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Clinical investigation of medical devices for human subjects

The European Standard EN 540 : 1993 has the status of a British Standard

Investigation clinique des disposifs médicaux sur les sujets humains

Klinische Prüfung von medizinischen Geräten für Versuchspersonen

UDC 615.471 : 615.478 : 620.1 : 62-78

Cooperating organizations

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Austria	Oesterreichisches Normungsinstitut
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United Kingdom	British Standards Institution

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Clinical investigation of medical devices for human subjects

Correction

Clause 6. Presentation of the results

In paragraph 2, line 5, after 'with' insert 'any'.

AMD 8162/March 1994

Contents

National foreword

This British Standard has been prepared under the direction of the Health Care Standards Policy Committee and is the English language version of EN 540 : 1993 *Clinical investigation of medical devices for human subjects*, published by the European Committee for Standardization (CEN).

EN 540 was produced as a result of international discussions in which the United Kingdom took an active part.

Compliance with a British Standard does not of itself confer immunity from legal obligations.

EUROPEAN STANDARD
NORME EUROPÉENNE
EUROPÄISCHE NORM

EN 540

June 1993

UDC 615.471 : 615.478 : 620.1 : 62-78

Descriptors: Medical equipment, safety, accident prevention, hazards, estimation, humans, clinical testing, specifications, commerce

English version

Clinical investigation of medical devices for human subjects

Investigation clinique des dispositifs médicaux sur les sujets humains

Klinische Prüfung von medizinischen Geräten für Versuchspersonen

This European Standard was approved by CEN on 1993-06-21. CEN members are bound to comply with the CEN/CENELEC Internal Regulations which stipulate the conditions for giving this European Standard the status of a national standard without any alteration.

Up-to-date lists and bibliographical references concerning such national standards may be obtained on application to the Central Secretariat or to any CEN member.

This European Standard exists in three official versions (English, French, German). A version in any other language made by translation under the responsibility of a CEN member into its own language and notified to the Central Secretariat has the same status as the official versions.

CEN members are the national standards bodies of Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and United Kingdom.

CEN

European Committee for Standardization
Comité Européen de Normalisation
Europäisches Komitee für Normung

Central Secretariat: rue de Stassart 36, B-1050 Brussels

Foreword

This European Standard was prepared by CEN TC 258 'CLINICAL INVESTIGATION OF MEDICAL DEVICES'.

This European Standard has been prepared under a Mandate given to CEN by the Commission of the European Communities (and the secretariat of the European Free Trade Association) and supports Annexes on Clinical Evaluation of relevant EC Directive(s).

In this European Standard, the words defined in clause **3** are written in capital letters.

International work is currently underway within ISO TC 194/WG 4, and this European Standard is in technical conformity with ISO CD 10993-8 which deals with the same subject.

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by December 1993, and conflicting national standards shall be withdrawn at the latest by December 1993.

According to the CEN/CENELEC Internal Regulations, the following countries are bound to implement this European Standard: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom.

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0 Introduction

This European Standard was prepared to define procedures to assist manufacturers, regulatory authorities, SPONSORS and CLINICAL INVESTIGATORS on the conduct and performance of the CLINICAL INVESTIGATION of MEDICAL DEVICES.

This European Standard is intended to protect SUBJECTS and ensure the scientific conduct of the CLINICAL INVESTIGATION.

1 Scope

1.1 This European Standard pertains to the CLINICAL INVESTIGATION in human SUBJECTS of those MEDICAL DEVICES whose the clinical PERFORMANCE needs assessment before being placed on the market.

This European Standard does not apply to in vitro diagnostic devices.

1.2 This European Standard specifies the requirements

- for the conduct of CLINICAL INVESTIGATIONS and documentation on whether the MEDICAL DEVICE achieves the performance intended by the SPONSOR;
- to determine any undesirable side effects, under normal conditions of use;
- to permit the assessment of the acceptable risks having regard to the intended PERFORMANCE OF THE MEDICAL DEVICE.

1.3 This European Standard provides a framework for the preparation of written procedures for the organization, design, implementation, data collection and documentation of the CLINICAL INVESTIGATION.

2 Normative references

This European Standard incorporates by dated or undated reference, provisions from other publications. These normative references are cited at the appropriate places in the text and the publications are listed hereafter. For dated references, subsequent amendments to or revisions of any of these publications apply to this European Standard only when incorporated in it by amendment or revision. For undated references the latest edition of the publication referred to applies.

World Medical Association Declaration of Helsinki; recommendations guiding physicians in biomedical research involving human subjects.

3 Terminology and definitions

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

3.1 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. This definition is taken from the Medical Device Directive.

3.2 device; 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.

3.3 clinical investigation

Any systematic study in human SUBJECTS, undertaken to verify the safety and PERFORMANCE of a specific MEDICAL DEVICE, under normal conditions of use.

3.4 clinical investigation plan; protocol

A document which includes detailed information on the rationale, aims and objectives, design and proposed analyses, methodology, and conduct of the CLINICAL INVESTIGATION.

3.5 clinical investigator

The investigator responsible for the conduct of a CLINICAL INVESTIGATION and who takes the clinical responsibility for the well-being of the SUBJECTS involved.

3.6 performance of the device

The action of a specific MEDICAL DEVICE with reference to its intended use when correctly applied to appropriate SUBJECTS.

3.7 ethics committee; research ethics committee; institutional review board; comité consultatif de protection des personnes dans la recherche biomédicale

An 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 particular CLINICAL INVESTIGATION are protected.

NOTE. The legal status, constitution and regulatory requirements pertaining to ETHICS COMMITTEES or similar institutions may differ among countries.

3.8 final report of clinical investigation

A comprehensive description of the CLINICAL INVESTIGATION on completion.

3.9 sponsor; promoter

An individual or an organization which takes responsibility for the initiation and/or implementation of a CLINICAL INVESTIGATION.

NOTE. When a CLINICAL INVESTIGATOR independently initiates and takes full responsibility for the CLINICAL INVESTIGATION, the CLINICAL INVESTIGATOR assumes the role of SPONSOR as well.

3.10 subject

A human being, either a patient or a non-patient volunteer, participating in a CLINICAL INVESTIGATION.

3.11 informed consent; consent

The voluntary confirmation and documentation of a SUBJECT's willingness (or his legal guardian or representative's permission) to participate in a particular investigation, after information has been given to the SUBJECT on the nature of the CLINICAL INVESTIGATION.

3.12 monitor

A person appointed by the SPONSOR and responsible to him for monitoring and reporting on the progress of the CLINICAL INVESTIGATION.

3.13 adverse event

Any undesirable clinical occurrence in a SUBJECT whether it is considered to be DEVICE related or not.

3.14 adverse device effect; undesirable side effect

A DEVICE related ADVERSE EVENT.

NOTE. An ADVERSE EVENT or an ADVERSE DEVICE EFFECT may be mild, moderate, or severe and are usually unexpected. If, as a result of an ADVERSE EVENT during a CLINICAL INVESTIGATION, a SUBJECT has to be hospitalized, or their hospitalization is unduly prolonged because of potential disability or danger to life or because an intervention has been necessitated or the event is terminal, the ADVERSE EVENT or ADVERSE DEVICE EFFECT is regarded as severe. For example, if an ADVERSE EVENT or ADVERSE DEVICE EFFECT causes foetal distress, foetal death or a congenital anomaly or malignancy results from the use of the DEVICE during a CLINICAL INVESTIGATION, this also would be classified as a severe ADVERSE EVENT or ADVERSE DEVICE EFFECT.

3.15 multicentre investigation

A CLINICAL INVESTIGATION, conducted according to a single CLINICAL INVESTIGATION PLAN, which takes place at different investigational sites.

3.16 principal clinical investigator

A CLINICAL INVESTIGATOR appointed by the SPONSOR to coordinate the work in a MULTICENTRE CLINICAL INVESTIGATION or that of several CLINICAL INVESTIGATORS at one site.

3.17 case report form

A set of documents, designed for complete recording of all relevant patient- and device-related data, as required by the CLINICAL INVESTIGATION PLAN,

3.18 clinical investigator's brochure

A collection of relevant information known prior to the onset of a CLINICAL INVESTIGATION.

4 General requirements

4.1 The Declaration of Helsinki and its subsequent amendments shall be the accepted basis for the ethical conduct of CLINICAL INVESTIGATIONS. It shall be applied by all parties involved and at every step in the CLINICAL INVESTIGATION from the first recognition of the need and justification to the publication of results.

4.2 At all times throughout the CLINICAL INVESTIGATION confidentiality shall be observed by all parties involved. All data shall be secured against unauthorized access (see **5.6.9**).

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

4.4 All relevant parties shall be appropriately qualified to perform their tasks.

4.5 In the event of unforeseen or increased risks to SUBJECTS, suspension or termination of the CLINICAL INVESTIGATION shall be considered.

4.6 The CLINICAL INVESTIGATION shall be designed to collect data to demonstrate whether the DEVICE is suitable for the population(s) for which it is intended.

4.7 A CLINICAL INVESTIGATION shall not start until, as appropriate to national policy, the opinion or approval of the ETHICS COMMITTEE(S) has been received.

4.8 All people involved in CLINICAL INVESTIGATIONS shall avoid any undue or improper influence on a SUBJECT.

4.9 The ETHICS COMMITTEE shall be provided with information to assess whether the risks to SUBJECTS, who cannot be expected to derive any direct therapeutic benefit, can be justified by the collective benefit.

5 Methodology

5.1 General

When any requirement given in **5.2** to **5.6** is not applicable, a justification shall be provided.

5.2 Requirements before commencement of the CLINICAL INVESTIGATION

5.2.1 Documentation outlining the basis and justification for the CLINICAL INVESTIGATION, shall be prepared before commencement of the CLINICAL INVESTIGATION.

It shall include the CLINICAL INVESTIGATOR'S BROCHURE and other documents.

5.2.1.1 The CLINICAL INVESTIGATOR'S BROCHURE shall contain:

a) a literature survey;

b) a general description of the DEVICE, and its functional components with the rationale of the design, and the scientific concepts on which it is based;

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

d) the description of the intended PERFORMANCE OF THE DEVICE;

e) a brief description of the manufacturing process of the DEVICE if this enhances the understanding of the DEVICE, as far as the safety is concerned;

f) previous CLINICAL INVESTIGATION or marketing history, if any, with any reason for recall relating to the safety of the DEVICE or the PERFORMANCE OF THE DEVICE;

g) a description of the materials used in the DEVICE, a summary of the in vitro, ex vivo and in vivo data relevant to the DEVICE, preclinical biological studies, non-clinical laboratory studies and any animal studies;

h) a list of standards, if any, complied with in full or in part;

i) a statement affirming that the DEVICE complies with relevant legal requirements apart from those requirements which the CLINICAL INVESTIGATION is intended to fulfil and that every reasonable precaution has been taken to protect the health and safety of SUBJECTS.

5.2.1.2 The other documents shall contain:

a) the CLINICAL INVESTIGATION PLAN with all documents for use in the CLINICAL INVESTIGATION, the details of the curriculum vitae of each of the CLINICAL INVESTIGATORS, and the name of the institution(s) in which the CLINICAL INVESTIGATION will be conducted;

b) ETHICS COMMITTEE opinion or approval in writing;

c) the agreement between the CLINICAL INVESTIGATOR(S) and the SPONSOR.

5.2.2 All CLINICAL INVESTIGATORS taking part in a CLINICAL INVESTIGATION shall have the right of access to relevant pre-CLINICAL INVESTIGATION information; requests made for further information shall be justified and the information shall be kept confidential.

5.2.3 There shall be an agreement between the SPONSOR, the MONITOR and the CLINICAL INVESTIGATOR which defines their responsibilities. The agreements shall include a confidentiality clause.

5.2.4 The provisions made to compensate SUBJECTS in the event of injury arising from participation in the CLINICAL INVESTIGATION shall be documented.

5.2.5 Before any SUBJECT is entered into the CLINICAL INVESTIGATION, his INFORMED CONSENT shall be obtained.

5.3 The CLINICAL INVESTIGATION PLAN

5.3.1 For any CLINICAL INVESTIGATION there shall be a written CLINICAL INVESTIGATION PLAN agreed between the SPONSOR and the CLINICAL INVESTIGATOR(S).

5.3.2 The CLINICAL INVESTIGATION PLAN shall be designed in such a way as to optimize the scientific validity of the results of the study.

5.3.3 The CLINICAL INVESTIGATION PLAN shall include:

a) references to and/or relevant literature;

b) the basis and justification for the CLINICAL INVESTIGATION;

c) the title of the project, identification of the DEVICE, names, qualifications and addresses, of the CLINICAL INVESTIGATOR(S) and other participants, SPONSOR, MONITOR and the location of the CLINICAL INVESTIGATION.

5.3.4 The proposed objective of the CLINICAL INVESTIGATION PLAN shall be related to establishing or verifying the safety and the PERFORMANCE OF THE DEVICE, when used for its intended purpose and according to the documented instructions.

5.3.5 The CLINICAL INVESTIGATION shall be conducted for the length of time sufficient to provide evidence of the safety and the PERFORMANCE OF THE DEVICE referred to in **5.3.4.**

5.3.6 The design of the CLINICAL INVESTIGATION shall be specified. The number of DEVICES to be used shall be stated. The procedures utilized to perform the CLINICAL INVESTIGATION shall be appropriate to the DEVICE under examination.

The number of SUBJECTS, the criteria for their inclusion, exclusion and withdrawal shall be specified together with the justification for the sample size chosen.

5.3.7 All relevant criteria of the PERFORMANCE OF THE DEVICE shall be established, appropriate to the DEVICE and its intended use, with methods of observation and quantification.

5.3.8 A CASE REPORT FORM shall be included in the CLINICAL INVESTIGATION PLAN.

5.3.9 The medication of SUBJECTS shall be documented

5.3.10 Where appropriate, statistical methods shall be applied before and if necessary throughout the entire CLINICAL INVESTIGATION, starting with the design of the CLINICAL INVESTIGATION PLAN and ending with the FINAL REPORT.

It shall be agreed between the SPONSOR and the CLINICAL INVESTIGATOR(S) whether the statistical work shall be carried out, and if so, by whom.

5.3.11 A description shall be given of the statistical design. The decision on how many SUBJECTS are needed (sample size) shall be based on scientific principles, although practical and ethical issues shall need consideration.

5.4 Role of the SPONSOR

5.4.1 The SPONSOR shall be responsible for selecting the CLINICAL INVESTIGATOR(S) in charge of the CLINICAL INVESTIGATION (see **3.5** and **5.6**).

The SPONSOR shall ensure that 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.

5.4.2 The SPONSOR shall either select a suitably trained and qualified person to monitor the CLINICAL INVESTIGATION and identify the MONITOR's responsibilities (see **5.5**), or he shall assume the responsibilities identified in **5.5** himself.

5.4.3 The SPONSOR shall be responsible for the preparation, assembly and maintaining of all preclinical data and documentation (see **5.2.1**).

In addition the SPONSOR shall be responsible for collection, storage, security and completion by the relevant parties, of the following documents:

- all preclinical data referred to in **5.2.1**;
- the CLINICAL INVESTIGATION PLAN;
- the CASE REPORT FORMS;
- a copy of the ETHICS COMMITTEE opinion or approval;
- all information on ADVERSE EVENTS and ADVERSE DEVICE EFFECTS reported to him;
- funding documents including all agreements related to the study;
- the data and statistical analyses;
- the FINAL REPORT of the CLINICAL INVESTIGATION.

5.4.4 The SPONSOR shall provide the CLINICAL INVESTIGATOR(S) with the CLINICAL INVESTIGATOR'S BROCHURE (see **5.2.1.1**), and other relevant information requested by the CLINICAL INVESTIGATOR(S).

5.4.5 The SPONSOR shall sign the CLINICAL INVESTIGATION PLAN.

5.4.6 The SPONSOR shall supply DEVICES appropriate to the CLINICAL INVESTIGATION PLAN.

5.4.7 The SPONSOR shall be responsible for ensuring that provisions for compensation in the event of injury arising from participation in the CLINICAL INVESTIGATION have been made.

5.4.8 The SPONSOR shall ensure that appropriate information and/or training is given to the CLINICAL INVESTIGATOR(S), in the use of the DEVICE in accordance with the CLINICAL INVESTIGATION PLAN.

5.4.9 The SPONSOR shall not offer improper inducement to the MONITOR, CLINICAL INVESTIGATOR(S) or their assistants.

5.4.10 The SPONSOR shall keep a record of any ADVERSE EVENT and ADVERSE DEVICE EFFECT reported to him during the CLINICAL INVESTIGATION.

5.4.11 The method of recording and analysing all ADVERSE EVENTS and ADVERSE DEVICE EFFECTS, together with the provisions for dealing with them shall be agreed between the SPONSOR and the CLINICAL INVESTIGATOR(S).

5.4.12 The SPONSOR shall be responsible for informing in writing all CLINICAL INVESTIGATORS about the severe ADVERSE EVENTS and all ADVERSE DEVICE EFFECTS occuring in MULTICENTRE CLINICAL INVESTIGATIONS, that have been reported to him. This information shall be transmitted to the CLINICAL INVESTIGATORS within ten days.

5.4.13 The SPONSOR shall consider jointly with the CLINICAL INVESTIGATOR(S) all ADVERSE EVENTS and ADVERSE DEVICE EFFECTS and if required shall report them to the appropriate authorities.

5.4.14 The SPONSOR shall be responsible for terminating the study and informing the CLINICAL INVESTIGATOR(S).

5.5 Role of the MONITOR

The MONITOR shall check and confirm that:

a) the CLINICAL INVESTIGATOR(S) is (are) informed of the investigational status of the DEVICE and the requirements necessary to verify the PERFORMANCE OF THE DEVICE;

b) by periodic communications, the compliance with the CLINICAL INVESTIGATION PLAN is maintained;

c) any deviation is discussed with the CLINICAL INVESTIGATOR(S) and reported to and agreed with the SPONSOR;

d) any CLINICAL INVESTIGATOR has, during the course of the CLINICAL INVESTIGATION, the staff and the facilities to conduct the CLINICAL INVESTIGATION safely and effectively;

e) any CLINICAL INVESTIGATOR has continued access to an adequate number of SUBJECTS to conduct the CLINICAL INVESTIGATION;

f) procedures exist for recording ADVERSE EVENTS and ADVERSE DEVICE EFFECTS, and reporting severe ADVERSE EFFECTS and all ADVERSE DEVICE EFFECTS to the SPONSOR;

g) the DEVICE is being used according to the documented instructions, and if modifications appear to be needed, either to the DEVICE or to the CLINICAL INVESTIGATION PLAN, this need is reported to the SPONSOR;

h) completion of the documentation is maintained;

i) an adequate supply of the DEVICE is maintained at the clinical investigation site;

j) INFORMED CONSENT has been obtained;

k) withdrawal and/or non-compliance by the SUBJECT is being documented;

l) the data in the CASE REPORT FORM conforms with that in the SUBJECT files;

m) any reason for the termination of the CLINICAL INVESTIGATION has been documented.

5.6 Role of the CLINICAL INVESTIGATOR(S)

5.6.1 The CLINICAL INVESTIGATOR(S) shall ask the SPONSOR for information as described in the CLINICAL INVESTIGATOR'S BROCHURE and any other information he judges essential for the conduct of the CLINICAL INVESTIGATION. He shall be well acquainted with the use of the DEVICE.

5.6.2 The CLINICAL INVESTIGATOR(S) shall be well acquainted with the CLINICAL INVESTIGATION PLAN before signing it.

5.6.3 The CLINICAL INVESTIGATOR(S) shall ensure that he and his team will be available to conduct and complete the CLINICAL INVESTIGATION.

Any other concurrent CLINICAL INVESTIGATION conducted by him shall not give rise to a conflict of interest or interfere with the specific CLINICAL INVESTIGATION in hand.

5.6.4 As far as the CLINICAL INVESTIGATION is concerned, the CLINICAL INVESTIGATOR(S) shall be responsible for the personal safety, and well being of SUBJECTS.

5.6.5 The CLINICAL INVESTIGATOR(S) shall make the necessary arrangements, including emergency treatment, to ensure the proper conduct of the CLINICAL INVESTIGATION.

5.6.6 The CLINICAL INVESTIGATOR(S) shall endeavour to ensure an adequate recruitment rate of SUBJECTS during the CLINICAL INVESTIGATION.

5.6.7 If appropriate, SUBJECTS enrolled in a CLINICAL INVESTIGATION shall be provided with some means of identification that they are taking part. Contact address/telephone numbers shall be given and the medical records shall be clearly marked.

NOTE. The SUBJECT's physician should, with the SUBJECT's agreement, be informed.

5.6.8 SUBJECTS who cannot be expected to derive any direct therapeutic benefit shall be examined to ascertain their state of health before entering the CLINICAL INVESTIGATION.

SUBJECTS shall be invited to confirm by a signed declaration that they have disclosed all matters concerning their health and any current medication shall be recorded.

5.6.9 The CLINICAL INVESTIGATOR(S) shall ensure that adequate information is given to the SUBJECT (or his guardian or legal representatives) both in oral and written form, on the nature of the CLINICAL INVESTIGATION.

This information shall be easily understandable by the SUBJECT.

This information shall include the aims, expected benefits for him and/or others, risks and inconveniences and an explanation of any alternative methods, and of possible consequences of any withdrawal from the CLINICAL INVESTIGATION.

Payment or any other form of inducement to SUBJECTS who cannot be expected to derive any direct therapeutic benefit, shall only be for expense, time and inconvenience.

The SUBJECT shall be made aware that there are procedures for compensation and treatment if he is injured/disabled by participating in the CLINICAL INVESTIGATION.

SUBJECTS shall be given the opportunity to enquire about the details of the CLINICAL INVESTIGATION. The information shall make clear to the SUBJECT that he remains free to refuse to participate or to withdraw from the CLINICAL INVESTIGATION at any stage without any sanction (see **5.6.10**).

SUBJECTS shall be allowed sufficient time to decide whether or not they wish to participate.

The SUBJECT shall be informed that his participation in the CLINICAL INVESTIGATION is confidential. He shall be made aware that the data relating to the study may be made available to third parties while maintaining anonymity.

5.6.10 A SUBJECT who wishes to withdraw from the CLINICAL INVESTIGATION shall be informed of the possible consequences of this withdrawal, by the CLINICAL INVESTIGATOR.

5.6.11 The CLINICAL INVESTIGATOR(S) shall obtain INFORMED CONSENT preferably in writing.

Following national policy, INFORMED CONSENT shall be documented either by the SUBJECT's dated signature or by the signature of an independent witness (see also **5.6.12**) who records the SUBJECT's assent.

NOTE. Obtaining INFORMED CONSENT from some categories of SUBJECTS raises particular ethical and legal issues which need special consideration (see the Declaration of Helsinki).

5.6.12 The CLINICAL INVESTIGATOR(S) shall document how INFORMED CONSENT will be obtained and recorded in emergency circumstances where the SUBJECT is unable to give it.

In the exceptional case when neither signed INFORMED CONSENT nor witnessed signed oral consent are possible, each case shall be documented and reported to the ETHICS COMMITTEE and the SPONSOR with the reasons, by the CLINICAL INVESTIGATOR(S).

5.6.13 The CLINICAL INVESTIGATOR(S) shall be responsible for submitting the CLINICAL INVESTIGATION PLAN for opinion or approval to an appropriate ETHICS COMMITTEE and shall transmit the results to the SPONSOR.

If not already included in the CLINICAL INVESTIGATION PLAN, the CLINICAL INVESTIGATOR(S) shall also provide the ETHICS COMMITTEE with at least information on the following:

a) an assessment of the scientific merit of the proposal, taking into account the preclinical data (see **5.2.1**);

b) possible effects on the health of the SUBJECTS;

c) possible hazards and the facilities available to deal with them;

d) the degree of discomfort or distress foreseen;

e) proposed method of supervision of the CLINICAL INVESTIGATION and the responsibilities of the CLINICAL INVESTIGATOR(S);

f) any monetary or other inducements, to be offered to the SUBJECTS;

g) arrangements to be made between the SPONSOR and the CLINICAL INVESTIGATOR(S);

h) the procedures for obtaining CONSENT from the SUBJECT or, where appropriate, their guardians or legal representatives;

i) provisions for compensation in the event of injury or death arising from participation in a CLINICAL INVESTIGATION and any insurance or indemnity to cover the liability of the CLINICAL INVESTIGATOR(S) and SPONSOR;

j) the methods of maintaining SUBJECT's confidentiality.

5.6.14 The CLINICAL INVESTIGATOR(S) shall inform the ETHICS COMMITTEE and ask for its opinion or approval regarding any significant change in the CLINICAL INVESTIGATION PLAN that has been approved by the SPONSOR, and the reasons for the change. The CLINICAL INVESTIGATOR(S) shall inform the ETHICS COMMITTEE of any severe ADVERSE DEVICE EFFECT.

5.6.15 The CLINICAL INVESTIGATOR(S) shall inform without undue delay the SPONSOR and the MONITOR (if applicable) about any severe ADVERSE EVENT, about all ADVERSE DEVICE EFFECTS, and provisions made.

5.6.16 The CLINICAL INVESTIGATOR(S) shall have primary responsibility for the accuracy, legibility and security of all CLINICAL INVESTIGATION data, documents and patient records both during and after the CLINICAL INVESTIGATION. The CASE REPORT FORM shall be signed by the CLINICAL INVESTIGATOR(S). Any alteration of the raw data shall be signed and dated, the original entry being retained for comparison.

5.6.17 The CLINICAL INVESTIGATOR(S) shall discuss with the SPONSOR any question of modification of the CLINICAL INVESTIGATION PLAN and shall obtain his written agreement (see **5.6.18**).

5.6.18 In any emergency situation the CLINICAL INVESTIGATOR(S) shall exercise his judgement to safeguard the SUBJECT's interests. In that case 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 and shall be reported to the SPONSOR.

5.6.19 The CLINICAL INVESTIGATOR(S) shall make sure that the CLINICAL INVESTIGATION PLAN is followed by all members of the investigation team, and by other parties involved in the execution of the CLINICAL INVESTIGATION. Any significant deviation shall be recorded.

5.6.20 The CLINICAL INVESTIGATOR(S) shall specify and document a procedure for recording ADVERSE EVENTS and ADVERSE DEVICE EFFECTS and reporting severe ADVERSE EFFECTS and all ADVERSE DEVICE EFFECTS to the SPONSOR.

5.6.21 The CLINICAL INVESTIGATOR(S) shall be responsible for the supervision and assignment of duties to the members of the CLINICAL INVESTIGATION team.

He shall be responsible for the measures needed to maintain confidentiality.

5.6.22 After the CLINICAL INVESTIGATION, the clinical records and investigation data shall be kept by the CLINICAL INVESTIGATOR(S) for an appropriate time and the SUBJECT's identity shall not be released to third parties without the SUBJECT's prior consent.

6 Presentation of the results

There shall be a FINAL REPORT of the CLINICAL INVESTIGATION.

The FINAL REPORT shall include a description of the methodology and design, data analysis together with a critical evaluation, a clinical appraisal signed by the SPONSOR and CLINICAL INVESTIGATOR(S), together with statistical analysis.

The FINAL REPORT shall take into account all data from each centre and for all enrolled SUBJECTS; no SUBJECT shall be identifiable either from the FINAL REPORT or published results.

This FINAL REPORT shall be signed by all CLINICAL INVESTIGATORS.

If any CLINICAL INVESTIGATOR does not sign the FINAL REPORT, a justification shall be provided.

Annex A (informative)

Bibliography

Directive on the approximation of the laws of the Member States relating to active implantable MEDICAL DEVICES (90/385/EEC — 20.07.1990).

Proposal of a directive of the Council on MEDICAL DEVICES (91/C 237/03 — JOCE 12.9.91 — presented to EEC on 30.08.91).

World Medical Association Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Assembly Helsinki, Finland, June 1964, amended by the 29th World Medical Assembly Tokyo, Japan, October 1975, 35th World Medical Assembly Venice, Italy, October 1983 and the 41st World Medical Assembly Hong Kong, September 1989.

National annex NA (informative)

Committees responsible

The United Kingdom participation in the preparation of this European Standard was entrusted by the Health Care Standards Policy Committee (HCC/-) to Technical Committee HCC/26, upon which the following bodies were represented:

Association of British Health-care Industries
Association of Clinical Pathologists
Association of Contact Lens Manufacturers
British Medical Association
British Orthopaedic Association
British Plastics Federation
British Society for Dental Research
British Surgical Trades Association
Department of Health
Department of Trade and Industry (Laboratory of the Government Chemist)
Disposable Hypodermic and Allied Equipment Manufacturers' Association (UK)
Electro Medical Trade Association Limited
Home Office
Medical Sterile Products Association
National Blood Transfusion Service
Plastics and Rubber Institute
Royal College of Pathologists
Royal College of Surgeons of England
Society for Tissue Viability
Sterilised Suture Manufacturers' Association
Surgical Dressings Manufacturers' Association

The following bodies were also represented in the drafting of the standard, through subcommittees and panels:

British Anaesthetic and Respiratory Equipment Manufacturers' Association
British Dental Association
Guild of Hospital Pharmacists
Royal Statistical Society
Society of Cardiothoracic Surgeons of Great Britain and Ireland

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