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Clinical investigation of medical devices for human subjects —

Part 2: Clinical investigation plans

*Investigation clinique des dispositifs médicaux pour sujets humains —
Partie 2: Plans d'investigation clinique*



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Foreword

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International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 14155-2 was prepared by the European Committee for Standardization (CEN) in collaboration with Technical Committee ISO/TC 194, *Biological evaluation of medical devices*, in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

Throughout the text of this document, read "...this European Standard..." to mean "...this International Standard...".

This first edition, together with the first edition of ISO 14155-1, cancels and replaces ISO 14155:1996, which has been technically revised.

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

- *Part 1: General requirements*
- *Part 2: Clinical investigation plans*

For the purposes of this part of ISO 14155, the CEN annex regarding fulfilment of European Council Directives has been removed.

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Foreword

This document (EN ISO 14155-2:2003) has been prepared by Technical Committee CEN/TC 258 "Clinical investigation of medical devices", the secretariat of which is held by AFNOR, in collaboration with Technical Committee ISO/TC 194 "Biological evaluation of medical devices".

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of an identical text or by endorsement, at the latest by November 2003, and conflicting national standards shall be withdrawn at the latest by November 2003.

This document has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association, and supports essential requirements of EU Directive(s).

Annex A is informative.

According to the CEN/CENELEC Internal Regulations, the national standards organizations of the following countries are bound to implement this European Standard: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal, Slovakia, Spain, Sweden, Switzerland and the United Kingdom.

Introduction

This standard is the second part of EN ISO 14155 "Clinical investigation of medical devices for human subjects", and should be read in conjunction with that standard.

The standard is intended to assist manufacturers, sponsors, monitors and clinical investigators in the design and conduct of clinical investigations. It is also intended to assist regulatory bodies and ethics committees in their roles of reviewing Clinical Investigation Plans (CIP). The CIP is a framework within which appropriate experience, insight, judgement, qualification and education need to be applied. The scientific rigour of a CIP can be verified and possibly improved by an independent review of the CIP.

1 Scope

This part of EN ISO 14155 provides requirements for the preparation of a Clinical Investigation Plan (CIP) for the clinical investigation of medical devices. The compilation of a CIP in accordance with the requirements of this standard and adherence to it will help in optimising the scientific validity and reproducibility of the results of a clinical investigation.

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

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 (including amendments).

EN ISO 14155-1:2003, *Clinical investigation of medical devices for human subjects — Part 1: General requirements. (ISO 14155-1:2001)*

3 Terms and definitions

For the purposes of this European Standard, the terms and definitions given in EN ISO 14155-1:2003 and the following apply.

3.1

end point - primary

principal indicator measured or determined to assess the primary objective of a clinical investigation

3.2

end point - secondary

indicator measured or determined in addition to the primary end-point to assess some other objective of a clinical investigation

3.3

point of enrolment

time at which, following recruitment, a subject has signed the informed consent form and is regarded as part of the study population

3.4

follow-up period

period of the clinical investigation after the application of the device under investigation in each subject during which the effects of the device are observed

3.5

recruitment

process of identifying subjects who may be suitable for enrolment into the clinical investigation

4 Requirements

4.1 General

All requirements of EN ISO 14155-1 apply.

4.2 Clinical Investigation Plan (CIP)

The CIP shall be a document developed by the sponsor and the clinical investigator(s). The CIP shall be designed in such a way as to optimise the scientific validity and reproducibility of the results of the study in accordance with current clinical knowledge and practice so as to fulfil the objectives of the investigation.

The CIP shall include the information specified in the subsequent clauses. Alternatively, if the required information is written in other documentation, for example the clinical investigator's brochure or the sponsor's standard operating procedures, such documentation shall be referenced in the CIP and shall be made available on request.

In the event of the sponsor deciding that any requirement given in 4.3 to 4.10 is not applicable, relevant or appropriate, a clear statement justifying the omission of the information specified shall be provided on each occasion.

4.3 General information

4.3.1 Identification of the clinical investigation plan

The CIP and any amended version shall state the title of the clinical investigation and its reference number. The CIP shall also include a version/issue number and date to ensure that it may be traced to the signatories (see 4.3.7). Each page of the CIP shall be referenced with the version number.

4.3.2 Clinical investigators, principal clinical investigator, co-ordinating clinical investigator, investigation centres/site(s)

The CIP shall state or refer to a list of the name(s), address(es), and professional position(s) of the clinical investigator(s), of the principal clinical investigator(s) and co-ordinating clinical investigator if appointed. The CIP shall document the name(s) and address(es) of the Institution(s) in which the clinical investigation will be conducted. Where it may affect the validity of the clinical investigation, the name(s) and address(es) of other establishments or persons involved in patient management, and associated testing and analysis shall be given.

4.3.3 Sponsor

The CIP shall state the name and address of the sponsor of the clinical investigation.

NOTE If the sponsor is not resident in the country (countries) in which the clinical investigation is to be carried out, the name and address of a representative in that country (those countries) may be required according to national or regional regulations.

4.3.4 Monitoring arrangements

The CIP shall state the monitoring arrangements to be followed during the investigation and the planned extent of source data verification.

4.3.5 Data and quality management

The CIP shall describe or refer to the procedures for database management, treatment of data, source data verification, data archiving, retention period and other aspects of quality assurance as appropriate.

4.3.6 An overall synopsis of the clinical investigation

The CIP shall provide a summary or overview of the clinical investigation.

NOTE It may be useful to include a flow chart showing the key stages of the clinical investigation or any other information that may be of value for the conduct of the investigation.

4.3.7 Approval and agreement to the clinical investigation plan

The sponsor, the co-ordinating investigator (if appointed) and the principal clinical investigator(s) in each centre shall agree to the CIP and any amendments and indicate their approval and agreement by signing and dating an appropriate document.

4.4 Identification and description of the medical device to be investigated

The CIP shall include or refer to a summary description of the device to be investigated and its intended purpose. The following information shall be given:

- a) the manufacturer of the device, its model or type number including software version and accessories, if any, to permit full identification and traceability. If this information is not known at the time the CIP is written, a description shall be given as to how traceability shall be achieved during and after the study;
- b) the intended purpose of the device as stated by the manufacturer including the clinical indications and contra-indications for use in the proposed study and the populations for which it is intended;
- c) a description of the device including any materials that will be in contact with tissues or body fluids. This shall include details of any medicinal products, human and/or animal tissues or their derivatives, or other biologically active substances;
- d) instructions for installation and use of the device including any necessary storage and handling requirements, preparation for use and any intended re-use (e.g. sterilization), any pre-use checks of safety and performance and any precautions to be taken after use, e.g. disposal;
- e) a summary of necessary training and experience needed for the use of the device under investigation;
- f) a description of the necessary medical or surgical procedures involved in the use of the device.

4.5 Preliminary investigations and justification of the study

4.5.1 Literature review

The CIP shall contain a critical review of the relevant scientific literature and/or unpublished data and reports together with a list of the literature reviewed. The conclusions from this review shall justify the design of the proposed investigation. The review shall be relevant to the intended purpose of the device to be investigated and the proposed method of use. It should also help in the identification of relevant end-points and confounding factors that should be considered, and the choice and justification of control methods.

NOTE Guidance on literature review and appraisal is provided in EN ISO 14155 – 1:2003, annex A.

4.5.2 Preclinical testing

The CIP shall summarise the preclinical testing that has been performed on the device to be investigated to justify its use in human subjects, together with an evaluation of the results of such testing. The summary shall include or refer to pre-clinical experimental data including, where applicable, the results of design calculations, in vitro tests, mechanical and electrical tests, reliability checks and the validation of software relating to the function of the device. Also to be included are the results of any performance tests, ex vivo testing, biological testing and/or safety tests in animals, including the relevance of tests and the timescale of such tests.

NOTE Guidance on the biological evaluation of medical devices is given in EN ISO 10993 [6].

4.5.3 Previous clinical experience

The CIP shall summarise the results from previous clinical investigations and clinical usage that are relevant to the proposed investigation and/or relevant experience with the device, or devices with similar features, including that relating to other indications for use of the device to be investigated. This shall include an analysis of adverse device effects and any history of modification or recall.

4.5.4 Device risk analysis and risk assessment

The CIP shall include the results of a risk analysis and assessment. This shall describe the balance of anticipated clinical benefit against the risks associated with the device itself and the procedures involved in its use, as identified by the risk assessment. Possible interactions with concurrent medical interventions shall be listed, together with a statement of the anticipated clinical benefit.

This shall include an analysis of adverse device effects and any history of modification or recall in relation to safety and clinical performance in relation to both the device under investigation and devices described in 4.5.3.

NOTE The process of risk analysis and risk assessment is described in EN ISO 14971 [1].

4.6 Objectives of the clinical investigation

The CIP shall identify clearly the hypothesis and objectives, primary and secondary, of the clinical investigation and the populations for which the device is to be used in the investigation. These shall include as appropriate the particular:

- a) claims and intended performance of the device that are to be verified;

NOTE 1 These may include claims implicit in the intended purpose of the device as well as those made explicit in labelling, instructions for use or promotional material.

NOTE 2 It should be clearly stated whether or not the determinations of the long-term effects are part of the objectives of the current clinical investigation (see also 4.7 p)).

- b) risks and foreseeable adverse device effects that are to be assessed;
- c) specific hypotheses to be accepted or rejected by statistical data from the clinical investigation.

4.7 Design of the clinical investigation

NOTE The scientific integrity of the clinical investigation and the credibility of the data from the investigation depend substantially on its design.

The CIP shall provide the following information:

- a) a description of the type of investigation to be performed (e.g. comparative double-blind, parallel design, with or without a control group) with rationale for the choice;
- b) a discussion of the controls;
- c) a description of the measures to be taken to minimise or avoid bias;
- d) the primary and secondary end-points, with rationale for their selection;
- e) the variables to be measured with rationale for selecting these to demonstrate the achievement of the end-points;
- f) the methods and timing for assessing, recording, and analysing variables;

- g) the test equipment to be used for the assessment of study variables and the arrangements for monitoring the maintenance and calibration;
- h) the inclusion criteria for subject selection;
- i) the exclusion criteria for subject selection;
- j) the point of enrolment (see 3.3);
- k) a detailed description of the procedure(s) that the subjects undergo during the investigation, as well as a list of any other device or medication to be used either during the application of the device or during the follow-up period;
- l) the criteria and procedures for withdrawal and discontinuation of subjects from the investigation and how they are accounted for, together with procedures for the follow-up of these subjects, if possible (see also clauses 4.8 f) and 4.9).
- m) the number of subjects required to be included in the clinical investigation together with the estimated time needed to include this number and the number of devices to be used and a justification for these figures, (see also 4.8 a)). In multi-centre investigations, the minimum number of subjects to be included for each centre shall be specified and justified. Where it may affect the validity of the study results, considerations shall be made on the minimum and maximum number of subjects to be included in each centre;

NOTE The period for enrolment should not be so great as to confound comparison of data relating to subjects enrolled at different times.

- n) the procedures for recording and investigating adverse events, adverse device effects and/or outcomes;
- o) the period of use of the device or its control and its follow-up period in a particular subject within the clinical investigation and the justification for this;

NOTE The follow-up period of the clinical investigation should permit the demonstration of performance over a period of time sufficient to represent a realistic test of the performance of the device and allow identification and risk assessment of any associated adverse device effects over that period.

- p) any known or foreseeable factors that may compromise outcomes or the interpretation of results. These may include, for example, subject baseline characteristics, concomitant medication, the use of other devices, or subject-related factors such as age, gender or lifestyle. The methods for addressing these factors in the investigation, for example by subject selection, study design (such as stratified randomisation) or by statistical analysis shall be described.

4.8 Statistical considerations

The CIP shall include a description and justification of hypothesis and statistical design, method and the analytical procedures to be used. This shall include:

- a) the reasons for the choice of sample size, including the level of significance to be used, the power of the trial and expected drop-out rates, together with the justification for these aspects;

NOTE Special reasoning and sample sizes may apply for the early phases of clinical experience e.g. feasibility studies.

- b) pass/fail criteria to be applied to the results of the investigation;;
- c) provision for an interim analysis, where applicable, and the criteria for the termination of the investigation on statistical grounds;
- d) procedures for reporting any deviation(s) from the original statistical plan; (Any deviation(s) from the original statistical plan shall be described and justified in the CIP or final report, as appropriate);
- e) the criteria for the selection of subjects to be included in the analyses with justification;

- f) the procedures for accounting for all data, together with treatment of missing, unused or spurious data, including drop-outs and withdrawals, together with a justification for excluding particular information from the testing of the hypothesis, if relevant.

4.9 Deviations from the clinical investigation plan

Any deviation from the CIP shall be recorded together with an explanation for the deviation. Deviations shall be reported to the sponsor who is responsible for analysing them and assessing their significance.

The reasons for withdrawal and discontinuation of any subject from the investigation shall be recorded. If such discontinuation is because of problems of safety or lack of effectiveness, that subject shall still be followed up in the investigation, if possible;

NOTE When relevant, ethics committees, competent authorities or the appropriate regulatory bodies should be informed.

4.10 Amendments to the clinical investigation plan

All amendments to the CIP shall be agreed between the sponsor and the clinical investigator(s) and be recorded with a justification for the amendments. Deviations should be reviewed to determine the need to amend the CIP or to terminate the investigation.

However, when there are changes to the initial list of clinical investigators and centres (4.3.2) this list will not be formally updated by amendments at each change; the sponsor will maintain an updated list which will be available on request. The definitive list of all centres and investigators shall be provided with the final report.

NOTE When relevant, ethics committees, competent authorities or the appropriate regulatory bodies should be informed.

4.11 Adverse events and adverse device effects

The CIP shall include:

- a) emergency contact details for reporting serious adverse events and serious adverse device effects;
- b) details of foreseeable adverse events and adverse device effects e.g. serious/non-serious, device related/non-device related, their likely incidence and the methods to be used for their management;
- c) details of the procedures for reporting all adverse events and adverse device effects to the sponsor, ethics committee and regulatory authority, in accordance with applicable regulations, including a specification of those types of events, device related and non-device related, that shall be reported and the timing for such reporting.

4.12 Early termination or suspension of the investigation

The CIP shall specify the criteria and arrangements for early termination or suspension of the investigation. This may apply to the whole clinical investigation or simply to one or more sites.

If the clinical investigation involves blinding techniques, the criteria for access to and breaking the code shall be stated.

Where appropriate, the CIP shall specify the subject follow-up required following an early termination or suspension.

4.13 Publication policy

The CIP shall specify whether the results of the investigation will be submitted for publication or the extent to which and conditions under which the results of the clinical investigation will be offered for publication.

NOTE It is highly desirable that all results should be offered for publication in scientific journals.

4.14 Case Report Forms

The Case Report Form (CRF) provides the practical means to implement the CIP by way of a list of all the information to be recorded. The CRF shall reflect the contents of the CIP and make clear the version number of the CIP to which it relates. The CRF and any amendment to it shall bear a version number and each page shall be identifiable by the study number and identification of the subject whose data the CRF records. When it is necessary to amend the CRF, the sponsor shall review the CIP to determine whether or not an amendment to the CIP is necessary.

NOTE Guidance on the content of a CRF is given in annex A.

Annex A (informative)

Case Report Forms

Case Report Forms (CRF) are established to implement the CIP and to facilitate subject observation and to record subject and device data during the clinical investigation according to the CIP. They can exist as printed, optical, or electronic documents. The CRF shall reflect the CIP and take account of the nature of the device under investigation. In establishing a CRF, the following items should be considered:

- a) the date, place and identification of the investigation, including the version number of the CIP;
- b) identification of the subject, date of enrolment, demographic data;
- c) identification of the medical device by lot number and/or serial number;
- d) medical diagnosis for which the subject is to be treated with the device to be investigated together with any concomitant illness;
- e) subject compliance information for concurrent procedures measures and for any emergency;
- f) relevant previous medication and/or procedures;
- g) subject baseline characteristics;
- h) concomitant medication and/or procedures;
- i) compliance with the inclusion/exclusion criteria;
- j) dated clinical and non-clinical findings according to the CIP;
- k) procedural data;
- l) subject assessment during the use of the device and follow-up with dates;
- m) reported adverse events and adverse device effects with dates;
- n) date of the end of follow-up;
- o) signature(s) of the clinical investigator(s) at the completion of follow-up.

Bibliography

- [1] EN ISO 14971, *Medical devices – Application of risk management to medical devices. (ISO 14971:2000)*
- [2] Essential Principles – Global Harmonization Task Force, 1999.
- [3] EU Medical Devices Directive 90/385/EEC Active implantable medical devices.
- [4] EU Medical Devices Directive 93/42/EEC Medical devices.
- [5] Guideline for Good Clinical Practice. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), 1996.
- [6] EN ISO 10993 (all parts), *Biological evaluation of medical devices.*

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