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ISO 14155

Clinical investigation of medical devices for human subjects — Good clinical practice

Investigation clinique des dispositifs médicaux pour sujets humains — Bonne pratique clinique

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ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Email: copyright@iso.org
Website: www.iso.org

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO document should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

ISO draws attention to the possibility that the implementation of this document may involve the use of (a) patent(s). ISO takes no position concerning the evidence, validity or applicability of any claimed patent rights in respect thereof. As of the date of publication of this document, ISO had not received notice of (a) patent(s) which may be required to implement this document. However, implementers are cautioned that this may not represent the latest information, which may be obtained from the patent database available at www.iso.org/patents. ISO shall not be held responsible for identifying any or all such patent rights.

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For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 194, *Biological and clinical evaluation of medical devices*, in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 206, *Biological and clinical evaluation of medical devices*, in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This fourth edition cancels and replaces the third edition (ISO 14155:2020), which has been technically revised.

The main changes are as follows:

— changed definition of clinical performance (3.12);

— clarified deviations from eligibility criteria not being permitted but subject to CIP amendment (see 5.6.4);

— clarified informed consent to be obtained where applicable from subject's legally designated representative (see 5.8.1);

— clarified subject must be given opportunity to discuss participation with others e.g. family members (see 5.8.2);

— clarified risk management by making clear distinction between risks related to the use of the device and risks related to the procedures required by the CIP which are not part of routine clinical practice (see 6.2.1);

— included required assessment of residual risks (see 6.2.2);

— corrected reference to risks related to the use of the investigational device (see 6.2.1, 7.4.4, 8.2, Annex F, Annex H and 3.2);

— added requirements (previously in Annex A) to 6.4;

— added requirement for data monitoring committee to confirm conditions for suspending or stopping the clinical investigation (see 6.11);

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— included new section on clinical events committee (see 3.8, 6.12 and Clause A.14);

— clarified situations of reduced adverse events reporting requirements (see 7.4.2);

— included management of risks related to clinical procedures required by the CIP (see 7.4.5);

— clarified process of suspension or premature termination of the clinical investigation also in line with updated 7.4.4 and Figure H.1 (see 8.2);

— updated procedure section in CIP with methods and timing for assessing, recording and analysing variables and added requirement for calibration of equipment (see A.6.4);

— clarified requirements for non-inferiority margins and missing data (see Clause A.7);

— added requirement to justify absence of DMC involvement (see Clause A.14);

— added requirement for subject follow up and continued care to include those different from normal practice (see Clause A.16);

— clarified aspects of local representative for better harmonisation with national regulatory requirements (see 9.2.1);

— included requirement for implant card (see 9.2.2);

— moved general requirements to 6.4 on objective and study design (see Clause A.5);

— updated adverse events categorization clarifying terminology in Figure F.1;

— updated Annex H in line with 6.2.1 and updated Figure H.1;

— included principles of estimands and their attributes (see 6.4, Clause A.5, Clause A.6, Clause A.7 and Annex K);

— included precautions (see Clause B.5), information on training on the use of investigational device (see Clause B.2), and in-silico tests (see Clause B.3).

— added an adverse event associated with a device deficiency – both Figure F.1 and Figure F.2 now apply.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

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Introduction

For the purpose of this document, the use of the term compliance is applied when compliance to clinical investigation requirements and good clinical practice as per this document is required. In case of requirements outlined in regulatory documents or other standards the term ‘conformance with’ is applied.

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Clinical investigation of medical devices for human subjects — Good clinical practice

1 Scope

This document specifies good clinical practice (GCP) for the design, conduct, recording and reporting of clinical investigations carried out in human subjects to assess the clinical performance or effectiveness and safety of medical devices.

For post-market clinical investigations, the principles set forth in this document are intended to be followed as far as relevant, considering the nature of the clinical investigation (see Annex I).

This document specifies the general requirements intended to

— protect the rights, safety and well-being of human subjects, users or other persons,

— ensure the scientific conduct of the clinical investigation and the credibility of the clinical investigation results,

— define the responsibilities of the sponsor and principal investigator, and

— assist sponsors, investigators, ethics committees, regulatory authorities and other bodies involved in the conformity assessment of medical devices.

Other standards or national requirements can also apply to the investigational device(s) under consideration or the clinical investigation(s).

NOTE For Software as a Medical Device (SaMD), where appropriate, demonstration of the analytical validity (the SaMD's output is accurate for a given input), the scientific validity (the SaMD's output is associated to the intended clinical condition/physiological state), and clinical performance (the SaMD's output yields a clinically meaningful association to the target use) of the SaMD, the requirements of this document apply as far as relevant (see Reference [5]). Justifications for exemptions from this document can consider the uniqueness of indirect contact between subjects and the SaMD.

This document does not apply to in vitro diagnostic medical devices. However, there can be situations, dependent on the device and national or regional requirements, where users of this document can consider whether either specific sections or requirements of this document, or both, can be applicable.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 14971, *Medical devices — Application of risk management to medical devices*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

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3.1
adverse device effect
ADE
adverse event (3.2) related to the use of an *investigational medical device* (3.30)

Note 1 to entry: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation or any *malfunction* (3.34) of the investigational medical device.

Note 2 to entry: This definition includes any event resulting from *use error* (3.53) or from intentional misuse of the investigational medical device.

Note 3 to entry: This definition applies to *'comparator'* (3.13) if the comparator is a medical device.

3.2
adverse event
AE
untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including abnormal laboratory findings) in *subjects* (3.51), users or other persons, whether or not related to the use of the *investigational medical device* (3.30) and whether anticipated or unanticipated

Note 1 to entry: This definition includes events related to the use of the investigational medical device or the *comparator* (3.13) and the clinical procedure(s) required by the *clinical investigation plan* (*CIP*) (3.10) that are outside to routine clinical practice but not related to the use of the device.

Note 2 to entry: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

3.3
audit
systematic examination of activities and documents related to a *clinical investigation* (3.9) performed by (an) *independent* (3.27) person(s), to determine whether these activities were conducted, and the data recorded, analysed and accurately reported, in compliance with the *clinical investigation plan* (*CIP*) (3.10), standard operating procedures, this document and in conformance with applicable regulatory requirements

3.4
audit trail
documentation that allows reconstruction of the course of events

3.5
blinding
masking
procedure in which one or more parties to the *clinical investigation* (3.9) are kept unaware of the treatment assignment(s)

Note 1 to entry: Single blinding usually refers to the *subject(s)* (3.51) being unaware of the treatment assignment(s). Double blinding usually refers to the subject(s), *investigator(s)* (3.31), monitor and, in some cases, centralized assessors being unaware of the treatment assignment(s).

Note 2 to entry: A clinical investigation is termed 'observer blind', if at least the *primary endpoint(s)* (3.23) is/are assessed without knowledge of whether an *investigational medical device* (3.30) or *comparator* (3.13) has been used to treat a subject.

3.6
case report form
CRF
set of printed, optical or electronic documents for each *subject* (3.51) on which information to be reported to the *sponsor* (3.50) is recorded, as required by the *clinical investigation plan* (*CIP*) (3.10)

3.7
certified copy
copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information including data that describe the context, content and structure, as the original

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3.8
clinical events committee
CEC
central events committee
clinical adjudication committee
CAC
endpoint adjudication committee
EAC
independent (3.27) committee of clinical experts that can be established by the *sponsor* (3.50) to ensure consistent event assessment across participating centres and mitigate inadequate reporting risks

3.9
clinical investigation
clinical trial
clinical study
systematic investigation in one or more human *subjects* (3.51), undertaken to assess the *clinical performance* (3.12), *effectiveness* (3.20) or safety of a *medical device* (3.35)

3.10
clinical investigation plan
CIP
protocol
document that states the rationale, *objectives* (3.38), design and pre-specified analysis, methodology, organization, *monitoring* (3.36), conduct and record-keeping of the *clinical investigation* (3.9)

Note 1 to entry: As the term "protocol" has many different meanings, some not related to clinical investigation, and as these can differ from country to country, the term CIP is used in this document.

3.11
clinical investigation report
clinical study report
document describing the design, conduct, statistical analysis and results of a *clinical investigation* (3.9)

3.12
clinical performance
ability of a *medical device* (3.35), resulting from any direct or indirect medical effects which stem from its technical or functional characteristics, including diagnostic characteristics, to achieve its intended purpose as claimed by the manufacturer, thereby leading to a clinical benefit for *subject(s)* (3.51), when used as intended by the manufacturer

Note 1 to entry: Clinical performance can be defined under national regulations.

Note 2 to entry: Not all clinical investigations have clinical benefits to subjects e.g. healthy volunteers, clinical investigations only gathering data etc.

3.13
comparator
medical device (3.35), therapy (e.g. active treatment, routine clinical practice), placebo, sham or no treatment, used in the *control group* (3.15) in a *clinical investigation* (3.9)

3.14
contract research organization
CRO
person or organization contracted by the *sponsor* (3.50) to perform one or more of the sponsor's clinical investigation-related duties and functions

3.15
control group
group of *subjects* (3.51) that receives the *comparator* (3.13)

Note 1 to entry: A control group may be concurrent or historical, or subjects may serve as their own control.

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3.16
coordinating investigator
national investigator
global investigator
investigator (3.31) who is appointed by the *sponsor* (3.50) to assist in coordinating the work in a multicentre *clinical investigation* (3.9)

3.17
data monitoring committee
DMC
data and safety monitoring board
DSMB
independent data monitoring committee
IDMC
data and safety monitoring committee
DSMC
independent (3.27) committee that can be established by the *sponsor* (3.50) to assess, at intervals, the progress of the *clinical investigation* (3.9), the safety data or the critical *clinical performance* (3.12) or *effectiveness* (3.20) *endpoints* (3.23, 3.24) and to recommend to the sponsor whether to continue, suspend, modify or stop the clinical investigation

3.18
deviation
instance of failure to follow, intentionally or unintentionally, the requirements of the *clinical investigation plan* (*CIP*) (3.10)

3.19
device deficiency
inadequacy in the identity, quality, durability, reliability, usability, safety or performance of a *medical device* (3.35), including *malfunctions* (3.34), *use errors* (3.53) or inadequacy in the information supplied by the manufacturer including labelling

Note 1 to entry: This definition includes device deficiencies related to the *investigational medical device* (3.30) or the *comparator* (3.13).

3.20
effectiveness
achievement of a clinically meaningful intended result in a defined portion of the target population when the *investigational medical device* (3.30) is used within its intended uses and in compliance with its instructions for use, the *investigator's brochure* (3.32) and the *clinical investigation plan* (*CIP*) (3.10), as determined by documented scientific evidence

3.21
electronic clinical data system
hardware and software (including associated documents, such as a user manual) that creates, modifies, maintains, archives, retrieves or transmits in digital form information related to the conduct of a *clinical investigation* (3.9)

3.22
electronic record
combination of text, graphics, data, audio, imaging, or other information in digital form that is created, modified, maintained, archived, retrieved or distributed by an *electronic clinical data system* (3.21)

EXAMPLE An electronic case report form (CRF).

3.23
endpoint
<primary> principal indicator(s) used for providing the evidence for *clinical performance* (3.12), *effectiveness* (3.20) or safety in a *clinical investigation* (3.9)

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3.24
endpoint
<secondary> indicator(s) used for assessing the secondary *objectives* (3.38) of a *clinical investigation* (3.9)

3.25
ethics committee
EC
research ethics committee
independent ethics committee
institutional review board
independent (3.27) body whose responsibility it is to review *clinical investigations* (3.9) in order to protect the rights, safety, and well-being of human *subjects* (3.51) participating in a clinical investigation

Note 1 to entry: The regulatory requirements pertaining to ethics committees or similar institutions vary by country or region.

3.26
hypothesis
testable statement, derived from the *objective* (3.38) of the *clinical investigation* (3.9) to draw a conclusion about this objective, based on a pre-specified statistical test

Note 1 to entry: The primary hypothesis is formulated based on the pre-defined *primary endpoint* (3.23) and is usually used to calculate the sample size.

3.27
independent
not involved in the development of the investigational device or the conduct of a *clinical investigation* (3.9), except for their specifically assigned responsibilities, in order to avoid bias or a conflict of interest

3.28
informed consent
process by which an individual voluntarily confirms willingness to participate in a particular *clinical investigation* (3.9), after having been informed of all aspects of the investigation that are relevant to the decision to participate

3.29
investigation site
investigation centre
institution or site where the *clinical investigation* (3.9) is carried out

3.30
investigational medical device
investigational device
medical device (3.35) being assessed for safety, *clinical performance* (3.12) or *effectiveness* (3.20) in a *clinical investigation* (3.9)

Note 1 to entry: This includes medical devices already on the market that are being evaluated for new intended uses, new populations, new materials or design changes.

Note 2 to entry: This includes medical devices already on the market that are being evaluated within their intended use in a post-market clinical investigation (interventional or non-interventional).

3.31
investigator
individual member of the *investigation site* (3.29) team designated and supervised by the *principal investigator* (3.40) at an investigation site to perform clinical investigation-related procedures or to make important clinical investigation-related and medical treatment decisions

Note 1 to entry: An individual member of the investigation site team can also be called “sub-investigator” or “co-investigator”.

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3.32
investigator's brochure
IB
compilation of the current clinical and non-clinical information on the *investigational medical device(s)* (3.30), relevant to the *clinical investigation* (3.9)

3.33
legally designated representative
individual, judicial, or other body authorized under applicable law to consent, on behalf of a prospective *subject* (3.51), to the subject's participation in the *clinical investigation* (3.9)

Note 1 to entry: "legally authorized representative" or "legally acceptable representative" are other terminologies used under national regulations for "legally designated representative" but not used in this document.

3.34
malfunction
failure of an *investigational medical device* (3.30) to perform according to its intended purpose when used in compliance with the instructions for use or *clinical investigation plan* (*CIP*) (3.10), or *investigator's brochure (IB)* (3.32)

3.35
medical device
instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific purpose(s) of:

— diagnosis, prevention, *monitoring* (3.36), treatment or alleviation of disease;

— diagnosis, monitoring, treatment, alleviation of or compensation for an injury;

— investigation, replacement, modification, or support of the anatomy or of a physiological process;

— supporting or sustaining life;

— control of conception;

— disinfection of medical devices;

— providing information by means of in vitro examination of specimens derived from the human body;

and does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means

Note 1 to entry: Products which may be considered to be medical devices in some jurisdictions but not in others include:

— disinfection substances;

— aids for persons with disabilities;

— devices incorporating animal and/or human tissues;

— devices for in vitro fertilization or assisted reproduction technologies.

[SOURCE: ISO 13485:2016, 3.11, modified — "medical" has been deleted in "the specific medical purpose(s)".]

3.36
monitoring
act of overseeing the progress of a *clinical investigation* (3.9) to ensure that it is conducted, recorded and reported in compliance with the *clinical investigation plan* (*CIP*) (3.10), written procedures, this document and in conformance with the applicable regulatory requirements

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Note 1 to entry: Centralized monitoring provides additional monitoring capabilities remotely for evaluation of the accumulated data and the overall study compliance and can complement or reduce the extent and frequency of on-site monitoring.

3.37
multicentre investigation
clinical investigation (3.9) that is conducted according to a single *clinical investigation plan* (*CIP*) (3.10) and takes place at two or more *investigation sites* (3.29)

3.38
objective
main purpose for conducting the *clinical investigation* (3.9)

3.39
point of enrolment
time at which, following *recruitment* (3.44) and before any clinical investigation-related procedures are undertaken, a *subject* (3.51) signs and dates the *informed consent* (3.28) form

3.40
principal investigator
qualified person responsible for conducting the *clinical investigation* (3.9) at an *investigation site* (3.29)

Note 1 to entry: If a clinical investigation is conducted by a team of individuals at an investigation site, the principal investigator is responsible for leading the team.

Note 2 to entry: Whether this is the responsibility of an individual or an institution can depend on national regulations.

3.41
quality assurance
planned and systematic actions that are established to ensure that the *clinical investigation* (3.9) is performed, and that the data are generated, documented (recorded) and reported in compliance with this document and in conformance with the applicable regulatory requirement(s)

3.42
quality control
operational techniques and activities undertaken within the *quality assurance* (3.41) system to verify that the requirements for quality of the clinical investigation-related activities have been fulfilled

3.43
randomization
process of assigning *subjects* (3.51) to the *investigational medical device* (3.30) or *control groups* (3.15) using an established recognized statistical method based on an element of chance to determine the unforeseeable assignment in order to reduce bias

3.44
recruitment
active efforts to identify *subjects* (3.51) who can be suitable for enrolment into the *clinical investigation* (3.9)

3.45
serious adverse device effect
SADE
adverse device effect (3.1) that has resulted in any of the consequences characteristic of a *serious adverse event* (3.46)

3.46
serious adverse event
SAE
adverse event (3.2) that led to any of the following:

a) death,

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b) serious deterioration in the health of the *subject* (3.51), users, or other persons as defined by one or more of the following:

   1) a life-threatening illness or injury, or

   2) a permanent impairment of a body structure or a body function including chronic disease, or

   3) in-patient or prolonged hospitalization, or

   4) medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function

c) foetal distress, foetal death, congenital abnormality or birth defect including physical or mental impairment

Note 1 to entry: Planned hospitalization for a pre-existing condition, or a procedure required by the *clinical investigation plan* (*CIP*) (3.10), without serious deterioration in health, is not considered a *serious adverse event* (3.46).

3.47
serious health threat
signal from any *adverse event* (3.2) or *device deficiency* (3.19) that indicates an imminent risk of death or a serious deterioration in the health in *subjects* (3.51), users or other persons, and that requires prompt remedial action for other subjects, users or other persons

Note 1 to entry: A serious health threat would include events that are of significant and unanticipated nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

3.48
source data
information in original records, *certified copies* (3.7) of original records of clinical findings, observations or other activities in a *clinical investigation* (3.9), necessary for the reconstruction and evaluation of the clinical investigation

Note 1 to entry: This definition includes source data initially recorded in an electronic format.

3.49
source document
original or *certified copy* (3.7) of printed, optical or electronic document containing *source data* (3.48)

EXAMPLE Hospital records, laboratory notes, device accountability records, photographic negatives, radiographs, records kept at the *investigation site* (3.29), at the laboratories and at the medico-technical departments involved in the *clinical investigation* (3.9).

3.50
sponsor
individual, company, institution or organization taking responsibility and liability for the initiation and management of a *clinical investigation* (3.9), and arranging the financial setup

Note 1 to entry: When an *investigator* (3.31) initiates, implements and takes full responsibility for the clinical investigation, the investigator also assumes the role of the sponsor and is identified as the sponsor-investigator.

3.51
subject
individual who is or becomes a participant in a *clinical investigation* (3.9), either as a recipient of the *investigational medical device* (3.30) or a *comparator* (3.13)

Note 1 to entry: A subject can be a healthy volunteer.

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3.52
unanticipated serious adverse device effect
USADE
serious adverse device effect (3.45) which by its nature, incidence, severity or outcome has not been identified in the current risk assessment

Note 1 to entry: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, and its severity or outcome has been identified in the risk assessment.

3.53
use error
user action or lack of user action while using the *medical device* (3.35) that leads to a different result than that intended by the manufacturer or expected by the user

Note 1 to entry: Use error includes the inability of the user to complete a task.

Note 2 to entry: Use errors can result from a mismatch between the characteristics of the user, user interface, task or use environment.

Note 3 to entry: Users might be aware or unaware that a use error has occurred.

Note 4 to entry: An unexpected physiological response of the patient is not by itself considered a use error.

Note 5 to entry: A malfunction of a medical device that causes an unexpected result is not considered a use error.

[SOURCE: ISO 14971:2019, 3.30]

3.54
validation
confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled

3.55
verification
confirmation by examination and provision of objective evidence that specified requirements have been fulfilled

3.56
vulnerable subject
individuals who are unable to fully understand all aspects of the clinical investigation that are relevant to the decision to participate, or who can be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response determined by physical, social, economic and environmental factors or processes

4 Summary of good clinical practice principles

Good clinical practice principles for clinical investigations carried out in human subjects assessing medical devices is summarized as follows:

a) Clinical investigations shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (see Reference [8]), and that are consistent with this document.

b) Before a clinical investigation is initiated, foreseeable risks and inconveniences shall be weighed against the anticipated benefit for the individual subject and society. A clinical investigation shall be initiated and continued only if the anticipated benefits justify the risk.

c) The rights, safety and well-being of human subjects are the most important considerations and shall prevail over interests of science and society.

d) The available non-clinical and clinical information on the investigational device shall be adequate to support the proposed clinical investigation.

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