INTERNATIONAL STANDARD

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Clinical investigation of medical devices for human subjects —

Part 1: General requirements

Investigation clinique des dispositifs médicaux pour sujets humains —

Partie 1: Exigences générales

Reference number
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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 14155-1 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*.

This first edition of ISO 14155-1, together with ISO 14155-2, cancels and replace ISO 14155:199 6, which has been technically revised.

ISO 14155 consists of the following parts, under the general title *Clinical investigation of medical devices for human subjects:*

— *Part 1: General requirements*

— *Part 2: Clinical investigation plans*

Introduction

This part of ISO 14155 is intended to be applied worldwide to clinical investigations of medical devices in order to fulfil the technical aspects of the various national, regional and international regulatory requirements. As the legal regulatory requirements presently differ throughout the world, regulatory specifics have been excluded from the scope of this part of ISO 14155. They are part of national or regional legislative texts and can be referenced in the national or regional forewords, as appropriate.

Clinical investigation of medical devices for human subjects —

Part 1:
General requirements

1 Scope

This part of ISO 14155 defines procedures for the conduct and performance of clinical investigations of medical devices. It specifies general requirements intended to

— protect human subjects,

— ensure the scientific conduct of the clinical investigation,

— assist sponsors, monitors, investigators, ethics committees, regulatory authorities and bodies involved in the conformity assessment of medical devices.

This part of ISO 14155

a) specifies requirements for the conduct of a clinical investigation such that it establishes the performance of the medical device during the clinical investigation intended to mimic normal clinical use, reveals adverse events under normal conditions of use, and permits assessment of the acceptable risks having regard to the intended performance of the medical device,

b) specifies requirements for the organization, conduct, monitoring, data collection and documentation of the clinical investigation of a medical device,

c) is applicable to all clinical investigation(s) of medical devices whose clinical performance and safety is being assessed in human subjects.

This part of ISO 14155 is not applicable to *in vitro* diagnostic medical devices.

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 14155-2, *Clinical investigation of medical devices for human subjects — Part 2: Clinical investigation plans*

3 Terms and definitions

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

3.1
adverse device effect
any untoward and unintended response to a medical device

NOTE 1 This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device.

NOTE 2 This definition includes any event that is a result of a user error.

3.2
adverse event
any untoward medical occurrence in a subject

NOTE This definition does not imply that there is a relationship between the adverse event and the device under investigation.

3.3
case report form
document designed to record all information to be reported to the sponsor on each subject as required by the clinical investigation plan

3.4
clinical investigation
any designed and planned systematic study in human subjects undertaken to verify the safety and/or performance of a specific device

3.5
clinical investigation plan
CIP
document that states the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation

NOTE The word “protocol” is often used synonymously with the term “clinical investigation plan”. However, it has many different meanings, some not related to clinical investigations, and these may differ from country to country. Therefore, it is not used in this part of ISO 14155.

3.6
clinical investigator
individual and/or institution responsible for the conduct of a clinical investigation who and/or which takes the clinical responsibility for the well-being of the subjects involved

NOTE Whether this is an individual or an institutional responsibility may depend on national legislation.

3.7
clinical investigator's brochure
compilation of the clinical and non-clinical information on the device(s) under investigation, that is relevant to the investigation in human subjects

3.8
clinical performance
behaviour of a specific medical device and/or its performance in relation to its intended use when correctly applied to appropriate subjects

3.9
coordinating clinical investigator
clinical investigator who is appointed by the sponsor to coordinate work in a multicentre clinical investigation

3.10
ethics committee
independent and properly constituted competent body whose responsibility is to ensure that the safety, well-being and human rights of the subjects participating in a clinical investigation are protected

NOTE For the purposes of this part of ISO 14155, “ethics committee” is synonymous with “research ethics committee” or “institutional review board”. The regulatory requirements pertaining to ethics committees or similar institutions may differ from country to country.

3.11
final report
description, results and evaluation of the clinical investigation after its completion

3.12
informed consent
legally effective, documented confirmation of a subject's (or his/her legal guardian or representative) voluntary agreement to participate in a particular clinical investigation after information has been given to the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate

3.13
investigation centre
investigation site
institution or site where the clinical investigation is carried out

3.14
medical device
any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application, intended by the manufacturer to be used on human beings for the purpose of

— diagnosis, prevention, monitoring, treatment or alleviation of disease,

— diagnosis, monitoring, treatment, alleviation or compensation for an injury or handicap,

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

— control of conception,

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

NOTE The term “medical device” is usually defined by national law. In order to inform the user of this part of ISO 14155, the definition from reference [1] is listed (see Bibliography). More information is given in reference [3].

3.15
monitor
individual appointed by the sponsor responsible for assessing the investigator's compliance with the clinical investigation plan and for performing source-data verification

NOTE The monitor is also responsible for reporting to the sponsor on the progress of the clinical investigation, including the compliance of the investigators.

3.16
multicentre investigation
clinical investigation which is conducted according to a single clinical investigation plan and which takes place at two or more sites

3.17
principal clinical investigator
clinical investigator responsible for the organization of the clinical investigation at one site

3.18
serious adverse device effect
adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune

3.19
serious adverse event
adverse event that

a) led to a death,

b) led to a serious deterioration in the health of the subject that

   1) resulted in a life-threatening illness or injury,

   2) resulted in a permanent impairment of a body structure or a body function,

   3) required in-patient hospitalization or prolongation of existing hospitalization,

   4) resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function.

c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

3.20
source data
all information in original and identified records and 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

3.21
source documents
original documents, data and records

NOTE This may be for example, hospital records, laboratory notes, pharmacy dispensing records, copies or transcriptions certified after verification as being accurate copies, photographic negatives, radiographs, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical investigation.

3.22
sponsor
individual or organization who or which takes responsibility for the initiation and/or implementation of a clinical investigation

NOTE 1 For the purposes of this part of ISO 14155 the word “sponsor” is synonymous with the word “promoter”.

NOTE 2 When a clinical investigator independently initiates, implements and takes full responsibility for the clinical investigation, the clinical investigator also assumes the role of the sponsor.

3.23
subject
individual who participates in a clinical investigation, either as a recipient of the device under investigation or as a control

4 Justification for a clinical investigation

In order to determine the justification and optimal design for a clinical investigation, an objective review of published and available unpublished medical and scientific data and information shall be conducted and documented.

NOTE 1 Guidance for such a literature review is given in Annex A.

The decision to embark upon a clinical investigation of a medical device requires *inter alia* the residual risks to be balanced against the anticipated benefits of the clinical investigation.

NOTE 2 For further information, see ISO 14971 [6].

5 Ethical considerations

5.1 Declaration of Helsinki

The rights, safety and wellbeing of clinical investigation subjects shall be protected consistent with the ethical principles laid down in the Declaration of Helsinki. This shall be understood, observed and applied at every step in the clinical investigation.

5.2 Improper influence or inducement

The sponsor and the clinical investigator(s) shall avoid improper influence or inducement of the subject, monitor, the clinical investigator(s) or other parties participating in or contributing to the clinical investigation.

5.3 Compensation and additional health care

The sponsor shall state what provision will be made for compensation of subjects in the event of injury arising from participation in the clinical investigation and this shall be documented. Arrangements for additional health care for subjects required as a result of an adverse device effect shall be made and documented.

NOTE This may be the subject of national legislation.

5.4 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 investigation.

6 General requirements

6.1 Formal agreement(s)

There shall be agreement(s) between the sponsor, the clinical investigator(s) and other relevant parties which define(s) their responsibilities. All formal agreements shall be recorded in writing and signed by all parties involved.

6.2 Qualifications

All parties participating in the conduct of the clinical investigation shall be appropriately qualified by education and/or experience to perform their tasks.

6.3 Clinical investigation plan

A clinical investigation plan shall be compiled in accordance with ISO 14155-2.

6.4 Design of the clinical investigation

The clinical investigation shall be designed to evaluate whether the 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 will support the clinical investigation objectives.

6.5 Confidentiality

At all times throughout the clinical investigation confidentiality shall be observed by all parties involved. All data shall be secured against unauthorized access.

Privacy and confidentiality of information about each subject shall be preserved in the reports and any publication of the clinical investigation data.

Lists of subjects' names and identifying information should, wherever possible, be maintained separately from case report forms.

6.6 Start of clinical investigation

No clinical investigation shall start until

a) a clinical investigation plan has been written and signed,

b) the opinion and/or approval of the ethic(s) committee(s) has been obtained,

c) regulatory clearance or approval, if applicable, has been obtained.

6.7 Informed consent

6.7.1 General

Informed consent shall be obtained in writing and documented before a subject is enrolled into the clinical investigation.

NOTE The consent form usually consists of an information part and an approval/signature part. These two parts can either be combined in one document (patient information and consent form) or separated into a patient information sheet and a patient consent form.

6.7.2 Process of obtaining informed consent

The process of obtaining informed consent shall

a) avoid any coercion of or undue influence of subjects to participate,

b) not waive or appear to waive subject’s legal rights,

c) use language that is non-technical and understandable to the subject or his/her legal representative,

d) provide ample time for the subject to consider participation,

e) include dated signatures of the subject or the subject's legal representative and of the clinical investigator,

f) show how informed consent will be obtained and recorded in circumstances in which the subject is unable to give it,

NOTE A subject intended for the participation in a clinical investigation may be unable to make the necessary decisions (foetus, infant, child and juvenile, the seriously ill or unconscious, mentally ill, mentally handicapped). In such circumstances, informed consent can only be given by the legal guardian or representative.

g) be documented in the clinical investigation plan.

6.7.3 Information to be provided to the subject for the purpose of obtaining informed consent

At least the following information shall be provided in writing and in non-technical language that is understandable to the subject (or the subject's legal representative):

a) description/purpose:

   1) the investigation involves research;

   2) the objective of the investigation;

   3) the anticipated duration and involvement of subject participation in the investigation;

   4) description of the device under investigation ;

   5) description of procedures, emphasising any that are experimental.

b) foreseeable risks:

   1) description of any foreseeable risks and inconveniences;

   2) possible side effects.

c) potential benefits:

   1) description of potential benefits to the subjects;

   2) description of potential benefits to others.

d) alternative therapy:

   1) information on alternative treatments or procedures available.

e) confidentiality:

   1) statement that subject participation is confidential;

   2) statement that subject allows access to medical records by regulatory authorities and sponsor ’s delegates;

   3) statement that investigation results may be published without disclosing the subject ’s identity.

f) compensation (medical/financial):

   1) information about provisions for compensation in the event of injury arising from participation in the clinical investigation and additional health care to be provided to subjects as a result of an adverse device effect;

   2) information on financial compensation for participation, if applicable.

g) questions and/or termination:

   1) whom to contact with questions about the investigation;

   2) whom to contact in the event of injury;

   3) circumstances under which subject's participation may be terminated by the investigator, if applicable.

h) new findings:

   1) statement that new findings relevant to the subject 's confirmed participation shall be made available.

6.7.4 Informed consent statement

The statement of informed consent shall contain the following in writing:

a) statement that subject's participation is voluntary;

b) statement that refusal of participation incurs no penalty for the subject;

c) statement that discontinuation at any time incurs no penalty for the subject;

d) statement on possible consequences of withdrawal;

e) acknowledgement of the information provided.

6.7.5 Informed consent agreement

In signing the consent form, the subject or his/her legal representative shall

a) agree to participate in and comply with the clinical investigation,

b) agree to his/her personal physician being informed of his/her participation, or state his/her disagreement to the release of this information,

c) agree to the use of his/her relevant personal data for the purpose of the clinical investigation.

6.8 Suspension or early termination of the clinical investigation

If an investigation is terminated prematurely or suspended, the sponsor shall promptly inform the clinical investigators/investigation centres of the termination or suspension and the reason(s) for this. The ethics committee shall also be informed promptly and provided with the reason(s) for the termination or suspension by the sponsor or by the clinical investigator/investigation centres.

NOTE Depending on the type of investigation, regulatory authorities and the personal physicians of the subjects may also need to be informed.

6.9 Document and data control

All documents and data shall be produced and maintained in such a way as to assure control of documents and data and to protect the subject's privacy as far as reasonably practicable.

A case report form shall be developed to capture the data for the individual subject required by the clinical investigation plan.

6.10 Accounting for subjects

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

6.11 Access to preclinical and clinical information

Each clinical investigator taking part in the clinical investigation shall have the right of access to the relevant preclinical and safety information. All information given shall be kept confidential.

The monitor shall have access to the source documents and other information needed to ensure investigator compliance with the clinical investigation plan and applicable rules and regulations, and to assess the progress of the clinical investigation.

6.12 Auditing

The clinical investigator(s) shall allow auditing of their clinical investigation procedures.

7 Documentation

7.1 General

Documentation in 7.2 and 7.3 shall be prepared before commencement of the clinical investigation. The information supplied to the clinical investigator shall be documented.

7.2 Clinical investigator's brochure

The clinical investigator's brochure shall contain

a) a summary of the literature and an evaluation supporting the rationale for the intended use of the device and the design of the clinical investigation,

b) a general description of the device and its components in accordance with ISO 14155-2,

c) a description of the mechanism of action of the device, along with supporting scientific literature including, if relevant, the manufacturer's instructions for use and installation,

   This should include possible risks, contra-indications, warnings, etc. for the device.

d) a description of the intended clinical performance,

e) a description of the materials used in the device,

f) a summary and evaluation of the *in vitro* and/or *ex vivo* and/or *in vivo* data relevant to the device, including preclinical data such as biological studies, non-clinical laboratory studies and any animal studies,

g) a summary of relevant previous clinical experience with the device and with other devices with similar features,

h) a list of International Standards, if any, complied with in full or in part,

i) results of the risk analysis.

The clinical investigator's brochure shall be updated throughout the course of the clinical investigation as significant new information becomes available, and shall be communicated to the investigators.

7.3 Other documents

As a minimum, the following documents shall be maintained in investigator and/or sponsor files:

a) the clinical investigation plan;

b) a current, signed and dated curriculum vitae of each of the clinical investigators;

c) the name(s) of the institution(s) in which the clinical investigation will be conducted;

d) the ethics committee opinion and/or approval, in writing, and relevant correspondence;

e) correspondence with authorities as required by national legislation;

f) the agreement between the principal and coordinating investigator(s) and the sponsor;

g) appropriate insurance certificates, if applicable;

h) informed consent forms and other information provided to the subjects;

i) case report forms;

j) forms for reporting adverse events and adverse device effects;

k) names/contact addresses of monitor(s).

8 Sponsor

8.1 General

Prior to initiating a clinical investigation, the sponsor shall define, establish, allocate and communicate all investigation-related duties and functions.

The sponsor shall ensure documentation of the compliance of the investigator, sponsor and monitor with this part of ISO 14155, the applicable clinical investigation plan and subsequent amendments and with all applicable regulatory requirements through a quality system.

8.2 Responsibilities of sponsor

The sponsor shall

a) select the clinical investigator(s) and investigation centre(s) for the particular investigation, and if appropriate a coordinating clinical investigator,

b) select and appoint a monitor for the clinical investigation or otherwise assume the responsibilities of the monitor,

   The ultimate responsibility for monitoring remains with the sponsor even if those activities are outsourced or delegated. Instructions should be available from the sponsor to the monitor on how to handle non-compliances and missing data.

c) prepare, and keep up to date, the clinical investigator's brochure,

d) provide the clinical investigator with the clinical investigation plan and subsequent approved amendments, and with the clinical investigator's brochure,

e) sign the approved clinical investigation plan,

f) supply fully characterized devices which are the subject of the clinical investigation,

g) ensure that appropriate information and/or training is given to the clinical investigator, if necessary, in the use of the device in accordance with the clinical investigation plan,

h) ensure that all deviations from the clinical investigation plan are reviewed with the appropriate clinical investigator(s) and reported in the case report forms and the final report for the clinical investigation,

i) ensure that all adverse events and all adverse device effects are reported and reviewed with the clinical investigator(s) and, where appropriate, that all serious adverse events and all serious adverse device effects are reported to the relevant authorities and ethics committee(s) and/or safety monitoring committee(s),

j) during the course of the clinical investigation, inform in writing all principal clinical investigators about all serious adverse events and all serious adverse device effects occurring in (multicentre) clinical investigations, that have been reported to the sponsor. This information shall be sent to the clinical investigator(s) based on perceived risk,

k) promptly inform the clinical investigator(s), when a clinical investigation is prematurely terminated or suspended, and, where applicable, inform the regulatory authority(ies) and ethics committee(s) of the termination or suspension and the reason(s) for the termination or suspension,

l) inform the clinical investigator(s) of the developmental status of the device and the requirements necessary to verify the performance and the safety of the device,

m) review and approve any deviation from the clinical investigation plan and take any appropriate corrective or preventive actions,

n) collect, store, keep secured and ensure completion by the relevant parties of the following documents:

   1) all documents listed in Clause 7 (documentation);

   2) copies of signed and dated case report form(s);

   3) records of any adverse events and adverse device effects reported to the sponsor during the clinical investigation;

   4) any statistical analyses and underlying supporting data;

   5) final report of the clinical investigation.

o) ensure accurate device accountability and traceability systems.

9 Monitor

9.1 Responsibilities of monitor

The monitor shall verify that

a) compliance with the clinical investigation plan is maintained and any deviation from the clinical investigation plan is discussed with the clinical investigators, documented and reported to the sponsor,

b) the device is being used according to the clinical investigation plan, and if modifications are required either to the device or its method of use or to the clinical investigation plan, this need is reported to the sponsor,

c) the clinical investigator(s) has(have) and continue(s) to have staff and facilities to conduct the clinical investigation safely and effectively,

d) the clinical investigator(s) has (have) and continue(s) to have access to an adequate number of subjects and devices,

e) signed and dated informed consent forms have been obtained from each subject at the time of enrolment and before any study-related procedures are undertaken,

f) the data in the case report forms are complete, are recorded in a timely manner and are consistent with the source data,

g) the procedures for recording and reporting adverse events and adverse device effects to the sponsor are followed,

h) there is a process in place for device accountability and traceability and that it is maintained,

i) maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is performed and documented,

j) subject withdrawal and/or non-compliance is documented and discussed with the clinical investigator and reported to the sponsor,

k) findings of non-compliance or required modifications shall be reviewed with the investigator and disclosed in a written monitoring report to the sponsor.

10 Clinical investigator

10.1 General

If the clinical investigator is an institution, it shall appoint a person with the qualification and responsibility of the clinical investigator mentioned in 10.2 and 10.3.

10.2 Qualification of clinical investigator

The clinical investigator shall be

a) an appropriately qualified practitioner legally entitled to practice,

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

c) familiar with the background and requirements of the clinical investigation methodology,

d) trained in the proper method of obtaining informed consent.

10.3 Responsibilities of clinical investigator

The clinical investigator shall be responsible for the day to day conduct of the clinical investigation as well as for the safety and well-being of the human subjects involved in the clinical investigation. The clinical investigator shall

a) have the resources to conduct the clinical investigation properly,

b) ensure that conducting the clinical investigation will not give rise to a conflict of interest,

c) obtain from the sponsor the information which the clinical investigator judges essential about the device and be familiar with this information,

d) be well acquainted with the clinical investigation plan before signing it,

e) support the monitor and auditor, if applicable, in their activities to verify compliance with the clinical investigation plan, to perform source data verification and to correct the case report form where inconsistencies or missing values are identified,

f) discuss with the sponsor and the monitor any question of modification of the clinical investigation plan and obtain the written approval of the sponsor,

g) make sure that the clinical investigation plan is followed by all responsible for the conduct of the clinical investigation at his institution. Any deviation shall be documented and reported to the sponsor,

h) make the necessary arrangements to ensure the proper conduct and completion of the clinical investigation,

i) make the necessary arrangements for emergency treatment, as needed, to protect the health and welfare of the subject,

j) ensure that appropriate ethics committee approval has been received to start the clinical investigation at his centre,

NOTE Examples of information for the ethics committee are given in Annex B.

k) provide the results from the ethics committee to the sponsor,

l) inform the ethics committee and ask for its opinion and/or approval regarding any significant change in the clinical investigation plan that has been approved by the sponsor and the reasons for the change,

m) inform the ethics committee about any serious adverse device effects,

n) inform the sponsor about all adverse events and adverse device effects in a timely manner,

o) endeavour to ensure an adequate recruitment of subjects,

p) ensure that the subject has adequate information to give informed consent,

q) ensure that informed consent is obtained and documented,

r) ensure that clinical records shall be clearly marked to indicate that the subject is enrolled in a particular clinical investigation. If appropriate, subjects enrolled in the clinical investigation shall be provided with some means of showing their participation in the investigation, together with identification and compliance information for concurrent treatment measures. Contact address/telephone numbers shall be given.

   If appropriate, the subject's personal physician should, with the subject's agreement, be informed.

s) provide subjects with well defined procedures for any emergency situation and safeguard the subject's interest. Under these circumstances deviations from the clinical investigation plan shall not require the prior approval of the sponsor or the ethics committee. Such deviations shall not be considered as a breach of agreement but shall be documented and reported to the sponsor,

t) ensure that information which becomes available as a result of the clinical investigation which may be of importance to the health of the subject and the continuation in the clinical investigation shall be made known to the sponsor and, if pertinent to the safety or wellbeing of the subject, the subject and the subject's private clinician,

u) inform the subject and/or the subject's physician about any premature termination or suspension of the clinical investigation with a rationale for the study termination,

v) have primary responsibility for the accuracy, legibility and security of all clinical investigation data, documents and patient records at his investigation site both during and after the clinical investigation. The case report form shall be signed by the clinical investigator(s). Any alteration of the data shall be made only by authorized personnel, and initialled and dated by the same, the original entry being retained for comparison,

w) ensure that the basic data are kept for the minimum time specified in the clinical investigation plan,

x) be responsible for the supervision and assignment of duties to all responsible for the conduct and evaluation of the clinical investigation for the clinical investigation centre involved,

y) ensure that all devices that are the subject of the clinical investigation are accounted for.

The quantity of the devices received should be reconciled with the quantities of devices used, discarded or returned.

11 Final report

11.1 Presentation of results

A final report of the clinical investigation shall be completed, even if the clinical investigation is prematurely terminated.

11.2 Contents of the final report

A final report shall be presented in written form. This shall be signed by the sponsor and the coordinating investigator (if appointed) and the principal clinical investigator(s) in each centre and made available, upon request, to all the clinical investigators and the ethics committee(s).

The final report of the clinical investigation shall include thorough identification of the device(s), a description of the methodology and design of the clinical investigation, any deviations from the clinical investigation plan, data analysis with any statistical analysis and a critical appraisal in relation to the aims of the investigation.

The final report shall take into account all data from each investigation centre/site and for all enrolled subjects. No subject shall be identifiable either from the final report or published results.

All clinical investigators shall have the opportunity to review and comment on the final report. The sponsor shall maintain records confirming that investigators have been provided with the final report for review and any comments. If a clinical investigator does not agree with all or parts of the final report, his/her comments shall be recorded and communicated to the other investigators.

If the coordinating investigator or any of the principal clinical investigator(s) does not sign the final report, a justification shall be provided for not signing the final report.

NOTE Further guidance for the content of the final report is given in Annex C.

Annex A
(informative)

Suggested procedure for literature review

A.1 Introduction

A review and evaluation of the literature is essential for justification and planning of any clinical investigation of a medical device. The aim of such a review is to provide a basis for drafting the clinical investigation plan in order to determine scientific background for the clinical investigation. It also provides essential information for assessing risk/benefits and achieving the ethical conduct of the planned investigation.

NOTE Such a literature review may also be helpful to assess whether the relevant clinical data available in the literature are sufficient to demonstrate safety and performance of the device in question without the need to generate further data from a specifically designed clinical investigation or conclude that the available data are not sufficient.

Performing a literature survey is a scientific activity that should be done with rigour and objectivity, and should allow for verification by third parties.

A.2 Methodology

A.2.1 General

Prior to performing the literature review, a plan should be established for the identification, selection, collation and review of all available studies/data. This plan should be documented and preferably be based on recognized practice for systematic review of the scientific literature.

A.2.2 Objective(s)

The objective(s) of the literature review should be clearly defined. The types of studies that are relevant to these objective(s) should be specified, taking into account any already well-established knowledge of the device.

A.2.3 Selection criteria for documents

The criteria for selecting or excluding data should be defined with an appropriate rationale. Published data should be taken from recognized scientific publications. All available unpublished relevant data should also be taken into account in order to avoid publication bias. All data should be referenced.

The literature review should state the sources of literature and data, and the extent of the searches of databases or other compilations of information.

A.2.4 Assessment of documents

A literature review should clearly assess the quality of the documents and the extent to which the literature relates to the specific characteristics and features of the device under consideration, taking into account the intended use of the device.

The following shall be considered:

a) similarity of the device in the selected documents to the device under consideration based on technology, critical performance, design and principles of operation, so that the applicability of the literature can be assessed;

b) the patient or study populations in the documents and the medical purpose, indications for use and severity and type of disease or condition compared to those intended for the device under assessment;

c) conditions of use of the device in the documents and the intended use of the device in question.

The literature review should make an assessment of the significance and weight of studies of different designs and between published and unpublished data. If unpublished data are being included in the assessment, the literature review will need to distinguish between the significance that is attached to these.

Factors include

1) whether the author's conclusions are substantiated by the available data,

2) whether the literature reflects the current medical practice and state of the art technologies,

3) whether references are taken from recognized scientific publications and whether or not they have been reported in peer reviewed journals,

4) the extent to which the published literature is the outcome of a study/studies that have followed scientific principles.

Ideally, evidence should be generated from a controlled clinical investigation, properly designed cohort- or case-controlled investigation, well-documented case histories conducted by appropriate experts, or reports of significant experience with the marketed device.

A.2.5 Critical evaluation of the literature

The literature review should contain a critical evaluation of the literature.

After documents are obtained and assessed, the selection criteria that are applied and the exclusion of any documents from this critical evaluation must be justified. A review is then completed as it relates to the device in question and its intended use, and a structured report of the review should be written, consisting of

a) a short description of the medical device including its intended functions, the type of device, technology and features and a description of the intended method of use,

b) an analysis of all the selected literature and data, both favourable and unfavourable,

c) a critical evaluation of the hazards, associated risks and appropriate safety measures for patients, medical staff and third parties,

d) a description of the methods of weighting the different papers and the statistical methods of analysis employed, taking into account the assessment methods, the type and duration of study and the heterogeneity of the population included within the study. Particular attention should be given to circumstances where there are repeated publications on the same group of patients by the same authors, in order to avoid over-weighting multiple publications of the same test subjects,

e) a list of publications appropriately cross-referenced in the evaluation,

f) a conclusion with a justification, including an assessment of any probable benefit to health from the use of the device as intended by the manufacturer, against probable risks of injury or illness from such use, taking account of the "state of the art". The conclusions should make it clear how the objectives of the literature review have been met and identify any gaps in the evidence necessary to cover all relevant aspects of safety and performance. If a clinical investigation is considered necessary, the conclusion should also give details on the relevant objectives and design of such an investigation, based on results of the literature review;

g) the signature(s) of the reviewer(s) and date.

Annex B
(informative)

Information for the ethics committees

The following information can be of relevance for the ethics committee:

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

b) a summary of how the health status of subjects may be affected;

c) an assessment of possible risks, methods and facilities proposed for dealing with them;

d) an assessment of any expected discomfort or distress;

e) proposed method of supervision of the clinical investigation, and the qualifications and experience of the clinical investigator(s) to conduct the clinical investigation;

f) all details of the proposed informed consent procedure, including an information sheet written in non-technical language which the subject or his/her guardian or legal representative can understand, including the aims, expected benefits for the subject and/or others, risks, inconveniences and an explanation of alternatives;

g) an outline of procedures that will ensure confidentiality;

h) documentation of how informed consent will be obtained from the subject and recorded in emergency circumstances in which the subject is unable to give consent;

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

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

k) the clinical investigation plan and any amendments;

l) the clinical investigator's brochure;

m) progress report and the final report;

n) all reports on serious adverse events and all adverse device effects.

Annex C
(informative)

Final reports of clinical investigations with medical devices

C.1 General

This annex specifies the structure and contents of clinical investigation reports.

C.2 Title page

The title page should contain the following information:

a) title of investigation;

b) identification of the medical devices including names, models, etc. as relevant for complete identification;

c) name of sponsor;

d) clinical investigation plan (CIP) identification;

e) statement indicating whether the investigation was performed in accordance with this part of ISO 14155;

f) date of report;

g) author(s) of report.

C.3 Summary

A structured abstract should be provided, presenting the essentials of the study in the following sections:

Title, introduction, objectives, subjects, methods, results, conclusions.

The key dates should be given, including the investigation initiation dates (first subject in) and investigation completion date (last subject out) or date of early termination, if applicable.

C.4 Table of contents

C.5 Introduction

A brief statement placing the study in the context of the development of the medical device and an identification of guidelines followed in the development in the clinical investigation plan should be provided.

C.6 Materials and methods

C.6.1 Device description

Summary description of the device and its intended use. Any modification of the device during the investigation should be described.

C.6.2 Clinical Investigation Plan (CIP) summary

A summary of the CIP should be provided. Any modification of the CIP during the investigation should be described. The summary should include a brief description of

a) the clinical investigation objectives,

b) the investigation design,

   1) type of investigation

   2) investigation endpoints

c) ethical considerations,

d) data quality assurance,

e) subject population for the investigation,

   1) inclusion/exclusion criteria

   2) sample size

f) treatment and treatment allocation,

g) investigation variables,

h) concomitant medications/treatments,

i) duration of follow-up,

j) statistical analysis.

   1) investigation hypothesis or pass/fail criteria

   2) sample size calculation

   3) statistical analysis methods

C.7 Results

This section should contain summary information with a description of the analysis and results.

This section should include

a) the investigation initiation date,

b) the investigation completed/suspension date,

c) the disposition of patients/devices,

d) the patient demographics,

e) CIP compliance,

f) the analysis, which includes

1) safety report comprising a summary of all adverse events and adverse device effects (device related or not) seen in the investigation, including a discussion of the severity, treatment needed, resolution, and assessment by the investigator of relation to treatment provided as part of the investigation,

2) performance analysis provided for in the CIP,

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

4) a description of how missing data (including patients lost to follow-up or withdrawn for any reason) were dealt with in the analysis.

C.8 Discussion and overall conclusions

The performance and safety results of the study and the relationship of risks and benefit should be briefly summarized and discussed. The clinical relevance and importance of the results should also be discussed in the light of other existing data. Any specific benefits or special precautions required for individual subjects or at-risk groups and any implications for the conduct of future studies should be identified.

C.9 Abbreviated terms and definitions

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

C.10 Ethics

It should be confirmed that the CIP and any amendments to it were reviewed by an ethics committee. A list of all consulted ethic committees should be given in an annex to the report (see C.13).

C.11 Investigators and administrative structure of investigation

A brief description of the organization of the study should be included in the report. A list of investigators should be given in an annex, including their affiliations. The name and address of the sponsor's representative should be provided.

C.12 Signature block

The signature provisions given in 11.2 should apply.

C.13 Annex to the report

There should be an annex to the report containing the following:

a) the CIP including amendments;

b) a list of investigators and their institutions of affiliation;

c) a list of other parties involved (e.g. core labs, contract research organistations (CROs), experts, etc.);

d) a list of monitors;

e) a list of ethics committees;

f) a tabulation of all relevant data sets, including all CIP deviations, all adverse events and adverse device effects, withdrawals and discontinuations.

Bibliography

[1] European Directives on medical devices, 93/42/EEC from 14 June 1993 and on active implantable medical devices, 90/385, EEC from 20 July 1990, as amended

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

[3] *Essential Principles* — Global Harmonization Task Force, 1999

[4] International Conference on Harmonisation, *Harmonised Tripartite Guideline for Good Clinical Practice* , 2nd edition, May 1996

[5] *Ethical principles for medical research involving human subjects* , World Medical Association, available at <http://www.wma.net/e/approvedhelsinki.html >

[6] ISO 10993 (all parts), *Biological evaluation of medical devices*

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