



FINAL DOCUMENT

Global Harmonization Task Force

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

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This document was produced by the Global Harmonization Task Force, a voluntary international group of representatives from medical device regulatory authorities and trade associations from Europe, the United States of America (USA), Canada, Japan and Australia.

The document is intended to provide non-binding guidance to regulatory authorities for use in the regulation of medical devices, and has been subject to consultation throughout its development.

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Preface

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1.0 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 GHTF's Essential Principles of Safety and Performance of Medical Devices (EPs). As IVD medical devices are used for the examination of specimens derived 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 IVD medical device achieves its intended performance during normal conditions of use by the intended user in the intended environment (e.g. laboratories, physician's offices, healthcare centers, home environments) and in the intended use population.

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/or 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 patient safety and data integrity along the entire process of the study.

2.0 Scope

The primary purpose of this document is to provide guidance for manufacturers of IVD medical devices, Regulatory Authorities (RA) and Conformity Assessment Bodies (CAB) in relation to:

- the selection of a clinical performance study design
- considerations to be made when undertaking a clinical performance study; and
- protocol, conduct and report of a clinical performance study

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, this document may also apply to studies conducted in the post-market phase.

NOTE: This document should not be used in isolation but read together with *the documents 'Clinical evidence for IVD medical devices – Key Definitions and Concepts' and 'Clinical evidence for IVD medical devices – Scientific Validity Determination and Performance Evaluation'* as well as the document *'Essential Principles of Safety and*

Performance of Medical Devices’ and the document ‘Summary Technical Documentation (STED) for Demonstrating Conformity to the Essential Principles of Safety and Performance of In Vitro Diagnostic Medical Devices’ (references provided in the reference section).

3.0 References

GHTF/SG1/N071:2012 Information Document Concerning the Definition of the Term ‘Medical Device’

GHTF/SG1/N068:2012 Essential Principles of Safety and Performance of Medical Devices

GHTF/SG1/N45:2008 Principles of In Vitro Diagnostic Medical Devices Classification.

GHTF/SG1/N046:2008 Principles of Conformity Assessment for in vitro Diagnostic (IVD) Medical Devices

GHTF/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/SG5/N6:2012 Clinical Evidence for IVD Medical Devices – Key Definitions and Concepts

GHTF/SG5/N7:2012 Clinical Evidence for IVD Medical Devices – Scientific Validity Determination and Performance Evaluation

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

4.0 Definitions

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/N71:2012 *Definition of the Terms ‘Medical Device’ and ‘In Vitro Diagnostic (IVD) Medical Device’*.

5.0 Purpose of Clinical Performance Studies

The purpose of a clinical performance study is to establish or confirm aspects of IVD medical device performance which cannot be determined by analytical performance studies, literature and/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*’). These studies are typically undertaken in the pre-market phase of the IVD medical device to support its compliance with the EPs, but may also be undertaken in the post-market phase.

6.0 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 potential biases.

Designs of IVD medical device clinical performance studies are either observational or interventional. An observational study refers to a study in which test results obtained during the study are not used for patient management and do not impact treatment decisions. An interventional study refers to a study in which test results obtained during the study 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:

- **Cross-sectional design (single time-point design)** – testing of one or few specimens/samples per patient that are collected at a single time-point
- **Longitudinal design** – testing of multiple specimens/samples per patient that are collected over an extended period of time (e.g. weeks, months, years)
- **Retrospective design** – testing of previously collected specimens for which the analyte status and the patient’s clinical status is known (characterized specimens) prior to the commencement of the study
- **Prospective design** – testing of specimens collected before or during the study but for which both the analyte status and the patient’s clinical status are established during the study
- **Prospective-retrospective design** – testing of previously collected specimens for which the clinical status is known but the analyte status is unknown and will be established during the study

NOTE: The terminology for the various study designs can be used in the context of either diagnostic or epidemiologic studies, and these terms are associated with definitions that vary accordingly. The definitions and methodologies described in this document refer to diagnostic test designs, not epidemiological designs.

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.

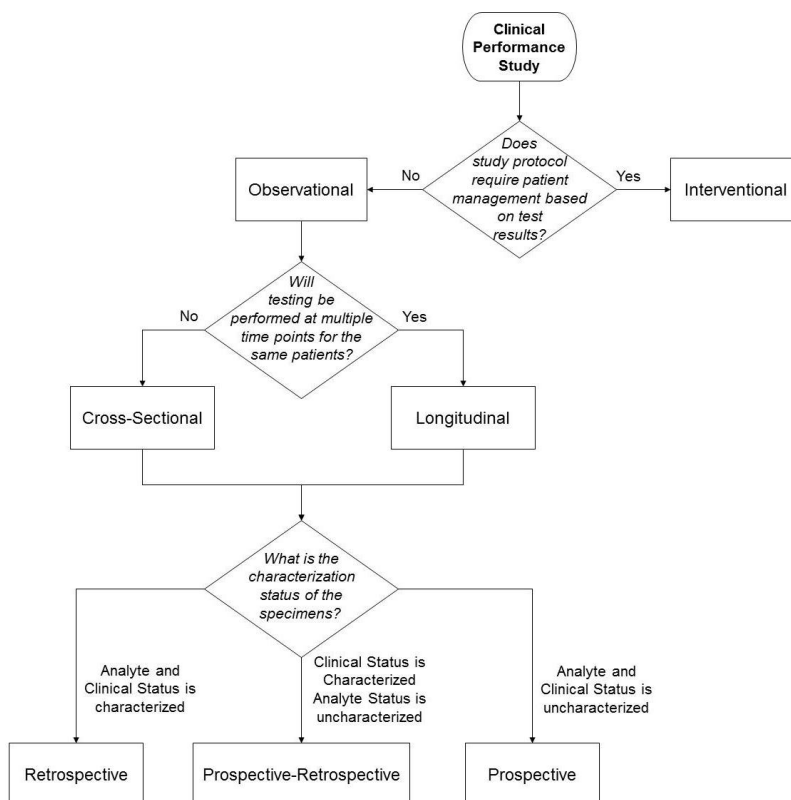


Figure 1: Decision tree for clinical performance study design

NOTE: In some cases it may be necessary to use a combination study design which includes both characterized and uncharacterized specimens.

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 management 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 leftover specimens that would otherwise have been discarded (also called surplus specimens); and/or
- additional specimens collected specifically for the study purposes

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

6.1.1 Cross-sectional Designs

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

Example 1 (Diagnosis): Troponin for the diagnosis of myocardial infarction.

Example 2 (Screening): Detection of Human Papilloma Virus (HPV) 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): Breast cancer gene expression profile test to determine the risk for distant metastasis.

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

NOTE: Refer to Appendix for a description of the common test purposes (e.g. screening, diagnosis, monitoring) for IVD medical devices.

In some cases, it is necessary to follow a modified version of cross-sectional design whereby testing is performed only at the initial time point, but patients are evaluated at later time points (follow-up) to determine their clinical status. This modification is known as a ‘delayed cross-sectional design’ and would apply in the following situations:

- the IVD medical device is used to evaluate the likelihood of future states (i.e. predisposition, prognosis and prediction); or
- there exists no applicable method to establish the clinical state at the time of testing or the method is deemed too invasive, thereby requiring follow-up to determine clinical outcome

6.1.2 Longitudinal Designs

Longitudinal clinical performance studies involve multiple patient measurements of the same analyte 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 patients at risk of renal failure, 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): Determination of the somatic mutation rate to estimate the risk of developing cancer.

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, significant decrease of BCR-ABL mRNA levels over time is predictive of continued treatment response.

6.1.3 Retrospective and Prospective Designs

This section describes clinical performance studies that follow a retrospective design, studies that follow a prospective design, studies that follow prospective-retrospective study design and studies that combine multiple designs.

Retrospective studies are appropriate if the following criteria are addressed:

- the specimens are representative of the intended use population (e.g. reflects variability of the clinical condition not just typical cases);
- the specimens are derived from a sufficiently large number of study subjects to reflect a random sampling;
- there is adequate data related to the clinical status of patients;
- the samples span the assay range (if applicable);
- there is minimal bias due to specimen/sample selection; and
- the analyte is stable over time.

When the criteria for retrospective study design eligibility are not met, the clinical performance study would need to follow a prospective design.

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 or a prospective-retrospective design could be used if specimen collection protocols were controlled to ensure that results are not biased or confounded.

A prospective-retrospective study employs a design that uses specimens that were collected previously under another protocol. These specimens will not be characterized for the analyte in question but will be clinically characterized. The specimens are collected retrospectively and are analytically characterized prospectively during the study.

Randomized controlled trials for therapeutic agents present a potential valuable source of specimens for a prospective-retrospective study as the patient outcome is known. Use of these specimens for prognosis or prediction is subject to the following considerations:

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

For certain clinical conditions (e.g. low disease prevalence), it may be necessary to design a clinical performance study that combines retrospective and prospective study designs. For example, a clinical performance study of an HIV-1/2 assay intended for donor screening may involve random blood donors (i.e. prospective uncharacterized specimens), HIV/AIDS patients (i.e. retrospective specimens characterized according to clinical status), and HIV-2 antibody-positive specimens (i.e. retrospective specimens characterized according to analyte status).

6.2 Interventional Designs

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

- there exists no established method for making decisions on patient management and the use of archived specimens would not be suitable to demonstrate the intended performance claims; or
- the manufacturer intends to demonstrate that the use of the IVD medical device impacts patient clinical outcome; 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 correct infectious disease identification (e.g. Hepatitis A versus Hepatitis B) 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 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 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)

7.0 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; 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, measuring interval (range), cutoff)
- expected clinical performance characteristics (e.g. sensitivity, specificity)
- novelty of the technology and/or clinical use (e.g. relevant previous experience)
- availability of an appropriate method to establish the clinical status of the patient.

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). 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 regarding 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, leftover specimens, or archived 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 (i.e. fresh) 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 status and/or clinical status of the patient are known, some specimens or samples may be archived without first

establishing their analyte/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 leftover or archived specimens 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 leftover or archived specimens if they were collected, handled and stored appropriately (i.e. good integrity) and if the information available for the specimens meets the study design requirements. Care must be taken to avoid introducing a selection bias through the use of leftover or archived specimens. Documentation should exist to support the integrity of the selected specimens in the clinical performance studies.

Attention needs to be given when using leftover or archived specimens to evaluate certain prognostic or predictive tests due to the potential that treatment regimens may bias results. It is generally more appropriate to use leftover or archived specimens 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's 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 manufacturer's site; in this case a justification for this decision should be provided. For example, a study to determine expected values can often be performed entirely at the manufacturer's site.

Sites are often chosen to serve as specimen collection sites only and do not perform testing. Similarly, sites can perform testing using the investigational IVD medical device but do not have the ability to perform testing using the reference method. In these cases, extra care is needed to minimize bias between study sites.

It is important to ensure that the collection and testing sites are 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) for estimation of clinical performance measures (e.g. sensitivity and specificity) with confidence intervals
- 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 such as selection bias, spectrum bias, verification bias (e.g. specimen/sample selection, collection, handling and storage; blinding of operator to clinical status of patient)
- criteria for re-examination and resolution (e.g. equivocal results, discrepant results)
- criteria for data exclusion (e.g. protocol deviation)
- analysis methodology
- clinically relevant performance characteristics (e.g. sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, negative predictive value, prevalence, percent agreement, correlation to clinical endpoints/outcomes, expected values)

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.

For clinical performance studies in which there is a risk to patients, clinical performance studies should only be performed once the analytical performance of the device has been established and determined to be acceptable. For example, in clinical performance studies for companion diagnostics, the way in which the biomarker status impacts treatment decisions may pose a risk to the patients.

7.6 Ethical Considerations for Clinical Performance Studies

As a general principle, the rights, safety and well-being of subjects participating in IVD medical device clinical performance studies shall be protected in accordance 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 leftover or archived 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 apply or may be waived.

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, there may be a need to communicate clinical performance study results to clinicians and/or public health institutions during or after the study. This can be the case when test results may have an immediate health impact (e.g. no routine testing exists) to the patient, patient's relatives 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 the detection of SARS is undergoing a clinical performance study. Specificity is assessed using prospectively-collected patient specimens. 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.

8.0 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 and if applicable, clinical endpoints/outcomes, and requirements for patient follow-up.

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.

9.0 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:

- independence of study personnel
- qualification and training of study personnel
- adequate infrastructure
- appropriate calibration procedures and means of control
- relevant method for determining the true clinical status of patient specimens

Raw data of a clinical performance study should be maintained based on the Quality Management System (QMS) requirements.

10.0 Clinical Performance Study Report

The protocol, results and conclusions of a clinical performance study should be documented in a Clinical Performance Study report. The results and conclusions should be transparent, free of bias, and clinically relevant. The report should contain sufficient information to enable it to be understood by an independent party without reference to other documents.

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

The level of detail of the clinical performance study report will vary based on the class of the IVD medical device:

- Class A – A clinical performance study would not be expected hence a report would not be required.
- Class B – The study report would be limited to a summary of study protocol, results and conclusion.
- Class C – The complete study report includes the method of data analysis, the study conclusion and relevant details of the study protocol.
- Class D – The complete study report includes the method of data analysis, the study conclusion, relevant details of the study protocol, and typically the individual data points (formatted raw data).

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. 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"> ▪ genetic test for the diagnosis of Tay-Sachs ▪ HBs antigen confirmatory assay to verify positive screening results ▪ D-dimer assay for exclusion of deep vein thrombosis ▪ karyotype testing for the diagnosis of Trisomy 18 (Edward's syndrome) |
| 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 test is not the sole determinant.</p> <p>These tests are designed to evaluate a patient's current state.</p> | <ul style="list-style-type: none"> ▪ troponin test as an aid in myocardial infarction diagnosis ▪ genetic testing to aid in the diagnosis of familial hypercholesterolaemia (FH) ▪ thyroid-stimulating hormone test to evaluate thyroid function ▪ toxoplasma IgG avidity assay to determine likelihood of active infection ▪ ANA test for autoimmune disease determination ▪ test for genotyping of the Factor V Leiden mutation as an aid to diagnosis of thrombophilia |

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

| Test Purpose | Description | Examples |
|--------------|--|---|
| Screening | <p>Screening tests are used to determine the status of a disease, disorder or other physiological state in an asymptomatic individual.</p> <p>These types of tests include genetic screening assays, tests for physiological typing, 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>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 an individual's current state.</p> | <ul style="list-style-type: none"> ▪ test to detect hepatitis B surface antigen in donated blood ▪ prenatal rubella IgG screening in pregnant women ▪ prenatal genetic testing for trisomy 21 (Down's syndrome) ▪ newborn genetic testing for phenylketonuria ▪ tests for the determination of HLA, blood groups and blood group factors for donor matching |
| Monitoring | <p>Monitoring tests are used for the measurement of analyte levels for the purpose of adjusting treatments/interventions as required. Monitoring tests include the following:</p> <ul style="list-style-type: none"> ▪ Assays which are used to ensure that an analyte remains within physiological levels or within an established therapeutic drug range. These types of monitoring tests are designed to evaluate an individual's current state. ▪ Assays which are used for serial measurement, whereby multiple determinations are taken over time. These types of monitoring tests are typically used for the detection/assessment of disease progression/regression, disease recurrence, minimum residual disease, response/resistance to therapy, and/or adverse effects due to therapy. These types of monitoring tests are designed to evaluate changes in an individual's state | <ul style="list-style-type: none"> ▪ intraoperative iPTH monitoring during parathyroidectomy surgery to confirm removal of abnormal tissue ▪ self-test glucose monitoring to allow for quick responses to hyperglycemia or hypoglycemia ▪ therapeutic drug monitoring of immunosuppressants to prevent rejection of transplanted organs ▪ viral load testing of patients known to be infected with HIV to determine treatment response and adjust therapy if necessary ▪ monitoring of CA 15-3 levels in breast cancer patients in remission to detect recurrence ▪ test for the detection of BCR-ABL transcripts to monitor response/resistance in patients undergoing treatment for acute lymphoblastic leukemia (ALL) or chronic myeloid leukemia (CML) ▪ test for immunoglobulin and T-cell receptor gene rearrangements for the detection of minimal residual disease in cancer patients. |

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

| Test Purpose | Description | Examples |
|--|--|--|
| 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"> ▪ genetic test for apolipoprotein E to assess the risk of developing Alzheimer's disease ▪ 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) |
| 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"> ▪ high sensitive C-reactive protein measurement for the risk stratification of patients with acute coronary syndromes to determine the likelihood of future cardiac events ▪ measurement of baseline HIV-1 RNA level to assess patient prognosis ▪ cancer gene expression profile testing for metastasis risk to tailor treatment aggressiveness |
| 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"> ▪ HER-2/neu testing in breast cancer patients to assess likelihood of response to hormone therapy ▪ identification of variations in cytochrome P450 genes (i.e. metabolizer status) to determine potential therapeutic benefits and/or adverse reactions to antiplatelet treatment |
| Determination of Physiological Status | <p>Physiological status determination 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"> ▪ hCG test for the determination of pregnancy |

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, a single genetic test may be used to detect the genotype (i.e. screening) as well as providing the likelihood of developing the condition (i.e. predisposition).