List of Titles

American National Standard

ANSI/AAMI/ISO 14155:1996

Clinical investigation of medical devices

AAMI Association for the Advancement of Medical Instrumentation

List of Titles

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14155 Clinical investigation of medical devices

American National Standard

ANSI/AAMI/ISO 14155—1996

Clinical investigation of medical devices

Approved 12 June 1996 by
Association for the Advancement of Medical Instrumentation
Approved 13 August 1996 by
American National Standards Institute, Inc.

Abstract:

This standard pertains to the clinical investigation in human subjects of those medical devices for which clinical performance needs to be assessed. It 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. It also provides the framework for systematic written procedures for the organization, design, implementation, data collection, documentation, and conduct of the clinical investigation.

Committee representation

Association for the Advancement of Medical Instrumentation

The adoption of ISO 14155:1996 as an American National Standard was initiated by the AAMI Biological Evaluation Committee, which also functions as a U.S. Technical Advisory Group to the relevant work in the International Organization for Standardization (ISO). U.S. representatives from the AAMI Clinical Investigations Working Group (U.S. Sub-TAG for ISO/TC 194/WG 4), cochaired by Robert L. Fuson, MD, of Bristol-Myers Squibb, played an active part in developing the ISO standard.

The AAMI **Biological Evaluation Committee** has the following members:

Cochair: Paul Didisheim, MD

Members: James M. Anderson, MD, PhD, Case Western Reserve University
Sumner A. Barenberg, Bernard Technologies
Arthur J. Coury, PhD, Society for Biomaterials
Roger Dabbah, PhD, U.S. Pharmacopeial Convention, Inc.
Paul Didisheim, MD, National Heart, Lung, Blood Institute
Robert L. Fuson, MD, Bristol-Myers Squibb
Donald F. Gibbons, PhD, 3M
Jean A. Goggins, PhD, Meadox Medicals, Inc.
Sharon Northup, PhD, Baxter Healthcare Corporation
Barry F. Page, Consultant, Garner, NC
Harold Stanley, DDS, American Dental Association
Mel Stratmeyer, PhD, FDA Center for Devices and Radiological Health

Alternates: John G. Miller, DVM, National Institutes of Health

Edward Mueller, FDA Center for Devices and Radiological Health

The AAMI **Clinical Investigations Working Group** has the following members:

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Members: James M. Anderson, MD, PhD, Case Western Reserve University
James Chesebro, MD, Massachusetts General Hospital
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Linda Graham, Virginia Medical Center at Cleveland
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Alternate Paul J. Upman, North American Science Associates, Inc.

Note—Participation by federal agency representatives in the development of this standard does not constitute endorsement by the federal government or any of its agencies.

Background of ANSI/AAMI proposed adoption of ISO 14155:1996

Clinical investigation of medical devices

As indicated in the foreword to the main body of this document (page v) the International Organization for Standardization (ISO) is a worldwide federation of national standards bodies. The United States is one of the ISO members that took an active role in the development of this standard, which was developed by ISO Technical Committee 194, *Biological evaluation of medical devices*, to fill a need for the international harmonization of test methods for various kinds of biological aspects of medical devices.

U.S. participation in this ISO TC is organized through the U.S. Technical Advisory Group for ISO/TC 194, administered by the Association for the Advancement of Medical Instrumentation (AAMI). The U.S. TAG for ISO/TC 194 supports the international harmonization of methods used in evaluating the biocompatibility of medical devices in order to help reduce unnecessary repetition of testing.

AAMI and ANSI procedures require that standards be reviewed and, if necessary, revised every 5 years to reflect technological advances that may have occurred since publication.

AAMI (and ANSI) have adopted other ISO standards. See the Glossary of Equivalent Standards for a list of ISO standards adopted by AAMI that gives the corresponding U.S. designation and the level of equivalency with the ISO standard.

The concepts incorporated in this standard should not be considered inflexible or static. This standard, like any other, must be reviewed and updated periodically to assimilate progressive technological developments. To remain relevant, it must be modified as technological advances are made and as new data come to light.

Suggestions for improving this standard are invited. Comments and suggested revisions should be sent to Standards Department, AAMI, 3330 Washington Boulevard, Suite 400, Arlington, VA 22201.

NOTE—Beginning with the ISO foreword on page v, this American National Standard is identical to ISO 14155:1996.

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).

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 fetus, 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 multicenter 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 multicenter 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 labeling 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 multicenter 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 multicenter investigations, reports on the differences in methods between centers;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;

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 upon 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 non-compliance 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 resume 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) endeavor 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 judgment 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 multicenter investigation, the final report shall take into account all relevant information from each center. 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 etiology 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.

A.2.4 Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

A.2.5 Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

A.2.6 The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

A.2.7 Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

A.2.8 In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

A.2.9 In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

A.2.10 When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

A.2.11 In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

A.2.12 The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

A.3 Medical research combined with professional care (clinical research)

A.3.1 In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

A.3.2 The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

A.3.3 In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method.

A.3.4 The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

A.3.5 If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (A.2.2).

A.3.6 The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

A.4 Nontherapeutic biomedical research involving human subjects (nonclinical biomedical research)

A.4.1 In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

A.4.2 The subjects should be volunteers—either healthy persons or patients for whom the experimental design is not related to the patient's illness.

A.4.3 The investigator or the investigating team should discontinue the research if in his/her/their judgment it may, if continued, be harmful to the individual.

A.4.4 In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

Annex B
(informative)

Rationale

B.1 Introduction

The requirements and recommendations of this International Standard represent a compromise. The various anomalies in terminology and interpretations among nations, legal definitions and established procedures had to be integrated. The following highlights those issues which might require clarification and explanation.

B.2 Legal aspects

National requirements and legal practices vary greatly. Therefore, these are not discussed in International Standards. Wherever national practice or regulation dictates some legal requirement, the requirement takes precedence over this International Standard.

B.3 Terminology

Choice of terminology is a difficult task. The use of terms differs from country to country and the cognitive meaning of the same words differs in various cultures.

For example, the term “clinical trial” could be inappropriately translated as experimentation with humans. Therefore “clinical investigation” has been chosen as a better description of the procedure. To assist the user, the choices used in this International Standard are listed in table B.1.

B.4 Methodology

Consultation with biostatisticians is recommended in the development of necessary criteria: population of subjects, inclusion and exclusion and discontinuation criteria, size and sampling procedures, randomization, criteria for monitoring, and others.

B.5 Auditing

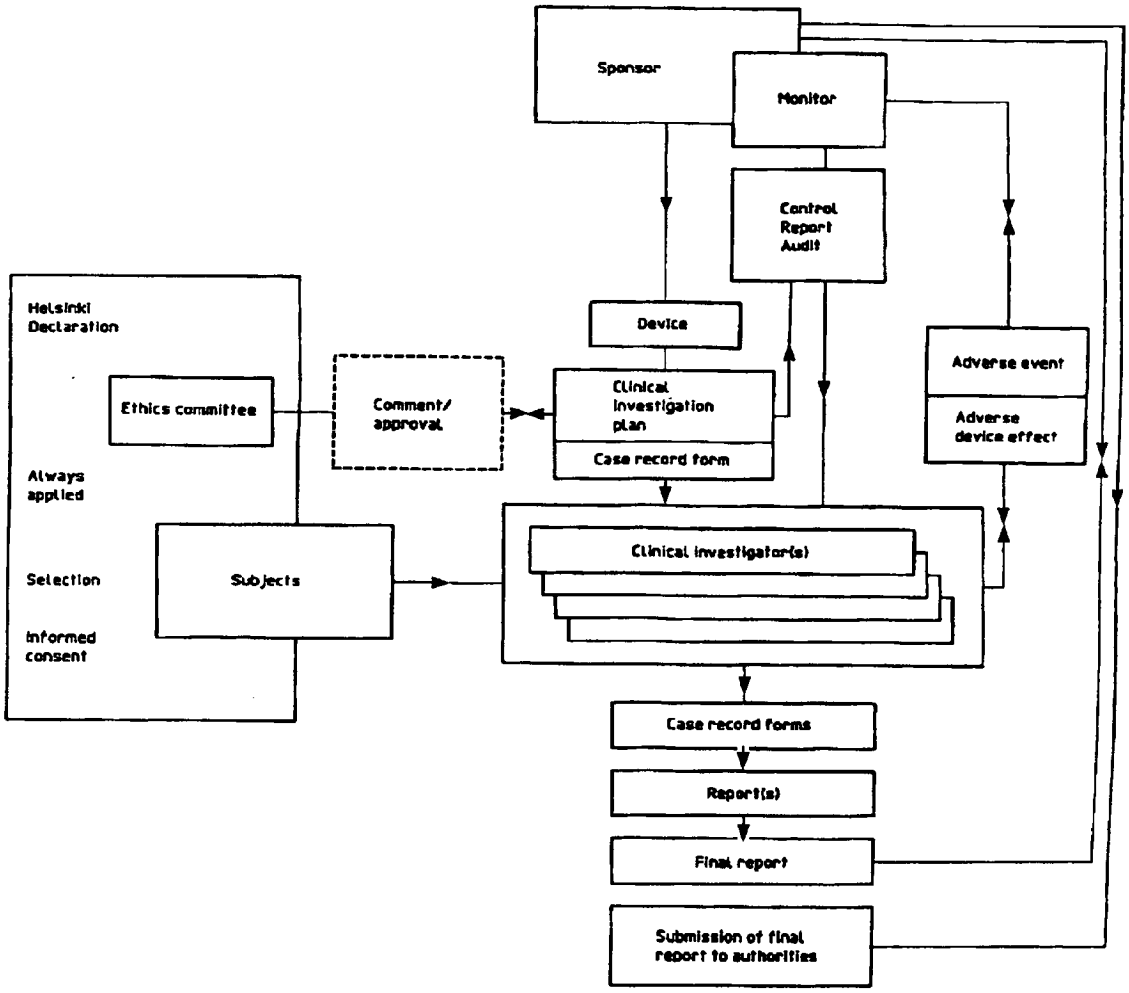
It is recommended that, in accordance with good clinical practice, clinical investigations are accessible to audit.

Table B.1

Terms not used	Terms recommended
Clinical trial, clinical study, clinical testing	Clinical investigation
Protocol, clinical study design	Clinical investigation plan
Promoter	Sponsor
Research ethics committee, institutional review board	Ethnic committee
Undesirable side effect	Adverse event

Annex C
(informative)

Flow chart for clinical investigation of medical devices



NOTE 5 ® ¬ in the flow chart indicates bidirectional flow of information or tasks.

Annex D
(informative)

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[10] *Good clinical practice for the trials on medical devices,* Appendix 4. Japanese Ministry of Health and Welfare. PAB Notification, 1 July 1992, Japan.

[11] Article 80-2, *Pharmaceutical Affairs Law of Japan,* 1949.

[12] *Recommended format for protocol for clinical research programs on dental materials,* International Dental Federation, 7 Carlisle Street, London W1V 5RG, UK.

Annotations from 14155.pdf

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Annotation 1; Label: AAMI; Date: 10/02/2000 9:26:47 AM
1 This definition is in accordance with [3] in annex D.

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Annotation 1; Label: AAMI; Date: 10/02/2000 9:29:11 AM
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.