IVD Clinical Performance Studies for FDA & EU

At present, the regulatory discussion pretty much focuses on MDR Regulation (EU) 2017/745 on medical devices. However, it seems the impact of Regulation (EU) 2017/746 on in vitro medical devices (IVDR) on the industry is expected to be much more intense. With the updated in vitro diagnostic medical devices (IVD) classification, at least 80% of IVDs will be moving under Notified Body scrutiny, compared to 20% previously. Therefore, most manufacturers should now be gearing up to shift from self-certification to notified body oversight as IVDR will be fully enforceable on May 2022.

According to the IVDR, clinical evidence must support the intended purpose of the device as stated by the manufacturer and be based on a continuous process of performance evaluation, following a performance evaluation plan. The performance evaluation reports should demonstrate the following elements:

- **Scientific validity**
- **Analytical performance**
- **Clinical performance**

As far as clinical performance is concerned, Clinical Performance Studies are the studies undertaken to establish or confirm the clinical performance of an IVD medical device. The purpose of a clinical performance studies is to establish or confirm aspects of 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 general safety and performance requirements with respect to clinical performance. The data obtained from clinical performance studies is used in the performance evaluation process as a part of the clinical evidence for the IVD.

The two important aspects of clinical performance studies are clinical validity and clinical utility studies.

Clinical Validity Studies is the ability of a test to accurately and reliably predict the clinically defined disorder or phenotype of interest. The clinical validity studies consist of the test parameters such as clinical sensitivity, clinical specificity, positive predictive value and negative predictive value.

The clinical validity studies are classified as below based on the objective types:

Study objectives	Term used	Example
» **Evaluation of how well the test can detect a target analyte**	• Analytical Validity	• Evaluation of precision, cross-reactivity • Evaluation of measuring interval • Evaluation against a comparator device
» **Evaluation of how well the test can detect a target analyte**	• Clinical Validity • Clinical Performance	• Estimation of measures of clinical performance • For a binary qualitative test, these measures are clinical sensitivity and specificity, positive and negative likelihood ratios, positive and negative predictive values for prevalence • For a qualitative test with multiple outputs, these measures are pretest risk, post-test risks for each output, likelihood ratio for each output, and percent of patient
» **Evaluation of the ability of the test to direct clinical management and improve patient outcomes**	• Diagnostic Thinking Efficacy • Benefit-Risk Analysis • Clinical Validity/ Clinical Utility	• Impact on clinician's judgment about diagnosis & prognosis • Impact on the choice of management
» **Evaluation of the ability and magnitude of the test to improve patient outcomes**	• Clinical Utility	• Impact on mortality or morbidity
» **Evaluation of the test to benefit society as a whole**	• Societal Efficacy/ Clinical Utility	Cost-effectiveness analysis

Clinical Utility is the ability of a test to implicitly improve patient health outcomes, when used to inform and support clinical decisions that increase the chances of improved patient outcomes.

Clinical Utility Studies include:

- Outcome measures that assess both potential benefits and harms of testing from the patient perspective
- Recognizing that these outcomes may occur at different time points and are the result of clinical management decisions guided by test results
- These outcome measures include such as clinical assessments of disease remission and progression, response to therapy, functional status as well as adverse events
- Clinical utility studies may also include important endpoints such as survival and downstream health care resource utilization

Clinical utility will vary with each new IVD based on its intended use, existing tests. Although it is common to separate the terms clinical validity and clinical utility, a clear-cut separation is not always possible since the clinical validity of the tests depends on the intended use or the claims made on the use of the test.

The designs of IVD clinical performance studies could be two types - Observational and Interventional study

- **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. The observational study design includes cross-sectional design, longitudinal design, retrospective design, prospective design and prospective-retrospective design.
- **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.

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

- If there is no established method for making decisions on patient management
- If the use of archived specimens would not be suitable to demonstrate the intended performance claims
- If it intends to demonstrate that the use of the IVD medical device impacts patient clinical outcome
- If an IVD medical device is co-developed alongside a therapeutic product

The clinical performance studies require a clinical performance study report, which will include the study plan, procedure, results, and conclusions. These reports will have to contain enough information to be understood by an independent party without reference to other documents. As planning, execution and collection of the data on clinical performance studies take considerable amount of time; the IVD manufacturers should seriously look into the need of clinical performance studies of their IVD products based on the clinical data available with them.

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