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

National foreword

This British Standard is the UK implementation of ISO 20916:2019.

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A list of organizations represented on this committee can be obtained on request to its secretary.

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

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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 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.

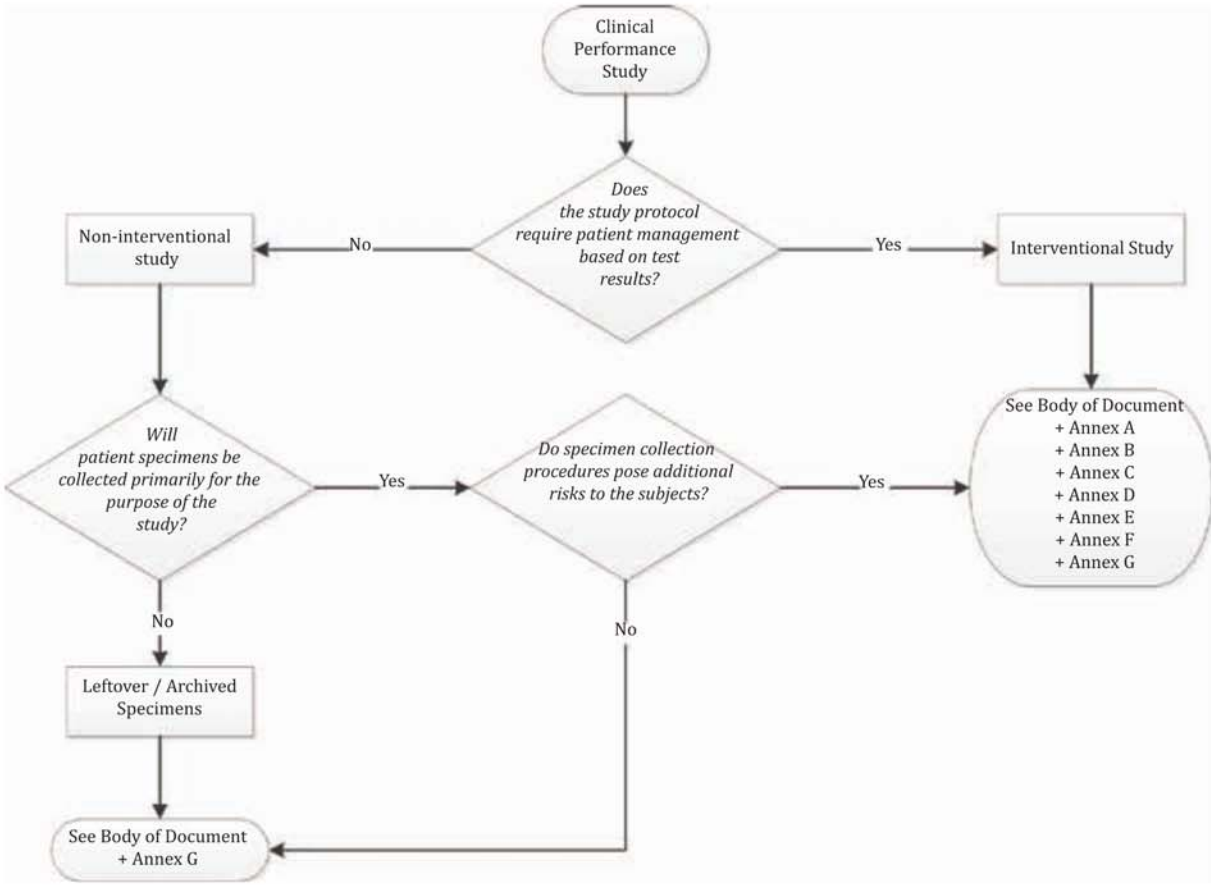

Figure 1 — Clinical performance study flow chart

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).

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INTERNATIONAL STANDARD ISO 20916:2019

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]

3.37
risk
combination of the probability of occurrence of harm and the severity of that harm

[SOURCE: ISO/IEC Guide 51:2014, 3.9]

3.38
risk analysis
systematic use of available information to identify hazards and to estimate the *risk* (3.37) to study subjects and users of the IVD medical device under investigation

Note 1 to entry: Risk analysis includes examination of different sequences of events that can produce hazardous situations and harm.

Note 2 to entry: For IVDs, the risk analysis should take into consideration risks associated with reporting of inaccurate test results in an interventional study.

[SOURCE: ISO/IEC Guide 51:2014, 3.10, modified — The definition has been adapted for IVDs, Note 1 to entry has been modified and Note 2 to entry has been added.]

3.39
risk assessment
overall process comprising a *risk analysis* (3.38) and a *risk evaluation* (3.40)

[SOURCE: ISO/IEC Guide 51:2014, 3.11]

3.40
risk evaluation
process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk

[SOURCE: ISO 14971: —[2)], 3.23]

3.41
safety
freedom from unacceptable risk

[SOURCE: ISO/IEC Guide 51:2014, 3.14]

3.42
sample
one or more representative parts taken from a *specimen* (3.47), which are intended to provide information

EXAMPLE A portion of serum taken from a specimen of coagulated blood.

[SOURCE: ISO 18113-1:2009, 3.64, modified — The wording in the definition changed.]

3.43
serious adverse device effect
adverse device effect (3.1) that has resulted in any of the consequences characteristic of a *serious adverse event* (3.44)

[SOURCE: MEDDEV 2.7.1, rev 4, 2016]

3.44
serious adverse event
SAE
adverse event that led to any of the following

a) death,

2) Under preparation. Stage at the time of publication: ISO/FDIS 14971:2019.

b) serious deterioration in the health of the subject, 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 diseases, or

   3) in-patient or prolonged hospitalisation, 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 or a congenital abnormality or birth defect including physical or mental impairment

Note 1 to entry: Planned hospitalisation for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

[SOURCE: ISO 14155:—[1)], 3.45]

3.45
source data
all information in original records, certified copies of original records of clinical findings, observations, device results or other activities in a clinical performance study, necessary for the traceability and evaluation of the clinical performance study

[SOURCE: ISO 14155:—[1)], 3.47, modified — Adapted for IVD devices, Note to entry removed.]

3.46
source document
printed or electronic document or other media containing *source data* (3.45)

EXAMPLE Hospital records, laboratory notes, test results, patient's surveys, device accountability records, photographic evidence, records kept at the study site, at the laboratories and at the medico-technical departments involved in the clinical performance study.

3.47
specimen
discrete portion of a body fluid or tissue taken for examination, study, or analysis of one or more quantities or characteristics to determine the character of the whole

[SOURCE: ISO 18113-1:2009, 3.54, modified — "Specimen" is the first preferred terms, Notes to entry have been removed.]

3.48
specimen collection procedure
all the steps involved in collecting a specimen from a human subject. This includes all preparatory steps, the actual collection and any after-treatment, and the disposal of any procedure-related materials

EXAMPLE Fasting, pre-medication, anaesthesia procedures, blood draw, biopsy, disposal of sharps.

3.49
sponsor
individual or organization taking responsibility and liability for the initiation, implementation and oversight of a clinical performance study

Note 1 to entry: when an investigator initiates, conducts and takes full responsibility for a clinical performance study, the investigator also assumes the role of sponsor and is identified as the sponsor-investigator.

3.50
study site
institution(s) or location(s) where the clinical performance study is carried out, under the supervision of a *principal investigator* (3.32)

Note 1 to entry: For the purpose of this document, "study site" is synonymous with "study centre".

Note 2 to entry: Study sites include testing locations and specimen collection sites but not commercial procurement entities, e.g. providers of archived specimens (such as biobanks).

3.51
subject
human who participates in a clinical performance study or whose specimen is used in the study

Note 1 to entry: Depending on the study, a subject can be either a healthy individual or a patient.

3.52
unanticipated serious adverse device effect
serious adverse device effect (3.43) which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report

[SOURCE: ISO 14155:—[1)], 3.51, modified — The second preferred term and Notes to entry have been removed.]

3.53
use error
act or omission of an act that results in an IVD medical device output which differs from 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 subject is not by itself considered use error.

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

[SOURCE: ISO 14971:—[2)], 3.30, modified — Adapted for IVD medical devices.]

3.54
validation
verification (3.55) that the specified requirements are adequate for an intended use

[SOURCE: ISO 18113-1:2009 3.72, modified — The definition has been reworded, the EXAMPLE and Note to entry have been removed.]

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

[SOURCE: GHTF/SG3/N99-10:2004]

3.56
vulnerable subject
individual whose willingness to volunteer in a clinical investigation could be unduly influenced by expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate

EXAMPLE Individuals with lack or loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees and those incapable of giving informed consent. Other vulnerable subjects include members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the sponsor, members of the armed forces and persons kept in detention.

[SOURCE: ISO 14155:—[1)], 3.55]

4 Ethical considerations

4.1 General

Clinical performance studies shall be conducted in accordance with ethical principles, e.g. the Declaration of Helsinki[14].

Clinical performance studies shall be designed and conducted in such a way that the rights, safety, dignity and well-being of the subjects participating in such clinical performance studies are protected and prevail over all other interests and the data generated are scientifically valid, reliable and robust.

4.2 Improper influence or inducement

The sponsor shall avoid improper influence on, or the inducement of, subjects, monitors, investigators or other parties participating in, or contributing to, the clinical performance study.

All investigators shall avoid improper influence on, or inducement of, subjects, sponsors, monitors, other investigators or other parties participating in, or contributing to, the clinical performance study.

4.3 Responsibilities

All parties involved in the conduct of the clinical performance study shall share the responsibility for its ethical conduct in accordance with their respective roles in the clinical performance study.

4.4 Ethics committee involvement

Before commencing a clinical performance study, the sponsor shall determine and take into account the requirements for ethics committee approval of the clinical performance study and/or the participating sites. It is the responsibility of the sponsor to ensure that specimens have been collected following ethical requirements. The ethics committee can choose to exempt certain IVD medical device clinical performance studies from their approval, and/or can waive informed consent.

For those studies described in A.1, additional requirements for communication with the ethics committee are specified in Annex E.

The principal investigator shall:

a) provide the sponsor with copies of any clinical performance study related communications between the principal investigator and the ethics committee, when they exist;

b) obtain the written and dated approval/favourable opinion, or a waiver of the ethics committee for the clinical performance study before initiating and implementing all subsequent amendments;

NOTE In certain jurisdictions, no response from the ethics committee after a defined time limit constitutes a waiver.

c) perform adverse event recording and reporting as specified in Annex G.

The communication with the ethics committee can be performed by the sponsor, partly or in full, in which case the sponsor shall keep the principal investigator informed.

4.5 Informed consent

For those studies described in A.1, requirements for informed consent are specified in Annex F.

Informed consent for leftover or archived specimens can be acquired and documented in different ways appropriate in the context of this document, depending on the local regulations and ethics committee requirements, such as:

— signed informed consent, when a form is dated and signed by the specimen donor/subject;

— authenticated electronic confirmation of consent documented together with date, which can be in the form of a timestamp in an electronic database;

— confirmation of the specimen donor/subject when unable to physically provide a signature; in this situation usually a witness is present or an audio or video recording of the consent is made; or

— where a jurisdiction requires opt-out for use of residual specimens for medical research, no objection is registered by the specimen donor/subject.

In some countries, a waiver can be obtained from the ethics committee.

NOTE 1 There can be cases when the ethics committee has no jurisdiction in evaluating the study proposal, for example when the proposed study has no impact on donor risk. Sometimes, the ethics committee delegates the evaluation to another committee.

For leftover and archived specimens, informed consent might exist in a general form to cover the use of the specimens in any clinical performance studies. Sponsors might not have direct access to this original informed consent, but should be able to obtain and verify the institution's informed consent policy.

For best practice, specimens should be de-identified, unless it is absolutely necessary to identify the subjects.

The principal investigator shall ensure that there is a procedure to identify the applicable regulatory requirements and ethical principles for the process of informed consent, when required.

Ethics committee approval should be sought when there are doubts surrounding the validity and applicability of the original informed consent.

NOTE 2 For the purposes of this subclause and all other clauses in this document, the word "signed" includes secure electronic signatures.

5 Clinical performance study planning

5.1 General

Clinical performance studies shall be conducted in a manner in which every precaution has been taken to protect the rights and the health and safety of the subject, user and other persons, considering all regulatory and ethical requirements, using valid scientific principles. When conflict of interest or bias cannot be avoided, there shall be full disclosure that is appropriately documented and justified. Clinical performance studies shall be undertaken under an effective quality management system to ensure that these principles are met. The study sponsor shall take responsibility for ensuring that these principles are met.

The sponsor shall define the roles and responsibilities of all parties including those of the sponsor, monitor, principal investigator and study team members in accordance with this document.

All parties participating in the conduct of the clinical performance study shall be qualified to perform their tasks by education, training or experience, and this shall be documented appropriately (see 6.2).

Quality assurance and quality control principles shall apply to the processes of the clinical performance study. The sponsor shall

a) implement and maintain written procedures to ensure that

   1) the clinical performance study is designed, conducted and monitored,

   2) all devices and other study-related materials are properly accounted for, and

   3) data generated are documented, recorded, reported and archived in conformity with this document and the CPSP all subsequent amendments to the CPSP.

b) maintain records to document the conformity of all parties involved in the clinical performance study,

c) ensure that the auditing requirements of Annex I are met, when applicable, and

d) justify and document significant exceptions to the requirements of this document.

Quality assurance and quality control aspects for clinical performance studies can be integrated in the sponsor's overall quality system.

In certain circumstances, it might be appropriate to perform the testing only at the manufacturer's site; in this case, a justification for this decision should be documented. For example, a study to determine reference values can often be performed entirely at the manufacturer's site. Studies conducted internally at a manufacturer's site can rely upon the manufacturer's quality system policies, processes, and procedures to meet the applicable requirements of this document. When used, these quality system documents should be referenced within the CPSP.

The sponsor can transfer any or all of the duties and functions related to the clinical performance study, including monitoring, to an external organization (such as a contract research organization or individual contractor), but the ultimate responsibility for the quality and integrity of the clinical performance study data shall reside with the sponsor. All the requirements in this document applying to a sponsor shall also apply to the external organization in as much as this organization assumes the clinical performance study-related duties and functions of the sponsor.

The sponsor shall specify in a written agreement any clinical performance study-related duty or function assumed by the external organization, retaining any clinical performance study-related duties and functions not specifically transferred to, and assumed by, the external organization.

The sponsor shall be responsible for verifying the external organization has and adheres to written study-related procedures.

NOTE For additional information, see ISO 13485[3].

5.2 Risk evaluation

Before conducting a clinical performance study, the sponsor shall undertake and document an assessment of the risks associated with the participation in and/or conduct of the study.

The risk analysis should include or refer to an objective review of published and, when available, unpublished medical or scientific data.

The anticipated adverse events based on the risk assessment shall be documented in the CPSP.

NOTE 1 Such anticipated adverse events are expected to be rare in most studies but could be expected to occur in the studies described in A.1

NOTE 2 There could also be risks to the staff members performing the collection procedures. These are not included in the scope of this document, but are covered by other medical laboratory and laboratory safety standards[1][12][13].

5.3 Design of the clinical performance study

Clinical performance studies shall be carried out using product representative of the final manufactured IVD medical device intended for commercialisation, using controlled and accepted processes and procedures, though scale up might not yet be completed.

The choice of the design for the clinical performance study can depend on the following considerations:

a) study objectives;

b) the outcome of the risk evaluation;

c) intended use, specifically:

   1) test purpose(s) (e.g. diagnosis, screening, monitoring);

   2) target population(s) (e.g. age, race, gender, geography, clinical condition, treatment status);

   3) specimen type(s) (e.g. serum, plasma, urine, whole blood);

   4) intended user(s)/operator(s) (person performing the test e.g. lay person).

d) specimen/sample handling and storage conditions (e.g. sample cannot be frozen);

e) sample size estimate, and description of planned statistical analysis;

f) quality, availability and accessibility of specimens (e.g. limited number of leftover specimens available);

g) testing location (e.g. point-of-care setting, central laboratory);

h) intended use setting's environmental conditions;

i) established analytical performance characteristics (e.g. precision, interference, measuring interval (range), cut-off, limit of detection, limit of quantification);

j) intended clinical performance characteristics (e.g. sensitivity, specificity, positive predictive value, negative predictive value, reference intervals, cut-off);

k) prevalence of the clinical condition/physiological or pathological state;

l) novelty of the technology and/or clinical use (e.g. relevant previous experience);

m) availability of appropriate method(s) to establish the clinical status of the subject;

n) availability of quality control material;

o) mechanisms to avoid bias.

5.4 Investigator brochure

For studies other than those described in Annex A, the instructions for use may replace the investigator brochure.

For those studies described in A.1, requirements for content of the investigator brochure shall be in accordance with Annex C.

5.5 Clinical Performance Study Protocol (CPSP)

5.5.1 General

The purpose of the CPSP is to ensure the clinical performance study is performed to yield high quality, accurate and reliable data for the IVD medical device under investigation. The CPSP shall be developed by investigators or sponsors appropriately qualified by education, training, or experience. An appointed representative of the sponsor shall sign and date the protocol, indicating sponsor acceptance. The CPSP and all subsequent amendments to the CPSP shall be agreed upon between the sponsor and all principal investigators, and shall be recorded with a justification for each amendment.

For studies described in A.1, use the requirements additional to those set out below specified in Annex B.

5.5.2 Principal investigator responsibilities

The principal investigator(s) shall

a) indicate his/her acceptance of the CPSP in writing,

b) manage the day-to-day conduct and ensure ethical conduct of the clinical performance study in conformity with the CPSP,

c) keep any agreement, contract, or register that stipulates the responsibilities, attributions and functions of all those involved in the clinical performance study,

d) maintain source documents throughout the clinical performance study and make them available as requested during monitoring visits or audits,

e) ensure that the IVD medical device under investigation is used in accordance with the CPSP and instructions for use,

f) not implement any modifications to the CPSP without agreement from the sponsor, and when required, ethics committee,

g) document and explain any deviation from the approved CPSP that occurred during the course of the clinical performance study, and define corrective actions to prevent further deviations,

h) document and explain any adverse events, actions taken, and report to the sponsor,

i) ensure the accuracy, integrity, completeness, legibility and timeliness of the data reported to the sponsor,

j) maintain the device accountability records,

k) maintain records of specimen accountability and specimen integrity,

l) allow and support the sponsor to perform monitoring and auditing activities,

m) be accessible to the monitor and respond to questions during monitoring visits,

n) allow and support the ethics committee when performing auditing activities,

o) ensure that all clinical performance study related records are retained,

p) disclose potential conflicts of interest, including financial, that could interfere with the conduct of the clinical performance study or interpretation of results, and

q) document relevant study-related communications.

5.5.3 Contents of the CPSP

5.5.3.1 General

The CPSP shall include the relevant information specified below. The content of a CPSP and any subsequent amendments shall include all the topics listed in this subclause together with a description for each topic that is not self-explanatory.

5.5.3.2 Identification of the clinical performance study protocol

a) Title of the clinical performance study.

b) Reference number identifying the specific clinical performance study, if any.

c) Version or date on each page of the CPSP.

d) Summary of the revision history in the case of amendments.

e) Page number and the total number of pages on each page of the CPSP.

5.5.3.3 Identification and description of the IVD medical device under investigation

a) Summary description of the IVD medical device under investigation and its intended use.

b) Name of the IVD medical device, including software and accessories, if any, intended use including populations and indications of the IVD medical device under investigation in the proposed clinical performance study.

c) Summary of the necessary training and experience needed to use the IVD medical device under investigation, when applicable.

5.5.3.4 Sponsor

Name and address of the sponsor of the clinical performance study, when testing is occurring externally to the sponsor's site.

When the sponsor is not resident in the country (countries) in which the testing related to the clinical performance study is to be carried out, the name and address of a representative in that country (those countries) can be required according to national or regional regulations.

5.5.3.5 Study site(s)

Individual sites need not be identified in the CPSP, however, the sponsor shall maintain an updated list of principal investigators, study sites, and institutions. This list can be kept separately from the CPSP. The final list shall be provided with the clinical performance study report.

5.5.3.6 Overall synopsis of the clinical performance study

A summary or overview of the clinical performance study shall include all the relevant information regarding the clinical performance study design, such as inclusion/exclusion criteria, number of specimens and, when applicable, subjects, duration of the clinical performance study, objective(s), endpoint(s).

5.5.3.7 Objectives of the clinical performance study

a) Objectives, primary and secondary, if applicable.

b) Relevant primary and secondary endpoints.

c) Claims and intended performance of the IVD medical device under investigation that are to be evaluated.

d) Risks and anticipated adverse device effects that are to be assessed.

5.5.3.8 IVD medical device under investigation and comparator(s)

When used, list the comparator(s). When the comparator is a commercial assay, include name and manufacturer, and when applicable, the version or catalogue number. When the comparator is a reference method or "gold standard", provide adequate published references supporting the methodology.

5.5.3.9 Specimens and when applicable, subjects providing specimens

a) Validated specimen type (for example only plasma collected using validated anticoagulant).

b) Inclusion criteria.

c) Exclusion criteria.

d) Information necessary to characterise the subject/specimen (e.g. status of other analytes, concomitant medications).

e) Number of specimens and/or subjects.

f) Specimen storage, handling, transport, and disposal.

5.5.3.10 Procedures

a) When applicable, description of all study-related procedures that the specimens will undergo during the clinical performance study.

b) When applicable, description of procedure for determining when and how incidental findings should be reported to subjects/physicians.

5.5.3.11 Monitoring plan

General outline of the monitoring plan to be followed, including access to source data and the extent to which source data will be verified (e.g. confirmation of quality control results, calibration).

5.5.3.12 Data management

— Procedures used for data review, database cleaning, and issuing and resolving data queries.

— Procedures for verification, validation, and securing of electronic clinical data systems, when applicable.

— Procedures for data retention.

— Specified data retention period.

— Other aspects of quality assurance, as appropriate.

When electronic databases or remote electronic data systems are used, written procedures shall be implemented to

a) establish and document requirements for the electronic data system to receive, transfer and process data – information/data transferred to the sponsor shall be without personal individual identifiers,

b) verify and validate that the requirements for the electronic data system can be consistently met,

c) ensure traceability, completeness, reliability, consistency and logic of data entered,

d) ensure accuracy of reports,

e) ensure that data changes are documented and that there is no deletion of entered data (i.e. maintain an audit trail, data trail, edit trail),

f) maintain a security system that prevents unauthorized access to the data, both internally and externally,

g) maintain a list of individuals who have access to the electronic data system as well as the dates of access and privileges granted to each user,

h) ensure that all completed documents are signed by the principal investigator or authorized designee,

i) maintain adequate backup, retention and retrievability of the data, and

j) provide documented training of users on proper use of the system.

NOTE It is possible to provide a detailed plan for data management separate from the CPSP.

5.5.3.13 Statistical considerations

The description of and justification for

a) statistical design, method and analytical procedures,

b) sample size,

c) level of significance and power of the clinical performance study,

d) pass/fail criteria to be applied to the results of the clinical performance study,

e) provision for an interim analysis, when applicable,

f) procedures that ensure that all the data is taken into account, and

g) treatment of missing, unused or spurious data.

NOTE It is possible to provide a detailed plan for statistical considerations separate from the CPSP.

5.5.3.14 Amendments to the CPSP

Description of the procedures to amend the CPSP.

5.5.3.15 Deviations from clinical performance study protocol

a) Statement specifying that the investigator is not allowed to deviate from the CPSP, except when a deviation is necessary to protect subject's rights, safety and well-being, or the scientific integrity of the clinical performance study.

b) Procedures for recording, reporting and analysing CPSP deviations.

c) Descriptions of procedures for corrective and preventive actions for repeated and/or major CPSP deviations.

5.5.3.16 Accountability of IVD medical devices under investigation

Description of the procedures for the accountability of IVD medical devices under investigation, including procedures to ensure that access to IVD medical devices under investigation shall be controlled and these devices shall be used only in the clinical performance study and according to the CPSP.

The sponsor shall keep records to document the physical location of all IVD medical devices under investigation from shipment of the devices to the study site until return or disposal.

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the IVD medical devices under investigation, which shall include, when applicable,

a) the date of receipt,

b) the identification of each IVD medical device (e.g. batch number, serial number or unique code),

c) the expiry date,

d) the date or dates of use,

e) the date on which the IVD medical device under investigation was returned or disposed of, when applicable, and

f) the date of return of unused, expired or malfunctioning IVD medical devices under investigation, when applicable.

NOTE Written procedures can be required by national regulations.

5.5.3.17 Statements of conformity

a) Statement specifying that the clinical performance study shall be conducted in accordance with ethical principles, e.g. the Declaration of Helsinki[14].

b) Statement specifying that the clinical performance study shall not begin until the required approval/favourable opinion or waiver from the ethics committee and/or regulatory authority has been obtained, when applicable.

5.5.3.18 Informed consent process

a) Description of the general process for obtaining informed consent, including the process for providing subjects with new information, as needed.

b) Description of the informed consent process in circumstances when the subject is unable to give it.

5.5.3.19 Adverse events, adverse device effects and device deficiencies

Description of how to categorise, evaluate and report adverse events and device deficiencies which could result in a serious adverse event.

When the clinical performance study uses leftover/archived specimens, subjects will not be at risk from adverse events of any kind.

Where the study uses specimen collection procedures that pose no additional risk to the subject, in exceptional cases, there might be adverse events impacting the subjects.

It is also possible that a user/operator experiences an adverse device effect. In such cases, elements from Annex G might be appropriate.

5.5.3.20 Bibliography

List of bibliographic references pertaining to the clinical performance study, when applicable.

5.6 Case report forms

For clinical performance studies in which clinical information is not recorded, a Case Report Form (CRF) is not required, as the relevant information is captured by other means (data collection forms,

instrument printouts, etc.). The need for a CRF should be discussed as part of the study planning phase. When a CRF is required, information on the requirements included in Annex A shall be used.

5.7 Recording of specimen information

A standardized method of capturing and securing the information for each specimen used in the clinical performance study as required by the CPSP shall be implemented. Study sites shall record required information for all the specimens in the study, e.g. in study sample log.

No subject's personally identifiable information shall be included within the sponsor's records.

NOTE Traceability could be available from the institution from which the specimen was originally collected.

The principal investigator or institution shall provide direct access to source data during and after the clinical performance study for monitoring, audits and when relevant, ethics committee review and regulatory authority inspections. As required, the principal investigator or institution shall obtain permission for direct access to source documents from the subject and/or hospital administration before starting the clinical performance study.

5.8 Specimen accountability and integrity

The clinical performance study shall be conducted so as to ensure accountability, traceability, suitability and quality of all specimens during the steps of the clinical performance study, from collection through testing and result reporting. All relevant information should be documented and maintained for the duration of the study to ensure accuracy and reliability of the clinical performance study data.

Specimens shall be collected, transported, used and stored in the conditions identified in the CPSP.

5.9 Study site selection

5.9.1 Site qualification

The sponsor is responsible for the choice of study site(s). Site selection criteria shall be established based on the design or characteristics of the study and the intended use of the IVD medical device under investigation. These criteria can include

a) adequate qualifications of the principal investigator and related staff,

b) adequate resources, including facilities, laboratories, appropriately validated equipment and procedures,

c) access to an adequate number of suitable characterized specimens, and/or

d) use of a laboratory with an appropriate quality management system.

5.9.2 Site assessment

A site assessment shall be performed based on the selection criteria as set in 5.9.1.

5.9.3 Site selection

Outcomes of the site selection process shall be documented, including the rationale for the study site selection. Study site selection rationale is based on the site assessment, including factors such as prior experience of the sponsor with the principal investigator or the study site.

5.10 Monitoring plan

Study monitoring shall ensure

a) investigators adhere to the CPSP,

b) study data are accurate and complete, and

c) ethical conduct of the study, e.g. the rights and well-being of study subjects are protected.

One or more qualified monitors shall be appointed.

Monitors shall be

— qualified through training and experience as well as scientific or clinical knowledge,

— knowledgeable on the specific activities to be monitored, the CPSP, and any other relevant requirements, and

— trained on the relevant quality assurance procedures as well as any special procedures for monitoring a specific clinical performance study. Training shall be documented in the files.

The sponsor shall assess the extent and nature of monitoring appropriate for the clinical performance study, based on the assessment of the risk of the study. The sponsor shall also assess the strategy for source data verification, based on considerations such as the objective, design, complexity, sample size, critical data points and endpoints of the clinical performance study. Results of this assessment shall be used to develop a monitoring plan. Monitoring can occur during and/or after the clinical performance study.

The sponsor can determine and document the rationale for remote monitoring (without visiting the study site), in conjunction with procedures such as investigator's documented training, meetings, and extensive written guidance or telephone communication.

5.11 Agreements

There shall be an agreement between the sponsor and the principal investigator(s)/study site(s) and any other relevant parties (e.g. investigators, contract research organization(s) and laboratories), which defines the roles and responsibilities of each party in the clinical performance study (see 5.1). Disclosures of financial or other conflicts of interest shall be provided by principal investigators and investigators. All agreements shall be recorded in writing, signed and dated by all parties involved.

Principal investigator disqualification criteria can be described in the agreement.

5.12 Labelling

For an IVD medical device that is not commercially available in the country in which it is being studied, the labelling shall indicate that the IVD medical device under investigation is exclusively for use in a clinical performance study.

6 Study site initiation

6.1 General

An initiation visit for each participating study site, or alternatively, an investigator meeting shall be conducted (in person or remotely) and documented by the sponsor or monitor at the beginning of the clinical performance study. Names, signatures, functions and designated authorizations for the principal investigator and members of the study site team shall be documented.

6.2 Prerequisites

In initiating the study site, it shall be determined that

a) documentation is prepared and approved by the appropriate persons by dated signature; when required, copies shall be provided to all parties involved, and dated signatures obtained as appropriate,

b) the accuracy of the translation of documents is ensured, when relevant,

c) a supply of IVD medical devices under investigation is available in a timely manner for the clinical performance study; IVD medical devices under investigation shall not be made available to the principal investigator until all requirements to start the clinical performance study are met. Material for training and proficiency testing may be shipped prior to initiating studies,

d) any financial arrangements between the principal investigator or the study site and the sponsor are documented,

e) any required application(s) to begin the clinical performance study in a given country have been submitted to the appropriate regulatory authority(ies) for review, acceptance or permission (as per applicable regulatory requirement[s]),

f) ethics committee's approval/favourable opinion or waiver has been obtained and documented when required, and that appropriate provisions are made to meet any conditions imposed by the ethics committee, and

g) any modification(s) required by the ethics committee or regulatory authority are made and documented by the principal investigator, and have gained the approval/favourable opinion of the ethics committee or regulatory authority.

6.3 Training

Documentation of training, experience and scientific or clinical knowledge shall be ensured for all involved parties in order to adequately conduct the clinical performance study, including training, as applicable to each role:

a) the use of the IVD medical device(s) under investigation;

b) the device accountability procedures;

c) the CPSP;

d) the method of obtaining and maintaining specimen data and result information;

e) the written informed consent form and informed consent process as well as other written information provided to subjects, when applicable; and

f) the sponsor's written procedures, this document and any regulatory requirements, as applicable.

Any additional members of the study team shall receive appropriate training on clinical performance study requirements and such training shall be documented.

6.4 Initiation of the study site

The monitor or designee shall initiate each study site to ensure that the principal investigator and study site team

a) have successfully completed all training,

b) have access to an adequate number of IVD medical devices under investigation, and

c) are familiar with the responsibilities of the principal investigator and study team.

The monitor or designee shall also ensure that all pre-study documentation is completed, e.g. ethics committee approval/favourable opinion, written clinical performance study agreements, etc.

7 Clinical performance study conduct

7.1 General

When written approval/favourable opinion from the ethics committee and/or the relevant regulatory authorities of the countries where the clinical performance study is taking place is required, the clinical performance study shall not commence until that approval/opinion has been received.

The clinical performance study shall be conducted in accordance with the CPSP.

7.2 Responsibilities of the sponsor

The sponsor shall be responsible for

a) accountability of IVD medical devices under investigation throughout the clinical performance study,

b) establishing a review mechanism to ensure that the principles described in 5.1 are respected at all times during the study,

c) documenting correspondence with all parties involved in the clinical performance study including, when applicable, ethics committees and regulatory authorities,

d) ensuring that the clinical performance study is appropriately monitored as defined by the monitoring plan,

e) reviewing the monitoring report(s) and following up any action(s) required in the monitoring report(s),

f) taking prompt action to secure conformity with all clinical performance study requirements,

g) when applicable, submitting progress reports, including safety summary, deviations and/or relevant changes in study team, to all reviewing ethics committees and the regulatory authorities,

h) ensuring that appropriate mechanisms are in place to cover the liability of the sponsor for the study (e.g. insurance), and

i) maintaining the integrity of any study samples that are also required for the standard of care.

7.3 Study site monitoring

7.3.1 General

The purpose of clinical performance study monitoring is to verify that the conduct of the study conforms to the CPSP, subsequent amendment(s), this document and the applicable ethical and regulatory requirement(s).

The conduct of the clinical performance study shall be monitored according to the monitoring plan.

7.3.2 Routine monitoring

The monitor shall perform routine monitoring activities to verify that

a) conformity with the CPSP, any subsequent amendment(s) and this document is maintained; deviations shall be discussed with the principal investigator(s) or authorized designee, documented and reported to the sponsor,

b) only authorized individuals are participating in the clinical performance study,

c) the IVD medical device under investigation is being used according to the CPSP or instructions for use,

d) when issues arise with the device, its method of use, or the CPSP, these are documented and reported to the sponsor,

e) study site resources, including laboratories, equipment and the study site team, remain adequate throughout the duration of the clinical performance study,

f) the principal investigator and the study team continue to have access to an adequate number of specimens and IVD medical devices under investigation,

g) when applicable, signed and dated informed consent forms have been obtained from each subject at the point of enrolment or before any clinical performance study related procedures are undertaken,

h) clinical performance study records are accurate, complete, up to date, stored and maintained appropriately,

i) all adverse events are recorded and reported to the sponsor and when applicable, reported to the ethics committee and regulatory authorities in a timely manner or as defined by the relevant authority (see Annex G),

j) all device deficiencies are reported to the sponsor,

k) the storage and accountability of the IVD medical device under investigation and specimens are correct and the traceability process is being followed,

l) all other records, reports, notifications, applications, submissions and correspondence are maintained in the investigator's files and are accurate, complete, timely, legible, dated and identify the clinical performance study,

m) maintenance and calibration of the equipment relevant to the conduct and assessment of the clinical performance study is appropriately performed and documented, when applicable,

n) subject and/or specimen withdrawal has been documented,

o) any non-conformity with the requirements stated in the informed consent or CPSP has been documented,

p) the principal investigator and study site team are informed and knowledgeable of all relevant documented updates concerning the clinical performance study, and

q) any corrective and preventive actions, as needed, have been implemented and are effective.

7.3.3 Monitoring reports

All monitoring activities including communications related to the clinical performance study shall be documented in a written report to the sponsor and shall include

a) the date, study site identification, name of the monitor and name of the principal investigator or other individuals contacted, and

b) a summary of what the monitor reviewed and his/her observation(s) with regard to the completion of previous action items, significant findings, facts, deviations, conclusions, and recommended actions to be taken to secure conformity.

A copy of the monitoring report or a summary of key findings shall be shared with the principal investigator in writing, including electronic communication.

7.4 Security and confidentiality of data

Confidentiality of data shall be observed by all parties involved at all times throughout the clinical performance study. All data shall be secured against unauthorized access.

The privacy of each subject providing specimens for the clinical performance study and confidentiality of his/her information shall be preserved in reports and when publishing any data.

NOTE Requirements for data confidentiality and disclosure can vary by jurisdiction.

8 Close-out of the clinical performance study

8.1 Close-out activities

Routine close-out activities shall be conducted under the terms of the study agreement, and documented to ensure that the principal investigator's records are complete, all documents needed for the sponsor's files are retrieved, remaining clinical performance study materials are disposed of or returned to the sponsor, previously identified issues have been resolved and all parties are notified of study closure. This can be done through a site visit or remotely. All close-out activities are completed for terminated studies.

a) Completing the records includes ensuring that

   1) all essential documents are up to date, complete and signed,

   2) all outstanding queries are resolved,

   3) the status of all ongoing adverse events is documented,

   4) arrangements are made for archival and record retention, and

   5) the disposition of any of the following is documented:

      i) IVD medical devices under investigation;

      ii) remaining specimens (e.g. blood or tissue) taking into account the ownership;

      iii) other clinical performance study materials.

b) Notification of study closure includes, when required

   1) notification to ethics committee, and/or

   2) notification to regulatory authorities.

8.2 Clinical performance study report

After the close-out of the clinical performance study, including premature termination, a report of the study shall be completed, containing the information listed below. For those studies described in A.1, use the additional requirements for content of the clinical performance study report specified in Annex D.

a) the clinical performance study report shall be in written form (including electronic or hard copy);

b) the title page should contain the following information:

   1) title of the clinical performance study;

   2) identifiers of the clinical performance study (e.g. study number) where applicable;

   3) brief identification of the IVD medical device(s) under investigation, including names, models, etc., as relevant for complete identification;

   4) when relevant, statement indicating whether the clinical performance study was performed in accordance with this document or any other applicable guidelines and applicable regulations;

   5) date of report;

6) author(s) of report.

c) a table of contents, where included, shall include the page number or locate information of each section; the introduction shall contain a brief statement placing the clinical performance study in the context of the development of the IVD medical device under investigation and relating the critical features of the clinical performance study (e.g. objectives and hypotheses, target population, treatment and follow-up duration) to that development.

Guidelines or standards that were followed in the development of the CPSP, or any other agreements or meetings between the sponsor and regulatory authorities that are relevant to the particular clinical performance study, shall be identified or described.

d) a description of the IVD medical device under investigation, containing the following points:

1) a description of the IVD medical device under investigation, including device identifier;

2) the intended use of the IVD medical device(s) under investigation;

3) any changes to the IVD medical device while under investigation during the clinical performance study.

NOTE Any change could be a critical change that invalidates the study when performance is affected.

e) a summary of or a reference to the CPSP, including any subsequent amendment(s) with a rationale for each amendment, shall be provided. The latest version of the CPSP may be appended to the report;

f) the results of the clinical performance study covering the following points:

1) the clinical performance study initiation date;

2) the clinical performance study completion/suspension date;

3) a listing of the clinical performance study sites where the study was conducted, dates for each, and details of conduct for each site, e.g. collection, testing;

4) a description of study-specific training received by site staff;

5) the disposal of specimens and IVD medical devices under investigation;

6) the subject demographics/specimen characterisation, when applicable;

7) CPSP conformity (including number and type of protocol deviations);

8) an analysis, which includes

i) a statistical analysis of the data resulting from the CPSP,

ii) the statistical analysis method used and the acceptance criteria,

iii) a summary of all adverse device effects,

iv) a table compiling all observed device deficiencies that could have led to a serious adverse device effect, and any corrective actions taken during the clinical performance study, if any,

v) any needed subgroup analyses for special populations (i.e. gender, racial/cultural/ethnic subgroups), as appropriate, and

vi) an accountability of all subjects and specimens, as applicable to the study, with a description of how missing data or deviations(s) were dealt with in the analysis e.g. specimens not passing screening tests, invalid results.

g) a discussion of the study and overall conclusions. The conclusions shall include the following points:

1) a critical appraisal of the study results to determine whether the aims of the study have been met;

2) the safety or performance results and any other endpoints;

3) any specific benefits or special precautions required for individual subjects or groups considered to be at risk;

4) any implications for the conduct of future clinical performance studies;

5) any limitations of the clinical performance study.

h) a list of abbreviated terms, and definitions of specialized or unusual terms;

i) a section on ethics which shall include the following points:

1) a confirmation that the CPSP and any amendments to it were reviewed by the ethics committee (when required);

2) a list of all ethics committees consulted in relation to the clinical performance study.

j) an overview of the administrative structure which shall include the following points:

1) a brief description of the organization of the clinical performance study;

2) a list of investigators, including their affiliations and potential conflict of interests;

3) the names and complete contact details for any third parties that were directly involved in the conduct of the study.

When applicable, the clinical performance study report shall be made available in a documented manner to all principal investigators for review and comments recorded.

Publication of the outcomes of the clinical performance study is encouraged to help guide future research, device development and medical treatment.

NOTE Additional requirements for the content of the clinical performance study report for certain studies are given in Annex D.

8.3 Document retention

The sponsor and principal investigator shall be aware of the applicable regulatory requirement(s) when maintaining the clinical performance study documents. They shall take measures to prevent accidental or premature destruction of these documents. The principal investigator or sponsor may transfer custody of records to another person/party and document the transfer at the study site or at the sponsor's facility.

In the absence of regulatory requirements, the sponsor shall maintain documents in accordance with the documentation requirements of the relevant QMS system (e.g. ISO 13485).

8.4 Suspension or premature termination of the clinical performance study

The sponsor can suspend or prematurely terminate either a clinical performance study in an individual study site or the entire clinical performance study for significant and documented reasons. All affected

investigators shall be informed accordingly and when the study is terminated, close-out activities shall be performed.

NOTE Legal notification requirements and specific time limits can apply.

9 Auditing

For IVD medical device studies, auditing is encouraged, particularly for more complex studies. For further details, see Annex I.

Annex A
(normative)

Additional general requirements for certain studies

A.1 Introduction

In addition to requirements set out in the body of this document, the requirements below apply to any clinical performance study

a) that is an interventional clinical performance study, or

b) in which specimen collection is done primarily for the purpose of the clinical performance study and where the specimen collection procedures pose additional risks to the subject, or

c) when the conduct of the study involves additional risks for the subjects of the studies.

A.2 Ethics committee approval

For IVD medical devices under investigation as described in A.1, ethics committee approval shall be obtained. Requirements for initial and continuing communication with the ethics committee shall be set out as in Annex E.

A.3 Informed consent

Requirements for obtaining informed consent shall be set out as in Annex F.

A.4 Accounting for subjects

All subjects enrolled in the clinical performance study (including those withdrawn from the clinical performance study or lost to follow-up) shall be accounted for and documented.

When a subject withdraws from the clinical performance study, the reason(s) shall be recorded. When such withdrawal is due to problems related to the safety or performance of the IVD medical device under investigation, the investigator shall ask for the subject's permission to follow his/her status outside the clinical performance study, when applicable. (Refer to Annex G for AE reporting requirements.)

A.5 Case report forms

Case report forms (CRFs) shall be developed to capture the data for each enrolled subject/specimen as required by the CPSP. The CRFs shall include information on each subject/specimen at commencement, and during the course of the clinical performance study, use of the IVD medical device under investigation and any other relevant information.

When it is necessary to amend the CPSP, the sponsor shall review the CRFs to determine if an amendment of these forms is also necessary.

A.6 Suspension or termination of a clinical performance study

A.6.1 Procedure for suspension/termination

A principal investigator, ethics committee, or regulatory authority can suspend or prematurely terminate participation in a clinical performance study at the study sites for which they are responsible.

When suspicion of an unacceptable risk to subjects arises during the clinical performance study, the sponsor shall suspend the clinical performance study while the risk is assessed. The sponsor shall terminate the clinical performance study when an unacceptable risk is confirmed.

The sponsor shall consider terminating or suspending the participation of a particular study site or investigator when monitoring or auditing identifies serious or repeated deviations on the part of an investigator.

When suspension or premature termination occurs, the terminating party shall justify its decision in writing and promptly inform the other parties with whom they are in direct communication. The principal investigator and sponsor shall keep each other informed of any communication received from either the ethics committee or the regulatory authority.

NOTE The usual lines of communication are between sponsor and principal investigator, sponsor and ethics committee, and sponsor and regulatory authority.

When, for any reason, the sponsor suspends or prematurely terminates the clinical performance study at an individual study site, the sponsor shall ensure that the ethics committee is notified, either by the principal investigator or by the sponsor. When the suspension or premature termination was in the interest of safety, the sponsor shall inform all other principal investigators.

When suspension or premature termination occurs,

a) the sponsor shall remain responsible for providing resources to fulfil the obligations from the CPSP and existing agreements for following up the subjects enrolled in the clinical performance study, and

b) the principal investigator or authorized designee shall promptly inform the enrolled subjects at his/her study site, when applicable.

NOTE The method and the timing of this communication will depend on the circumstances and the perceived risks.

All activities listed in 8.1 shall also be conducted.

A.6.2 Procedure for resuming the clinical performance study after temporary suspension

When the sponsor concludes an analysis of the reason(s) for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, the sponsor shall inform the relevant parties of the rationale and provide them with the relevant data supporting this decision.

NOTE The usual lines of communication are between sponsor and principal investigator, sponsor and ethics committee, and sponsor and regulatory authority.

When subjects have been informed of the suspension, the principal investigator or authorized designee shall inform them of the reasons for resumption.

The sponsor shall promptly report any deviation from the CPSP that affects the rights, safety or well-being of the subject or the scientific integrity of the clinical performance study, including those that occur under emergency circumstances.

A.7 Medical care of subjects

The CPSP shall specifically address what medical care, if any, will be provided for the subjects after the clinical performance study has been completed.

The principal investigator shall

a) provide adequate medical care to a subject during and after a subject's participation in a clinical performance study in the case of adverse events, as described in the informed consent,

b) inform the subject of the nature and possible cause of any adverse events experienced,

c) provide the subject with the necessary instructions on proper use, handling, storage and return of the IVD medical device under investigation, when it is used or operated by the subject,

d) inform the subject of any new significant findings occurring during the clinical performance study, including the need for additional medical care that might be required,

e) provide the subject with well-defined procedures for possible emergency situations related to the clinical performance study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical performance studies as needed,

f) ensure that clinical records are clearly marked to indicate that the subject is enrolled in a particular clinical performance study,

g) when applicable, provide subjects enrolled in the clinical performance study with some means of documenting their participation in the clinical performance study, together with identification and conformity information for concomitant treatment measures (contact address and telephone numbers shall be provided),

h) inform, with the subject's approval, the subject's personal physician about the subject's participation in the clinical performance study, and

i) make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from the clinical performance study while fully respecting the subject's rights.

A.8 Compensation

Compensating subjects for costs resulting from participation in the clinical performance study (e.g. transportation) can be appropriate, but the compensation amount shall not be so large as to unduly encourage the subjects to participate.

Compensation and indemnification arrangements shall be mentioned in the informed consent form, as applicable.

Arrangements for additional health care for subjects who suffer from an adverse event as a result of participating in the clinical performance study shall be made and described in the informed consent form, or a reference to subject's insurance.

NOTE Such arrangements can be subject to national regulations.

A.9 Vulnerable populations

These clinical performance studies shall be designed specifically to address health problems that occur in the vulnerable population, and offer the possibility of direct health-related benefit to the vulnerable population.

Annex B
(normative)

Clinical performance study protocol (CPSP)

B.1 General

This annex specifies the content required of a CPSP, in addition to those requirements set forth in 5.5, for those studies described in A.1. The content of a CPSP and any subsequent amendments for such studies shall include all the topics listed in this annex, together with a description for each topic that is not self-explanatory.

B.2 Identification and description of the IVD medical device under investigation

In addition to the requirements of 5.5.3.7, the name and address of the manufacturer of the IVD medical device under investigation is required.

B.3 Identification of the clinical performance study protocol

Version/issue number and reference number on each page of the CPSP.

B.4 Sponsor

Address of the sponsor of the clinical performance study.

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

B.5 Principal investigator and study site(s)

a) Name, address, and professional position of principal investigator(s).

b) Name and address of the study site(s) in which the clinical performance study will be conducted.

c) Name(s) and address(es) of other institutions involved in the clinical performance study.

The sponsor shall maintain an updated list of principal investigators, study sites, and institutions. This list can be kept separately from the CPSP. The final list shall be provided with the clinical performance study report.

B.6 Overall synopsis of the clinical performance study

The synopsis of the clinical performance study shall include relevant information regarding, when applicable, follow-up of subjects providing specimens.

B.7 Risks and benefits of the IVD medical device under investigation and clinical performance study

a) Anticipated adverse device effects.

b) Anticipated adverse events associated with the study other than those associated with the IVD medical device, e.g. during specimen collection.

c) Residual risks associated with the study, as identified in the risk analysis report.

d) Steps that will be taken to control or mitigate the risks.

e) Risk-to-benefit rationale.

B.8 Design of the clinical performance study

B.8.1 General

a) Justification for the need for an interventional study design or the need for specimens primarily collected for the study which pose additional risks for the subject.

b) Rationale for the choice of the type and design of clinical performance study to be performed in relation to the intended use of the IVD medical device under investigation.

c) Description of the measures to be taken to avoid bias (considerations of bias from, for instance, population, test protocol, reference measurement procedure, interpretation and analysis), including when applicable randomization and blinding/masking.

B.8.2 IVD medical device under investigation and comparator(s)

Justification of the choice of comparator(s).

B.8.3 Specimens and when applicable, subjects providing specimens

a) Method of specimen collection.

b) Inclusion criteria for subjects providing specimens.

c) Exclusion criteria for subjects providing specimens.

d) Criteria and procedures for subject withdrawal or discontinuation.

e) Total expected duration of the clinical performance study.

f) When applicable, expected duration of each subject's participation.

g) Volume of specimens to be collected, and number of subjects providing specimens required to be included in the clinical performance study.

h) When applicable, estimated time needed to select this number (i.e. enrolment period).

i) Specimen storage, handling, processing, transport, and disposal.

B.8.4 Procedures

Description of all clinical performance study related procedures subjects will undergo during the clinical performance study.

B.8.5 Monitoring plan

Detailed plan to be followed for monitoring the clinical performance study, including access to source data and the extent to which source data will be verified.

NOTE It is possible to provide a detailed plan for monitoring arrangements separately from the CPSP.

B.8.6 Data management

Detailed plan to be followed for data management for the clinical performance study, including access to source data and the extent to which source data will be verified.

B.8.7 Statistical considerations

The description of and justification for:

a) expected drop-out rates, when applicable;

b) criteria for the termination of the clinical performance study on statistical grounds, when applicable;

c) the specification of subgroups for analysis;

d) the treatment of data, including drop-outs and withdrawals.

NOTE Special reasoning and sample size(s) can apply for early clinical performance studies, e.g. feasibility clinical performance studies.

B.8.8 Deviations from clinical performance study protocol

The description of and justification for:

a) procedures for reporting any deviation(s) from the original statistical plan;

b) emergency contact details for reporting serious adverse events and serious adverse device effects;

c) notification requirements and time frames.

B.8.9 Accountability of IVD medical devices under investigation

No additional requirements.

B.8.10 Insurance

Statement specifying the type of insurance that shall be provided for subjects, when applicable.

B.8.11 Adverse events, adverse device effects and device deficiencies

For this annex, both subject and user/operator can be exposed to adverse events.

a) definitions of adverse events and adverse device effects;

b) definition of device deficiencies;

c) definitions of serious adverse events and serious adverse device effects and, when applicable, unanticipated serious adverse device effects;

d) list of foreseeable adverse events and anticipated adverse device effects, together with their likely incidence, mitigation or treatment;

e) time period in which the principal investigator shall record and report all adverse events and device deficiencies to the sponsor;

f) details of the process for investigator recording and reporting adverse events (date of the adverse event, treatment, resolution, assessment of both the seriousness and the relationship to the IVD medical device under investigation);

   In the case of interventional studies, details of reporting AEs shall be delineated (e.g. an IVD medical device manufacturer and a pharmaceutical manufacturer).

g) details of the process for assessment and reporting device deficiencies;

h) emergency contact details for reporting serious adverse events and serious adverse device effects.

B.8.12 Vulnerable population

a) Description of the vulnerable population, when applicable.

b) Rationale for including vulnerable population, when applicable.

c) Description of the ethics committee's specific responsibility.

d) Description of what medical care or other care (e.g. transport, counselling etc.), if any, will be provided for subjects after the clinical performance study has been completed.

B.8.13 Suspension or premature termination of the clinical performance study

a) Criteria and arrangements for suspension or premature termination of the entire clinical performance study or of the clinical performance study at one or more study sites.

b) Criteria for access to and breaking the blinding/masking code in the case of suspension or premature termination of the clinical performance study, when the clinical performance study involves a blinding/masking technique.

c) Details of process and requirements needed to restart a suspended study.

d) Requirements for subject follow-up, if applicable.

B.8.14 Publication and Communication policy

Statement indicating the conditions under which the results of the clinical performance study will be offered for publication.

NOTE If publication of the results is planned, the clinical performance study might need to be listed on a public database.

B.8.15 Bibliography

List of bibliographic references pertaining to the clinical performance study, when applicable.

Annex C
(normative)

Investigator brochure

C.1 Introduction

C.1.1 General

This annex specifies the content required of an investigator brochure for those studies that are described in A.1. Relevant content for an IVD clinical performance study should be incorporated in the investigator brochure. The investigator brochure includes the results of studies conducted on the product, and is updated on a regular basis.

When the required information of the investigator brochure is provided in other documentation (e.g. the CPSP or instructions for use) such documents shall be referenced in the investigator brochure and shall be made available upon request.

The content of the investigator brochure shall contain, as a minimum, all topics listed in this annex.

C.1.2 Identification of the investigator brochure

a) Name of the IVD medical device under investigation.

b) Document reference number, if any.

c) Version or date of the investigator brochure.

d) Confidentiality statement, when applicable.

e) Summary of the revision history in the case of amendments, when applicable.

f) A version/issue number and reference number, when any, with the page number and the total number of pages on each page of the investigator brochure.

C.1.3 Sponsor

a) Name and address of the sponsor of the IVD medical device under investigation.

b) Name and address of the legal representative or contact person, as applicable.

C.2 Information on IVD medical device under investigation

a) Summary of the literature and evaluation supporting the rationale for the design and intended use of the IVD medical device under investigation.

b) Statement concerning the regulatory classification of the IVD medical device under investigation, when relevant.

c) General description of the IVD medical device under investigation and its components.

d) Description of the intended use of the IVD medical device under investigation, along with supporting scientific literature.

e) Manufacturer's instructions for installation and use of the IVD medical device under investigation, including any necessary storage and handling requirements, preparation for use, any pre-use safety

or performance checks and any precautions to be taken after use (e.g. disposal, decontamination), when relevant.

f) Description of the intended clinical performance characteristics, when applicable.

C.3 Analytical testing

Summary of the analytical testing that has been performed on the IVD medical device under investigation, together with an evaluation of the results of such testing, justifying its use in the clinical performance study.

C.4 Existing clinical performance data

a) Summary of relevant previous clinical experience with the IVD medical device under investigation and with IVD medical devices that have similar characteristics, including such characteristics that relate to other intended uses of the IVD medical device under investigation.

b) Analysis of adverse device effects and any history of modification or recall.

C.5 Risk management

a) Summary of the risk analysis for the IVD medical device, including identification of residual risks.

b) Result of the risk assessment (risk chart).

c) Anticipated risks, warnings, hazards, etc., for the IVD medical device under investigation.

d) A plan for reporting results to clinicians or public health institutions in cases for which a result might have an immediate public health effect (e.g. emerging infectious disease).

NOTE See ISO 14971 and ISO/TR 24971 for guidance on risk assessment and management.

C.6 Regulatory and other references

a) List of International Standards, if any, conformed with in full or in part.

b) Statement of conformity with national regulations, when applicable.

c) List of references, when relevant.

Annex D
(normative)

Clinical performance study report

D.1 General

This annex specifies the content required of a clinical performance study report, in addition to those requirements set forth in 8.2, for those studies that are described in A.1. The CPSR should describe the design, execution, statistical analysis and results of a clinical performance study.

The format given here may be used in interim, progress, annual, or final reports when such reports are required.

D.2 Signature page

The sponsor and coordinating investigator can be asked to provide their signatures, indicating their agreement with the content of the clinical investigation report. If no coordinating investigator is appointed, the signature of the principal investigator(s) shall be obtained.

D.3 Cover page

The title page should contain the name and contact details of sponsor or sponsor's representative.

D.4 Table of contents

The table of contents should include a list of appendices and their location.

D.5 Summary

The summary should contain the following items:

a) the title of the clinical performance study;

b) an introduction;

c) the purpose of the clinical performance study;

d) description of the clinical performance study population;

e) the number of study sites;

f) the statistical method used;

g) the study acceptance criteria;

h) the results of the clinical performance study;

i) the conclusion;

j) the date of the clinical performance study initiation;

k) the completion date of the clinical performance study or, when the clinical performance study is discontinued, the date of premature termination.

D.6 Introduction

The introduction should contain a brief statement placing the clinical performance study in the context of the development of the IVD medical device under investigation and relating the critical features of the clinical performance study (e.g. objectives and hypotheses, target population, treatment and follow-up duration) to that development.

Guidelines or standards that were followed in the development of the CPSP, or any other agreements or meetings between the sponsor and regulatory authorities that are relevant to the particular clinical performance study, should be identified or described.

D.7 IVD medical device under investigation and methods

D.7.1 Description of the IVD medical device under investigation

The description of the IVD medical device under investigation should contain the following points:

a) previous intended uses, when relevant;

b) any changes to the IVD medical device while under investigation during the clinical performance study, including

   1) raw materials,

   2) software,

   3) components,

   4) shelf-life,

   5) storage conditions,

   6) instructions for use, and

   7) other changes.

NOTE Any of the above changes could be critical changes that invalidate the study when performance is affected.

D.7.2 Clinical performance study protocol (CPSP)

No additional requirements other than described in Clause 5.

D.8 Results

The results report should include the following points:

a) a listing of the clinical performance;

b) details of enrolment for each site;

c) qualification of the study site operators, received when applicable or required per the protocol;

d) an analysis, which includes:

   1) a summary of all adverse events and adverse device effects, including a discussion of the severity, corrective action required, resolution and relevant principal investigator's judgment concerning the causal relationship with the IVD medical devices under investigation or procedure;

2) an accountability of all specimens with a description of how missing data or deviation(s) were dealt with in the analysis, including invalid, indeterminate and other missing results such as those from subjects:

   i) not passing screening tests;

   ii) lost to follow-up;

   iii) withdrawn or discontinued from the clinical performance study and the reason;

3) an assessment of risks and benefits.

D.9 Discussion and overall conclusions

The conclusions should include a discussion of the clinical relevance and importance of the results in the light of other existing data.

D.10 Abbreviated terms and definitions

No additional requirements.

D.11 Ethics

No additional requirements.

D.12 Investigators and administrative structure of clinical performance study

The overview of the administrative structure should include the names and addresses of the sponsor(s) or sponsors' representative(s).

D.13 Annexes to the report

Annexes to the report could contain the following information:

a) the CPSP, including amendments;

b) the instructions for use, including those used for the reference measurement or comparative procedure;

c) the list of principal investigators and their affiliated clinical performance study sites, including a summary of their qualifications or a copy of their curricula vitae;

d) the list of names and complete contact details for any third parties (such as core laboratories, contract research organizations, consultants or other contractors) that contributed to the clinical performance study;

e) the list of monitors;

f) the tabulation of all relevant data sets, including:

   1) CPSP deviations that could have affected the rights, safety or well-being of the subject or the scientific integrity of the clinical performance study,

   2) all adverse events, adverse device effects and device deficiencies, and

   3) withdrawals and discontinuations.

Annex E
(normative)

Communication with the ethics committee

E.1 Introduction

This annex specifies the requirements for communication with the ethics committee for those studies that are described in A.1, in addition to those requirements set forth in 4.4 of the main text. These requirements can also apply to other studies in situations for which national or regional requirements for ethics committee approval of the clinical performance study and/or the participating sites exist.

E.2 Initial ethics committee submission

As a minimum, the following information and any amendments shall be provided to the ethics committee:

a) CPSP;

b) investigator's brochure or equivalent documentation;

c) informed consent form and any other information to be provided to subjects in native language and translated version;

d) procedures for recruiting subjects, when relevant, and advertising materials, if any, in native language and translated version;

e) a copy of the curriculum vitae of the principal investigator(s) for which the ethics committee has oversight.

The following documents might also need to be provided to the ethics committee, depending on the clinical performance study design and national or regional requirements:

f) documents related to payments and compensation available to subjects;

g) proposed compensation to the institution or principal investigator;

h) documentation related to any conflict of interest, including financial, on the part of an investigator, as per national regulations;

i) evidence of the clinical performance study insurance.

E.3 Information to be obtained from the ethics committee

Before beginning the clinical performance study, the sponsor shall obtain documentation of the ethics committee's approval/favourable opinion identifying the documents and amendments on which the opinion was based.

NOTE The sponsor can request the ethics committee opinion voting list for the clinical performance study to document that members of the study site team were not part of the voting.

E.4 Continuing communication with the ethics committee

The following information shall be provided to the ethics committee, if required by national regulations, the CPSP or the ethics committee, whichever is more stringent:

a) serious adverse events;

b) requests for deviations, and reports of deviations, whether the deviation affects subjects' rights, safety and well-being, or the scientific integrity of the clinical performance study;

c) progress reports, including safety summary and deviations;

d) amendments to any documents already approved by the ethics committee;

NOTE For non-substantial changes (e.g. minor logistical or administrative changes, change of monitor(s), telephone numbers, renewal of insurance) not affecting the rights, safety and well-being of human subjects or not related to the clinical performance study objectives or endpoints, a simple notification to the ethics committee and, when applicable, regulatory authorities might be sufficient.

e) when applicable, notifications of suspensions or premature termination;

f) when applicable, justification and request for resuming the clinical performance study after a suspension;

g) clinical performance study report or its summary.

E.5 Continuing information to be obtained from the ethics committee

As a minimum, during the clinical performance study, the following information shall be obtained in writing from the ethics committee before implementation;

a) approval/favourable opinion of amendments, as stated in E.4 d);

b) approval of the request for deviations that can affect the subject's rights, safety and well-being, or the scientific integrity of the clinical performance study, as stated in E.4 b);

c) approval for resumption of a suspended clinical performance study, as stated in E.4 f), when applicable.

Annex F
(normative)

Informed consent

F.1 General

Informed consent is required for those studies described in A.1. The process for obtaining informed consent shall be documented. Informed consent shall be obtained from the subject and documented before any procedure specific to the clinical performance study is applied to the subject, or their specimen, except when special circumstances described in F.3 apply.

The informed consent documentation consists of provided information (e.g. form, electronic presentation) (see F.4) and an informed consent signature form (see F.5). This documentation may be provided in electronic form: the documentation of the electronic confirmation of consent together with date may be in the form of a timestamp, retained in an electronic database.

F.2 Process of obtaining informed consent

The general process for obtaining informed consent shall be documented in the CPSP and shall:

a) ensure that the principal investigator or authorized designee conducts the informed consent process,

b) require the principal investigator to ensure and document appropriate training when an authorized designee is appointed to conduct the informed consent process,

c) include all aspects of the clinical performance study that are relevant to the subject's decision to participate throughout the clinical performance study,

d) avoid any coercion or undue improper influence on, or inducement of, the subject to participate,

e) not waive or appear to waive the subject's legal rights,

f) use native, non-technical language that is understandable to the subject,

g) provide ample time for the subject to review and understand the informed consent form and to consider participation in the clinical performance study,

h) include personally dated signatures of the subject and the principal investigator or an authorized designee responsible for conducting the informed consent process,

i) provide the subject with a copy of the signed and dated informed consent form and any other written information,

j) provide complete information on a contact that can provide answers to questions or concerns that can arise,

k) show how informed consent will be obtained and recorded in special circumstances (see F.3) in cases in which the subject is unable to provide it him or herself, and

l) ensure important new information is provided to new and existing subjects throughout the clinical performance study.

The above requirements shall also apply with respect to informed consent obtained from a subject's legally authorized representative.

F.3 Special circumstances for informed consent

F.3.1 General

The provisions given in F.3.2 to F.3.3 are subject to national regulations.

F.3.2 Subject needing legally authorized representatives

Informed consent may be given by the legally authorized representative only when a subject is unable to make the decision to participate in a clinical performance study (e.g. infant, child, juvenile, seriously ill or unconscious subject, mentally ill person, mentally impaired person). In such cases, the subject shall also be informed about the clinical performance study within his/her ability to understand.

F.3.3 Subject unable to read or write

Informed consent shall be obtained through a supervised oral process when a subject or legally authorized representative is unable to read or write. An independent witness shall be present throughout the process. The written informed consent form and any other information shall be read aloud and explained to the prospective subject or his/her legally authorized representative and either individual shall sign and personally date the informed consent form. The witness also signs and personally dates the informed consent form attesting that the information was accurately explained and that informed consent was freely given.

F.4 Information to be provided to the subject

All information pertinent to the clinical performance study, including at least the following, shall be provided in native, non-technical language that is understood by the subject (or the subject's legally authorized representative).

a) Description and purpose:

   1) statement that the clinical performance study involves research;

   2) purpose of the clinical performance study;

   3) anticipated duration of the clinical performance study, and extent of the involvement and responsibilities of each subject during the clinical performance study;

   4) description of the IVD medical device under investigation and comparator, if any;

   5) for an interventional clinical performance study using an IVD medical device that is not commercially available in the country in which it is being studied, the informed consent form shall indicate that subject will be tested using an IVD medical device under investigation (i.e. not approved for general use);

   6) description of all procedures involving the subject, including the type and number of specimens and the specimen collection method;

   7) aspects of the clinical performance study (not related to the IVD medical device) that are experimental (i.e. not approved for marketing in the study location);

   8) description of the clinical performance study, including a mention of any comparison groups and method of assignment to each group, as applicable;

   9) number of subjects expected to participate in the clinical performance study;

   10) whether the specimens might be used for future studies;

   11) instructions for subject's withdrawal of consent, if desired; and

12) information on if/when results of the study will be provided to the subject.

b) Potential benefits:

1) description of benefits for the subject that can reasonably be expected (when there is no direct therapeutic benefit anticipated, this shall be noted);

2) description of potential benefits for others.

c) Risks and inconveniences for the subject, and when applicable, for an embryo, foetus, or nursing infant:

1) description of residual risks identified by the risk analysis;

2) description of risks associated with the clinical procedures required by the CPSP;

3) for an interventional clinical performance study, the risk of false results (e.g. false positive or false negative) being used for inappropriate patient management decisions;

4) description of the risks associated with specimen collection procedures;

5) statement that unanticipated risks might occur;

6) description of inconveniences.

d) Alternative procedure(s):

Information on alternative treatments or procedures that might be available to the subjects, and their potential risks and benefits.

e) Confidentiality:

1) statement confirming that subject participation is confidential;

2) statement confirming that records identifying the subject will be kept confidential to the extent allowed by the law;

3) statement confirming that the subject understands that regulatory authorities, ethics committee representatives and sponsor's representatives involved in the clinical performance study will have direct access to medical records;

4) statement indicating that clinical performance study results might be published without disclosing the subject's identity.

NOTE Additional requirements regarding personal data protection can be requested as per national or regional regulations.

f) Compensation:

1) information about provisions for compensation available in the event of injury arising from participation in the clinical performance study;

2) information about additional health care for subjects who suffer from an adverse event as a result of participating in the clinical performance study;

3) information on financial compensation for participation, when applicable.

g) Anticipated expenses, if any, to be borne by the subject for participating in the clinical performance study.

h) Information on the role of sponsor's representative in the clinical performance study.

i) Contact persons:

   1) whom to contact with questions about the clinical performance study;

   2) whom to contact in the event of injury;

   3) whom to contact with questions about subject's rights.

j) Statement declaring that new findings or the reason for any amendment to the CPSP that could affect the subject's continued participation shall be made available to the subject.

k) Information on if and when results will be returned.

l) Termination:

   1) circumstances under which the subject's participation can be terminated by the principal investigator, when applicable;

   2) circumstances under which the sponsor can suspend or prematurely terminate the clinical performance study.

F.5 Informed consent signature

The informed consent signature form shall contain the following:

a) the voluntary agreement to participate in the clinical performance study and follow the investigator's instructions;

b) a statement declaring that refusal of participation or withdrawal incurs no penalty for the subject (e.g. the subject will not lose their right to the appropriate standard of care);

c) a statement declaring that discontinuation at any time incurs no penalty for the subject;

d) a statement with regard to the possible consequences of withdrawal;

e) an acknowledgement of the information provided and confirmation that all the subject's questions were answered;

f) a statement confirming that the subject or his/her legally authorized representative agrees to the use of the subject's personal data for the purpose of the clinical performance study;

g) a statement confirming that the subject or his/her legally authorized representative agrees that the sponsor's representatives, regulatory authorities and ethics committee representatives will be granted direct access to the subject's medical records.

F.6 New information

When new information (e.g. newly identified risks related to participation in the study) becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the subject(s) affected in written form. When relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing.

Annex G
(normative)

Adverse event categorization

G.1 Direct and indirect harms

A failure or malfunction of an IVD medical device can lead to indirect or direct harms.

Indirect harms occur when inaccurate test results from an IVD medical device (e.g. false positive, false negative) lead to inappropriate patient management decisions, impacting the subject. In the context of a clinical performance study, this would apply, for example, when in an interventional study, the inaccurate test result leads to inappropriate stratification of treatment groups leading to harm.

Direct harms occur when failure or malfunction of an IVD medical device injures a user or other person. In addition, in the context of a clinical performance study, direct harms can also occur when additional specimen material is collected primarily for the purpose of the study, and results in harm to the subject.

G.2 Categories of adverse events

All applicable adverse events shall be reported in an interim or final report of the clinical performance study. See Table G.1 for adverse event categories.

Table G.1 — Categories of adverse events

<table>
<tr><th>ADVERSE EVENTS</th><th>Non-device-related</th><th colspan="2">Device-related</th></tr>
<tr><td></td><td>Applies to:
— Interventional studies
— Sampling procedure causes direct harm to the subject</td><td colspan="2">Applies to:
— Interventional studies: inaccurate test result leads to indirect harm to the subject
— All studies: device causes direct harm to user or other person</td></tr>
<tr><td>Non-serious</td><td>Adverse event[a]
(3.2)</td><td colspan="2">Adverse device effect
(3.1)</td></tr>
<tr><td rowspan="3">Serious</td><td rowspan="3">Serious adverse event[b]
(3.44)</td><td colspan="2">Serious adverse device effect
(3.43)</td></tr>
<tr><td>Anticipated</td><td>Unanticipated</td></tr>
<tr><td>Anticipated serious adverse device effect
(3.5)</td><td>Unanticipated serious adverse device effect
(3.52)</td></tr>
<tr><td colspan="4">[a] Includes all categories.
[b] Includes all categories that are serious.</td></tr>
</table>

G.3 Safety evaluation and monitoring

The sponsor is responsible for the classification of adverse events and ongoing safety evaluation of the clinical performance study and shall

a) review the investigators assessment of all adverse events and determine and document in writing their seriousness and relationship to the IVD medical device under investigation; in case of disagreement between the sponsor and the principal investigator(s), the sponsor shall communicate both opinions to concerned parties, as defined in c), d) and e) below,

b) review all device deficiencies and determine and document in writing whether they could have led to a serious adverse device effect; in case of disagreement between the sponsor and the principal investigator(s), the sponsor shall communicate both opinions to concerned parties, as defined in c), d) and e) below,

c) ensure to report, to the ethics committee by the principal investigator(s), all serious adverse events and device deficiencies that could have led to a serious adverse device effect, when required by the CPSP or by the ethics committee,

d) ensure to report to regulatory authorities, within the required time period, all serious adverse events and device deficiencies that could have led to a serious adverse device effect, when required by national regulations or the CPSP,

e) in the case of a multicentre clinical performance study, inform all principal investigators in writing of all serious adverse events at all study sites that have been reported to the sponsor, and ensure that they are reported to their ethics committee, when required by national regulations or the CPSP or by the ethics committee, whichever is more stringent; this information shall be sent to all the principal investigators within a time frame established based on the perceived risk as defined in the risk analysis report,

f) ensure that the ethics committee and the regulatory authorities are informed of significant new information about the clinical performance study, and

g) in case of serious adverse device effects and device deficiencies that could have led to serious adverse device effects, determine whether the risk analysis needs to be updated and assess whether corrective or preventative action is required.

G.4 Safety recording and reporting

The principal investigator shall

a) record every adverse event and observed device deficiency, together with an assessment as to whether the IVD medical device or sampling procedure were a cause of the event,

b) report to the sponsor, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect; this information shall be promptly followed by detailed written reports, as specified in the CPSP,

c) ensure to report to the ethics committee serious adverse events and device deficiencies that could have led to a serious adverse device effect, when required by the national regulations or CPSP or by the ethics committee, and

d) ensure to report to regulatory authorities serious adverse events and device deficiencies that could have led to serious adverse device effect, as required by national regulations, and supply the sponsor, upon sponsor's request, with any additional information related to the safety reporting of a particular event.

Figures G.1 and G.2 provide guidance on questions that can be asked to categorize adverse events and device deficiencies, but are not intended to show the interrelationship of categories.

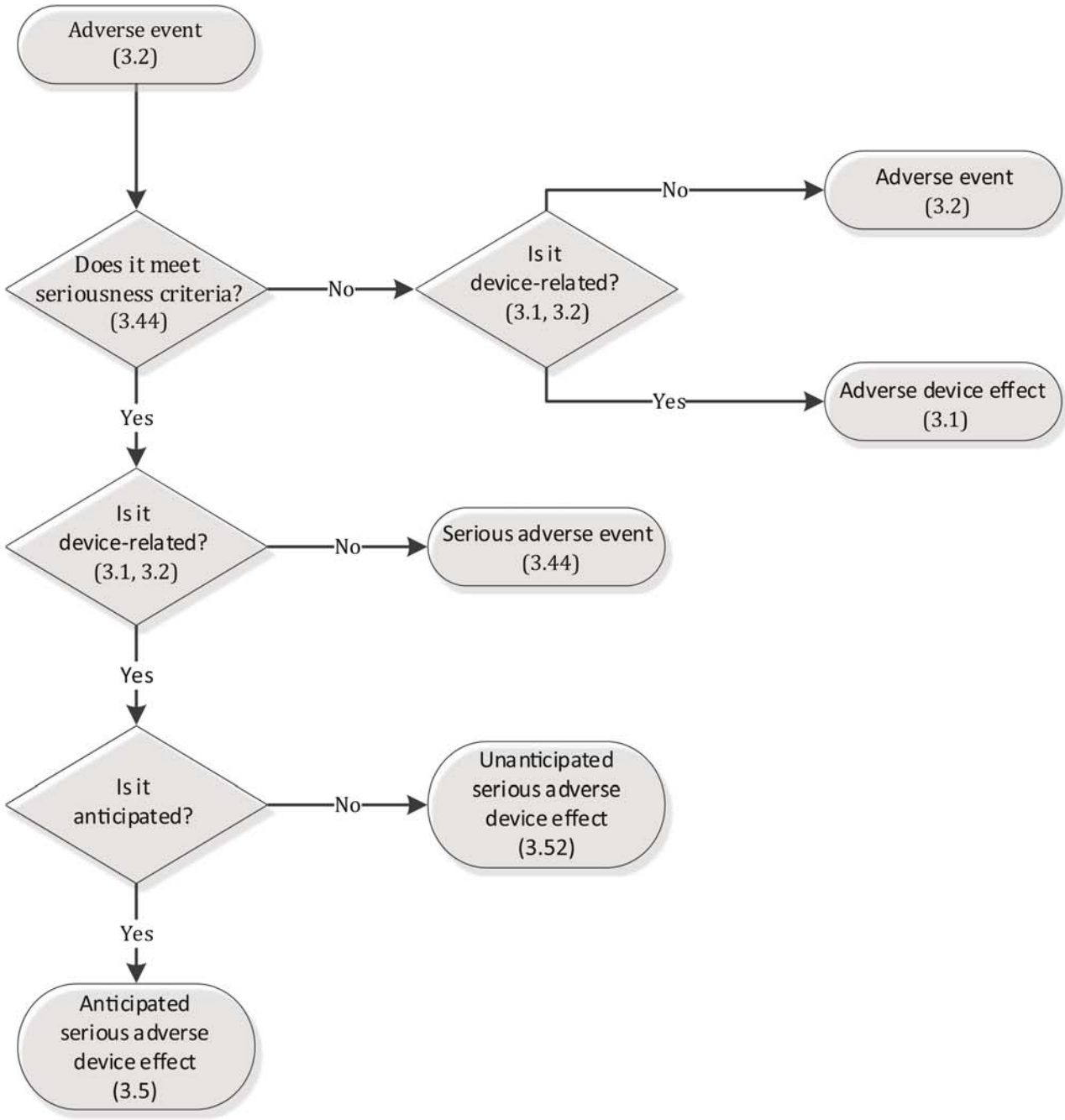

Figure G.1 — Adverse events categorization chart

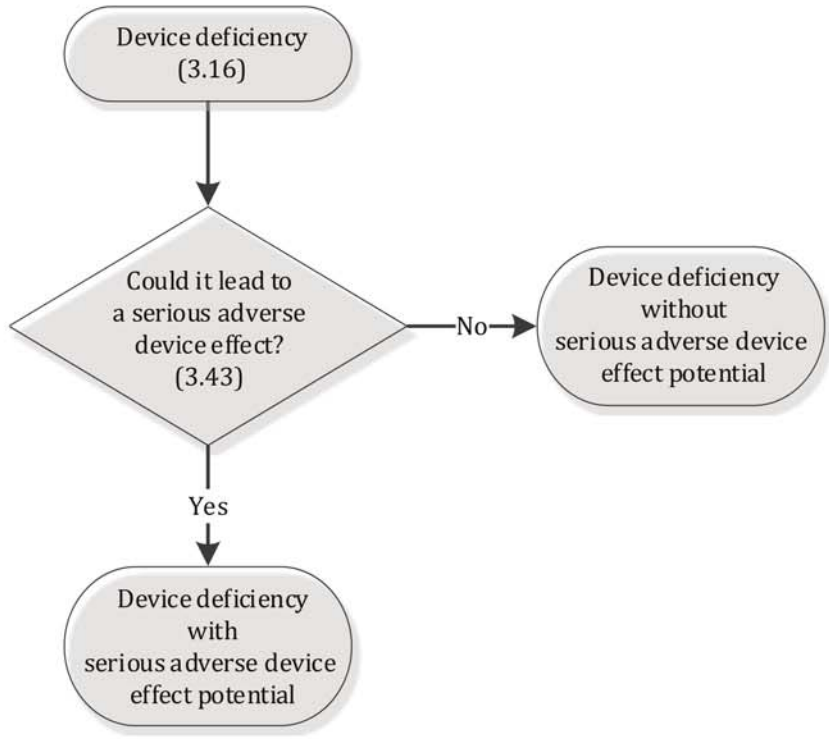

Figure G.2 — Device deficiency categorization chart

Annex H
(informative)

Good clinical performance study documentation

Due to the specific nature of IVD medical devices, in order to demonstrate good clinical performance study practices, a distinct and separate set of documentation to that required for other medical devices [such as that described in ISO 14155:-[1]), Annex E] has been developed.

The following list describes the type of documentation that can be compiled in order to demonstrate good clinical performance study practices. The specific documents listed below might not apply to all studies, and it might be possible to consolidate information from multiple documents into a single document.

For any of the documentation mentioned in this list, source documents should be maintained throughout the duration of the study.

Table H.1 lists documentation required for different types of studies.

How to use Table H.1:

— Set A refers to studies using leftover/archived specimens or studies where specimens were primarily collected for the purposes of the study and for which the collection procedure pose no additional risks to the subject.

— Set B refers to interventional studies or studies where the specimens were primarily collected for the purposes of the study and for which the collection procedure poses additional risks to the subject.

The columns "Relevant clause set A" and "Relevant clause set B" reference the clauses within this document where the requirements are described.

Table H.1 — Documentation demonstrating good study practice

No.	Documentation	Purpose or comment	Relevant clause (set A)	Reference clause (set B)
H.1	Ethics committee notification, correspondence and opinion/approval	Gives evidence that a qualified, independent ethics committee has reviewed the clinical performance study and is maintaining oversight	4.4 4.5 5.5.3.18 b) 6.2 f) and g) 6.4 7.1 7.2 c) 7.3.2 i) 8.1 b) 1) 8.2 j)	4.4 4.5 5.5.3.18 b) 6.2 f) and g) 6.4 7.1 7.2 c) 7.3.2 i) 8.1 b) 1) 8.2 j) A.2 A.6.1 A.6.2 B.8.11 e) Annex E

No.	Documentation	Purpose or comment	Relevant clause (set A)	Reference clause (set B)
H.2	Reports of adverse events, adverse device effects and device deficiencies	Documents the occurrence and resolution of adverse events, adverse device effects and device deficiencies.	4.4 c) G.4	4.4 c) G.4
H.3	Sample of approved informed consent forms, where used, information for the subjects and advertisements, including translations and amendments, if made	Gives evidence of the content of the informed consent forms and of the information provided to the subject during the clinical performance study.	4.5 5.5.3.19 7.3.2 g)	4.5 5.5.3.19 7.3.2 g) A.3 E.2 c) Annex F
H.4	Evidence of informed consent	Verifies that informed consent has been given. This document should remain only at the site.	4.5 7.3.2 g)	4.5 7.3.2 g) Annex F
H.5	Documentation of principal investigator's adequate qualifications (updated if there is a new principal investigator)	Identifies the principal investigator.	5.1 5.9.1 a) 6.3 6.4	5.1 5.9.1 a) 6.3 6.4 E.2 e)
H.6	Documentation of roles and responsibilities of principal investigator and key members of study site team at each study site	Documents the attribution of responsibilities, with signature, title, and responsibilities in the clinical performance study.	5.1 5.11	5.1 5.11
H.7	Records of qualification of key members of the study site team: (updated as necessary for new members)	Identifies the key members of the study site team.	5.1 6.3 6.4	5.1 6.3 6.4
H.8	Investigator brochure, and a record of amendments, if applicable	Describes the IVD medical device under investigation, including instructions for use.	5.4	5.4 Annex C
H.9	Clinical Performance Study Protocol (CPSP)	Describes the clinical performance study design and procedures.	5.5	5.5 Annex B D.7.2
H.10	Monitoring documentation;	Provides evidence that adequate monitoring has taken place. Includes: — Monitoring plan — Site monitoring documentation — Names and qualifications of monitor(s), updated when necessary	5.5.2 d) 5.5.2 m) 5.10 7.2 e) 7.3.3	5.5.2 d) 5.5.2 m) 5.10 7.2 e) 7.3.3 D.13 e)

No.	Documentation	Purpose or comment	Relevant clause (set A)	Reference clause (set B)
H.11	Shipping records and accountability records for IVD medical devices under investigation	Verifies physical possession of devices, ensures integrity of device. Reconciles with sponsor's shipping and receipt records.	5.5.2 j) 5.5.3.17 8.1 a) 5)	5.5.2 j) 5.5.3.17 8.1 a) 5)
H.12	Records of specimen accountability and specimen integrity	Ensure accountability of all the specimens during the steps of the study	5.5.2 k) 8.1 a) 5)	5.5.2 k) 8.1 a) 5)
H.13	List of study site(s)	site(s)conducting the study with site names and addresses.	5.5.3.6 8.2 g)	5.5.3.6 8.2 g) B.5 D.5 e)
H.14	Documentation of IVD medical device under investigation return or disposal, where applicable	Documents the proper disposal of biohazardous materials or other materials that require special disposal.	5.5.3.17 8.1 a) 5)	5.5.3.17 8.1 a) 5)
H.15	Regulatory authority notification, correspondence and approval (where applicable)	Verifies information provided to regulatory authorities. Confirms notification or approval.	5.5.3.18 5.7 6.1 g)	5.5.3.18 5.7 6.1 g) A.6.1 A.6.2 B.8.11
H.16	Data collection tools	This can take the form of data collection form, instrument printouts, Case Report Forms (CRF). Blank set to evidence the content of data being collected.	5.6	5.6 A.5
H.17	Study sample log	Record required information for all specimens in the study	5.7	5.7
H.18	Maintenance and calibration records of equipment if relevant to the clinical performance study	Documents equipment maintenance and calibration, any changes of equipment and continuous maintenance and calibration throughout the clinical performance study.	5.9.1 b) 7.3.2 e) 7.3.2 m)	5.9.1 b) 7.3.2 e) 7.3.2 m)
H.19	Documentation of study site selection	Verifies that qualifications of investigator and study site have been reviewed.	5.9.3	5.9.3
H.20	Signed agreement between principal investigator(s)/study site(s) and sponsor	Demonstrates understanding of each party's respective responsibilities.	5.11 6.4 8.1	5.11 6.4 8.1
H.21	Signed agreements between sponsors and third parties, e.g. contract research organization, core laboratories	Demonstrates understanding of each party's responsibilities.	5.11	5.11
H.22	Disclosures of conflicts of interest, updated as necessary	Documentation of conflicts of interest, e.g. financial.	5.11 8.2 k) 2)	5.11 8.2 k) 2) E.2
H.23	Sample of labelling attached to IVD medical device under investigation	Confirms appropriate labelling.	5.12	5.12

No.	Documentation	Purpose or comment	Relevant clause (set A)	Reference clause (set B)
H.24	Documentation of clinical performance study initiation	Verifies that investigator and study site team have been trained to device use and CPSP conformity.	Clause 6 8.2 g)	Clause 6 8.2 g) D.5 j)
H.25	Financial agreements, if separate from agreements on responsibilities	Provides evidence of financial arrangements between investigator/study site and sponsor (can be kept separate from other site files).	6.2 d)	6.2 d)
H.26	Documentation of training	Provides evidence of training as specified in the relevant clauses of this document.	6.3 8.2 g) 4)	6.3 8.2 g) 4) F.2 b)
H.27	Correspondence related to the clinical performance study, including emails, letters, meeting notes and phone reports	This does not have to be in paper form.	7.2 c) 7.3.2 a)	7.2 c) 7.3.2 a)
H.28	Notification of clinical performance study close-out to the ethics committee and/or regulatory authority by principal investigators or sponsor, where required		8.1 b)	8.1 b) A.6.1
H.29	Clinical performance study report		8.2	8.2 d)
H.30	CRFs amendments	Gives evidence of any changes, additions, or corrections made to CRFs after data were initially recorded.		A.5
H.31	CRFs, fully executed	Evidences what data were collected and that their authenticity has been verified by principal investigator.		A.5
H.32	Decoding procedures for blinded/masked clinical performance studies, where applicable	Ensures in case of medical emergency that decoding can occur.		A.7 e)
H.33	Evidence of insurance, when applicable	Gives evidence that compensation to subject(s) for clinical performance study-related injuries will be available.	7.2 h)	7.2 h) A.8 B.8.10 E.2 i) E.4 d)
H.34	Description of randomization for randomized clinical performance studies	Verifies that randomization has been followed. Depending on the design of the clinical performance study, the list might not be available at the study site for blinded/masked clinical performance studies.		B.8.1 c)

Annex I
(informative)

Auditing

Audits of the clinical performance study can be conducted to evaluate conformity with the CPSP, written procedures and this document. These audits can cover all involved parties, systems and facilities and are independent of, and separate from, routine monitoring or quality control functions.

An audit is useful

a) as a routine part of the sponsor's quality assurance programme,

b) to assess the effectiveness of the monitoring activity,

c) whenever there are serious or repeated CPSP deviations or suspicion of fraud,

d) to ensure a study site is ready for an inspection, and

e) when requested or suggested by a regulatory authority.

When an audit is conducted, the auditors should be qualified by training and experience to conduct audits and have no direct responsibility for the study or site being audited.

The auditing of clinical performance study systems should be conducted in accordance with the sponsor's written procedures or specific plan on what to audit, how to audit, the frequency of audits and the form and content of audit reports.

The sponsor's audit plan and procedures for a clinical performance study audit should be guided by the type, complexity and risk of the clinical performance study, and any identified problem(s).

The audit results should be documented and communicated to relevant parties, when applicable. Also, should deficiencies be noted during the audit, corrective actions and a re-audit should be performed.

Bibliography

[1] ISO 15190:2003, *Medical laboratories — Requirements for safety*

[2] ISO 13131:2014, *Health informatics — Telehealth services — Quality planning guidelines*

[3] ISO 13485, *Medical devices — Quality management systems — Requirements for regulatory purposes*

[4] ISO 14971:-[2)], *Medical devices — Application of risk management to medical devices*

[5] ISO 14155:-[1)], *Clinical investigation of medical devices for human subjects — Good clinical practice*

[6] ISO 15193:2009, *In vitro diagnostic medical devices — Measurement of quantities in samples of biological origin — Requirements for content and presentation of reference measurement procedures*

[7] ISO 16142-2:2017, *Medical devices — Recognized essential principles of safety and performance of medical devices — Part 2: General essential principles and additional specific essential principles for all IVD medical devices and guidance on the selection of standards*

[8] ISO 18113-1:2009, *In vitro diagnostic medical devices — Information supplied by the manufacturer (labelling) — Part 1: Terms, definitions and general requirements*

[9] ISO/TR 24971, *Medical devices — Guidance on the application of ISO 14971*

[10] ISO/IEC Guide 51:2014, *Safety aspects — Guidelines for their inclusion in standards*

[11] Global Harmonization Task Force. Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device' [GHTF/SG1/N071:2012] available at: http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n071-2012-definition-of-terms-120516.pdf

[12] CLSI. *Protection of Laboratory Workers from Occupationally Acquired Infections; Approved Guideline — Fourth Edition.* CLSI document M29-A4. Wayne, PA: Clinical and Laboratory Standards Institute; 2014

[13] United States Department of Labor. Occupational Safety and Health Administration. *Part 1910.1030 – Bloodborne pathogens.* (Codified at 29 CFR § 1910.1030). US Government Printing Office; published annually, available at: https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_id=10051&p_table=STANDARDS

[14] Declaration of Helsinki. available at: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects

[15] Global Harmonization Task Force, Principles of In Vitro Diagnostic (IVD) Medical Devices Classification [GHTF/SG1/N077:2012], available at: http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n071-2012-definition-of-terms-120516.docx

[16] Global Harmonization Task Force, Essential Principles of Safety and Performance of Medical Devices [GHTF/SG1/N68:2012], available at: http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n68-2012-safety-performance-medical-devices-121102.pdf

[17] Global Harmonization Task Force. Clinical Evidence for IVD medical devices — Key Definitions and Concepts [GHTF/SG5/N6:2012], available at http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n6-2012-clinical-evidence-ivd-medical-devices-121102.pdf

[18] Global Harmonization Task Force. Clinical Evidence for IVD medical devices — Scientific Validity Determination and Performance Evaluation [GHTF/SG5/N7:2012], available at http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n7-2012-scientific-validity-determination-evaluation-121102.pdf

[19] GLOBAL HARMONIZATION TASK FORCE. Clinical Evidence for IVD Medical Devices — Clinical Performance Studies for In Vitro Diagnostic Medical Devices [GHTF/SG5/N8:2012], available at http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n8-2012-clinical-performance-studies-ivd-medical-devices-121102.pdfmay

[20] GLOBAL HARMONIZATION TASK FORCE. Quality Management Systems – Process Validation Guidance [GHTF/SG3/N99-10:2004], available at http://www.imdrf.org/docs/ghtf/final/sg3/technical-docs/ghtf-sg3-n99-10-2004-qms-process-guidance-04010.pdf

[21] EUROPEAN COMMISSION GUIDELINES ON MEDICAL DEVICES. Clinical Evaluation: A Guide For Manufacturers And Notified Bodies Under Directives 93/42/EEC and 90/385/EEC [MEDDEV 2.7/1 revision 4, June 2016], available at http://ec.europa.eu/DocsRoom/documents/17522/attachments/1/translations/

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