CEN TC 258 Committee Enquiry/ISO TC 194 Committee Draft

EN ISO 14155

CLINICAL INVESTIGATION OF MEDICAL DEVICES FOR HUMAN SUBJECTS

PART 2: CLINICAL INVESTIGATION PLANS

0 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.

European Foreword

This standard has been prepared under a mandate from the European Commission and is drafted in support of Annex VII of Directive 90/385 and of Annex X of Directive 93/42.
CONTENTS

0 Introduction ....................................................................................................................... 1
1 Scope .................................................................................................................................. 3
2 Normative references ........................................................................................................ 3
3 Terms and definitions ....................................................................................................... 4
4 Requirements ................................................................................................................... 5
4.1 General ............................................................................................................................ 5
4.2 General information ....................................................................................................... 6
4.3 Identification and description of the medical device to be investigated ....................... 8
4.4 Preliminary investigations and justification of the study .......................................... 9
4.5 Objectives of the Clinical Investigation ...................................................................... 10
4.6 Design of the Clinical Investigation .......................................................................... 11
4.7 Statistical considerations ............................................................................................. 13
4.8 Deviations from and amendments to the Clinical Investigation Plan ....................... 14
4.9 Adverse events ............................................................................................................. 14
4.10 Early termination or suspension of the investigation ............................................ 14
4.11 Publication policy ....................................................................................................... 15
4.12 Case report forms ...................................................................................................... 15
INFORMATIVE ANNEX ....................................................................................................... 15
Case Report Form ............................................................................................................... 15
Bibliography ...................................................................................................................... 16
1 Scope

This part of 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 only be judged by independent review of the CIP.

2 Normative references

The following normative documents contain provisions that, through reference in this text, constitute provisions of this part of ISO 14155. For dated references, subsequent amendments to, or revisions of, any of these publications do not apply. However, parties to agreements based on this part of ISO 14155 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 ISO, CEN and IEC maintain registers of currently valid International Standards.

EN ISO 14155 – 1 : 20XX, Clinical investigation of medical devices for human subjects.
3 Terms and definitions

For the purposes of this part of ISO 14155, the definitions given in EN ISO 14155 – 1 and the following apply.

3.1 clinical investigation plan (CIP)

document(s) that state the rationale, objectives, design and proposed analyses, methodology, conduct and record keeping of the clinical investigation.

3.2 duration of the study

period of investigation for each individual subject from the time of enrolment until the end of follow-up.

3.3 end point – primary

principal indicator measured in a subject or biological sample to assess the safety, efficacy or other objective of a clinical investigation.

3.4 End point – secondary

indicator measured in a subject or biological sample in addition to the primary end-point to assess some other objective of a clinical investigation.
3.5

Follow-up
period of the clinical investigation after the use of the device under investigation in each subject during which the effects of the device are observed.

3.7

Recruitment
process whereby the clinical investigator(s) uses inclusion and exclusion criteria and the informed consent process to enrol appropriate subjects into the clinical investigation.

3.8

Enrolment
point at which following recruitment a subject is considered to be enrolled in the clinical investigation.

3.9

Withdrawal of subjects
process whereby subjects may removed from the clinical investigation having been lost to follow-up or because of some adverse event, as decided by the sponsor.

4. Requirements

4.1 General

4.1.1 All requirements of EN ISO 14155 – 1 apply. In addition, the following sub-clause applies.

4.1.2 The Clinical Investigation Plan shall be a document agreed between the Sponsor and the Clinical Investigators. 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 in determining the safety and performance of a device, including undesirable side effects.

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 may be referenced in the CIP and shall be made available on request.

Where the Sponsor decides that any requirement given in Clauses 4.2 to 4.9 is not applicable, relevant or appropriate, a clear statement justifying the omission of the information specified shall be provided for each occasion.

4.2 General information

4.2.1 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 Clause 4.2.5). Each page of the CIP shall be referenced with a footnote stating the version number.

4.2.2 Investigators, Principal Investigator, Investigation Centres

The requirements of EN ISO 14155-1 Clauses 5.4, 6.3 and 10 shall apply. In addition, the CIP shall state the name(s), address(es), and professional position(s) of the Clinical Investigator(s) and of the principal clinical investigator if there is one. 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.

4.2.3 Sponsor

EN ISO 14155–1 Clause 8 shall apply. In addition, 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(ies) in which the Clinical Investigation is to be carried out, but has the name and address of a representative in that country may be required according to national or regional regulation.

4.2.4 Monitoring arrangements

The CIP shall state the monitoring arrangements to be used during the investigation and EN ISO 14155 – 1 Clause 9 shall apply. In addition, the CIP shall name the monitors (if known) appointed by the Sponsor together with details of the arrangements made to allow investigators to contact monitors and in particular details of contact point(s) in case of emergencies.

4.2.5 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. Any deviation(s) from the original procedures shall be described and justified in the CIP or final report, as appropriate. In addition there shall be a written agreement, either in the CIP or another document, that specifies that the investigators and their institutions will permit monitoring, audits, ethics committee review and regulatory inspections that are related to the clinical
investigation and that will provide direct access to the source data and documentation, provided the subjects consent where appropriate.

4.2.6 An overall summary or overview of the clinical investigation

The CIP shall provide a summary or overview. 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.

4.2.7 Approval and agreement to the Clinical Investigation Plan

The Sponsor and all Clinical Investigator(s) shall agree to the CIP and any amendments (see Clause 4.2.1 and 4.8.2) and indicate their approval by signing and dating a document.

4.3 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:

4.3.1 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.

4.3.2 The purpose of the device intended by the manufacturer including the clinical indications for use in the proposed study and the populations for which it is intended.

4.3.3 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.
4.3.4 Instructions for use of the device including any necessary storage and handling requirements, preparation for use and eventual 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.

4.3.5 A summary of necessary training and experience needed for the use of the device to be investigated.

4.3.6 A description of the necessary medical or surgical procedures involved in the use of the device.

4.4 Preliminary investigations and justification of the study

4.4.1 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 need for a clinical investigation and support 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 have to be considered, and the choice and justification of control treatments.

NOTE: Guidance on literature review and appraisal is provided in EN ISO 14155-1.
4.4.2 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, with justification for the choice of animal model used, the relevance of tests and the timescale of tests.

4.4.3 Previous clinical experience

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

4.4.4 Device risk analysis and management

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.

4.5 Objectives of the Clinical Investigation

The CIP shall identify clearly the objectives of the clinical investigation and the populations to be studied for which the device is to be used. This shall include as appropriate the particular:

a) Essential Requirements of the relevant Directive or Essential Principles against which compliance is to be verified.

b) claims and intended performance of the device that are to be verified.
NOTE: 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: 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 4.6.12).

c) risks and foreseeable adverse device events that are to be assessed.

d) any other specific hypotheses to be confirmed or refuted by the clinical investigation.

4.6 Design of the Clinical Investigation

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

The CIP shall specify the following:

4.6.1 a statement that clearly justifies the design of the investigation in the context of current clinical knowledge and practice;

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

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

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

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

4.6.6 the methods and timing for assessing, recording, and analysing variables, with rationale;

4.6.7 the test equipment to be used for the assessment of study variables and the arrangements for monitoring, maintenance and calibration;
4.6.8 pass/fail criteria to be applied to the results of the investigation, if appropriate. E.g. what number of devices or percentage of devices would need to succeed in order to fulfil the objectives of the investigation;

4.6.9 the inclusion criteria for subject selection, together with a description of the measurement methods to be applied;

4.6.10 the exclusion criteria for subject selection, together with a description of the measurement methods to be applied;

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

4.6.12 the criteria for withdrawal of subjects from the investigation (see also Clause 4.8). These criteria shall be defined and explained and such explanation shall include when and how subjects may be withdrawn from the clinical investigation, the type and timing of the data to be collected from these subjects and how these subjects will be subjected to follow-up;

4.6.13 the number of subjects required to be included in the clinical investigation together with the estimated time needed to enrol this number and the number of devices to be used and a justification for these figures. (See also 4.7.1). In multi-centre investigations, the minimum number of subjects to be enrolled for each centre shall be specified. Where it may affect the validity of the study results, considerations should be made on the minimum and maximum number of subjects to be enrolled 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;

4.6.14 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 duration of the clinical investigation should permit the demonstration of performance over a period of time sufficient to represent a realistic test of the device and allow identification and risk assessment of any associated adverse events over that period.
4.6.15 any known or foreseeable factors that may compromise outcomes or the interpretation of results. This may include for example subject baseline characteristics, concomitant medication or the use of other devices, subject related factors such as age, gender or lifestyle;

4.7 Statistical considerations

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

4.7.1 the reasons for the choice of sample size shall be stated, including the level of significance to be used, the power of the trial, possible differences in the incidence 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.

4.7.2 provision for an interim analysis, where applicable, and the criteria for the termination of the investigation on statistical grounds;

4.7.3 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);

4.7.4 the criteria for the selection of subjects to be included in the analyses with justification (e.g. full set analyses or protocol analyses);

4.7.5 the procedures for accounting for all data, together with treatment of missing, unused or spurious data, together with a justification for excluding particular information from the testing of the hypothesis.
4.8 Deviations from and amendments to the Clinical Investigation Plan

4.8.1 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. (See also EN ISO 14155 - 1 Clause 8).

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

4.8.2 All amendments to the CIP shall be agreed between the Sponsor and the Clinical Investigator and be recorded with a justification for the amendments.

4.9 Adverse events

4.9.1 The CIP shall include emergency contact details for reporting adverse events.

4.9.2 The CIP shall include details of foreseeable adverse events (e.g. serious/non-serious or device related/non-device related), their likely incidence and the methods to be used for their management.

4.9.3 Details of the procedures for reporting all adverse events to the sponsor, ethics committee and regulatory authority, in accordance with applicable regulations, including a specification of those types of events (device and non-device related) that shall be reported and the timing for such reporting.

4.10 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.

4.11 Publication policy

The CIP shall specify 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.

4.12 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 shall bear a version number. 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.

Guidance on the content of a CRF is given in the Informative Annex.

INFORMATIVE ANNEX

Case Report Form

Case Report Forms (CRF) are established to facilitate patient observation and to document patient 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 should include the following information as a minimum:

the date, place and identification of the investigation;
identification of the subject, demographic data;
identification of the medical device by lot number;
medical diagnosis of the subject;
subject compliance information for concurrent treatment measures and for any emergency;
clinical indication for which the medical device is used;
previous medication and/or treatment;
subject baseline characteristics;
concomitant medication and/or treatment;
adherence to the inclusion/exclusion criteria;
examination and laboratory findings according to the CIP;
subject assessment during the use of the device and follow-up;
reported adverse events.

Bibliography

See also EN ISO 14155-1, Bibliography.


