SLOVENSKI STANDARD
SIST EN 540:2000

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Klinične raziskave medicinskih pripomočkov za ljudi

Clinical investigation of medical devices for human subjects

Klinische Prüfung von medizinischen Geräten für Versuchspersonen

Investigation clinique des dispositifs médicaux sur les sujets humains

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CEN

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

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Contents list

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of an identical text or by endorsement, at the latest by December 1993, and conflicting national standards shall be withdrawn at the latest by December 1993.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.

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.

Clinical investigation of medical devices for human subjects

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 organisation, 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 purpose 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** : and 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 hospitalised, 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 co-ordinate 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 unauthorised 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 manufacturers 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 ar 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.