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STANDARD

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

*Investigation clinique des dispositifs médicaux pour sujets humains —
Bonnes pratiques cliniques*

forbis ISO
DOCUMENT



Reference number
ISO 14155:2011(E)

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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.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

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.

ISO 14155 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*.

This second edition cancels and replaces the first edition of ISO 14155-1:2003 and the first edition of ISO 14155-2:2003, which have been technically revised.

Guidelines for standardizing and official practice for the collection, analysis, recording and reporting of adverse events associated with human subjects for devices: the performance of medical devices

and not from the International Standard may apply to some of the investigations and should thus be seriously considering the nature of the concepts and the requirements of the investigation.

the dignity, safety and well-being of humans by
expanding the scientific content of the clinical research

and resources. It is also important to work closely with regulatory authorities and other bodies involved in the timely management of outbreaks.

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It is indispensable for the application of this document. For more aspects for related references, the latest edition of the references is available.

— Application of the Dose-Response Method to the Evaluation of Chemical Carcinogens

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

1 Scope

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

The principles set forth in this International Standard also apply to all other clinical investigations and should be followed as far as possible, considering the nature of the clinical investigation and the requirements of national regulations.

This International Standard 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.

It does not apply to *in vitro* diagnostic medical devices.

NOTE Standards developed by ISO/TC 194 are intended to be applied to medical devices. Users of this International Standard will need to consider whether other standards and/or requirements also apply to the investigational device(s) under consideration.

2 Normative references

The following referenced documents are indispensable for the application 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 14971:2007, *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.

3.1

adverse device effect

ADE

adverse event related to the use of an investigational medical device

NOTE 1 This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

NOTE 2 This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

3.2

adverse event

AE

any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device

NOTE 1 This definition includes events related to the investigational medical device or the comparator.

NOTE 2 This definition includes events related to the procedures involved.

NOTE 3 For users or other persons, this definition is restricted to events related to investigational medical devices.

3.3

audit

systematic independent examination of activities and documents related to clinical investigation to determine whether these activities were conducted, and the data recorded, analysed and accurately reported, according to the CIP, standard operating procedures, this International Standard and applicable regulatory requirements

3.4

blinding/masking

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

NOTE Single blinding usually refers to the subject(s) being unaware of the treatment assignment(s). Double blinding usually refers to the subject(s), investigator(s), monitor and, in some cases, centralized assessors being unaware of the treatment assignment(s).

3.5

case report forms

CRFs

set of printed, optical or electronic documents for each subject on which information to be reported to the sponsor is recorded, as required by the CIP

3.6

clinical investigation

systematic investigation in one or more human subjects, undertaken to assess the safety or performance of a medical device

NOTE "Clinical trial" or "clinical study" are synonymous with "clinical investigation".

3.7

clinical investigation plan

CIP

document that state(s) the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation

NOTE The term "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 International Standard.

3.8

clinical investigation report

document describing the design, execution, statistical analysis and results of a clinical investigation

3.9

clinical performance

behaviour of a medical device or response of the subject(s) to that medical device in relation to its intended use, when correctly applied to appropriate subject(s)

3.10

comparator

medical device, therapy (e.g. active control), placebo or no treatment, used in the reference group in a clinical investigation

3.11

contract research organization

CRO

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

3.12

coordinating investigator

investigator who is appointed by the sponsor to coordinate work in a multicentre clinical investigation

3.13

data monitoring committee

DMC

independent committee that may be established by the sponsor to assess, at intervals, the progress of the clinical investigation, the safety data or the critical performance endpoints and to recommend the sponsor whether to continue, suspend, modify, or stop the clinical investigation

NOTE

Examples of DMCs are "data safety monitoring board (DSMB)" or "data safety monitoring committee (DSMC)".

3.14

deviation

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

3.15

device deficiency

inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance

NOTE

Device deficiencies include malfunctions, use errors, and inadequate labelling.

3.16

endpoint(s)

(primary) principal indicator(s) used for assessing the primary hypothesis of a clinical investigation

3.17

endpoint(s)

(secondary) indicator(s) used for assessing the secondary hypotheses of a clinical investigation

3.7

clinical investigation plan**CIP**

document that state(s) the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation

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endpoint(s)

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3.17

endpoint(s)

(secondary) indicator(s) used for assessing the secondary hypotheses of a clinical investigation

3.18

ethics committee

EC

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

NOTE For the purposes of this International Standard, "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.

3.19

hypothesis

testable statement, resulting from the objective, regarding the investigational medical device safety or performance that is used to design the clinical investigation and that can be accepted or rejected based on results of the clinical investigation and statistical calculations

NOTE The primary hypothesis is the determinant of the investigational medical device safety or performance parameters and is usually used to calculate the sample size. Secondary hypotheses concerning other points of interest can also be evaluated.

3.20

independent

not involved in the conduct of a clinical investigation, except for their specifically assigned responsibilities, in order to avoid bias or a conflict of interest

3.21

informed consent process

process by which an individual is provided information and is asked to voluntarily participate in a clinical investigation

NOTE Informed consent is documented by means of a written, signed and dated informed consent form.

3.22

investigation site

institution or site where the clinical investigation is carried out

NOTE For the purpose of this International Standard, "investigation site" is synonymous with "investigation centre".

3.23

investigational medical device

medical device being assessed for safety or performance in a clinical investigation

NOTE 1 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 In this International Standard, the terms "investigational medical device" and "investigational device" are used interchangeably.

3.24

investigator

individual member of the investigation site team designated and supervised by the principal investigator at an investigation site to perform critical clinical-investigation-related procedures or to make important clinical-investigation-related decisions

NOTE An individual member of the investigation site team can also be called "sub-investigator" or "co-investigator".

3.25

investigator's brochure

IB

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

3.26

legally authorized representative

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

3.27

malfunction

failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP

3.28

medical device

any instrument, apparatus, implement, machine, appliance, implant, software, material, or other similar or related article

a) intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of

- 1) diagnosis, prevention, monitoring, treatment or alleviation of disease,
- 2) diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury,
- 3) investigation, replacement, modification, or support of the anatomy or of a physiological process,
- 4) supporting or sustaining life,
- 5) control of conception,
- 6) disinfection of medical devices, and

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

NOTE The term "medical device" is usually defined by national regulations. For the purposes of this International Standard, this definition does not list "*in vitro* diagnostic medical devices" (see ISO 13485:2003, definition 3.7^[1]).

3.29

monitoring

act of overseeing the progress of a clinical investigation and to ensure that it is conducted, recorded, and reported in accordance with the CIP, written procedures, this International Standard, and the applicable regulatory requirements

3.30

multicentre investigation

clinical investigation that is conducted according to a single CIP and takes place at two or more investigation sites

3.31

objective

main purpose for conducting the clinical investigation

3.32

point of enrolment

time at which, following recruitment, a subject signs and dates the informed consent form

3.33

principal investigator

qualified person responsible for conducting the clinical investigation at an investigation site

NOTE 1 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 Whether this is the responsibility of an individual or an institution can depend on national regulations.

3.34

randomization

process of assigning subjects to the investigational medical device or comparator groups using an established recognized statistical methodology to determine the assignment in order to reduce bias

3.35

recruitment

active efforts to identify subjects who may be suitable for enrolment into the clinical investigation

3.36

serious adverse device effect

SADE

adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event

3.37

serious adverse event

SAE

adverse event that

- a) led to death,
- b) led to serious deterioration in the health of the subject, that either resulted in
 - 1) a life-threatening illness or injury, or
 - 2) a permanent impairment of a body structure or a body function, 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) led to foetal distress, foetal death or a congenital abnormality or birth defect

NOTE Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

3.38

source data

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

3.39

source document

printed, optical or electronic document containing source data

EXAMPLES Hospital records, laboratory notes, device accountability records, photographic negatives, radiographs, records kept at the investigation site, at the laboratories and at the medico-technical departments involved in the clinical investigation.

3.40**sponsor**

individual or organization taking responsibility and liability for the initiation or implementation of a clinical investigation

NOTE When an investigator 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.

3.41**subject**

individual who participates in a clinical investigation

NOTE A subject can be either a healthy volunteer or a patient.

3.42**unanticipated serious adverse device effect****USADE**

serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report

NOTE Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

3.43**use error**

act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user

NOTE 1 Use error includes slips, lapses, and mistakes.

NOTE 2 An unexpected physiological response of the subject does not in itself constitute a use error.

[ISO 14971:2007, definition 2.27]

3.44**vulnerable subject**

individual whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate

EXAMPLE Individuals with lack of or loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving informed consent. Other vulnerable subjects include, for example, members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the sponsor, members of the armed forces, and persons kept in detention.

4 Ethical considerations

4.1 General

Clinical investigations shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (see Reference [8]). These principles protect the rights, safety and well-being of human subjects, which are the most important considerations and shall prevail over interests of science and society. These principles shall be understood, observed, and applied at every step in the clinical investigation.

4.2 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.

4.3 Compensation and additional health care

Compensating subjects for costs resulting from participation in the clinical investigation (e.g. transportation) may be appropriate if allowed by national regulations, but the compensation shall not be so large as to unduly encourage the subjects to participate.

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 arrangements can be subject to national regulations.

4.4 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.

4.5 Communication with the ethics committee (EC)

4.5.1 General

If national or regional EC requirements are less strict than the requirements of this International Standard, the sponsor shall apply the requirements of this International Standard to the greatest extent possible, irrespective of any lesser requirements, and shall record such efforts.

4.5.2 Initial EC submission

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

- a) CIP;
- b) IB or equivalent documentation;
- c) informed consent form and any other written information to be provided to subjects;
- d) 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) sample or draft CRFs, including other data collection tools, as required by the CIP;
- g) documents related to payments and compensation available to subjects;
- h) proposed compensation to the institution or principal investigator;
- i) documentation related to any conflict of interest, including financial, on the part of an investigator;
- j) evidence of the clinical investigation insurance.

4.5.3 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 members of the investigation site team were not part of the voting.

4.5.4 Continuing communication with the EC

The following information shall be provided to the EC, if required by national regulations, 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) progress reports, including safety summary and deviations;
- d) amendments to any documents already approved by the EC;

NOTE 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.

- e) if applicable, notifications of suspensions or premature termination;
- f) if applicable, justification and request for resuming the clinical investigation after a suspension;
- g) clinical investigation report or its summary.

4.5.5 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 4.5.4 d);
- 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 4.5.4 b);
- c) approval for resumption of a suspended clinical investigation, as stated in 4.5.4 f), if applicable.

4.6 Vulnerable populations

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

4.7 Informed consent

4.7.1 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 4.7.3.4 apply.

The informed consent form consists of an information form (see 4.7.4) and an informed consent signature form (see 4.7.5). These two forms can either be combined in one document or separated into two documents.

4.7.2 Process of obtaining informed consent

The general process for obtaining informed consent shall be documented in the CIP and shall

- a) ensure that the principal investigator or his/her authorized designee conducts the informed consent process,
- b) include all aspects of the clinical investigation that are relevant to the subject's decision to participate throughout the clinical investigation,
- c) avoid any coercion or undue improper influence on, or inducement of, the subject to participate,
- d) not waive or appear to waive the subject's legal rights,
- e) use native non-technical language that is understandable to the subject,
- f) provide ample time for the subject to read and understand the informed consent form and to consider participation in the clinical investigation,
- g) include personally dated signatures of the subject and the principal investigator or an authorized designee responsible for conducting the informed consent process,
- h) provide the subject with a copy of the signed and dated informed consent form and any other written information,
- i) show how informed consent will be obtained and recorded in special circumstances (see 4.7.3) where the subject is unable to provide it him- or herself, and
- j) ensure important new information is provided to new and existing subjects throughout the clinical investigation.

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

4.7.3 Special circumstances for informed consent

4.7.3.1 General

The provisions given in 4.7.3.2 to 4.7.3.4 are subject to national regulations.

4.7.3.2 Subject needing legally authorized representatives

Informed consent may be given by the legally authorized 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, mentally ill person, mentally handicapped person). In such cases, the subject shall also be informed about the clinical investigation within his/her ability to understand.

4.7.3.3 Subject unable to read or write

Informed consent shall be obtained through a supervised oral process if a subject or legally authorized representative is unable to read or write. An independent 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 authorized representative and, whenever possible, either shall sign and personally date the informed consent form. The witness also signs and personally dates the informed consent form attesting that the information was accurately explained and that informed consent was freely given.

4.7.3.4 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 authorized representative, if present, shall be requested.

When it is not possible to obtain prior informed consent from the subject, and the subject's legally authorized 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 authorized 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.

The principal investigator may enroll a subject without obtaining the informed consent of the subject or his/her legally authorized 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 investigational device is used;
- f) anticipated risks are outweighed by the potential benefits of applying the investigational device;
- g) the legally authorized representative cannot be promptly reached and informed.

4.7.4 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 authorized representative).

- 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) aspects of the clinical investigation that are experimental;
- 7) description of the clinical investigation, including a mention of any comparison groups and the method of assignment to each group;
- 8) number of subjects expected to participate in the clinical investigation.

a) 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.

b) Risks and inconveniences for the subject and, when applicable, for an embryo, foetus, or nursing infant:

- 1) description of residual risks identified by the risk analysis;
- 2) description of risks associated with the clinical procedures required by the CIP;
- 3) statement that unanticipated risks may occur;
- 4) description of inconveniences.

c) Alternative procedure(s):

- 1) information on alternative treatments or procedures that may be available to the subject, and their potential benefits and risks.

d) Confidentiality:

- 1) statement confirming that subject participation is confidential;
- 2) statement confirming that records identifying the subject will be kept confidential to the extent allowed by the law;
- 3) statement confirming that the subject understands 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.

NOTE Additional requirements regarding personal data protection can be requested as per national or regional regulations.

e) 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.

f) Anticipated expenses, if any, to be borne by the subject for participating in the clinical investigation.

- g) Information on the role of sponsor's representative in the clinical investigation.
- h) Contact persons:
 - 1) whom to contact with questions about the clinical investigation;
 - 2) whom to contact in the event of injury;
 - 3) whom to contact with questions about subject's rights.
- i) 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.
- j) Statement indicating that, upon subject's approval, the subject's personal physician will be informed of the subject's participation in the clinical investigation.
- k) 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.

4.7.5 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;
- c) a statement declaring that discontinuation 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;
- f) a statement confirming that the subject or his/her legally authorized 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 authorized representative agrees that sponsor's representatives, regulatory authorities and EC representatives will be granted direct access to the subject's medical records.

4.7.6 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 subject(s) affected in written form. If relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing.

5 Clinical investigation planning

5.1 General

All parties participating in the conduct of the clinical investigation shall be qualified by education, training or experience to perform their tasks and this shall be documented appropriately (see 8.2.1).

5.2 Risk evaluation

Risks associated with the investigational device shall be estimated in accordance with ISO 14971 prior to conducting a clinical investigation. The risk analysis shall include or refer to an objective review of published and available unpublished medical and scientific data. A summary of the risk analysis, including an identification of residual risks, shall be included in the IB.

The decision to embark upon a clinical investigation of a 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 required by the CIP be balanced against the anticipated benefits to the subjects.

This risk analysis shall also be used as a basis for identifying anticipated adverse device effects characterized by their nature, incidence, severity and outcome.

The anticipated adverse device effects shall be documented in the CIP (see A.4), the IB (see B.5) and the informed consent form (see 4.7.4).

NOTE This enables compliance with any reporting requirements for anticipated and unanticipated SADEs.

5.3 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.

The clinical evaluation includes an assessment and analysis of clinical data concerning safety or performance of the investigational device or similar devices or therapies. The evaluation shall be relevant to the intended purpose of the investigational device and the proposed method of use. This is a scientific activity that shall be done with rigour and objectivity according to scientific standards using the principles of GHTF clinical evaluation (see Reference [6]).

The results of the clinical evaluation shall be used to determine 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 comparator(s).

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.

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

5.4 Clinical investigation plan (CIP)

The CIP shall include the information specified in Annex A.

The CIP and all subsequent amendments to the CIP are agreed upon between the sponsor, the coordinating investigator and all principal investigators, and are recorded with a justification for each amendment.

5.5 Investigator's brochure (IB)

The purpose of the IB is to provide the principal investigator 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, etc.).

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

The IB shall include the information specified in Annex B.

5.6 Case report forms (CRFs)

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).

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 forms is also necessary.

5.7 Monitoring plan

The sponsor shall assess the extent and nature of monitoring appropriate for the clinical investigation, 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. Results of this assessment shall be used to develop a monitoring plan.

5.8 Investigation site selection

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.

5.9 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 and signed and dated by all parties involved.

The agreement shall indicate that, by participating in a clinical investigation, the parties may share some regulatory responsibilities with the sponsor.

5.10 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, if required by national regulations.

NOTE See ISO 15223-1^[3], EN 1041^[4] and national or regional regulations for further information on labelling.

5.11 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 analysis, 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 responsibilities of the DMC shall be detailed in separate written procedures to establish the frequency of meetings, handling of emergency situations and documentation of such meetings.

6 Clinical investigation conduct

6.1 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 authorities of the countries where the clinical investigation is taking place has been received.

6.2 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 8.2.4).

A log shall be initiated identifying names, initials, signatures, functions, and designated authorizations for the principal investigator and members of the investigation site team.

6.3 Investigation site monitoring

The conduct of the clinical investigation shall be monitored according to the monitoring plan (see 8.2.4).

In general, there is a need for on-site monitoring before, during, and after the clinical investigation. However, in exceptional circumstances, the sponsor may determine that remote monitoring (without visiting the investigation site), in conjunction with procedures such as investigator's documented training, meetings, and extensive written guidance or telephone communication, can assure appropriate conduct of the clinical investigation. In such circumstances, the sponsor shall provide a justification for omitting the source document verification.

6.4 Adverse events and device deficiencies

6.4.1 Adverse events

All adverse events shall be documented in a timely manner throughout the clinical investigation and shall be reported as specified in 8.2.5 and 9.8.

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

6.4.2 Device deficiencies

All device deficiencies related to the identity, quality, durability, reliability, safety or performance of an investigational medical device shall be documented throughout the clinical investigation and appropriately managed by the sponsor.

Device deficiencies that did not lead to an adverse event but could have led to a medical occurrence

- 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 8.2.5 and 9.8.

6.5 Clinical investigation documents and documentation

6.5.1 Amendments

The IB, CIP, CRFs, informed consent form and other subject information, or other clinical investigation documents shall be amended as needed throughout the clinical investigation, and a justification statement shall be included with each amended section of a document. Proposed amendments to the CIP shall be agreed upon between the sponsor and principal investigator, or the coordinating investigator. 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 4.5.4). The version number and date of amendments shall be documented.

6.5.2 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 that identifies everyone who has been pre-screened for potential enrolment in the clinical investigation.

6.5.3 Source documents

Source documents shall be created and maintained by the investigation site team throughout the clinical investigation.

6.6 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 authorizations of new personnel shall be documented.

6.7 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 institution 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 institution shall obtain permission for direct access to source documents from the subject, hospital administration and national regulatory authorities before starting the clinical investigation.

6.8 Document and data control

6.8.1 Traceability of documents and data

All documents and data shall be produced and maintained in a way that assures control and traceability. Where relevant, the accuracy of translations shall be guaranteed and documented. 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.

The investigator shall assure the accuracy, completeness, legibility and timeliness of the data reported to the sponsor on the CRFs and in all required reports. Where copies of the original source document as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the investigation site team with a statement that it is a true reproduction of the original source document.

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. Established procedures for decoding blinded/masked clinical investigations shall be followed.

6.8.2 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. 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, initialed 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.

6.8.3 Electronic clinical data systems

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

- a) establish and document requirements for the electronic clinical data system to receive and process data,
- b) verify and validate that the requirements for the electronic clinical data system can be consistently met,
- c) ensure attributability, completeness, reliability, consistency and logic of the data entered,
- d) ensure accuracy of reports,
- e) ensure that data changes are documented and that there is no deletion of entered data (i.e. maintain an audit trail, data trail, edit trail),
- f) maintain a security system that prevents unauthorized access to the data, both internally and externally,
- g) maintain a list of individuals who have access to the electronic data system as well as the dates of access and privileges granted to each user,
- h) ensure that all completed CRFs are signed by the principal investigator or authorized designee,
- i) maintain adequate backup, retention and retrievability of the data, and
- j) train users on proper use of the system.

6.9 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 principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include

- a) the date of receipt,
- b) identification 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, and
- g) the date of return of unused, expired or malfunctioning investigational devices, if applicable.

NOTE Written procedures can be required by national regulations.

6.10 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 withdraws from the clinical investigation, the reason(s) shall be recorded. If such withdrawal is due to problems related to the investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside the clinical investigation.

6.11 Auditing

Audits of the clinical investigation may be conducted by the sponsor or third parties designated by the sponsor to evaluate compliance with the CIP, written procedures, this International Standard and the applicable regulatory requirements. These audits may cover all involved parties, systems and facilities and are independent of, and separate from, routine monitoring or quality control functions.

An audit is useful

- a) as a routine part of the sponsor's quality assurance programme,
- 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, and
- e) when requested or suggested by a regulatory authority.

The auditors shall be qualified by training and experience to conduct audits properly.

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

The sponsor's audit plan and 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.

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

7.1 Suspension or premature termination of the clinical investigation

7.1.1 Procedure for suspension or premature termination

The sponsor may suspend or prematurely terminate either a clinical investigation in an individual investigation site or the entire clinical investigation for significant and documented reasons.

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 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 is confirmed.

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

NOTE The usual lines of communication are sponsor <-> principal investigator or sponsor <-> EC, and sponsor <-> 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, 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 from the CIP and existing agreements 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 The method and the timing of this communication will depend on the circumstances and the perceived risks.

All activities listed in 7.2 shall also be conducted.

7.1.2 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.

7.2 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, and
- 2) notification to regulatory authorities, if required.

7.3 Clinical investigation report

After close-out of the clinical investigation, a report of the clinical evaluation shall be completed in accordance with the applicable regulations, even if the clinical investigation was terminated prematurely.

- 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 aims of the clinical investigation.

- c) 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.
- d) Where applicable, the clinical investigation report shall be made available to the coordinating investigator 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.
- e) Where required by national regulations, 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.
- f) In accordance with applicable requirements, the clinical investigation report shall be provided to the EC(s) and regulatory authorities.

NOTE 1 Further guidance for the content of the clinical investigation report is given in Annex D.

Publication of positive and negative results of the clinical investigation is encouraged to help guide future research, device development and medical treatment.

NOTE 2 In accordance with the national regulations, the intent to carry out a clinical investigation, as well as the results thereof, might need to be entered in a public database.

7.4 Document retention

The sponsor and principal investigator shall maintain the clinical investigation documents as required by the applicable regulatory requirement(s). 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 are detailed in Annex E.

8 Responsibilities of the sponsor

8.1 Clinical quality assurance and quality control

Quality assurance and quality control principles shall apply to the processes of the clinical investigation. The sponsor shall

- a) implement and maintain written clinical quality procedures to ensure that the clinical investigation is designed, conducted and monitored, and that data are generated, documented, recorded and reported in compliance with this International Standard, the CIP, any subsequent amendment(s), and any other applicable standards and regulatory requirements,
- b) maintain records to document the compliance of all parties involved in the clinical investigation,
- c) ensure that the auditing requirements of 6.11 are met, if applicable, and
- d) justify and document significant exceptions to the requirements of this International Standard.

Clinical quality assurance and quality control may be integrated in the sponsor's overall quality system.

NOTE For further information, see ISO 13485^[1].

8.2 Clinical investigation planning and conduct

8.2.1 Selection 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 5.9;
- b) select appropriately qualified principal investigators, as outlined in 5.8 and 9.2;
- c) select a coordinating investigator, if appropriate, as in the case of a multicentre investigation;
- d) receive disclosures of conflict of interest from principal investigators and investigators, where required by national regulations;
- e) ensure the members of the investigation site team and their designated authorization(s) are identified in a log with details, as defined in 6.2;
- f) designate or appoint one or more monitors, or otherwise assume the responsibilities of the monitor(s), and
- g) ensure documentation 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),
 - 2) device accountability procedures (see 6.9),
 - 3) IB,
 - 4) CIP,
 - 5) CRFs and instructions for completion,
 - 6) the written informed consent form and process as well as other written information provided to subjects, and
 - 7) sponsor's written procedures, this International Standard and any applicable regulatory requirements;
- h) ensure that, in multicentre investigations, all investigators and all other parties involved are given instructions on uniformly assessing and documenting clinical and laboratory findings;
- i) ensure that any clinical-investigation-related activities of 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 field engineers or sales representatives who will provide technical expertise in the implementation of the clinical investigation, are examples of sponsor representatives.

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

8.2.2 Preparation of documents and materials

Prior to commencement of the clinical investigation, the sponsor shall

- a) prepare the documents, as described in Clauses 4, 5 and 6, 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) assure the accuracy of the translation, where relevant,
- c) ensure that a supply of investigational devices, as characterized in 6.9, 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) provide insurance covering the cost of treatment of subjects in the event of clinical-investigation-related injuries, in accordance with the national regulations if applicable,
- e) document any financial arrangements between the principal investigator or the investigation site and the sponsor,
- f) submit any required application(s) to begin the clinical investigation in a given country to the appropriate regulatory authority(ies) for review, acceptance or permission [as per applicable regulatory requirement(s)],
- g) 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, and
- h) 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.

8.2.3 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) reviewing the monitoring report(s) and following up any action(s) required in the monitoring report(s) (see also 8.2.4.7),
- e) taking prompt action to secure compliance with all clinical investigation requirements, and
- f) submitting progress reports, including safety summary and deviations, when requested, to all reviewing ECs and the regulatory authorities.

8.2.4 Monitoring

8.2.4.1 General

The purpose of clinical investigation monitoring is to verify that the conduct of the clinical investigation complies with the approved CIP, subsequent amendment(s), this International Standard, and the applicable regulatory requirement(s).

8.2.4.2 Qualifications of the monitor

Monitors shall be:

- a) qualified in the field of this International Standard 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 4.7);
- c) trained on the sponsor's clinical quality assurance and quality control system as well as any special procedures for monitoring a specific clinical investigation.

Training shall be documented in the sponsor's files.

8.2.4.3 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.

8.2.4.4 Initiation of the investigation site

The monitor shall initiate each investigation site to ensure that the principal investigator and investigation site team

- a) have received and understood the requirements and contents of
 - 1) CIP,
 - 2) IB,
 - 3) the informed consent form,
 - 4) 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, and
- d) are familiar with the responsibilities of the principal investigator, as described in Clause 9.

NOTE In certain circumstances, an investigator meeting can be conducted instead of, or in addition to, the on-site initiation visit.

8.2.4.5 Routine on-site monitoring visits

The monitor shall perform routine on-site monitoring visits to verify that

- a) compliance with the CIP, any subsequent amendment(s), this International Standard 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 individuals, as described in 8.2.1 e), are participating in the clinical investigation,
- c) the investigational device is being used according to the CIP 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 at the point of enrolment or before any clinical-investigation-related procedures are undertaken,
- g) source documents 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,
- i) appropriate corrections, additions or deletions are made to the CRFs, dated, explained if necessary and initiated by the principal investigator or by his/her authorized designee; the monitor shall not make corrections, additions or deletions to the CRFs,
- j) 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,
- k) all serious adverse events and deviations are reported to the EC, if required,
- l) the storage and investigational device accountability are correct and the traceability process is being followed,
- m) all other 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,
- n) maintenance and calibration of the equipment relevant to the assessment of the clinical investigation is appropriately performed and documented, where applicable,
- o) current laboratory normal values, laboratory certifications, accreditations, or other validations are present in the investigator's file, if required,
- p) subject withdrawal has been documented; the monitor shall discuss this with the principal investigator or his/her authorized designee,
- q) 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,
- r) the principal investigator and investigation site team are informed and knowledgeable of all relevant document updates concerning the clinical investigation, and
- s) any corrective and preventive actions, as needed, have been implemented and are effective.

8.2.4.6 Close-out activities

The monitor shall perform close-out activities as described in Clause 7.

8.2.4.7 Monitoring reports

All monitoring activities shall be documented in a written report to the sponsor [see also 8.2.3 d)] and shall include

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

- b) a summary of what the monitor reviewed and his/her observation(s) with regard to 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.

8.2.5 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; 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) below,
- 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) 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 national regulations or the CIP or by the EC,
- 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, if required by national regulations or the CIP,
- 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 national regulations or 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 analysis report,
- g) ensure that the EC and the regulatory authorities are informed of significant new information about the clinical investigation, and
- 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.

8.2.6 Clinical investigation close-out

The sponsor shall

- a) ensure all clinical investigation close-out activities are properly conducted as described in Clause 7,
- b) provide a statistical analysis of the data,
- c) produce a clinical investigation report and submit it for review, as described in 7.3, and

- 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, as required by national regulations.

8.3 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 data shall reside with the sponsor. All requirements in this International Standard 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.

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.

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

8.4 Communication with regulatory authorities

The sponsor shall, if required

- a) notify or obtain approval from regulatory authorities in the country where the clinical investigation is conducted,
- b) report on the progress and status of the clinical investigation, and
- c) perform safety reporting as specified in 8.2.5.

9 Responsibilities of the principal investigator

9.1 General

The role of the principal investigator is to implement and manage 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.

If the sponsor contracts an institution to conduct the clinical investigation, the institution shall appoint an appropriately qualified person to be the principal investigator.

9.2 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 International Standard; evidence of such qualifications of the principal investigator and key members of the investigation site team shall be provided to the sponsor through up-to-date CVs or other relevant documentation,
- 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 interfere with the conduct of the clinical investigation or interpretation of results, and
- d) be knowledgeable with the method of obtaining informed consent.

9.3 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, and
- b) has one or more qualified investigators, a qualified investigation site team and adequate facilities for the foreseen duration of the clinical investigation.

9.4 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 4.5,
- c) obtain the written and dated approval/favourable opinion of the EC for the clinical investigation before recruiting subjects and implementing all subsequent amendments, if required,
- d) perform safety reporting as specified in 9.8, and
- 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, CIP or national regulations.

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.

9.5 Informed consent process

The principal investigator shall

- a) comply with the requirements specified in 4.7,
- b) ensure compliance with the applicable regulatory requirements and 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.

9.6 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,
- d) ensure that the investigational device is used solely by authorized users as specified in 6.2, 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) allow and support the sponsor to perform monitoring and auditing activities,
- m) be accessible to the monitor and respond to questions during monitoring visits,
- n) allow and support regulatory authorities and the EC when performing auditing activities,
- o) ensure that all clinical-investigation-related records are retained as specified in 7.4, and
- p) sign the clinical investigation report, as specified in 7.3.

9.7 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 [see 4.7.4. f)],
- 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 may 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, subjects enrolled in the clinical investigation shall be provided with some means of showing their participation in the clinical investigation, 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 or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation, and
- 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.

9.8 Safety reporting

The principal investigator shall

- a) record every adverse event and observed device deficiency, together with an assessment,
- 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 national regulations or CIP or by the EC,
- d) report to regulatory authorities serious adverse events and device deficiencies that could have led to a serious adverse device effect, as required by the national regulations, and
- e) supply the sponsor, upon sponsor's request, with any additional information related to the safety reporting of a particular event.

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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.

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.

A.1.3 Sponsor

Name and address of the sponsor of the clinical investigation.

NOTE 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 representative in that country (those countries) can be required according to national or regional regulations.

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

- a) Name, address, 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 other institutions involved in the clinical investigation.

The sponsor shall maintain an updated list of principal investigators, investigation sites, and institutions. 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 might 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 and its intended purpose.
- 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 products, human or animal tissues or their derivatives, or other biologically active substances.)
- h) Summary of the necessary training and experience needed to use the investigational device.
- i) Description of the specific medical or surgical procedures involved in the use of the investigational device.

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 evaluation, as specified in 5.3, and shall comprise

- a) an evaluation of the results of the relevant pre-clinical testing/assessment carried out to justify the use of the investigational device in human subjects, and
- b) an evaluation of clinical data that are relevant to the proposed clinical investigation.

A.4 Risks and benefits of the investigational device and clinical investigation

- a) Anticipated clinical benefits.
- b) Anticipated adverse device effects.
- c) Residual risks associated with the investigational device, as identified in the risk analysis report.
- d) Risks associated with participation in the clinical investigation.
- e) Possible interactions with concomitant medical treatments.

- f) Steps that will be taken to control or mitigate the risks.
- g) Risk-to-benefit rationale.

NOTE The risk management process, which includes risk analysis, risk-to-benefit assessment and risk control is described in ISO 14971.

A.5 Objectives and hypotheses of the clinical investigation

- a) Objectives, primary and secondary.
- b) Hypotheses, primary and secondary, to be accepted or rejected by statistical data from the clinical investigation.
- c) Claims and intended performance of the investigational device that are to be verified.
- d) Risks and anticipated adverse device effects that are to be assessed.

A.6 Design of the clinical investigation

A.6.1 General

- a) Description of the type of clinical investigation to be performed (e.g. comparative double-blind, parallel design, with or without a comparator group) with rationale for the choice.
- b) Description of the measures to be taken to minimize or avoid bias, including randomization and blinding/masking.
- c) Primary and secondary endpoints, with rationale for their selection and measurement.
- 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.

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) Justification of the choice of comparator(s).
- c) List of any other medical device or medication to be used during the clinical investigation.
- d) 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 discontinuation.

- d) Point of enrolment.
- e) Total expected duration of the clinical investigation.
- f) Expected duration of each subject's participation.
- g) Number of subjects required to be included in the clinical investigation.
- h) Estimated time needed to select this number (i.e. enrolment period).

A.6.4 Procedures

- a) Description of all the clinical-investigation-related procedures that subjects undergo during the clinical investigation.
- b) Description of those activities performed by sponsor representatives (excluding monitoring).
- c) Any known or foreseeable factors that may 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. 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.

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

The CIP shall specifically address what medical care, if any, will be provided for the subjects after the clinical investigation has been completed.

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.

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

A.7 Statistical considerations

With reference to A.5 and A.6, the description of and justification for

- a) statistical design, method and analytical procedures,
- b) sample size,
- c) the level of significance and the power of the clinical investigation,
- d) expected drop-out rates,
- e) pass/fail criteria to be applied to the results of the clinical investigation,
- f) the provision for an interim analysis, where applicable,
- g) criteria for the termination of the clinical investigation on statistical grounds,

- h) procedures for reporting any deviation(s) from the original statistical plan,
- i) the specification of subgroups for analysis,
- j) procedures that take into account all the data,
- k) the treatment of missing, unused or spurious data, including drop-outs and withdrawals,
- l) the exclusion of particular information from the testing of the hypothesis, if relevant, and
- m) in multicentre clinical investigations, the minimum and maximum number of subjects to be included for each centre.

Special reasoning and sample size(s) may apply for the early clinical investigation(s), e.g. feasibility clinical investigation(s).

A.8 Data management

- a) Procedures used for data review, database cleaning, and issuing and resolving data queries.
- b) Procedures for verification, validation and securing of electronic clinical data systems, if applicable.
- c) Procedures for data retention.
- d) Specified retention period.
- e) 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 4.5.4 b).
- 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

Description of the procedures for the accountability of investigational devices as specified in 6.9.

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 [8]).

- b) Statement specifying compliance with this International Standard 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 or 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.

A.13 Informed consent process

- a) Description of the general process for obtaining informed consent, including the process for providing subjects with new information, 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 4.7.3.4 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 and serious adverse device effects and, where appropriate, unanticipated serious adverse device effects.
- d) 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.
- e) 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).
- f) Details of the process for reporting device deficiencies.
- g) List of foreseeable adverse events and anticipated adverse device effects, together with their likely incidence, mitigation or treatment.
- h) Emergency contact details for reporting serious adverse events and serious adverse device effects.
- i) Information regarding the DMC, if established.

A.15 Vulnerable population

- a) Description of the vulnerable population.
- b) Description of the specific informed consent process.
- c) Description of the EC's specific responsibility.
- d) 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.

A.17 Publication policy

- a) Statement indicating whether the results of the clinical investigation will be submitted for publication.
- b) Statement indicating the conditions under which the results of the clinical investigation will be offered for publication.

A.18 Bibliography

List of bibliographic references pertaining to 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.

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

B.1.3 Sponsor/manufacturer

Name and address of the sponsor or manufacturer of the investigational device.

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 materials used.
- d) Summary of relevant manufacturing processes and related validation processes.
- e) Description of the mechanism of action of the investigational device, along with supporting scientific literature.
- f) Manufacturer's instructions for installation 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) 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 tests,
- d) reliability tests,
- e) validation of software relating to the function of the device,
- f) any performance tests,
- g) *ex vivo* tests, and
- h) an evaluation of biological safety.

NOTE Guidance on the biological evaluation of medical devices is given in ISO 10993-1^[2].

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

- a) Summary of the risk analysis, including identification of residual risks.
- b) Result of the risk assessment.
- c) Anticipated risks, contra-indications, warnings, etc. 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, if allowed by national regulations.
- 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").

NOTE 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 may 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).
- k) Unscheduled visit(s).
- l) Subject diary.
- m) Subject withdrawal or lost to follow-up.
- n) Form signifying the end of the clinical investigation, 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 (informative)

Clinical investigation report

D.1 General

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

The format given here may be used in interim, progress, annual, or final reports if such reports are required.

D.2 Cover page

The title page should contain the following information:

- a) title of the clinical investigation;
- b) identification of the investigational devices, including names, models, etc. as relevant for complete identification;
- c) if not clear from the title, a single sentence describing the design, comparison, period, usage method, and subject population;
- d) name and contact details of sponsor or sponsor's representative;
- e) CIP identification;
- f) name and department of coordinating investigator and names of other relevant parties, e.g. experts, biostatistician, laboratory personnel;
- g) statement indicating whether the clinical investigation was performed in accordance with this International Standard or any other applicable guidelines and applicable regulations;
- h) date of report;
- i) author(s) of report.

D.3 Table of contents

The table of contents should include the following information:

- 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 should contain the following items:

- a) the title of the clinical investigation;
- b) an introduction;
- c) the purpose of the clinical investigation;
- d) 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 should 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 should contain the following points:

- 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 rational for each amendment, should be provided. The summary should include a brief description of the following points:

- a) the clinical investigation objectives;
- b) the clinical investigation design including
 - 1) the type of clinical investigation, and
 - 2) the clinical investigation endpoints,
- 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 analysis including
 - 1) the clinical investigation hypothesis or pass/fail criteria,
 - 2) a sample size calculation, and
 - 3) statistical analysis methods.

D.7 Results

The results report should include the following points:

- a) the clinical investigation initiation date;
- b) the clinical investigation completion/suspension date;
- c) the disposal of subjects and investigational devices;
- d) the subject demographics;
- e) CIP compliance;

- f) an analysis, which includes
 - 1) a performance analysis provided for in the CIP,
 - 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,
 - iii) withdrawn or discontinued from the clinical investigation and the reason.

D.8 Discussion and overall conclusions

The conclusions should include the following points:

- a) the safety or performance results and any other endpoints;
- b) an assessment of risks and benefits;
- 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.

D.9 Abbreviated terms and definitions

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

D.10 Ethics

The ethics report should include the following points:

- a) a confirmation that the CIP and any amendments to it were reviewed by the EC (if required);
- b) a list of all ECs consulted (can be given in an annex; see D.13).

D.11 Investigators and administrative structure of clinical investigation

The overview of the administrative structure should include the following points:

- 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 third parties (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, should be provided. If no coordinating investigator is appointed, then the signature of the principal investigators should 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 information:

- 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 third parties (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.

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 International Standard
E.1.1	Investigator's brochure (IB)	Describes the investigational device, including instructions for device use.	X	X	5.5 Annex B
E.1.2	Clinical investigation plan (CIP)	Describes the clinical investigation design and procedures.	X	X	5.4 Annex A
E.1.3	Sample of labelling attached to investigational device	Confirms appropriate labelling.	—	X	5.10
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	4.5.2 e) 9.2 a) D.13 c)
E.1.5	CV of key members of the investigation site team: current, signed and dated	Identifies the key members of the investigation site team. The site has CVs for key members of investigation site team at that site.	X	X	9.2 a)
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	5.1 8.2.1 8.2.4.3
E.1.7	Log of principal investigator and key 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	6.2 8.2.1 e) 8.2.4.5 b)
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	Ethics committee (EC) notification, correspondence and opinion/approval	Gives evidence that a qualified, independent EC has reviewed the clinical investigation.	X	X	4.5.3 6.1 8.2.2 g) 9.4
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	4.5.3

Table E.1 (continued)

No.	Title of document	Purpose or comment	Site files	Sponsor files	Reference in this International Standard
E.1.11	Regulatory authority notification, correspondence and approval (where required)	Verifies information provided to regulatory authorities. Confirms notification or approval.	X ^a	X	6.1 8.2.2 f)
E.1.12	Signed agreement between principal investigator(s)/investigation site(s) and sponsor	Demonstrates understanding of each party's respective responsibilities.	X	X	5.9 8.2.1 a) 8.2.2 e)
E.1.13	Signed agreements between sponsors and third parties, e.g. CRO, core laboratories	Demonstrates understanding of each party's responsibilities.	—	X	5.9 8.2.1 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	8.2.2 e)
E.1.15	Insurance certificates, if applicable	Gives evidence that compensation to subject(s) for clinical investigation-related injuries will be available.	X	X	4.3 4.5.2 j) 8.2.2 d)
E.1.16	Shipping records for investigational devices	Verifies physical possession of devices.	X	X	6.9 8.2.2 c) 8.2.3 a) 8.2.4.5 l) 9.6 k)
E.1.17	Shipping records for clinical investigation-related documents and materials	Verifies physical shipment of documents and materials.	—	X	8.2.2 c) 8.2.4.4 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	4.5 4.7 8.2.2 a)
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	6.8.1
E.1.20	Decoding procedures for blinded/masked clinical investigations, where applicable	Might not take place on the investigation site depending on study design.	X	X	6.8.1 A.6.1 a) A.16 b)
E.1.21	Investigation site selection report	Verifies that qualifications of investigator and investigation site have been reviewed.	—	X	5.8 8.2.1 b) 8.2.4.3 8.2.4.7
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	6.2 8.2.4.7
E.1.23	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	8.2.4.7

Table E.1 (continued)

No.	Title of document	Purpose or comment	Site files	Sponsor files	Reference in this International Standard
E.1.24	Case report forms (CRF)	Blank set to evidence the content of data being collected.	X	X	5.6 Annex C
E.1.25	Adverse events forms	Documents all adverse events as required by the standard. Forms may or may not be part of the CRFs.	X	X	5.6 6.4.1 Annex C
E.1.26	Device deficiency forms	Document all device deficiencies. Forms may or may not be part of the CRFs.	X	X	5.6 6.4.2 Annex C
E.1.27	Names/contact information of monitor(s)	Document the person who has ensured continuing compliance of the clinical investigation.	X	X	5.1 8.2.1 a) 8.2.1 f) D.13 e)
E.1.28	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	8.2.1 g)
E.1.29	Normal value(s)/range(s) for clinical laboratory test, if relevant to the clinical investigation	Documents normal values.	X	X	8.2.4.5 o)
E.1.30	Confirmation of adequacy of equipment, if relevant to the clinical investigation	Documents equipment maintenance and calibration.	X	—	8.2.4.5 n)
E.1.31	— 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 the competence and responsibilities of the facility to perform the required test(s), and support the reliability of results.	X	X	5.1 6.11 8.1 8.2.1 8.2.4.5 o)
E.1.32	Disclosures of conflicts of interest	Documentation of conflicts of interest, e.g. financial.	X	X	8.2.1 d) 9.2 c)

^a Regulations may 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 International Standard
E.2.1	IB amendments, if any	Documents changes to the IB.	X	X	6.5.1
E.2.2	CIP amendments, if any	Describes changes to the clinical investigation design.	X	X	6.5.1
E.2.3	Sample of amendments to informed consent form		X	X	6.5.1
E.2.4	EC opinion/approval of any amendments		X	X	4.5.4 d) 4.5.5 a) 8.2.3 b) 8.2.4.5 m) 9.4 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 may 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	6.1 8.2.2 f) 8.2.2 h)
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	4.5.2 e) 9.2 a) D.13 c)
E.2.7	CV of new key members of the investigation site team: current, signed and dated	Identifies the new key members of the investigation site team. The investigation site has CVs for key members of investigation site team at that investigation site.	X	X	9.2 a)
E.2.8	Shipping records and investigational device accountability records		X	X	6.9 8.2.2 c), 8.2.3 a) 8.2.4.5 l) 9.6 k)
E.2.9	Shipping records for clinical investigation-related document materials		—	X	8.2.4.4 a)
E.2.10	Monitoring visit reports	Provides summary of key findings to the principal investigator.	(X)	X	8.2.3 d) 8.2.4.7
E.2.11	Correspondence related to the clinical investigation, including emails, letters, meeting notes and phone reports		X	X	8.2.3 b) 8.2.4.5 m) 9.6 o)
E.2.12	Updated log of the principal investigator and key 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	6.2 8.2.1 e) 8.2.4.5 b)

Table E.2 (continued)

No.	Title of document	Purpose or comment	Site files	Sponsor files	Reference in this International Standard
E.2.13	Signed, dated, and fully executed informed consent forms	Verifies that informed consent has been given.	X	—	4.7.1 7.4 8.2.4.5 f) 9.5
E.2.14	Source documents		X	—	6.5.3 6.8.2 9.6 o) 9.7 f)
E.2.15	CRFs, fully executed	Evidences what data were collected and that their authenticity has been verified by principal investigator.	X	X	6.3 6.8.1 6.8.2 8.2.4.5 i) 9.6 j)
E.2.16	Reports of adverse events, adverse device effects and device deficiencies	Documents the occurrence and resolution of adverse events and adverse device effects.	X	X	6.4 8.2.4.5 j), k) 8.2.5 9.8 D.13 g)
E.2.17	CRFs corrections	Gives evidence of any changes, additions, or corrections made to CRFs after data were initially recorded.	X	X	6.8 8.2.4.5 i) 9.6 j)
E.2.18	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	6.4 7.1 8.2.5 9.8
E.2.19	Reports of adverse events by principal investigator to EC or by sponsor, where required		X	X	4.5.4
E.2.20	Reports by sponsor to investigators of adverse events occurring at other investigation sites		X	X	8.2.5
E.2.21	Interim or annual reports by principal investigators to EC, where applicable		X	X	4.5.4 8.2.3 b) 8.2.4.5 m) 9.4 9.8
E.2.22	Subject screening log	Sponsor file only if anonymized.	X	X	6.5.2
E.2.23	Subject identification log		X	—	6.5.2
E.2.24	Accountability logs of investigational devices at the investigation site, where appropriate	Reconciles with sponsor's shipping and receipt records.	X	X	6.9 8.2.3 a) 8.2.4.5 l) 9.6 k)
E.2.25	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	8.2.1 a) 8.2.1 f) D.13 e)

Table E.2 (continued)

No.	Title of document	Purpose or comment	Site files	Sponsor files	Reference in this International Standard
E.2.26	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	8.2.4.5 o)
E.2.27	Updates to confirmation of adequacy of equipment, if relevant to the clinical investigation	Documents the changes of equipment and continuous maintenance and calibration throughout the clinical investigation.	X	—	8.2.4.5 n)
E.2.28	Updates of <ul style="list-style-type: none"> — 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	5.1 6.11 8.1 8.2.1 8.2.4.5 o)
E.2.29	Updates of disclosures of conflicts of interest	Documents conflicts of interest, e.g. financial.	X	X	8.2.1 d) 9.2 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 International Standard
E.3.1	Investigational device accountability at each investigation site, where applicable		X	X	6.9 7.2 a) 9.6 k) 9.6 o)
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	6.9 7.2 a) 9.6 k)
E.3.3	Completed subject identification log		X	—	6.5.2
E.3.4	Audit certificate (if required or conducted)		—	X	6.11 8.1 D.13 h)
E.3.5	Close-out monitoring report		—	X	8.2.4.7
E.3.6	Notification of clinical investigation close-out to the EC by principal investigators or sponsor, where required		X	X	4.5.4 7.1 7.2 8.2.6 d) 9.4
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	7.1 7.2 8.2.6 d)
E.3.8	Sponsor's statistical analyses and clinical investigation report	Investigation site file only if required by sponsor procedures.	X	X	7.3 8.2.6 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 procedure-related	
Non-serious	Adverse Event (AE) ^a (3.2)	Adverse Device Effect (ADE) (3.1)	
Serious	Serious Adverse Event (SAE) ^b (3.37)	Serious Adverse Device Effect (SADE) (3.36)	
		Anticipated	Unanticipated
		Anticipated Serious Adverse Device Effect (ASADE) (3.42, Note)	Unanticipated Serious Adverse Device Effect (USADE) (3.42)

a Includes all categories.
b Includes all categories that are serious.

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.

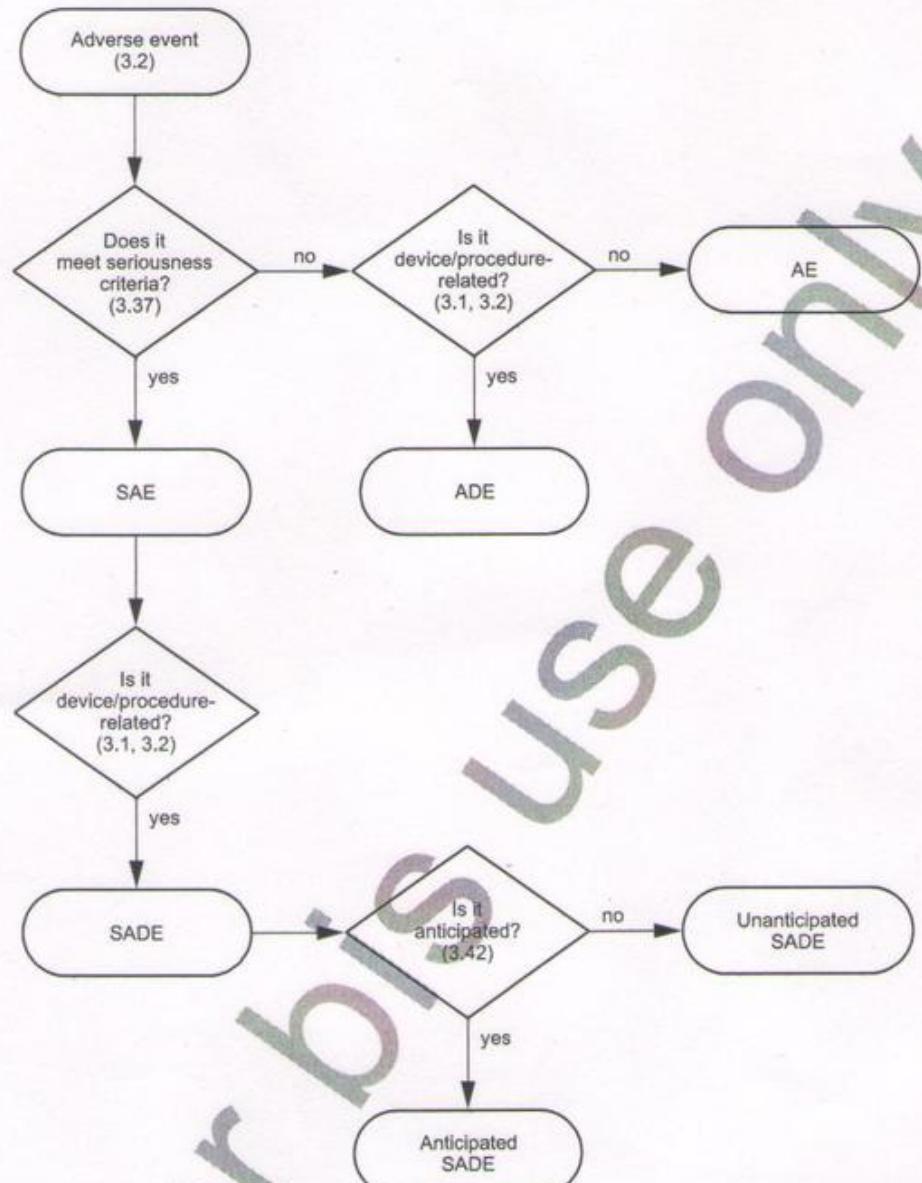


Figure F.1 — Adverse events categorization chart

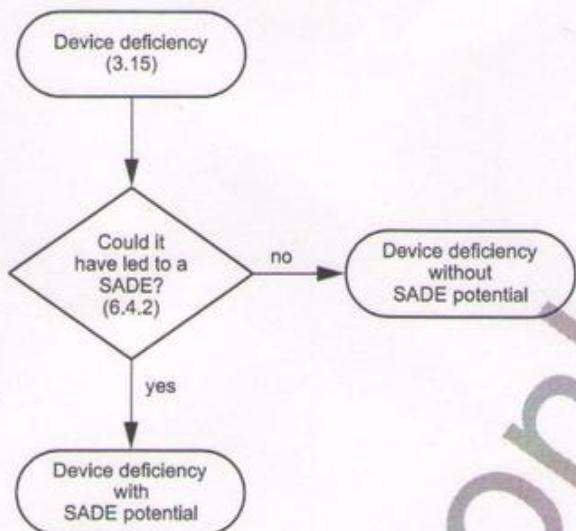


Figure F.2 — Device deficiency categorization chart

Bibliography

- [1] ISO 13485:2003, *Medical devices — Quality management systems — Requirements for regulatory purposes*
- [2] ISO 10993 (all parts), *Biological evaluation of medical devices*
- [3] ISO 15223-1, *Medical devices — Symbols to be used with medical device labels, labelling and information to be supplied — Part 1: General requirements*¹⁾
- [4] EN 1041, *Information supplied by the manufacturer of medical devices*
- [5] Global Harmonization Task Force, Information Document Concerning the Definition of the Term "Medical Device" [SG1/N29R16:2005], available at:
<http://www.ghtf.org/documents/sg1/sg1n29r162005.pdf>
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- [9] MEDDEV 2.7.1, Rev. 3, Dec. 2009, Clinical Evaluation: A Guide for Manufacturers and Notified Bodies, available at:
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1) To be published. (Revision of ISO 15223-1:2007)

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