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In vitro diagnostic medical devices — Clinical performance studies using specimens from human subjects — Good study practice

Dispositifs médicaux de diagnostic in vitro — Études des performances cliniques utilisant des prélèvements de sujets humains — Bonnes pratiques d'étude

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Foreword

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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 documents 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).

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. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

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 212, *Clinical laboratory testing and in vitro diagnostic test systems*.

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.

Introduction

In vitro diagnostic (IVD) medical devices are used to conduct tests outside of the human body to provide valuable information regarding a person's health or physiological status. They include tests and related devices, such as test strips and reagents, using specimens such as blood, tissue or urine, to carry out screening, diagnosis, prognosis, predictive testing, and monitoring of conditions. IVD medical devices are fundamentally different from other medical devices because they perform their function outside of the body on specimens taken from the human body. Human subjects are typically not exposed to risks with the performance testing of IVD medical devices, except for the risk associated with specimen collection procedures or when the obtained information is used for patient management. The specimens are obtained via normal body functions (e.g. urine) or through the use of invasive medical devices to allow for the specimen to be obtained (e.g. biopsy). The specimens are never reintroduced into the human body. These differences make the performance and risk characteristics of IVD medical devices different and unique from other medical devices.

Most of the studies for IVD medical devices are performed using samples resulting from the remnants of specimens taken for purposes of standard of care (leftover or archived). In these studies, there is no risk for the subjects arising from either the information provided by the IVD medical device or from the collection procedure of the specimen. However, when leftover specimens are not used, additional requirements should be considered

— when the specimens are collected specifically for the study and the specimen collection procedures present additional risk of direct harm for the subject (e.g. lumbar puncture or tissue biopsy, blood collection from neonates or critically ill patients), and/or

— when the information obtained from the IVD medical devices during the study is used to make patient management decision (i.e. interventional studies), presenting a risk of indirect harm for the subject (e.g. false negative or false positive result leading to inappropriate patient management decisions).

For the majority of IVD clinical performance studies, issues related to the use of vulnerable subjects might not arise but should be considered on a case by case basis.

Considering the reliance on specimens taken from the body and the absence of direct contact of the IVD with the patient, issues related to procedures for obtaining informed consent for IVD clinical performance studies differ from those associated with other medical devices, especially for studies with leftover or archived specimens. This document will provide guidance on the requirements for the various situations described above for IVD medical devices.

This document is intended for clinical performance studies as these studies involve specimens taken from the human body. When specimens other than leftover or archived specimens are used, there might be additional collection risks for the subject. Also in interventional studies, there might be a risk for the subject coming from the information provided by the result of the IVD under investigation.

This document is specific for IVD medical devices and therefore uses definitions and concepts that are appropriate for IVD medical devices. It is a stand-alone standard for clinical performance studies for IVD medical devices. In the situation for which there is an IVD medical device and a medical device used in an integrated system (e.g. a lancet, an IVD test strip and a glucose meter), the respective jurisdiction's regulation will define it as either an IVD medical device or a medical device and subsequently, aspects of both this document and ISO 14155 might need to be considered.

Except for these situations, this document should not be read in conjunction with ISO 14155, which excludes IVD medical devices from its scope.

The flowchart represented in Figure 1 provides guidance on how to use this document.

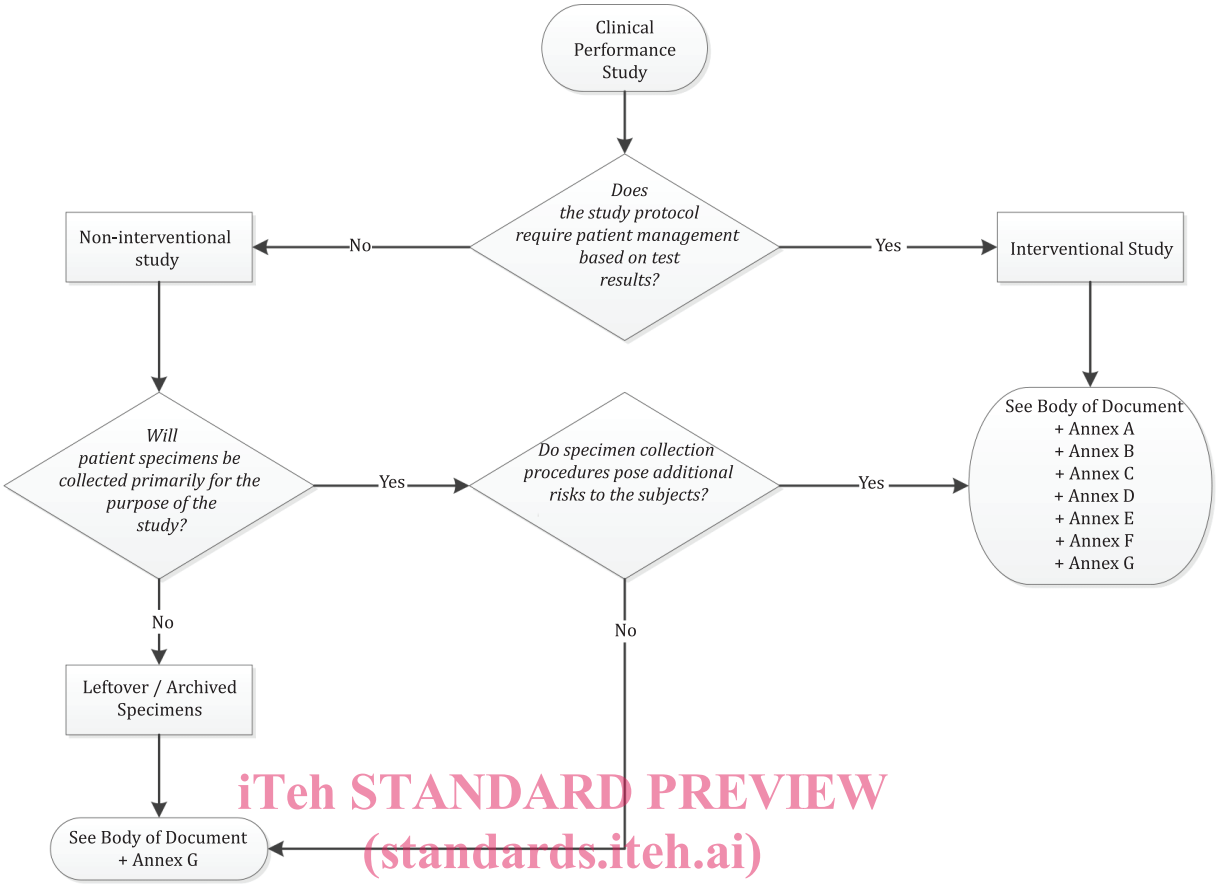

Figure 1 — Clinical performance study flow chart

The main body of the document, in addition to Annex G, includes minimum requirements for all studies. No additional requirements apply for studies using leftover/archived specimens or studies with specimen collection procedures that pose no additional risks to the subject.

However, additional requirements for interventional studies, and those studies in which the specimen collection procedures pose a risk to subjects primarily recruited for the study, are found in Annexes A to F. The nature of these studies warrants an increased level of stringency in the requirements for conduct of the study. The flowchart indicates the annexes which describe the additional requirements for each type of more complex studies. When necessary, the annexes describe differences in the requirements for the different types of study. Additionally, informative annexes are included to provide information on good study practice documentation (see Annex H) and auditing (see Annex I).

In vitro diagnostic medical devices — Clinical performance studies using specimens from human subjects — Good study practice

1 Scope

This document defines good study practice for the planning, design, conduct, recording and reporting of clinical performance studies carried out to assess the clinical performance and safety of in vitro diagnostic (IVD) medical devices for regulatory purposes.

NOTE 1 The purpose of these studies is to assess the ability of an IVD medical device in the hands of the intended user, to yield results pertaining to a particular medical condition or physiological/pathological state, in the intended population.

The document is not intended to describe whether the technical specifications of the IVD medical device in question are adequately addressed by the clinical performance study.

This document identifies the principles that underpin clinical performance studies and specifies general requirements intended to

— ensure the conduct of the clinical performance study will lead to reliable and robust study results,

— define the responsibilities of the sponsor and principal investigator,

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

— protect the rights, safety, dignity and well-being of the subjects providing specimens for use in clinical performance studies.

Analytical performance studies are out of the scope of this document.

NOTE 2 When the collection of specimens specifically for the analytical performance study creates an additional collection risk for subjects, some of the elements of this document (particularly the annexes) can be useful for ensuring subject safety.

Clinical performance studies that are performed for reasons other than pre- and post-market regulatory purposes, such as for re-imbursement purposes, are out of the scope of this document.

NOTE 3 Some of the elements of this document can be useful for the design of such studies, including subject safety and data integrity.

This document does not include safety information for laboratory workers or other personnel collecting the study specimens.

NOTE 4 Such information is included in other publications[1][12][13].

NOTE 5 Users of this document can consider whether other standards and/or requirements also apply to the IVD medical device which is the subject of the clinical performance study, for instance, in the situation for which there is an IVD medical device and a medical device used in an integrated system (e.g. a lancet, an IVD test strip, and a glucose meter), aspects of both this document and ISO 14155 can be considered.

2 Normative references

There are no normative references in this document.

3 Terms and definitions

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

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

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

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

3.1
adverse device effect
adverse event (3.2) related to the use of an IVD medical device under investigation

Note 1 to entry: This definition includes any adverse event resulting from insufficient or inadequate instructions for use, installation, operation, or any malfunction of the IVD medical device under investigation.

Note 2 to entry: This definition includes any event resulting from use error or from intentional misuse of the IVD medical device under investigation.

[SOURCE: ISO 14155:—[1)], 3.1, modified — Adapted for IVD medical devices.]

3.2
adverse event
AE
any untoward medical occurrence, inappropriate patient management decision, unintended disease or injury, or untoward clinical signs in subjects, users, or other persons, with any connection to study related activities, whether or not related to the IVD medical device under investigation

Note 1 to entry: Adverse events can be caused by, for instance, insufficient or inadequate instructions for use, deployment, installation, operation, or any malfunction of the IVD medical device under investigation.

Note 2 to entry: This definition includes the malfunction or deterioration of a device which has not yet caused death or serious injury, but which could lead to death or serious injury.

Note 3 to entry: This definition is not intended to be used in determining whether an event is reportable to a regulatory authority.

Note 4 to entry: For users or other persons, this definition is restricted to events related to investigational (IVD) medical devices.

Note 5 to entry: False negative or false positive results are not considered an adverse event unless in an interventional study, inappropriate patient management decisions are made based on those false results.

3.3
analytical performance
ability of an IVD medical device to detect or measure a particular analyte

[SOURCE: GHTF/SG5/N6:2012]

Note 1 to entry: Analytical performance can include analytical sensitivity (e.g. limit of detection), analytical specificity (e.g. interference, cross-reactivity), accuracy (derived from trueness and precision), linearity, etc.

3.4
analytical performance study
study undertaken to establish or confirm the ability of an IVD medical device to detect or measure a particular analyte

1) Under preparation. Stage at the time of publication: ISO/DIS 14155:2019.

3.5
anticipated serious adverse device effect
effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report

Note 1 to entry: Anticipated serious adverse device effects can also be described in the study protocol, investigator brochure, and subject informed consent, when applicable.

3.6
archived specimen
archived sample
specimen or *sample* (3.42) that was collected in the past and is obtained from repositories (e.g. tissue banks, commercial vendor collections)

[SOURCE: GHTF/SG5/N8:2012]

3.7
audit
systematic independent examination of activities and documents related to a clinical performance study to determine whether these activities were conducted, and the data recorded, analyzed and accurately reported according to the clinical study performance protocol, standard operating procedures, specified requirements

[SOURCE: ISO 14155:—[1)], 3.3, modified — Adapted for IVD medical devices.]

Note 1 to entry: Specified requirements are those described in this document and may include any other applicable requirements such as regulatory provisions.

3.8
blinding
masking
procedure in which one or more parties to the clinical performance study are kept unaware of any information related to the condition or physiological state, treatment, prior test results, demographics, etc., of the individual from whom the specimen for testing was obtained in order to reduce bias

3.9
case report forms
CRFs
set of printed or electronic documents for each subject on which information to be reported to a sponsor is recorded, as required by the clinical performance study protocol

[SOURCE: ISO 14155:—[1)], 3.6, modified — Adapted for IVD medical devices.]

3.10
clinical performance of an IVD medical device
ability of an IVD medical device to yield results that are correlated with a particular clinical condition or physiological/pathological process/state in accordance with the intended use (clinical test purpose, target population and intended user)

Note 1 to entry: In accordance with intended use, clinical performance can include expected values, diagnostic sensitivity and diagnostic specificity based on the known clinical condition or physiological/pathological process/state of the individual, and negative and positive predictive values based on the prevalence of the disease.

[SOURCE: GHTF/SG5/N6:2012]

3.11
clinical performance study
study undertaken to establish or confirm the *clinical performance of an IVD medical device* (3.10)

Note 1 to entry: Testing performed pre-market that is not designed to address clinical performance of an IVD medical device is not considered a clinical performance study (e.g. customer feedback studies, external analytical performance studies, research studies).

[SOURCE: GHTF/SG5/N6:2012]

3.12
clinical performance study protocol
CPSP
document that states the rationale, objectives, design, risk, proposed analysis, methodology, monitoring, conduct and record-keeping of the *clinical performance study* (3.11)

Note 1 to entry: The CPSP need not be a single document but a series of documents related and referenced to each other for the purpose of creating the CPSP.

[SOURCE: GHTF/SG5/N8:2012]

3.13
clinical performance study report
CPSR
document describing the objectives design, execution, statistical analysis, results and conclusion(s) of a clinical performance study

Note 1 to entry: Some elements of the clinical performance study report can be covered by stand-alone documents that are references in the clinical performance study report.

Note 2 to entry: The CPSR need not be a single document but a series of documents related and referenced to each other for the purpose of creating the CPSR.

[SOURCE: GHTF/SG5/N8:2012]

3.14
contract research organization
person or organization contracted by the *sponsor* (3.49) to perform one or more of the sponsor's clinical performance study-related duties and functions

3.15
device accountability records
records documenting the physical location of all IVD medical devices under investigation, from shipment of the devices to the study site until return or disposal, as well as records documenting the receipt, use, return and disposal of the IVD medical devices under investigation

3.16
device deficiency
inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance

Note 1 to entry: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.

Note 2 to entry: This definition includes device deficiencies related to the investigational medical device or the comparator.

[SOURCE: ISO 14155:—[1)], 3.19]

3.17
endpoint
principal (primary) or secondary indicator used in a clinical performance study to assess the performance of the *IVD medical device* (3.24)

Note 1 to entry: For example, endpoints can be statistical measures for performance or clinical events/outcomes.

3.18
ethics committee
EC
independent body whose responsibility it is to review clinical investigations in order to protect the rights, *safety* (3.41) and well-being of human subjects participating in a clinical investigation

[SOURCE: ISO 14155:—[1)], 3.24, modified — Note 1 to entry has been removed.]

3.19
informed consent
process by which an individual voluntarily confirms willingness to participate in a particular clinical performance study, after having been informed of all aspects of the study that are relevant for the decision to participate

[SOURCE: ISO 14155:—[1)], 3.27]

Note 1 to entry: For the purposes of this document, the permission is typically for providing specimens or participating in a clinical performance study.

Note 2 to entry: The informed consent document lists the risk(s) and benefit(s) to the subject, when applicable.

Note 3 to entry: The information provided can be broad in nature, allowing the specimen to be used for future undetermined studies, or the information can be specific to a particular study.

3.20
intended use
intended purpose

objective intent of the manufacturer regarding the use of a product, process or service as reflected in the specifications, instructions and information provided by the IVD manufacturer

Note 1 to entry: Intended use statements for IVD labelling can include two components: a description of the functionality of the IVD medical device (e.g. an immunochemical measurement procedure for the detection of analyte "*x*" in serum or plasma), and a statement of the intended medical use of the examination results.

[SOURCE: ISO 18113-1:2009, 3.31, modified]

3.21
interventional clinical performance study
study in which test results obtained during the study can influence patient management decisions and might be used to guide treatments

EXAMPLE Studies for companion diagnostics.

[SOURCE: GHTF/SG5/N8:2012]

3.22
investigator brochure
compilation of analytical and clinical performance data relevant to the clinical performance study

Note 1 to entry: The investigator brochure includes risk/benefit information of the IVD device under investigation and sampling procedures.

3.23
investigator
sub-investigator
co-investigator
individual member of the investigation study site team designated and supervised by the principal investigator at the study site to perform critical study-related procedures or to make important study-related decisions

3.24
IVD medical device
medical device (3.28), whether used alone or in combination, intended by the manufacturer for the in vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring, or compatibility purposes

Note 1 to entry: IVD medical devices include reagents, calibrators, control materials, specimen receptacles, software and related instruments or apparatus or other articles and are used, for example, for the following test purposes: diagnosis, aid to diagnosis, screening, monitoring, predisposition, prognosis, prediction, determination of physiological status.

[SOURCE: ISO 18113-1:2009, 3.27, modified — Note 1 to entry has been removed, GHTF/SG1/N071:2012.]

3.25
leftover specimen
leftover sample
unadulterated remnants of human derived specimens collected as part of routine clinical practice and after all standard analysis has been performed

Note 1 to entry: Such specimens/samples would be otherwise discarded as there is no remaining clinical need for them.

Note 2 to entry: This can include specimens collected for research or other purposes not connected to the clinical performance study in question.

3.26
legally authorized representative
legally designated representative
individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical investigation

[SOURCE: ISO 14155:—[1)], 3.32, modified — Note 1 to entry has been deleted, first preferred term has been added and "legally designated representative" has become an admitted term.]

3.27
malfunction
failure of an IVD medical device under investigation to perform in accordance with its *intended use* (3.20) when used in accordance with the instructions for use or *CPSP* (3.12)

[SOURCE: ISO 14155:—[1)], 3.33, modified — Adapted for IVD medical devices.]

3.28
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 medical purposes of

— diagnosis, prevention, monitoring, 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 state or process,

— supporting or sustaining life,

— control of conception,

— disinfection or sterilization of medical devices, or

— 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 can be assisted in its intended function by such means

[SOURCE: ISO 18113-1:2009, 3.47, modified — Terminology has been slightly changed; GHTF SG1/N071:2012]

3.29
monitor
person, qualified by education, training or experience, responsible for performing the *monitoring* (3.30) of the clinical performance study

3.30
monitoring
act of reviewing the progress of a clinical performance study and ensuring that it is conducted, recorded and reported in accordance with the CPSP, written procedures, procedures, specified requirements

Note 1 to entry: Specified requirements are those described in this document and may include any other applicable requirements such as regulatory provisions.

3.31
point of enrolment
time at which, following *recruitment* (3.34), a subject signs and dates the informed consent form, when required by the *ethics committee* (3.18), or otherwise begins participation in the study

[SOURCE: ISO 14155:—[1)], 3.38, modified — The definition has been lengthened.]

3.32
principal investigator

qualified person responsible for conducting the clinical performance study at a *study site* (3.50)

Note 1 to entry: When a clinical performance study is conducted by a team of individuals at a study 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.

3.33
protocol deviation
instance of failure to follow, intentionally or unintentionally, the requirements of the *clinical performance study protocol* (3.12)

3.34
recruitment
active efforts to identify *subjects* (3.51) who might be suitable for enrolment in a clinical performance study

3.35
reference measurement procedure
measurement procedure accepted as providing measurement results fit for their use in assessing measurement trueness of measured quantity values obtained from other measurement procedures for quantities of the same kind, in calibration, or in characterizing reference materials

[SOURCE: ISO 15193:2009, 3.7, modified — Notes to entry have been removed.]

3.36
regulatory authority
government agency or other entity that exercises a legal right to control the use or sale of medical devices within its jurisdiction, and can take legal action to ensure that medical devices marketed within its jurisdiction comply with legal requirements

[SOURCE: GHTF/SG1/N68:2012]