principal investigator to EC or by sponsor, where required		X	X	5.6.4 9.2.4.5 l) 9.2.5 c) 10.8 c)
E.2.21	Reports by sponsor to investigators of adverse events occurring at other investigation sites		X	X	9.2.5 f)
E.2.22	Interim or annual reports by principal investigators to EC, where applicable		X	X	5.6.4 d) 9.2.3 h) 9.2.4.5 o)
E.2.23	Subject screening log	Sponsor file only if anonymized.	X	X	7.5.2 - NOTE
E.2.24	Subject identification log		X	—	7.5.2
E.2.25	Accountability records of investigational devices at the investigation site, where appropriate	Reconciles with sponsor's shipping and receipt records.	X	X	7.9 9.2.3 a) 9.2.4.5 n) 10.6 k)
E.2.26	Updated names/contact information of monitor(s)	Documents the person who has ensured continuing compliance of the clinical investigation. The investigation site file contains dedicated monitors identification only.	X	X	9.2.1 g) D.13 e)
E.2.27	Updates to normal value(s)/range(s) for clinical laboratory test, if relevant to the clinical investigation	Documents the changes of normal values throughout the clinical investigation.	X	X	9.2.4.5 q)
E.2.28	Updates to confirmation of adequacy of equipment, if relevant to the clinical investigation	Documents the changes of equipment, continuous maintenance, and calibration throughout the clinical investigation.	X	X	9.2.4.5 p)
E.2.29	Updates of — certification accreditation or established quality control or external quality assessment or — other validation of the laboratory, if relevant to the clinical investigation or — identification and qualification of the laboratory director, if relevant to the clinical investigation	Documents adequacy of tests throughout the clinical investigation.	X	X	6.1 9.2.1 9.2.4.5 t)

Table E.2 *(continued)*

No.	Title of document	Purpose or comment	Site files	Sponsor files	Reference in this document
E.2.30	Updates of disclosures of conflicts of interest	Documents conflicts of interest, e.g. financial.	X	X	9.2.1 e) 10.2 c)

Table E.3 — Essential clinical investigation documents after clinical investigation

No.	Title of document	Purpose or comment	Site files	Sponsor files	Reference in this document
E.3.1	Investigational device accountability records at each investigation site, where applicable		X	X	7.9 8.3 a) 10.6 k) 10.6 q)
E.3.2	Documentation of investigational device return or disposal, where applicable	Documents the proper disposal of biohazardous materials or other materials that require special disposal.	X	X	7.9 8.3 a) 10.6 k)
E.3.3	Completed subject identification log		X	—	7.5.2
E.3.4	Audit certificate (if required or conducted)		—	X	7.11 9.1 D.13 h)
E.3.5	Close-out monitoring report		—	X	9.2.4.7
E.3.6	Notification of clinical investigation close-out to the EC by principal investigators or sponsor, where required		X	X	5.6.4 8.3 b) 9.2.6 d) 10.4 f)
E.3.7	Notification of clinical investigation close-out to the regulatory authorities by sponsor or principal investigators, where required	Investigation site file only where principal investigator is required to notify regulatory authorities.	X	X	8.3 b) 9.2.6 d)
E.3.8	Sponsor's statistical analyses and clinical investigation report	Investigation site file only if required by sponsor procedures.	X	X	8.4 9.2.6 c) Annex D

Annex F
(informative)

Adverse event categorization

Table F.1 presents categories of adverse events.

Table F.1 — Categories of adverse events

Adverse events	Non-device-related	Device- or investigational procedure-related	
Non-serious	Adverse event (AE)[a] (3.2)	Adverse device effect (ADE)[c] (3.1)	
Serious	Serious adverse event (SAE)[b] (3.45)	Serious adverse device effect (SADE) (3.44)	
		Anticipated	**Unanticipated**
		Anticipated serious adverse device effect (ASADE)[c] (3.1, Note 1 to entry)	Unanticipated serious adverse device effect (USADE) (3.51)

[a] Includes all categories.

[b] Includes all categories that are serious.

[c] Includes all categories that are related to the device or the investigational procedure.

Figures F.1 and F.2 provide guidance on questions that can be asked to categorize adverse events and device deficiencies but are not intended to show the interrelationship of categories. During any time of the process, attention should be paid to signals that can indicate a serious health threat.

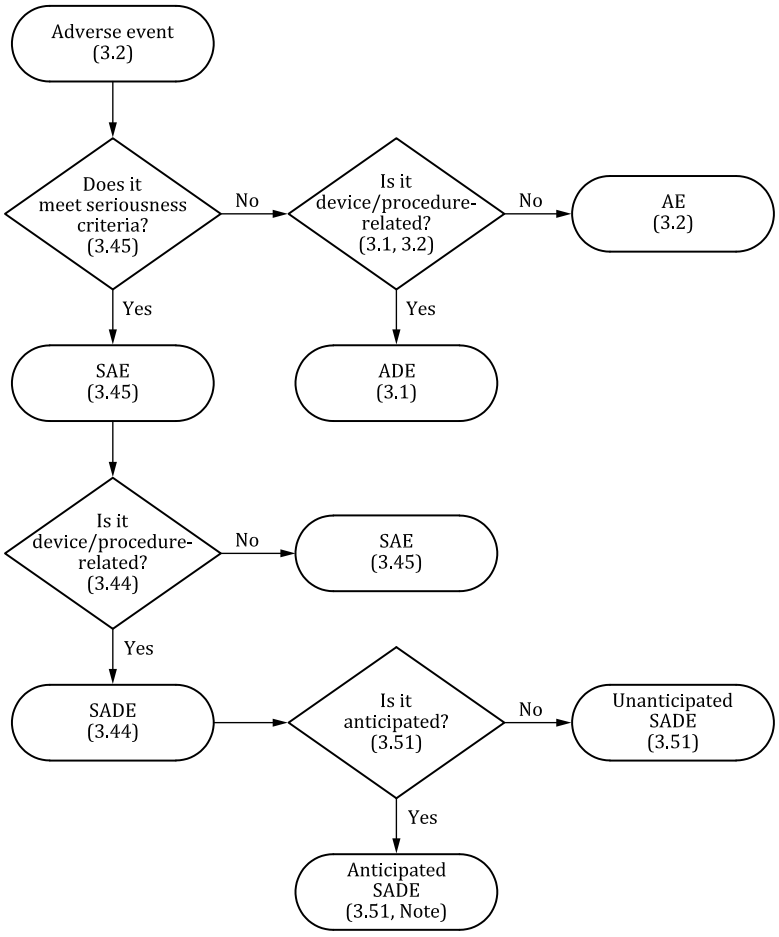

Figure F.1 — Adverse events categorization chart

The flowchart below on device deficiencies should only be used in case the device deficiency is not associated with an adverse event.

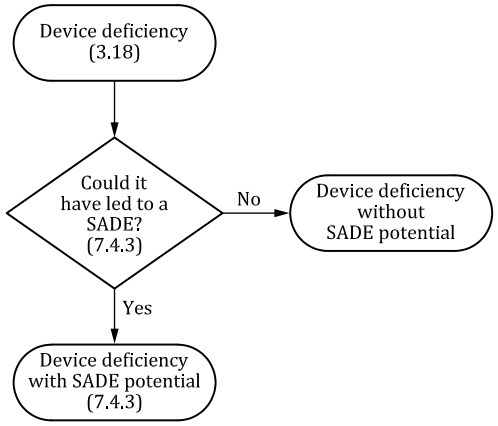

Figure F.2 — Device deficiency categorization chart

Annex G
(informative)

EC responsibilities

G.1 General

The content of this annex is intended to provide guidance on best practices for the operation of ECs involved in the review of clinical investigations of medical devices.

NOTE EC requirements are outlined in national or local regulations, where available (see 5.6.1).

G.2 Responsibilities

The purpose of an EC is to safeguard the rights, safety, and well-being of all clinical investigation subjects. Special attention should be paid to clinical investigations that may include vulnerable subjects.

The EC should obtain documents describing the proposed conduct of the clinical investigation as outlined in 5.6. The EC may require more information than described in 5.6 when the additional information would contribute meaningful to the protection of the rights, safety, and well-being of the subjects.

The EC should review a proposed clinical investigation within a reasonable timeframe and document its review in writing, clearly identifying the type and versions of the documents reviewed.

Where the CIP indicates that prior consent of the clinical investigation subject or the subject's legally designated representative is not possible, the EC should determine that the proposed CIP or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such clinical investigations (i.e. in emergency situations).

The EC should review both the amount and method of payment to subjects to ensure that neither presents problems of coercion or undue influence on the clinical investigation subjects with special attention to clinical investigations that may include vulnerable subjects. Payments to a subject should be prorated and not wholly contingent on completion of the clinical investigation by the subject. The EC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payments, is set forth in the informed consent form and any other written information provided to subjects. The way payment will be prorated should be specified.

The EC should consider the qualifications of the principal investigator and facilities for the proposed clinical investigation, as documented by a current CV or by any other relevant documentation the EC requests.

When a clinical investigation with no therapeutic benefit is to be carried out with the consent of the subject's legally designated representative, the EC should determine that the proposed clinical investigation plan or other documents adequately address relevant ethical concerns.

The EC should conduct continuing review of each ongoing clinical investigation at intervals appropriate to the degree of risk to subjects, but at least once per year.

G.3 Composition, functions, and operations

The EC should consist of members who collectively have the qualifications and experience to review and evaluate the scientific, medical, methodological, statistical and ethical aspects of the proposed clinical investigation. In some cases, the EC should be organized within each medical institution where the investigation is to be conducted. In other cases, one EC may be organized to serve a number of investigation sites conducting one multicentre investigation. It is recommended that an EC should include at least:

— five members;

— one lay person or member whose primary area of interest is non-scientific;

— one member who is independent of the investigation site;

— one member of each gender.

An EC may invite non-members with expertise in specific fields to participate in meetings when appropriate.

A list of all EC members and their qualifications should be maintained.

Only those EC members independent of both the principal investigator and the sponsor should vote on an investigation-related matter.

The EC should perform its functions according to written operating procedures, should maintain written records of its activities and minutes of its meetings, and should comply with GCP as described in this document.

An EC should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present. Decisions can include:

— approval/favourable opinion;

— conditional approval, modifications required prior to its approval/favourable opinion;

— disapproval/negative opinion;

— termination/suspension of any prior approval/favourable opinion.

The principal investigator or coordinating investigator may provide information on any aspect of the clinical investigation but should not participate in the deliberations of the EC or vote.

EC procedures should have provisions that the EC avoids any bias and conflict of interest including proof of independent review of sponsor-investigator clinical investigations.

Only members who participate in the EC review and discussion can vote. A list of all meeting attendees along with their qualifications should be maintained.

G.4 Information needed

The following information can be helpful when review of an initial submission of an investigation is requested and continuing review is performed, and should be provided to the EC as part of the CIP, the IB; the informed consent form, or separately in other clinical investigation documents:

a) an assessment of the scientific merit and justification of the clinical investigation project and of the investigation plan proposal;

b) a summary of how the health of subjects can be affected, including any benefits anticipated;

c) possible risks, and the plans for dealing with them;

d) an assessment of any anticipated discomfort or distress;

e) proposed plan for supervision of the investigation and the qualifications and experience of the principal investigator and key investigation site personnel;

f) the proposed informed consent procedure and sample forms;

g) an outline of procedures to ensure confidentiality;

h) document(s) provided for subject's identification and compliance information for concurrent treatment measures and for any emergency situation;

i) a copy of the patient insurance policy when legally relevant;

j) progress reports and final reports, for continued review;

k) all reports on serious adverse events and serious adverse device effects, for continued review;

l) information on vulnerable populations where applicable.

G.5 Procedures

The EC should establish and follow written procedures, on the following.

a) Chair and membership selection criteria and process, names and qualifications of current and past members and the authority under which it is established.

b) Scheduling of meetings and notification of members.

c) Conduct of meetings.

d) Timelines and scope of continuing review of investigations.

e) Criteria and process for expedited review and approval/favourable opinion of minor change(s) in ongoing investigations that have previous approval/favourable opinion of the EC.

f) Timeframe for EC review and approval in context of investigation start-up – including pre-investigation advertising, subject recruitment, patient/subject screening, early informed consent completion, and enrolment. No subject should be admitted to a clinical investigation before the EC issues written approval/favourable opinion of the investigation.

g) Submission and review of changes to the CIP and timeframe for implementation.

h) Specific items that the principal investigator should promptly report to the EC are

   1) deviations from, or changes of, the CIP to eliminate immediate hazards to the clinical investigation subjects,

   2) changes increasing the risk to subjects and/or affecting significantly the conduct of the investigation,

   3) all adverse events that are both serious and unexpected, and

   4) new information that can affect adversely the safety of the subjects or the conduct of the investigation.

i) Ensuring that the EC promptly notifies in writing the principal investigator of the elements listed in G.6.

G.6 EC approval/favourable opinion letters

The EC approval/favourable opinion letter should list the following elements:

a) identification of the clinical investigation under review;

b) identification of the documents and amendments on which the opinion was based;

c) date the meeting was held and the approval/favourable opinion date;

d) clear explanation of its decision/opinions related to the clinical investigation and the reasons thereof;

e) reporting obligations during the clinical investigation by the principal investigator/sponsor including timelines;

f) list of voting members present during the review meeting;

g) procedures for appeal of its decisions/opinions;

h) compliance statement to national regulations and where applicable accreditation/registration document under national regulations.

G.7 Records

The EC should retain all relevant records (e.g. written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) after the completion of the clinical investigation and receiving the final clinical investigation report including data on all investigation sites of a given clinical investigation and make them available upon request from the regulatory authorities.

NOTE National regulations can apply.

Annex H
(informative)

Application of ISO 14971 to clinical investigations

ISO 14971 provides a general framework to systematically manage risks associated with the use of medical devices. The risk management process associated with a clinical investigation allows the hazards and hazardous situations associated with the investigational device to be identified. The associated risks are estimated (risk analysis) and evaluated (benefit-risk analysis), and risks are reduced to an acceptable level where necessary (risk control). The effectiveness of risk control is evaluated throughout the product's lifecycle including during clinical investigations.

A clinical investigation is a method of providing clinical data to allow conclusions on the acceptability of the benefit-risk ratio. These conclusions are documented in the risk management report.

All individuals involved in clinical investigations (including the sponsor, investigators, other clinical investigation site staff, DMC members, monitors, and external organizations) play an important role in the process described in Figure H.1.

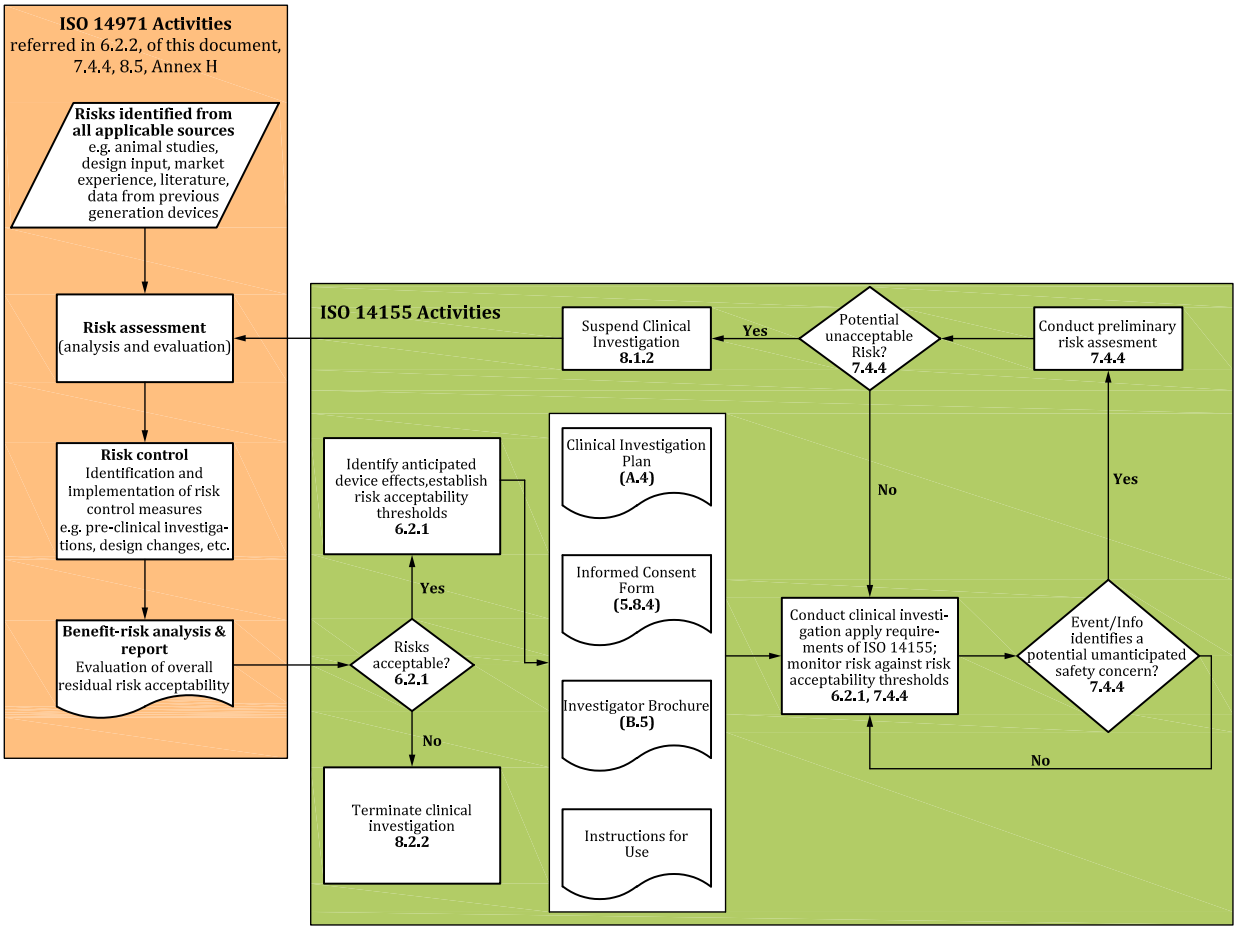

Figure H.1 — Application of ISO 14971 to the management of potential safety concerns in a clinical investigation

Annex I
(informative)

Clinical development stages

I.1 Background

This annex provides a general indication of the possible types of clinical investigations in different clinical development stages described hereunder and a schematic is given in the Table I.1.

Table I.1 — Synopsis of clinical development stages (terminology can vary across geographies)

Regulatory status	Pre-market		Post-market	
Clinical development stage	Pilot stage (I.3.2)	Pivotal stage (I.3.3)	Post-market stage (I.3.4)	
Type of design	Exploratory or confirmatory (I.4.2)	Confirmatory (I.4.3)		Observational (I.4.4)
Descriptors of clinical investigations	First in human clinical investigation (I.5.2) Early feasibility clinical investigation (I.5.3) Traditional feasibility clinical investigation (I.5.4)	Pivotal clinical investigation (I.5.5)	Post-market clinical investigation (I.2.3)	Registry[a] (I.5.6) Post-market clinical investigation[a] (I.2.3)
Burden to subject	Interventional (I.6.2)			Non-interventional (I.6.3)

[a] Registry data may be used for pre-market regulatory purposes (see I.5.6), this can also apply to the post-market clinical investigation data.

I.2 Regulatory status

I.2.1 General

The scope of this document indicates its applicability for both pre- and post-market clinical investigations which are defined hereunder.

I.2.2 Pre-market clinical investigation

A clinical investigation carried out before market approval of the investigational device.

NOTE 1 For the purpose of a pre-market clinical investigation, “market approval” is synonymous with “availability of the medical device in the market”.

NOTE 2 If marketed products are being investigated for new indications, other than described in the approved labelling, normative directions for pre-market clinical investigations apply.

I.2.3 Post-market clinical investigation

A clinical investigation carried out following market approval of a medical device, intended to answer specific questions relating to clinical performance, effectiveness or safety of a medical device when used in accordance with its approved labelling.

NOTE 1 For the purpose of post-market clinical investigation "market approval" is synonymous with "availability of the medical device in the market".

NOTE 2 Post-market clinical investigation can be part of a post-market clinical follow-up process.

If marketed medical devices are being investigated for new indications, other than described in the approved labelling, requirements for pre-market clinical investigations apply.

NOTE 3 National regulations can apply.

I.3 Clinical development stages

I.3.1 General

Based on the risk assessment, medical devices can undergo three general stages of clinical development. These stages can be dependent on each other and doing a thorough evaluation in one stage can make the next stage much more straightforward.

The clinical investigation population can be influenced by the type of clinical development stage, for example pilot stage population may come from a sub group of the total target population for which the device is eventually indicated. However, by the time the pivotal stage is reached, the clinical investigation population should more closely mirror the target population.

I.3.2 Pilot stage

If a pilot stage is necessary, (an) exploratory clinical investigation(s) will evaluate the limitations and advantages of the medical device and is commonly used to capture preliminary information on a medical device (at an early stage of product design, development, and validation) to adequately plan further steps of device development, including needs for design modifications or parameters for a pivotal clinical investigation.

This stage includes first in human and feasibility clinical investigations. Exploratory clinical investigations might not require pre-specified statistical hypotheses, although the design of the clinical investigation and the interpretation of the outcome can be more straightforward if statistical considerations are provided in the CIP.

I.3.3 Pivotal stage

In the pivotal stage, one or more confirmatory clinical investigations can be conducted to provide the information necessary to evaluate the clinical performance, effectiveness or safety of the investigational device. A confirmatory clinical investigation should be adequately designed with a pre-defined hypothesis for the primary endpoint(s) and a pre-specified sound statistical method for the analysis laid out in the CIP.

I.3.4 Post-market stage

The post-marketing stage can include additional confirmatory clinical investigations to establish clinical performance or effectiveness of the medical device in a broader population of users and subjects. Observational clinical investigations for better understanding of device safety, such as rare adverse events and long-term outcome, are also included in the post-marketing stage.

I.4 Type of clinical investigation design

I.4.1 General

Three main clinical investigation designs can be considered as referenced in I.3 and are further defined hereunder.

I.4.2 Exploratory clinical investigation

A clinical investigation, such as a first in human or feasibility clinical investigation as defined in this annex that might not have pre-specified primary hypotheses, and can be conducted to generate hypotheses, to be confirmed in subsequent clinical investigations.

I.4.3 Confirmatory clinical investigation

A confirmatory clinical investigation is an adequately controlled clinical investigation in which the hypotheses of the primary endpoint(s) are stated before the start of the clinical investigation in the CIP and are analysed in accordance with the CIP (i.e. sound confirmative statistical testing is pre-specified, intended, and applied).

I.4.4 Observational clinical investigation

Clinical investigation that draws inferences about the possible effect of an intervention on subjects, but the investigator has not assigned subjects into intervention groups and has not made any attempts to collect data on variables beyond those available throughout the course of normal clinical practice and burden to the subject.

I.5 Descriptors of clinical investigations

I.5.1 General

Throughout the above described clinical development stages, different descriptors of clinical investigations can apply, and the most common examples are defined hereunder.

I.5.2 First in human clinical investigation

A clinical investigation in which a medical device for a specific indication is evaluated for the first time in human subjects.

I.5.3 Early feasibility clinical investigation

A limited clinical investigation of a device early in development, typically before the device design has been finalized, for a specific indication (e.g. innovative device for a new or established intended use, marketed device for a novel clinical application). It can be used to evaluate the device design concept with respect to initial clinical safety and device clinical performance or effectiveness (if appropriate) as per intended use in a small number of subjects when this information cannot practically be provided through additional nonclinical assessments or appropriate nonclinical tests are unavailable. Information obtained from an early feasibility clinical investigation can guide device modifications. An early feasibility clinical investigation does not necessarily involve the first clinical use of a device.

NOTE Early feasibility clinical investigation can also be called proof of concept clinical investigation.

I.5.4 Traditional feasibility clinical investigation

A clinical investigation that is commonly used to capture preliminary clinical performance, effectiveness or safety information of a near-final or final device design to adequately plan an appropriate pivotal clinical investigation. Because the clinical investigation of a near-final or final device design takes place later in development than an early feasibility clinical investigation, more non-clinical or prior clinical

data are expected than in an early feasibility clinical investigation. A traditional feasibility clinical investigation does not necessarily need to be preceded by an early feasibility clinical investigation.

I.5.5 Pivotal clinical investigation

A confirmatory clinical investigation designed to collect data on the clinical performance, effectiveness or safety of a device for a specified intended use, typically in a statistically justified number of human subjects. It can or cannot be preceded by an early and/or a traditional feasibility clinical investigation.

I.5.6 Registry

An organized system that uses observational methods to collect defined clinical data under normal conditions of use relating to one or more medical devices to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure and that serves predetermined scientific, clinical or policy purpose(s).

NOTE 1 The term “registry study” is synonymous with “device registry” or “registry”.

NOTE 2 Individual registry studies can be used within the context of the IMDRF N33R1 ‘Patient registry; Essential Principles’ registry system (covering multiple applicable registries), see References [14] and [15].

I.6 Burden to subjects

I.6.1 General

Clinical investigations can further be categorized by their nature of interference with normal clinical practice as further defined hereunder. These categorisations are usually referred to for defining the requirements of ethical considerations (see further information in I.7).

I.6.2 Interventional clinical investigation

Interventional clinical investigation is a pre-or post-market clinical investigation where the assignment of a subject to a particular medical device is decided in advance by a CIP or diagnostic or monitoring procedures requested in the CIP are in addition to those available as normal clinical practice and burden the subject.

I.6.3 Non-interventional clinical investigation

Non-interventional clinical investigation is a post-market clinical investigation where the medical device is used in accordance with its approved labelling. The assignment of a subject to a particular medical device is not decided in advance by a CIP but falls within current clinical practice. The use of the medical device is clearly separated from the decision to include the subject in the clinical investigation. No additional invasive or burdensome diagnostic or monitoring procedures are applied to the subjects and epidemiological methods are used for the analysis of collected data.

NOTE In general, “observational” clinical investigations are “non-interventional”.

I.7 Applicability of this document’s principles

Depending on the clinical development stage and the type of the clinical investigation design, the principles of this document can be applied in full or in part. Significant exceptions from the requirements of this document should be duly justified and noted in the CIP or other sponsor regulatory files.

The following categories of applicability of the requirements of this document are expected to be taken into consideration in light of protection of subject’s rights, safety and well-being, the scientific outcome

and credibility of the clinical data, as well as the overall risk management of reaching the objectives of the clinical investigation.

a) Pre-market exploratory clinical investigation: all principles in this document apply with the exception that no mandatory (pre-)specification of a statistical hypothesis is required.

b) Pre-market confirmatory clinical investigations: all principles in this document apply.

c) Post-market confirmatory (interventional) clinical investigation: applicability in this document with justification for minimal exemptions, for example:

   1) device accountability for those clinical investigations where market approved medical devices are used within their approved indication;

   2) labelling specific for clinical investigations;

   3) IB, where sufficient information is available for the use of a medical device within its approved indication;

   4) reporting to the regulatory authorities.

      NOTE 1 National regulations can stipulate such reporting requirements.

d) Post-market observational (non-interventional) clinical investigation. Applicability of the requirements of this document with justification for exemptions, for example:

   1) device accountability for those clinical investigations where commercial products are used;

   2) labelling specific for clinical investigations;

   3) IB, where sufficient commercial product information is available;

   4) reporting to the regulatory authorities;

   5) informed consent if waived by the ethics committee, except consent applying requirements for personal data protection;

      NOTE 2 National regulations can stipulate different reporting requirements.

   6) CV of the members of the investigation site team.

NOTE 3 Some elements of normative annexes Annex A, B and D might not be required for certain types of clinical investigations with minimal requirements.

Annex J
(informative)

Clinical investigation audits

J.1 General

This annex provides general guidance on the areas that should be examined during the conduct of clinical investigation audits of sponsor, clinical investigator, and investigation site practices and procedures to determine compliance with this document and where appropriate, national regulations. The areas examined during inspections by national regulatory authorities depend upon the practices, procedures, and policies of those authorities.

The sponsor should provide evidence to ensure that the clinical investigation is being conducted in line with GCP, for instance through internal or external audits.

J.2 Sponsor

An audit of a sponsor's organization and documents is intended to evaluate compliance with the sponsor's own procedures, this document, and where appropriate, national regulations. The audit should include an examination of

a) the overall organization of the sponsor's clinical research activities and monitoring of the selected clinical investigations (see 9.1),

b) organizational charts that document the structure and responsibilities for all clinical investigation activities (see 9.2.1),

c) qualification and training of individuals involved at any stage of the clinical investigation process [see 9.2.1. g) and h)],

d) computer systems used in the conduct and management of the clinical investigation, and where applicable, the validation status of the systems (see 7.8.3),

e) clinical quality procedures (see 9.1), which address the following:

   1) planning; conduct and termination of the clinical investigation;

   2) investigation site selection process;

   3) required agreements;

   4) financial disclosure;

   5) CIP and management of amendments;

   6) management of CIP and regulatory deviations by investigation site;

   7) management of serious or continuous non-compliance with the CIP or regulations by investigation site, sponsor, contracted vendor, or third party;

   8) monitor selection criteria;

   9) monitoring procedures;

   10) investigational device control and accountability;

11) device deficiencies;

12) safety evaluation and adverse event reporting;

13) CRF design, data entry, and correction process;

14) data handling, data analysis and the control of these activities,

15) clinical investigation report;

16) document retention;

17) outsourcing of clinical investigation duties and functions;

18) computerized systems used in the conduct of clinical investigations;

f) documents related to a specific clinical investigation (see 9.2.2) on:

1) the planning, conduct and termination of the clinical investigation, such as internal approvals, assigning of responsibilities, documents issued, investigator selection, clinical investigation agreements, EC and regulatory authority approvals, and training;

2) the clinical investigation registration in a publicly accessible database;

3) the CIP and any amendment to the CIP;

4) monitor qualifications;

5) monitoring activities (e.g. monitoring plan, monitor qualifications and training, visit reports and review, follow-up on monitoring findings, and corrective actions);

6) device accountability (e.g. release of the investigational devices to investigation sites, tracking systems for the investigational device, and storage and shipment conditions);

7) facilities used for investigational device storage;

8) device deficiencies;

9) safety and adverse event reporting;

10) CRFs and evidence of adherence to the CIP and applicable clinical quality procedures;

11) documentation of management of serious or continuous noncompliance with the CIP or regulations by investigation site, and any suspensions or terminations of investigation sites;

12) data handling and clinical investigation report;

13) availability, accuracy, legibility, and completion of clinical investigation documents;

14) computerized systems used in the conduct of clinical investigations;

15) oversight of outsourced clinical duties, functions, and activities.

J.3 Investigation site

An audit of the investigation site is intended to evaluate compliance with applicable agreements, sponsor procedures, EC requirements, the CIP, the requirements of this document, and where appropriate, national regulations. The audit should include an evaluation of:

a) the regulatory approval status of the clinical investigation (e.g. availability of EC and regulatory approvals and correspondence, and insurance documents);

b) clinical site organization of personnel and facilities (e.g. delegation log, appropriate qualifications and experience of site staff, training records, availability of site staff, signed agreements between sponsor and investigator, suitability of facilities and equipment, equipment maintenance and calibration records, and validated site-specific computer systems);

c) financial disclosure and any updates;

NOTE National requirements regarding updates can differ.

d) data integrity, document retention, availability, completeness, and storage;

e) use of the CIP approved by the EC and regulatory authorities;

f) CIP deviations (e.g. documented reasons for deviations), management, approval (if applicable) and reporting of deviations;

g) informed consent (e.g. use of the informed consent form approved by the EC and regulatory authorities, as applicable, site practices for obtaining informed consent, evidence of compliance with informed consent requirements, and, if applicable, procedures of obtaining informed consent from vulnerable subjects);

h) available source documents (e.g. organization, condition, completeness, and legibility);

i) CRFs (e.g. process of obtaining and recording information on CRFs, any corrections made to the CRFs, compliance with clinical investigation procedures);

j) monitoring (e.g. monitoring visit logs, scope of visits and follow-up, accounting for subjects, source data verification, inclusion/exclusion criteria, subjects' visit schedules, safety, clinical performance or effectiveness data, processing of patient data, preservation of patient confidentiality, and provisions for records and data retention);

k) investigational device handling (e.g. device accountability log correspondence with source data verification and physical count, suitability of storage conditions, controlled access);

l) safety reporting (e.g. timeliness of investigator reports to sponsor, to ECs and regulatory authorities, as applicable).

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