



## **PROPOSED DOCUMENT**

### **Global Harmonization Task Force**

**Title:** Clinical Performance Studies for In Vitro Diagnostic Medical Devices

**Authoring Group:** Study Group 5

**Date:** January 26, 2012

## CONTENTS

	Preface.....	3
1	Introduction.....	4
2	Scope.....	4
3	References.....	5
4	Definitions.....	5
5	Purpose of Clinical Performance Studies .....	6
6	Clinical Performance Study Design Type.....	6
	6.1 Observational Designs .....	7
	6.1.1 Single Time-point Designs .....	8
	6.1.2 Longitudinal Designs .....	8
	6.1.3 Retrospective and Prospective Designs .....	9
	6.2 Interventional Designs .....	10
7	Clinical Performance Study Design Considerations.....	11
	7.1 Test purpose .....	11
	7.2 Specimen Collection and Handling .....	12
	7.3 Clinical Performance Study Site Location.....	13
	7.4 Statistical Design .....	13
	7.5 Potential Risks .....	14
	7.6 Ethical Considerations for Clinical Performance Studies.....	14
	7.6.1 Informed Consent.....	14
	7.6.2 Ethics Committee Involvement.....	15
	7.6.3 Communicating Test Results Outside of the Study .....	15
8	Clinical Performance Study Protocol.....	15
9	Conduct of Clinical Performance Studies.....	16
10	Clinical Performance Study Report .....	16
	Appendix.....	17

## **Preface**

The document herein was produced by the Global Harmonization Task Force, a voluntary group of representatives from medical device regulatory agencies and the regulated industry. The document is intended to provide non-binding guidance for use in the regulation of medical devices, and has been subject to consultation throughout its development.

There are no restrictions on the reproduction, distribution or use of this document; however, incorporation of this document, in part or in whole, into any other document, or its translation into languages other than English, does not convey or represent an endorsement of any kind by the Global Harmonization Task Force.

## 1 Introduction

When placing an IVD medical device on the market the manufacturer must have demonstrated through the use of appropriate conformity assessment procedures that the device complies with the Essential Principles of Safety and Performance of Medical Devices. As IVD medical devices are used on specimens taken from the human body, the characteristics of clinical evidence are different from medical devices other than IVD medical devices.

Generally, from a clinical perspective, it is expected that the manufacturer has demonstrated the device achieves its intended performance during normal conditions of use in the intended environment (e.g. blood-banks, hospitals, home environment). This could be done by a clinical performance study which is a scientific and operational process that represents one method of generating clinical performance data for demonstrating clinical evidence.

The objective of a clinical performance study is to evaluate whether the IVD medical device is suitable (i.e. meets the relevant Essential Principles of Safety and Performance) for the purpose(s) and the population(s) for which it is intended, when this cannot be addressed with the analytical performance data, literature and experience gained by routine diagnostic testing.

In general, clinical performance studies must be designed according to, and take into account scientific principles underlying the collection of clinical performance data along with accepted operational and ethical standards surrounding the use of human subjects. The clinical performance study objectives and design should be documented in a clinical performance study protocol. The data collection process must ensure data integrity along the entire process of the study.

## 2 Scope

The primary purpose of this document is to provide guidance for IVD medical devices in relation to:

- the selection of clinical performance study design based on the type and intended use of the IVD medical device; and
- considerations to be made when undertaking clinical performance studies

Given the wide diversity of IVD medical devices and their associated risks, this document is not intended to provide comprehensive guidance for clinical performance studies of specific IVD medical devices.

Clinical performance studies are typically performed in the pre-market phase. However, some aspects of this document may also apply to studies conducted in the post-market phase .

Pre-market testing that is not designed to address clinical performance of an IVD medical device is not considered a clinical performance study (examples of such studies are customer feedback studies, external analytical performance studies, research studies).

### 3 References

#### **GHTF final documents**

- SG1/N029:2005     *Information Document Concerning the Definition of the Term “Medical Device”*
- SG1/N041:2005     *Essential Principles of Safety and Performance of Medical Devices*
- SG1/N046:2008     *Principles of Conformity Assessment for in vitro Diagnostic (IVD) Medical Devices*
- SG1/N063:2011     *Summary Technical Documentation (STED) for Demonstrating Conformity to the Essential Principles of Safety and Performance of In Vitro Diagnostic Medical Devices*

#### **GHTF documents proposed for public comment**

- SG5(PD)/N6R3     *Clinical Evidence for IVD Medical Devices – Key Definitions and Concepts*
- SG5(PD)/N7R4     *Clinical Evidence for IVD Medical Devices – Scientific Validity Determination and Performance Evaluation*

#### **Other References**

*World Medical Association – Declaration of Helsinki - Ethical principles for medical research involving human subjects*

### 4 Definitions

#### **Clinical Evidence**

Clinical evidence for an IVD medical device is all the information that supports the scientific validity and performance for its use as intended by the manufacturer.

#### **Clinical Performance**

The ability of an IVD medical device to yield results that are correlated with a particular clinical condition/physiological state in accordance with target population and intended user.

#### **Clinical Performance Study**

A systematic investigation or study undertaken to demonstrate the clinical performance of an IVD medical device.

#### **Clinical Performance Study Protocol**

Document that states the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical performance study.

#### **IVD medical device**

Refer to GHTF/SG1(PD)/N71R4 the Definition of the Term ‘Medical Device’.

## 5 Purpose of Clinical Performance Studies

The purpose of a clinical performance study is to validate aspects of IVD medical device performance which cannot be determined by analytical testing, literature or previous experience gained by routine diagnostic testing. This information is used to demonstrate compliance with the relevant Essential Principles with respect to clinical performance. When a clinical performance study is conducted, the data obtained is used in the performance evaluation process and is part of the clinical evidence for the IVD medical device (see GHTF SG5/N7 – “*Clinical Evidence for IVD medical devices–Scientific Validity Determination and Performance Evaluation*”).

## 6 Clinical Performance Study Design Type

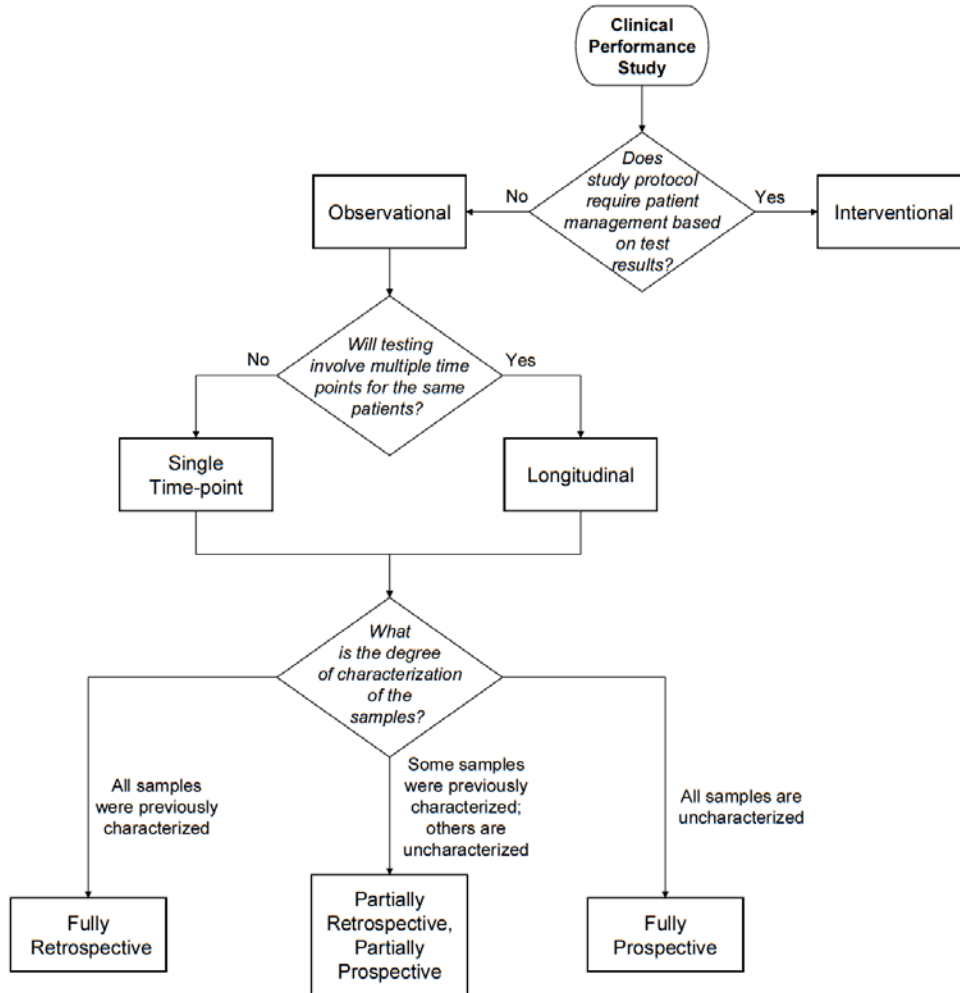
Clinical performance studies should be designed in such a way as to maximize the relevance of the data while minimizing confounding factors. Designs of IVD medical device clinical performance studies are either observational or interventional. An observational study refers to a study in which test results are not used for patient management and do not impact treatment decisions while in interventional studies, test results may influence patient management decisions and may be used to guide treatments.

Observational design can be further characterized as a combination of the following designs:

- **single time-point design** – testing of one or few samples per patient that are collected at a single time-point
- **longitudinal design** – testing of multiple samples per patient that are collected over an extended period of time (e.g. weeks, months, years)
- **retrospective design** – testing of samples for which the analyte (measurand) status and/or the patient’s clinical status is known (characterized samples)
- **prospective design** – testing of samples for which neither the analyte (measurand) status or the patient’s clinical status have been established (uncharacterized samples)
- **NOTE:** The terms ‘retrospective’ and ‘prospective’ have also been used in the context of clinical studies to describe sample collection methodology (i.e. retrospective samples = archived samples) and analysis methodology (i.e. retrospective analysis = meta-analysis). For the purpose of this document the use of the terms ‘retrospective’ and ‘prospective’ are limited to the characterizations status of the samples (i.e. analyte (measurand) and clinical status).

Figure 1 provides an illustration of the use of study design types for a single test purpose. Further clarifications on these study design types are presented below.

**FIGURE 1: Decision tree for clinical performance study design**



## 6.1 Observational Designs

The majority of IVD medical device clinical performance studies follow an observational design. This design is common and appropriate because such study results are not used to determine patient treatment decisions as they are done in parallel to the routine diagnostic testing. The specimens for these studies are derived from:

- previously-collected specimens, such as archived specimens or left over specimens that would otherwise have been discarded (also called surplus specimens); and/or
- additional specimens collected specifically for the study purposes

The following design types further characterize studies of an observational nature.

### 6.1.1 Single Time-point Designs

Single time-point performance studies are those where correlation of test results to clinical condition can be established at a single time-point. These studies are also called cross-sectional studies. Examples of single time-point clinical performance studies are presented below.

Example 1 (Diagnosis): CK-MB for the diagnosis of myocardial infarction.

Example 2 (Screening): Detection of infectious disease antigen in asymptomatic patients

Example 3 (Predisposition): Detection of single nucleotide polymorphisms (SNPs) in particular genes (e.g. *HSPA1A*) to estimate the risk of developing cardiac disease.

Example 4 (Prognosis): Determination of plasma HIV viral load to evaluate the likelihood of progression to AIDS.

Example 5 (Prediction): Detection of KRAS mutation as a marker of probable failure of epidermal growth factor receptor (EGFR)-targeted therapy.

### 6.1.2 Longitudinal Designs

Longitudinal performance studies involve multiple patient measurements of the same analyte (measurand) over time to validate the clinical performance of an IVD medical device. Examples of longitudinal clinical performance studies are presented below.

Example 1 (Diagnosis): In women less than 40 years old who have had amenorrhea for 4 months or more, serial FSH testing is useful for the diagnosis of primary ovarian insufficiency (i.e. two FSH measurements, obtained at least 1 month apart, in the menopausal range).

Example 2 (Screening): In diabetic patients, serial cystatin C measurements can be used to screen for early renal function decline.

Example 3 (Monitoring): In HIV infected patients the measurement of viral load after first establishing the baseline value can be used to assess treatment response.

Example 4 (Predisposition): serial testing to determine the change in an analyte (measurand) over time to estimate the risk of developing a disease.

Example 5 (Prognosis): In heart failure patients, a minimal change in B-type natriuretic peptide (BNP) levels upon initiation of therapy is associated with a low risk of mortality.

Example 6 (Prediction): For chronic myeloid leukemia (CML) patients undergoing imatinib treatment,  $\geq 2$ -log decrease of BCR-ABL mRNA levels by 6 months is predictive of continued treatment response.

### 6.1.3 Retrospective and Prospective Designs

This section describes performance studies that follow a retrospective design (i.e. using characterized samples) or a prospective design (i.e. using non-characterized samples).

Depending on the IVD medical device, clinical performance study designs may follow a fully retrospective design, a fully prospective design, or a combination of the two whereby both characterized and non-characterized samples are used to address different elements of clinical performance.

For many IVD medical devices, it is appropriate to test specimens derived from patients with known clinical status and/or for which test results of the analyte (measurand) are available. For example, a clinical performance study of a specific IgE assay intended for diagnosis of allergy could use well-characterized specimens from atopic and non-atopic patients to establish the clinical sensitivity and specificity of the device. In this case, prospective specimens (i.e. from unknown donors) would not be needed because the clinical performance of the assay would likely be sufficiently validated following a fully retrospective design.

Retrospective studies are appropriate if the following criteria are addressed:

- the samples are representative of the intended use population (e.g. reflects variability of the clinical condition not just typical cases);
- specimens were taken from a sufficiently large number of study subjects to reflect a random sampling;
- there is adequate data related to the follow-up of patients (e.g. no patients lost to follow-up);
- the samples span the assay range (if applicable); and
- there is minimal bias due to sample selection

Completed randomized controlled trials for therapeutic agents present a potential valuable source of samples for a retrospective study as the patient outcome is known. Use of these samples is subject to the following considerations:

- samples were collected prior to treatment;
- samples for testing reflect a relatively equal distribution from each of the study arms (treatment groups)

In other cases, it may be necessary to use a combination study design whereby some clinical performance characteristics are assessed in a prospective design and some clinical performance characteristics are assessed in a retrospective design. For example, a clinical performance study of an HIV-1/2 assay intended for donor screening may involve a prospective design for random blood donors with no known clinical status, and a retrospective design to evaluate well-characterized HIV-2 antibody-positive specimens. In this example, the retrospective design is justified for a portion of the study due to the difficulties in recruiting patients that have the particular clinical condition needed to be able to test for that performance characteristic.

In yet other cases, the clinical performance study would need to follow a fully prospective design (e.g. when the analyte (measurand) is not stable over time).

In the case of IVD medical devices used for the determination of a patient's future state (e.g. predisposition, prognosis, prediction), the clinical performance study will often be based on a prospective design. However, a retrospective design could be used if specimen collection protocols were controlled to ensure that results are not biased or confounded.

## 6.2 Interventional Designs

If performance claims for an IVD medical device cannot be demonstrated by an observational study design an interventional design will be appropriate when:

- no established method exist for making decisions on patient management and the use of archived samples would not be suitable to demonstrate the intended performance claims.

or

- an IVD medical device is co-developed alongside a therapeutic product such that the information provided by the IVD medical device will influence the patient treatment in a therapeutic clinical trial (e.g. stratification of treatment arm).

This design uses specimens specifically collected for the study and the results of the clinical performance study would be used in patient management decisions.

The following examples outline situations when an interventional design would be required:

Example 1 (Diagnosis): To determine if patient outcome (i.e. treatment efficacy) is improved by the correct disease subtype identification thereby facilitating selection of optimal treatment regimens.

Example 2 (Screening): To determine if prenatal screening for a particular genetic developmental disorder improves patient outcome (i.e. disease mitigation) because treatment can begin immediately following birth.

Example 3 (Monitoring): To determine if patient outcome (i.e. treatment efficacy) is improved by regular monitoring of changes to analyte (measurand) concentration.

Example 4 (Predisposition): To determine if prophylactic interventions and/or lifestyle changes improve outcomes for patients at high risk of developing late-onset genetic conditions.

Example 5 (Prognosis): To determine if patient outcome (i.e. treatment efficacy) is improved by accurate disease staging and more aggressive treatments for patients with worse prognosis.

Example 6 (Prediction): To prospectively determine if a marker predicts a differential efficacy or safety of a particular therapy based on the marker's status (e.g. to test if patients expressing the marker respond to the specific treatment or respond to a greater

degree than those without the marker or that some will respond negatively on the treatment; commonly termed “companion diagnostics”).

## 7 Clinical Performance Study Design Considerations

The design of a clinical performance study should provide the data necessary to address the clinical performance of the IVD medical device. The clinical performance study design should account for potential risks, should follow appropriate ethical principles, and should be compliant with all relevant legal and regulatory requirements;

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

- study objectives
- intended use, specifically
  - test purpose(s) (e.g. diagnosis, screening, monitoring, etc.). (Refer to Section 7.1 and Appendix)
  - target population(s) (e.g. age, race, gender, geography, clinical condition)
  - specimen type(s) (e.g. serum, plasma, urine)
  - intended user(s) (e.g. lay person)
- established analytical characteristics (e.g. precision, interference, assay range, cutoff)
- expected clinical performance characteristics (e.g. sensitivity, specificity);
- novelty of the technology and/or clinical use (e.g. relevant previous experience);

The following additional considerations will also need to be taken into account in designing the clinical performance study

- specimen collection and handling (Refer to Section 7.2)
- clinical performance study site (Refer to Section 7.3)
- statistical design (Refer to Section 7.4)
- potential risks (Refer to Section 7.5)
- ethics (Refer to Section 7.6)

### 7.1 Test purpose

An IVD medical device may be designed for a variety of intended uses with different test purposes (e.g. diagnosis, screening, monitoring etc). See Appendix for details.

The test purpose will directly influence the subject sample size (N) and selection criteria (including inclusion and exclusion) when planning and designing the clinical performance study. For example, if the disease state prevalence is low and the intent of the assay is to screen asymptomatic individuals, specimens from a large number of subjects may be required to

provide sufficient evidence of clinical performance. However, if the assay is to be used for diagnosis in symptomatic individuals, specimens from a smaller number of subjects may be adequate.

Where appropriate, there should be consideration about the timing of specimen collection such as prior to treatment or during treatment. For example a test for predisposition would require that the specimens should be drawn prior to the onset of the condition.

Where appropriate, the study should be designed to include patient follow-up to determine their clinical endpoint/outcome. This would be applicable for tests that identify future conditions such as tests for predisposition, prognosis and prediction.

Where appropriate, multiple test purposes might be evaluated simultaneously. In these cases more than one design type can be combined into a single clinical performance study. Such clinical performance studies should be designed and involve patient populations (with known or readily identifiable clinical status) that would sufficiently validate all of the potential test purposes.

## **7.2 Specimen Collection and Handling**

Samples used in clinical performance studies are derived from specimens which may be obtained from several sources, including purposefully-collected specimens, archived specimens, leftover specimens.

Purposefully-collected specimens refer to specimens that were drawn from patients with the specific intention of using them in a particular clinical performance study. These specimens or their derived samples may be tested immediately after collection or may be stored (e.g. refrigerated or frozen) for testing at a later date.

Leftover specimens are considered to be remnants of specimens collected for routine diagnostic testing that would otherwise have been discarded, or specimens that were previously collected for other research purposes (e.g. basic research studies, pharmaceutical clinical trials, previous IVD medical device clinical performance studies).

Archived specimens or samples refer to specimens or samples that were collected in the past and are obtained from repositories (e.g. tissue banks, commercial vendor collections). While archived specimens or samples tend to be well-characterized whereby the analyte (measurand) status and/or clinical status of the patient are known, some specimens or samples may be archived without first establishing their analytical/clinical status. Well-characterized archived specimens or samples are often the source for unique or rare specimens or samples in sufficient quantity, whereby without these specimens or samples, it would be difficult, if not impossible, to conduct the study in a reasonable timeframe.

For many IVD medical device clinical performance studies, it is appropriate to use archived or leftover specimens/samples in lieu of purposefully-collected specimens provided that sufficient information concerning specimen characterization is available (e.g. anticoagulant, known patient

treatment(s) that may influence test results, time of last treatment dose for therapeutic drug monitoring assays). Generally, clinical performance characteristics can be validated using archived or leftover specimens/samples if they were collected, handled and stored appropriately (i.e. good integrity) and if the information available for the specimen/sample meets the study design requirements. Documentation should exist to support the integrity of the selected specimens/samples in the clinical performance studies.

Greater care needs to be taken when using archived or leftover specimens/samples to evaluate certain prognostic or predictive tests due to the potential that treatment regimens may bias results. It is generally more appropriate to use archived or leftover specimens/samples when there is minimal treatment heterogeneity among the patient populations. Such an approach reduces the risk that variable treatment regimens will obscure the influence of prognostic or predictive markers on clinical outcomes.

### **7.3 Clinical Performance Study Site Location**

Clinical performance studies are generally performed at sites external to the manufacturer although the manufacturer site can be one of the testing sites included in the study. However, in certain circumstances it might be appropriate to perform the testing only at the manufacturing site, in this case a justification for this decision should be provided. In every case it is important to ensure that the testing environment is reflective of the intended use environment and/or intended user.

### **7.4 Statistical Design**

In designing the study, statistical considerations should be specified in advance and be based on sound scientific principles and methodology. Care must be taken in developing a statistical plan that includes consideration of, for example, the following:

- statistical significance levels, power
- appropriate sample size (N) to meet statistical significance
- appropriate subject inclusion and exclusion criteria (e.g. age, disease status)
- appropriate specimen/sample inclusion and exclusion criteria (e.g. specimen/sample integrity)
- minimization of bias (e.g. specimen/sample selection, collection, handling and storage; blinding of operator to clinical status of patient)
- criteria for re-examination and data exclusion
- analysis methodology
- clinically relevant performance characteristics (e.g. sensitivity, specificity, positive predictive value, negative predictive value, percent agreement, correlation to clinical endpoints/outcomes)

## **7.5 Potential Risks**

A variety of factors influence the potential risks to patients when conducting clinical performance studies for IVD medical devices.

When study specimens are obtained from specimens already taken for routine diagnostic testing there is no additional risk coming from the study. However, if the specimen is collected specifically for the study and involves invasive collection procedures the risks associated with these procedures should be taken into consideration. In doing so the level of invasiveness of the sampling procedures should also be taken into account (e.g. venipuncture versus spinal puncture).

Interventional studies carry higher risks as the results are used to manage patients. For these studies, appropriate procedures for adverse events monitoring and handling should be in place.

## **7.6 Ethical Considerations for Clinical Performance Studies**

As a general principle, the rights, safety and wellbeing of subjects participating in IVD medical device clinical performance studies shall be protected consistent with the ethical principles laid down in the Declaration of Helsinki.

It is ethically important in deciding to conduct a clinical performance study that it should generate new data and answer specific safety and/or performance questions that remain unanswered by the current body of knowledge. The desire to protect human subjects from unnecessary or inappropriate experimentation must be balanced with the need to protect public health through the use of clinical performance studies where they are indicated based on scientific needs (e.g. specific mutations in a given population). In all cases, however, care must be taken to ensure that the necessary data are obtained through a scientific and ethical manner that does not expose subjects to undue risks or discomfort. The rights, safety and well-being of subjects are paramount, and appropriate clinical performance study design and conduct is essential to generate meaningful data.

### **7.6.1 Informed Consent**

The requirement for patient informed consent should be based on the risk posed to subjects participating in the clinical performance study. For IVD medical devices, informed consent is required for specimens specifically collected for the purpose of a clinical performance study.

If the clinical performance study will solely use archived or leftover specimens that are not individually identifiable (i.e. devoid of information that would otherwise permit traceability to the patient of origin), the requirement for informed consent may not exist.

In some cases, informed consent may exist in a general form to cover the use of the specimens in any clinical performance studies.

The need for informed consent should be discussed with the ethics committee of each institution included in the study.

### 7.6.2 Ethics Committee Involvement

Prior to commencing a clinical performance study, the participating sites may require approval by their local ethics committee. This independent committee is formally designated to review, approve and monitor studies involving human subjects with the aim of protecting their rights and welfare.

The ethics committee may choose to exempt certain IVD medical device clinical performance studies from their approval.

### 7.6.3 Communicating Test Results Outside of the Study

In some rare instances during a clinical performance study there is a need to communicate study results to clinicians and/or public health institutions. This can be the case when:

- the IVD medical device is presumed to have enhanced performance compared to the current routine testing or where no routine testing exists; and/or
- test results may have an immediate health impact to the patient or the public.

The decision and the mechanism to report results to clinicians and or public health institutions should be discussed with the local ethics committee prior to beginning the clinical performance study.

Example: An IVD medical device for detection of B. anthracis is undergoing clinical performance testing. Specificity is assessed using prospectively-collected patient samples. During testing of the specificity population, a sample is reported as positive. This result is confirmed by testing with an alternate method. It is ethically appropriate to communicate such unexpected results to ensure appropriate patient treatment.

## 8 Clinical Performance Study Protocol

The clinical performance study protocol, sets out how the study is intended to be conducted. It contains important information about the study design such as the purpose, objectives, study population, description of test method(s) and interpretation of results, site training and monitoring, specimen type, specimen collection, preparation, handling and storage, inclusion and exclusion criteria, limitations, warning and precautions, data collection/management, data analysis, required materials, number of study sites.

In addition, the clinical performance study protocol identifies the key factors which may impact the completeness and significance of results, such as intended participant follow-up procedures,

decision algorithms, discrepancy resolution process, masking/blinding, approaches to statistical analyses, and methods for recording endpoints/outcomes and, where appropriate, communication of test results.

Discussion with regulatory authorities or a conformity assessment body may be appropriate when there is uncertainty as to whether the proposed clinical performance study protocol is adequate.

## **9 Conduct of Clinical Performance Studies**

A properly conducted clinical performance study, including compliance to the clinical performance study protocol and local laws and regulations (e.g. pre-study authorization for interventional studies by the RA), ensures the protection of subjects, the integrity of the data and that the data obtained is acceptable for the purpose of demonstrating conformity to the relevant Essential Principles of Safety and Performance.

Considerations for the conduct of a clinical performance study may include:

- appropriate calibration procedures and means of control
- relevant method for determining the true clinical status of patient specimens/samples
- independence of study personnel

Raw data of a clinical performance study should be maintained based on the QMS requirements.

## **10 Clinical Performance Study Report**

The protocol, results and conclusions of a clinical performance study should be documented in a Clinical Performance Study report.

Such a report should also include as appropriate any protocol deviations, and data exclusions with the appropriate rationale.

## Appendix

The table below lists the most common test purposes and provides examples to illustrate their differences.

**TABLE 1: DESCRIPTION OF COMMON TEST PURPOSES FOR IVD MEDICAL DEVICES**

Test Purpose	Description	Examples
Diagnosis	<p>Diagnostic tests are used to determine, verify or confirm a patient's clinical condition as a sole determinant. The nature of the test may be qualitative (presence/absence of analyte) or quantitative (amount/concentration of analyte (measurand)). This type of testing also includes sole confirmatory assays (to verify results of previous testing) and sole exclusion assays (to rule out a particular condition).</p> <p>These tests are designed to evaluate a patient's current state.</p>	<ul style="list-style-type: none"> <li>▪ genetic test for the diagnosis of Tay-Sachs</li> <li>▪ HBs antigen confirmatory assay to verify positive screening results</li> <li>▪ D-dimer assay for exclusion of deep vein thrombosis</li> </ul>
Aid to Diagnosis	<p>Aid to Diagnosis tests are used to provide additional information to assist in the determination or verification of a patient's clinical status. The nature of the test may be qualitative (presence/absence of analyte) or quantitative (amount/concentration of analyte (measurand)).</p> <p>The test is not the sole determinant.</p> <p>This type of testing also includes supplemental assays</p> <p>These tests are designed to evaluate a patient's current state.</p>	<ul style="list-style-type: none"> <li>▪ troponin test as an aid in myocardial infarction diagnosis</li> <li>▪ genetic testing to aid in the diagnosis of familial adenomatous polyposis (FAP)</li> <li>▪ thyroid-stimulating hormone test to evaluate thyroid function</li> <li>▪ toxoplasma IgG avidity assay to determine likelihood of active infection</li> <li>▪ ANA test for Auto-immune disease determination</li> <li>▪ Test for genotyping of the Factor V Leiden mutation as an aid to diagnosis of thrombophilia</li> </ul>

**TABLE 1: DESCRIPTION OF COMMON TEST PURPOSES FOR IVD MEDICAL DEVICES**

Test Purpose	Description	Examples
Screening	<p>Screening tests are used to detect the presence or absence of an analyte (measurand) in asymptomatic patients. They include tests for genetic screening, tests for early detection of disease, and tests used to reduce the risk of infectious disease transmission, such as assays for prenatal screening and donor screening (transfusion or transplantation).</p> <p>They are designed to be highly sensitive.</p> <p>Depending on the nature of the condition and the targeted patient population, screening tests may be used routinely or may be restricted to "at risk" patients.</p> <p>These tests are designed to evaluate a patient's current state.</p>	<ul style="list-style-type: none"> <li>▪ test to detect hepatitis B surface antigen in donated blood</li> <li>▪ PSA screening for prostate cancer</li> <li>▪ antenatal rubella IgM screening in pregnant women</li> <li>▪ prenatal genetic testing for trisomy 21 (Down's syndrome)</li> <li>▪ newborn genetic testing for phenylketonuria</li> <li>▪ tests for the determination of blood groups and blood group factors for donor match</li> <li>▪ HLA typing for donor match</li> </ul>
Monitoring	<p>Monitoring tests are used for the serial measurement of analyte (measurand) levels</p> <p>They are typically used to detect/assess disease progression, regression, recurrence, minimal residual disease, and/or response/resistance to therapy.</p> <p>Tests for monitoring are often used to guide treatment over time.</p> <p>These tests are designed to evaluate changes in a patient's state.</p>	<ul style="list-style-type: none"> <li>▪ viral load testing of patients known to be infected with HIV to determine treatment response and adjust therapy if necessary</li> <li>▪ monitoring of CA 15-3 levels in breast cancer patients in remission to detect recurrence</li> <li>▪ therapeutic drug monitoring to ensure pharmaceutical concentrations remain within a therapeutic window</li> <li>▪ test for the detection of BCR-ABL transcripts in patients treated for acute lymphoblastic leukaemia (ALL)</li> </ul>
Predisposition	<p>Predisposition assays are used to determine the likelihood of disease onset (i.e. assessing the risk of developing the disease in future) in presymptomatic patients.</p> <p>For patients at sufficient risk (as determined by test results), preventive interventions may be taken.</p> <p>These tests are designed to evaluate a patient's future state.</p>	<ul style="list-style-type: none"> <li>▪ genetic test for apolipoprotein E to assess the risk of developing Alzheimer's disease</li> <li>▪ BRCA1/BRCA2 mutation status testing to assess the risk of developing breast cancer (patient may choose to have prophylactic mastectomy if they are at sufficient risk)</li> </ul>

**TABLE 1: DESCRIPTION OF COMMON TEST PURPOSES FOR IVD MEDICAL DEVICES**

Test Purpose	Description	Examples
Prognosis	<p>Prognostic tests are used to measure factors linked to clinical outcome irrespective of treatment. Such tests may be used to estimate the natural progression of a disease (i.e. outcome in the absence of treatment), or to determine the likelihood of a clinical outcome irrespective of therapeutic intervention.</p> <p>These tests are designed to evaluate a patient's future state.</p>	<ul style="list-style-type: none"> <li>▪ high sensitive C-reactive protein measurement for the risk stratification of patients with acute coronary syndromes to determine the likelihood of future cardiac events</li> <li>▪ measurement of baseline HIV-1 RNA level to assess patient prognosis</li> <li>▪ cancer gene expression profile testing for metastasis risk to tailor treatment aggressiveness</li> </ul>
Prediction (of Treatment Response or Reaction)	<p>Predictive tests are used to measure factors that determine the likelihood of patient responses or adverse reactions to a specific therapy.</p> <p>Predictive tests designed specifically for use with a targeted therapy are sometimes termed "companion diagnostics" or "personalized medicine".</p> <p>These tests are designed to evaluate a patient's future state.</p>	<ul style="list-style-type: none"> <li>▪ HER-2/neu testing in breast cancer patients to assess likelihood of response to hormone therapy</li> <li>▪ identification of variations in cytochrome P450 genes (i.e. metabolizer status) to determine potential therapeutic benefits and/or adverse reactions to antiplatelet treatment</li> </ul>
Determination of Physiological Status	<p>Tests are used to evaluate the physiological state of an individual for the purpose of identifying a human condition or characteristic.</p> <p>These tests are designed to evaluate a patient's current state.</p>	<ul style="list-style-type: none"> <li>▪ hCG test for the determination of pregnancy</li> </ul>

Depending on its intended use, an IVD medical device may have one or more test purposes. For example, a nucleic acid-based infectious disease assay may be used for diagnosis (testing in patients suspected to be infected), screening (testing in asymptomatic patients) and monitoring (determination of viral load to assess effectiveness of treatment).

In some cases, it may be difficult to define a distinct test purpose, especially when one is dependent on (or linked to) another. For example, genetic testing is typically used for screening (i.e. testing in presymptomatic patients to detect genetic changes). However, very few genetic changes have complete penetrance and expressivity<sup>1</sup>. For most genetic-based conditions, testing serves to both detect the genotype (i.e. screening) and address the likelihood of developing the condition (i.e. predisposition).

---

<sup>1</sup> Penetrance refers to whether a genotype is expressed or not, and is considered complete (100%) if everyone with the genotype displays the phenotype. Expressivity describes the magnitude of the phenotype, if a particular trait is known to be mild, moderate or severe (or any degree in between).

