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INTERNATIONAL ORGANIZATION FOR STANDARDIZATION • МЕЖДУНАРОДНАЯ ОРГАНИЗАЦИЯ ПО СТАНДАРТИЗАЦИИ • ORGANISATION INTERNATIONALE DE NORMALISATION

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

ICS 11.100

ISO/CEN PARALLEL ENQUIRY

This draft International Standard is a draft European Standard developed within the European Committee for Standardization (CEN) in accordance with subclause 5.2 of the Vienna Agreement. The document has been transmitted by CEN to ISO for circulation for ISO member body voting in parallel with CEN enquiry. Comments received from ISO member bodies, including those from non-CEN members, will be considered by the appropriate CEN technical body. **Accordingly, ISO member bodies who are not CEN members are requested to send *a copy* of their comments on this DIS directly to CEN/TC 258** (AFNOR, Avenue Francis de Pressensé, F-93571 Saint Denis La Plaine Cedex) **as well as returning their vote and comments in the normal way to the ISO Central Secretariat.** Should this DIS be accepted, a final draft, established on the basis of comments received, will be submitted to a parallel two-month FDIS vote in ISO and formal vote in CEN.

Contents

Foreword

The text of prEN ISO 14155-2:2001 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 document is currently submitted to the parallel Enquiry.

This European Standard 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).

For relationship with EU Directive(s), see informative Annex ZA, which is an integral part of this standard.

Introduction

This standard is the second part of EN ISO 14155, Clinical Investigation of Medical Devices for Human Subjects and shall 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.

1 Scope

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

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

NOTE 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 possible improved by an independent review of the CIP.

2 Normative references

The following normative documents contain provisions which, through reference in this text, constitute provisions of this European Standard. For dated references, subsequent amendments to, or revisions of, any of these publications do not apply. However, parties to agreements based on this European Standard are encouraged to investigate the possibility of applying the most recent editions of the normative documents indicated below. For undated references, the latest edition of the normative document referred to applies. Members of CEN and CENELEC maintain registers of currently valid European Sandards (including amendments).

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

3 Terms and definitions

For the purposes of this part of prEN ISO 14155, the terms and definitions given in prEN ISO 14155-1:2001 and the following apply.

3.1
end point - primary
principal indicator measured to assess the primary objective of a clinical investigation

3.2
end point - secondary
indicator measured 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 prEN ISO 14155-1 apply.

4.2 Clinical Investigation Plan

The Clinical Investigation Plan shall be a document agreed between 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.

Where the Sponsor decides 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 for 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, Clinical Investigation Centres/site(s)

The CIP shall state the name(s), address(es), and professional position(s) of the Clinical Investigator(s), and 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 regulation.

4.3.4 Monitoring arrangements

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

4.3.5 Data and quality management

The CIP shall describe the procedures for database management, treatment of data, source data verification, data archiving and 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.

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, all Clinical Investigator(s), and other parties having a significant role in the clinical investigation shall agree to the CIP and any amendments (see 4.2, 4.3.1 and 4.9) and indicate their agreement by signing and dating a 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 the 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 to be investigated;

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 together with a list of the literature considered. 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 its method of use. It should also help in the identification of relevant endpoints 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 prEN ISO 14155 - 1.

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 the results of design calculations, in vitro tests, mechanical and electrical tests, reliability checks and the validation of any software. Also to be included are the results of any performance tests, ex vivo testing, toxicological testing and/or safety tests in animals, including the relevance of tests and the timescale of tests.

4.5.3 Previous clinical experience

The CIP shall summarise the results from previous clinical investigations that are relevant to the proposed investigation and/or relevant experience of the device, including that relating to other indications for use of the device to be investigated.

4.5.4 Device risk analysis

The CIP shall summarise the results of a risk analysis on the device to be investigated that takes into account the risks associated with the device itself and the procedures involved in its use and possible interactions with concurrent medical interventions.

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. This 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 l)).

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 specify the following:

a) a description of the type of investigation to be performed (e.g. comparative double-blind, parallel design, any control group) with rationale for the choice;

b) a discussion of the control population or procedures, and the procedures allocation scheme, if applicable;

c) a description of the measures to be taken to minimise or avoid bias;

d) the primary and secondary endpoints, with rationale for their selection;

e) the variables to be measured with rationale for selecting these to demonstrate the achievement of the endpoints;

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 at which subjects are considered to be enrolled in the investigation;

k) a detailed description of the procedure(s) the subjects will be subjected to during the investigation, as well as any other device or medication to be used either during the application of the device or during the follow-up period;

l) the criteria for withdrawal of subjects from the investigation and how they are accounted for (see also Clauses 4.8 f) and 4.9). These criteria shall be defined and explained and such explanation shall include when and how subjects may be withdrawn from the analysis of the clinical investigation, the type and timing of the data to be collected from these subjects and how these subjects will be followed-up;

m) the reason for 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;

n) 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. 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.

o) the procedures for recording and investigating adverse events, adverse device effects and/or outcomes;

p) the period of use of the device 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.

q) any known or foreseeable factors that may compromise outcomes or the interpretation of results. This 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 statistical design and hypothesis, 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, possible differences in the incidence and prevalence of investigation variables in the study population 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, if appropriate, and the justification for these, e.g. what number of devices or percentage of devices would need to succeed in order to fulfil the objectives 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 and amendments to the Clinical Investigation Plan

All deviations 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.

NOTE 1 Deviations should be reviewed to determine the need to amend the CIP or to terminate the investigation.

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.

NOTE 2 Where relevant, Ethics Committees, Competent Authorities or the appropriate regulatory bodies should be informed.

4.10 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.

4.11 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 just 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.

4.12 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.

4.13 Case report forms

The Case Report Form (CRF) shall reflect the contents of the CIP and make clear the version number of the CIP to which it relates. The CRF itself 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. Where 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 facilitate subject observation and to record subject and device data during the clinical investigation according to the Clinical Investigation Plan. They can exist as a printed, optical, or electronic document. In establishing a CRF, the following items should be considered. The CRF shall reflect the CIP and take account of the nature of the device under investigation.

The CRF may include one or more of the following:

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) 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.