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Clinical investigation of medical devices

Investigations cliniques des dispositifs médicaux

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Contents

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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.

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.

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

Annex A forms an integral part of this International Standard. Annexes B, C and D are for information only.

Introduction

This International Standard was prepared to assist sponsors, regulatory authorities, and investigators in the conduct and performance of the clinical investigation of medical devices.

The text of this International Standard contains general requirements; it is intended to protect human subjects and ensure the scientific conduct of the investigation.

Clinical investigation of medical devices

1 Scope

This International Standard

a) pertains to the clinical investigation in human subjects of those medical devices whose clinical performance needs assessment;

b) specifies the requirements for the conduct of the clinical investigation and documentation on whether the medical device achieves the performance intended by the sponsor, determines any undesirable side effects under normal conditions of use and permits assessment of the acceptable risks relating to the intended performance of the device;

c) provides the framework for systematic written procedures for the organization, design, implementation, data collection, documentation and conduct of the clinical investigation.

2 Normative reference

The following standard contains provisions which, through reference in this text, constitute provisions of this International Standard. At the time of publication, the edition indicated was valid. All standards are subject to revision, and parties to agreements based on this International Standard are encouraged to investigate the possibility of applying the most recent edition of the standard indicated below. Members of IEC and ISO maintain registers of currently valid International Standards.

World Medical Association's Declaration of Helsinki, *Recommendations guiding physicians in biomedical research involving human subjects* (see annex A).

1) This definition is in accordance with [3] in annex D.

3 Definitions

For the purposes of this International Standard, the following definitions apply.

3.1 clinical investigation: Any systematic study in subjects undertaken to verify the performance of a specific device under normal conditions of intended use.

3.2 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.[1)]

3.3 device (intended for clinical investigation): Any medical device intended for use by an appropriately qualified practitioner when conducting clinical investigations in an adequate clinical environment.

3.4 clinical performance: Effects achieved by a device in relation to its intended use, when correctly applied to appropriate subjects.

3.5 clinical investigation plan: Principal document which includes detailed information on the rationale, including risk versus benefit analysis, objectives, design and proposed analyses, methodology and conduct of the clinical investigation.

NOTE 1 The word "protocol", often used synonymously with the term "clinical investigation plan", has many different meanings, some not related to clinical investigations, and is translated differently in various countries. Therefore, it is not used in this International Standard.

3.6 sponsor: Individual or organization which takes responsibility for the initiation and/or implementation of a clinical investigation.

NOTE 2 For the purposes of this International Standard, the word "sponsor" is synonymous with the word "promoter". When a clinical investigator independently initiates and takes full responsibility for the clinical investigation, the clinical investigator assumes the role of the sponsor as well.

3.7 clinical investigator: Individual and/or institution responsible for the conduct and integrity of a clinical investigation.

The clinical investigator is

— an appropriately qualified practitioner legally entitled to practice,

— trained and experienced in the field of application of the device under consideration,

— familiar with the background to and the requirements of the clinical investigation.

3.8 subject: Human being participating in a clinical investigation.

3.9 informed consent: Process and documentation of obtaining the confirmation of the willingness of a subject (or his/her legal guardian or representative) to participate in a particular clinical investigation after information has been given to the subject on the nature of the clinical investigation.

NOTE 3 A subject intended for the participation in a clinical investigation may be unable to make the necessary decisions (the fœtus, infant, child and juvenile, the severely ill or unconscious, mentally ill, mentally handicapped). In such circumstances, informed consent shall only be given by the legal guardian or representative.

3.10 monitor: Qualified person appointed by the sponsor responsible for ensuring the investigator's compliance with the clinical investigation plan and for reporting on the progress of the clinical investigation.

3.11 ethics committee: Independent and properly constituted body of medical professionals and non-medical members, appointed in accordance with current practice, whose responsibility is to ensure that the safety, well-being and human rights of the subjects participating in a proposed clinical investigation are protected.

NOTE 4 For the purposes of this International Standard, "ethics committee" is synonymous with "research ethics committee" or "institutional review board". The legal status, constitution, and regulatory requirements pertaining to ethics committees or similar institutions may differ among countries.

3.12 multicentre investigation: Clinical investigation, conducted according to a single clinical investigation plan, which takes place at multiple sites.

3.13 principal clinical investigator: Clinical investigator who is appointed by the sponsor to coordinate the work in a multicentre clinical investigation or that of several clinical investigators at one site.

3.14 case record form: Set of documents, as part of the clinical investigation plan, designed for the recording of all relevant patient and device-related data. It shall be produced in a way which guarantees controlled document numbering and the subject's anonymity.

3.15 adverse event: Any undesirable clinical occurrence in a subject.

3.16 adverse device effect: Device-related adverse event.

3.17 final report: Comprehensive description and results of the clinical investigation after its completion, including a description of the methodology and design, the data analysis together with a critical evaluation, a clinical appraisal signed by the sponsor and clinical investigator(s), and the statistical analysis, if any.

3.18 clinical investigator's brochure: Collection of all relevant information known prior to the commencement of a clinical investigation.

4 Ethical considerations

4.1 The Declaration of Helsinki, as amended, is the accepted basis for the ethics of clinical investigations. This shall be understood, observed, and applied at every step in the clinical investigation, from the first recognition of the need and justification to the publication of results.

4.2 The clinical investigator is responsible for the safety and welfare of human subjects as far as the clinical investigation is concerned, but all involved share responsibility for the ethical conduct of the clinical investigation.

5 General requirements

5.1 At all times throughout the clinical investigation, strict confidentiality by all parties involved shall be maintained.

5.2 All formal agreements shall be recorded in writing and signed by all relevant parties.

5.3 No clinical investigation shall start until

a) the opinion and/or approval of the ethics committee has been received as appropriate to national policy and/or regulation;

b) regulatory clearance is provided by appropriate authorities, if applicable.

5.4 Before any subject is entered into the clinical investigation, informed consent shall be obtained. The process of obtaining informed consent includes the provision of an understandable explanation in oral and/or written form of the aims and benefits, risks, inconvenience, information on treatments or alternatives, if any, and right of withdrawal without penalty.

5.5 In the event of unanticipated or increased risks to subjects, suspension or termination of the clinical investigation shall be considered.

5.6 Data collected from a clinical investigation shall demonstrate whether the device is suitable or not for the population(s) for which it is intended.

5.7 All subjects enrolled in the clinical investigation (including those who dropped out of the investigation or were lost to follow-up) shall be accounted for.

6 Methodology

6.1 Documentation

Documentation shall be prepared before commencement of the clinical investigation. It shall include the clinical investigator's brochure and other documents.

6.1.1 The clinical investigator's brochure shall contain

a) a literature survey summary;

b) a general description of the device;

c) an explanation of how the device functions and the manufacturer's instructions for use and installation, if relevant;

d) a description of the proposed clinical performance and proposed labelling claims;

e) a summary of the *in vitro* and *in vivo* data relevant to the safety of the device;

f) a summary of any previous clinical performance of the device;

g) a list of applicable standards and regulatory requirements.

6.1.2 Other documents include the following:

a) an agreed clinical investigation plan with all documents for use in the clinical investigation;

b) the 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;

e) the agreement between the clinical investigator(s) and the sponsor.

6.2 Access to information

Each clinical investigator taking part in the clinical investigation shall have access to relevant preclinical investigation information; requests made for further information shall be justified and the information given shall be kept confidential.

6.3 Additional health care

Arrangements for additional health care for subjects required as a result of an adverse device effect shall be made and documented.

6.4 Clinical investigation plan

6.4.1 For single and multicentre investigations there shall be a written clinical investigation plan which sets out in detail the aims and objectives of the clinical investigation. This shall be agreed between the sponsor and all clinical investigators.

6.4.2 The clinical investigation plan shall be designed in such a way as to ensure that the results obtained have clinical relevance and scientific validity.

6.4.3 The clinical investigation plan shall include the information in 6.4.3.1 and 6.4.3.2.

6.4.3.1 General and administrative information, including:

a) title of the project;

b) background to the investigation;

c) names, qualifications and addresses of the clinical investigator and other participants, sponsor and monitor;

d) names, addresses and emergency contact numbers of the location(s) of the clinical investigation;

e) definition of responsibilities;

f) documentation of how informed consent shall be obtained;

g) mechanism for reporting significant adverse device effects;

h) statistical methods to be used;

i) copies of the informed consent and case record form(s).

6.4.3.2 Scientific information, including:

a) the objectives of the clinical investigation;

b) general design, including success and failure criteria and types of controls to be used, if any;

c) duration of the investigational treatment and follow-up, and rationale for the choice;

d) subject selection with inclusion and exclusion criteria, the number of subjects and rationale for the choice, and procedure for subject accountability including methods for determination of loss to follow-up;

e) criteria for early termination of the clinical investigation, if any;

f) methods of assessment of the clinical performance and the benefit to the patient; when appropriate, use of quantifiable characteristics;

g) documentation of adjunctive medication of subjects or other therapy related to the device;

h) in case of multicentre investigations, reports on the differences in methods between centres[2)];

i) statistical and other data analysis procedures to be used, rationale and validity for using the proposed scheme of analysis.

6.4.4 The clinical investigation plan should state that a final report shall be written.

6.5 Role of sponsor

The sponsor shall be responsible for

a) selecting the clinical investigators;

b) appointing the monitor;

c) preparing, assembling and maintaining all preclinical data and documentation;

d) collecting, storing, guarding, and ensuring completion by the relevant parties of the following documents:

1) the clinical investigation plan,

2) a set of the case record forms,

3) the ethics committee's opinion and/or approval,

4) records of any adverse device effect reported to the sponsor during the clinical investigation,

5) any statistical analyses, underlying data, and

6) the final report;

e) providing the clinical investigator with the clinical investigator's brochure and clinical investigation plan;

2) For example, differences in methods may consist of the use of different documentation equipment or the use of different supplementary products or medication for the same indication.

f) agreeing and signing the clinical investigation plan;

g) supplying fully characterized devices;

h) ensuring that appropriate training is given to the clinical investigator, if necessary, in the use of the device;

i) ensuring that adverse device effects are recorded, reported to appropriate authorities, reviewed and considered with the clinical investigator(s);

j) considering jointly with the clinical investigator(s) termination of the clinical investigation.

6.6 Role of monitor

The monitor shall ensure that

a) compliance with the clinical investigation plan is maintained and any deviation from the clinical investigation plan is reported to and agreed with the sponsor;

b) the device is being used according to the clinical investigation plan, and if modifications appear to be needed, either to the device 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) good clinical practice is followed;

e) the clinical investigator(s) has (have) and continue(s) to have access to an adequate number of subjects;

f) informed consent is obtained;

g) the data in the case record forms are recorded in a timely manner and are consistent with the data in the subject's records in accordance with national regulations;

h) the procedures for recording and reporting adverse events and adverse device effects to the sponsor are followed;

i) documentation on subject withdrawal and/or noncompliance and on any reason for the termination of the clinical investigation is being maintained.

6.7 Role of clinical investigator

The clinical investigator shall

a) ask for and receive from the sponsor information which the clinical investigator, who shall be acquainted with the use of the device, judges essential about the device;

b) be acquainted with the clinical investigation plan;

c) have the time and resources to conduct and complete the clinical investigation;

d) ensure that any other concurrent investigation being conducted by the clinical investigator will not give rise to a conflict of interest or interfere with the specific clinical investigation at hand;

e) make the necessary arrangements, including emergency treatment, to ensure the proper conduct and completion of the clinical investigation;

f) generate for the ethics committee the following information:

1) an assessment of the scientific merit of the proposal,

2) a resumé of how the health status of subjects may be affected,

3) an assessment of possible risks, proposed methods and adequate facilities for dealing with them,

4) an assessment of discomfort or distress foreseen,

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

6) all details of proposed informed consent procedure, including a "plain language" information sheet,

7) an outline of procedures that will ensure confidentiality,

8) ensure that adequate information (written in nontechnical language which the subject can understand, including the aims, expected benefits for him and/or others, risks and inconveniences and an explanation of alternatives) are available to the subject,

9) document how consent will be obtained and recorded in emergency circumstances in which the subject is unable to give consent;

g) submit the clinical investigation plan for comment, opinion, and/or approval to an appropriate ethics committee and provide the results to the sponsor;

h) ask the ethics committee for its opinion and/or approval if a reevaluation of the ethical aspects of the clinical investigation is called for;

i) endeavour to ensure an adequate recruitment of subjects;

j) ensure that the subject has adequate information to obtain informed consent;

k) shall provide, if appropriate, subjects enrolled in a clinical investigation with documents which prove that they are taking part. Contact address/telephone numbers shall be given and the medical records shall be clearly marked. The subject's physician should, with the subject's consent, be informed;

l) in an emergency situation, exercise clinical judgement and safeguard the subject's interest in all cases, if necessary deviating from the clinical investigation plan; such deviations shall not be considered as a breach of agreement but shall be reported and accounted for in the final report;

m) 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 clinical investigator and/or the clinician;

n) inform the ethics committee, in agreement with the sponsor, on any change in the clinical investigation plan potentially affecting the patients' safety or the scientific soundness of the clinical investigation, and the reasons for the change;

o) inform the sponsor, the monitor and national regulatory authorities, if applicable, about any severe adverse event and about all adverse device effects in a timely manner;

p) inform the subject and/or his clinician about the termination of the clinical investigation in the event of unanticipated or increased risk;

q) carry the primary responsibility for the accuracy, legibility and security of all documentation relevant to the clinical investigation;

r) ensure that any alteration of the raw data is signed and dated by authorized personnel, the original entry being retained for comparison;

s) ensure that the basic data are kept for the appropriate time (as required by national laws and regulations).

7 Presentation of results

A final report of the clinical investigation shall be presented.

For a multicentre investigation, the final report shall take into account all relevant information from each centre. The final report shall account for all enrolled subjects.

Annex A
(normative)

World Medical Association Declaration of Helsinki: Recommendations guiding physicians in biomedical research involving human subjects

This text was adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, and amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, the 35th World Medical Assembly, Venice, Italy, October 1983, and the 41st World Medical Assembly, Hong Kong, September 1989, and is herewith reproduced in full.

A.1 Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

A.2 Basic principles

A.2.1 Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

A.2.2 The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor, provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

A.2.3 Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his/her consent.