IVD medical device clinical performance (evaluation) studies

From performance evaluation studies to clinical performance studies

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Introduction

When placing in vitro diagnostic devices (IVDs) on the European market, manufacturers need to demonstrate that their IVDs perform as claimed. This requires “adequate” performance evaluation (PE) data supporting manufacturers’ IVD performance claims. What qualifies as “adequate” PE data is, however, the most pressing question asked by manufacturers when designing, manufacturing or placing devices on the EU market, or when putting them into service via CE Marking.

The In Vitro Diagnostics Directive 98/79/EC (IVDD) demands that adequate PE data “should originate from studies in a clinical or other appropriate environment or result from relevant biographical references” (IVDD Annex III).

Since 2017, further specifications regarding the adequacy of IVD PE data have been provided by the European In-vitro Medical Devices Regulation (EU) 2017/746 (IVDR). The Regulation states that PE of a device is “a continuous process by which data are assessed and analysed to demonstrate the scientific validity, analytical performance and clinical performance of that device for its intended purpose as stated by the manufacturer” (IVDR Annex XIII).

The IVDR also states that performance data can be obtained from state-of-the-art literature (scientific validity) as well as “correct detection or measurement of the particular analyte (analytical performance)” and “results that are correlated with the particular clinical condition or a physiological or pathological process or state in accordance with the target population and intended user (clinical performance).” The analytical and clinical performance of an IVD has to be established in analytical performance studies and clinical performance (CP) studies using methodologically sound procedures, unless any omission can be justified as not applicable (Annex I). This concept is identical under the current IVDD and the upcoming IVDR.

IVD manufacturers have done/should do their utmost to meet their obligation to provide adequate PE data, but most companies have never undergone an audit under the current IVDD, and it remains uncertain whether this performance data will be considered "adequate" by Notified Bodies (NB) under the IVDR.

While this might appear to be a significant change, the EU Commission stated in an IVDR fact sheet published in 2018 that, "In terms of impact on manufacturers and products, the IVDD and the IVDR largely share the same basic regulatory process. No existing requirements have been removed, but the IVDR adds new requirements."[1]

This white paper focuses on requirements for clinical performance (evaluation) studies, conducted to obtain adequate performance data for demonstrating clinical performance, and summarizes our understanding of the main obstacles to tackle for existing or new clinical performance (evaluation) studies.

Requirements for IVD performance evaluation studies: Current or past?

Information on specific requirements for IVD performance evaluations, including definitions for different types of PE studies, was quite limited in previous EU guidance documents and standards.[2] For example, the IVDD does not include a definition for PE studies. However, the definition given for the "devices for performance evaluation" does indirectly address these PE studies, indicating that PE studies include "studies in laboratories or medical analyses or studies in other appropriate environments outside the own premises of the IVD medical device manufacturer." That's why these PE studies are often called "external" PE studies.

The EN 13612 standard "Performance evaluation of in vitro diagnostic medical devices," published in October 2002, provided more guidance on these "external" PE studies and furnished information about when PEs should be performed. This standard refers directly to the IVDD, which requires "that the manufacturer provides evidence in his technical documentation that the IVD medical device performs as claimed, whether these claims are of a technical, analytical or diagnostic nature.

Such evidence can be shown by data already available to the manufacturer or by scientific literature or by data originating from performance evaluation studies in a clinical or other appropriate environment in accordance with the intended use."

EN 13612 also defines:

- Preconditions, which need to be fulfilled before conducting a PE study[3]
- When to perform PE studies; PE studies are part of the design validation or may be required after a design change, so typically will be done on a frozen or changed design at the end of the IVD design development
- General terms applicable to PE studies

EN 13612 also provides information on:

- The requirement to establish certain roles and functions such as the coordinator or investigator of a PE study
- Generating PE- specific documents such as the evaluation plan and evaluation report

While EN 13612 describes many of the PE study elements, it leaves the specific study planning and conduct up to the manufacturer, as these efforts depend on the level of complexity of the IVD and the design of the intended PE study.

In 2003, the ISO 14155 standard "Clinical investigation of medical devices for human subjects - Good clinical practice (GCP)" was published, specifying general guidance on conducting clinical investigations with medical devices on human subjects; this standard was first updated in 2011. Even though ISO 14155 excludes IVD medical devices from its scope, it was common understanding that, next to compliance to EN 13612, compliance to ISO 14155 needed to be considered for those IVD clinical PE studies which posed risks to involved subjects, whether due to methods of sample taking or if the outcome of the IVD assessment affected the subjects' treatment.

In addition, requirements for conducting clinical investigations and PE studies were introduced into national country legislations in many EU member states over time. Many of these national regulations include Good Clinical Practice (GCP) requirements for studies in humans as described in ISO 14155, which apply regardless of whether medical devices or IVDs are involved. It is worth mentioning that manufacturers and clinical study sponsors must always consider these country legislations when a clinical site in the respective EU member state is involved in a PE study, even if "only samples were taken" at that site.

What has changed?

In May 2017, the IVDR was adopted, and will replace the IVDD on May 26, 2022 in the European Union. The new Regulation will likely roll out progressively, with compliance deadlines dependent upon the IVD product's risk class.

The IVDR introduces the concept that "Clinical performance studies shall be performed unless due justification is provided for relying on other sources of clinical performance data," which will increase the number of necessary clinical performance studies (CP studies, known as PE studies under the IVDD).

Specifically, IVDR Chapter VI, Annex XIII, Section 2, and Annex XIV describe elements required for CP studies such as an establishment of a purpose for the planned CP study, ethical considerations, methods to be used in the study and the study design. A clinical performance study plan (CPSP) must address most of these elements, but certain information can also be provided in stand-alone documents. The results and conclusions need to be provided in a clinical performance study report (CPSR). CP studies, which do not meet the IVDR Annex XIII requirements, might be considered as "other sources of clinical data." A sound rationale for why such data supports CP needs to be provided by the manufacturer.

The IVDR also referred to ISO 14155 in recital 66, underlining the expectation that compliance to ISO 14155 should be considered for CP studies. To provide further guidance, a new standard, ISO 20916, "In vitro diagnostic medical devices - Clinical performance studies using specimens from human subjects - Good study practice," was published in 2019, and the IVDR was updated with its first corrigendum to cite ISO 20916 instead of ISO 14155. Recital (66) now states:

The rules on performance studies should be in line with well-established international guidance in this field, such as the international standard ISO 20916 on clinical performance studies using specimens from human subjects, currently under development…

The establishment of ISO 20916 and the IVDR introduces clear definitions of different types of CP studies as well as roles and responsibilities of all involved parties (e.g., sponsor, study site, ethical committees, etc.). In addition, it provides guidance for the compliant conduct of respective clinical performance studies. This guidance allows manufacturers to more efficiently plan the compliant conduct of respective CP studies and enables Competent Authorities as well as Notified Bodies to establish their respective controls regarding when such studies are started and whether they support CE Marking.

For the compliant study conduct, manufacturers need to establish and/or maintain well-defined processes for applying ISO 20916. Additionally, they need to maintain more thorough and compliant documentation regarding these studies' conduct and results (e.g., generating the CPSR), which will eventually need to be provided to the Notified Bodies when applying for CE Marking.

ISO 20916 at a glance

General

As mentioned above, the ISO 20916 standard provides detailed guidance on CP studies, including appropriate IVD definitions and insights into the roles and responsibilities of all involved parties in line with CP study requirements included in the IVDR. ISO 20916 also differentiates between:

Interventional CP studies: Studies in which test results obtained during the study can influence patient management decisions and might be used to guide treatments

Non-interventional CP studies, which are further divided into studies:

- In which specimen collection is primarily done for the purpose of the CP study, and the specimen collection procedures pose additional risks to the subject

or

- When the conduct of the study involves additional risks for the subjects and studies
- Which do not pose a risk to the participants — e.g., studies with leftover archived specimens

ISO 20916 and specifically Annex G of the standard (adverse event categorization) should be considered for all CP studies. Depending on the IVD and the planned study's complexity, Annexes A through F also require respect, as they are applicable for higher-risk CP studies. Thus, the first questions each sponsor of a planned CP study with an IVD should ask are:

- Is the planned CP study interventional or non-interventional?
- Does the study pose additional risks to the subjects?

Answering these questions will define applicable CP study processes (see also normative Annex A: additional general requirements for certain studies) and is essential for the planning, conduct and closeout of the anticipated CP study.[4]

Ethical considerations

As with any clinical study involving human subjects, CP studies shall always be conducted in accordance with ethical principles such as the Declaration of Helsinki[5] to protect the study participants' rights, safety, dignity and well-being and to ensure that the data generated are scientifically valid, reliable and robust.

Normative Annex E of ISO 20916 describes the general documents needed for ethics committee (EC) submission as well as information to be provided to the EC before, during and after the study.[6]

CP studies: Planning

To ensure that the CP study is planned and conducted adequately, a clinical performance study protocol (CPSP) (named clinical performance study plan in the IVDR) should be generated.

Topics usually included in the CPSP are described in ISO 20916 Section 5.5.3 and normative Annex B, and include, among other items, information on:[7]

- Sponsor(s)
- Study IVD (and comparator, if applicable) and intended use
- Specimens and, when applicable, subjects providing specimens
- Objectives and endpoints (primary and secondary)
- Procedure involved
- Informed consent process
- Statistical consideration
- Monitoring and data management
- (Serious) adverse event, (serious) adverse device effects and device deficiency documentation and reporting

Other activities and documents required during the setup of the CP study are:[8]

- Risk evaluation to assess the risks associated with study participation
- Site selection (selection, assessment and qualification of study staff and study sites)
- Monitoring plan
- Case report forms
- Contracts (with all involved parties)
- Labeling
- Good Clinical Practice (GCP) study documentation (see ISO 20916 Annex H)

CP studies: Conduct

The CP study can only be started following written approval or favorable opinion from the involved EC(s) and, where applicable, approval from the respective NCA.

Site initiation: Prior to full initiation of involved study sites, sponsors must ensure that required study site documentation is in place, including signed contract(s) and respective approval(s). The IVD needs to be available at the study site. In addition, sponsors must confirm that the study site personnel have received adequate training on general study requirements (e.g., study site personnel responsibilities) and specific CP study requirements (e.g., the CPSP and proper use of the IVD).

Site monitoring: Once CP study sites begin enrolling participants, sponsors should conduct clinical monitoring to verify that the study is conducted according to the CPSP, ISO 20916 and any other applicable requirements. During routine monitoring, it will be verified, among others that:

- The IVD is being used according to CPSP or instruction for use
- The IVD is available and IVD accountability is performed accurately
- Study records are correct, complete and up to date
- Safety event (device deficiency, (serious) adverse event, (serious) adverse device effect) documenting and reporting is done appropriately to country legislation
- The General Data Protection Regulations (GDPR) are respected

Activities conducted as well as findings or observations should be documented in a monitoring report (see ISO 20916 Section 7.3.3).

CP study closeout

Closeout activities will be conducted for each study site to ensure that the site records are complete, all sponsor records are retrieved, remaining IVDs are returned or destroyed, issues have been resolved and relevant parties are informed about the end of the study.

A clinical performance study report (CPSR) will be generated for every CP study. ISO 20916 Section 8.2 outlines a CPSR's expected content. The results section, for example, should include information on the statistical analysis used as well as performance and safety results. The CPSR results section should also provide an accounting of all subjects included in the study and specimens collected, plus a discussion and overall conclusion on the outcome of the study.

Normative Annex D provides further guidance for CPSR generation for certain higher-risk CP studies.

ISO 20916 also covers other topics including document retention, premature study termination and auditing.

Studies with companion diagnostics

General

There seems to be some uncertainty about study requirements on the part of the sponsor when it comes to studies in which the clinical performance of an IVD, e.g., companion diagnostics (CDx), is tested along with an investigational medicinal product (IMP) in one study. CDx are a specific type of IVD, unfortunately not defined in the current IVDD since the CDx concept emerged only after the IVDD came into effect in 1998. The IVDR as well as ISO 20916, however, closed this gap by defining CDx (Article 2 (f)): being a device which is essential for the safe and effective use of a corresponding medicinal product to:

(a) identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or
(b) identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product[9]

The IVDR and ISO 20916 further define requirements for CP studies with CDx.[10]

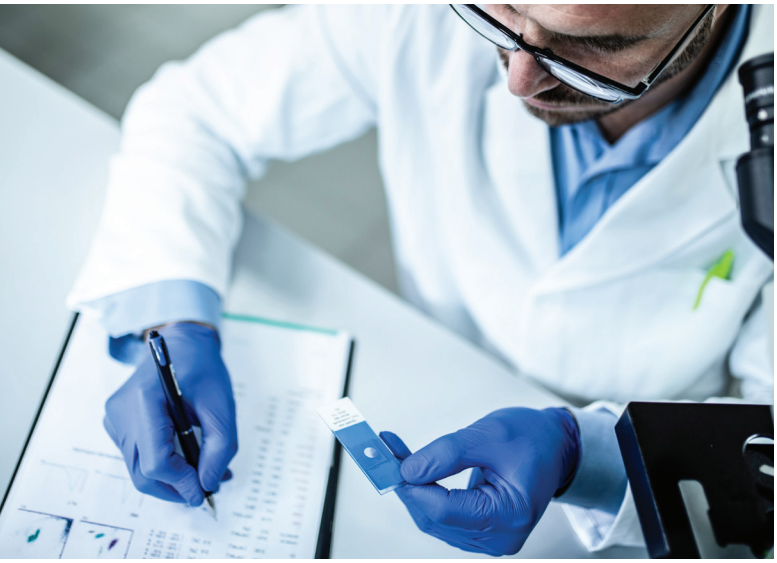
Requirements for CP studies with companion diagnostics

As mentioned above, CP studies in which test results obtained during the study are used for patient management decisions and to guide treatments are considered interventional clinical performance studies. This applies to most studies involving CDx products.

According to ISO 20916 Annex A, these interventional studies involve additional general requirements. Those studies require a CPSP, investigator's brochure (IB), informed consent (ICF) and other essential study documents as specified in Annex H. EC approval will need to be obtained as well as NCA approval in many EU member states. Therefore, compliance with these general ISO 20916 requirements should be considered to ensure that the ethical principles addressed above are met. Another important aspect is the establishment of proper IVD safety event documentation and reporting. Finally, a CPSR needs to be generated.[11]

Challenges for CP studies with companion diagnostics

The CDx manufacturer and the investigational medicinal product developer are often separate companies and roles, and responsibilities for the planned study are not clearly contractually defined between these two companies. The pharmaceutical company usually drives studies with CDx while the CDx manufacturer plays a supporting role in the study's setup and execution. Medicinal product studies with CDx are then conducted according to general and national medicinal product regulations and requirements.



Among pharmaceutical companies or their involved partners such as contract research organizations (CRO), there is often a certain unawareness regarding the applicability of ISO 20916 for CP studies with a CDx since the current IVDD does not reference this standard. In addition, national legislative requirements for CP studies are often hard to identify (national regulations are frequently written in national languages only). Furthermore, the written procedures of CDx manufacturers and involved pharmaceutical companies might not adequately address CP study processes.

Not sufficiently addressing these challenges, along with higher NCA, EC and Notified Body scrutiny, may lead to significant delays of the respective studies.

Considerations for CP studies with CDx

Overall medicinal product study requirements and CP study requirements need to be addressed when conducting a study with an investigational medicinal product and a CDx. The following issues should be considered:

- Along with requirements for medicinal product studies, understand and follow national legislation applicable to CP studies with CDx. This applies to all involved parties.
- Review your written processes to close eventual gaps (processes for medicinal product studies are not that different from those for CP studies).
- Define roles and responsibilities for the pharmaceutical company and CDx manufacturer for conducting these studies. Ensure that all necessary tasks are covered and documented.
- Consider ALL applicable ISO 20916 aspects for developing the essential study documents. Two study protocols might be expected; however, if only one protocol is written, ensure that the study protocol identifies the IVD involved as IVD for PE (including respective labeling) and includes required IVD CP study-specific elements. The same applies to other essential study documents like informed consent covering both study elements. The CDx requires an additional investigator's brochure (IB).
- Ensure that study site personnel are qualified to conduct CP studies and are trained on the appropriate study requirements, and that qualified infrastructure is established as requested by the NCA and EC.[12]
- Set up appropriate safety recording and reporting processes defining who will be responsible for recording and reporting safety events (IVD-related and/or IMP related) as well as when to report according to the medicinal product regulations and/or IVD regulations (e.g., safety events due to the inclusion of subjects based on "false" IVD results). Reach out to the NCA for guidance, if needed.
- Ensure that all required EC and NCA study approvals for the medicinal product and the CDx study components are obtained. Besides "medicinal product EC" approvals, commonly additional "CP study EC" approvals need to be obtained for all study sites involved in medicinal product studies with CDx, even if the samples are shipped outside of the respective country for analysis.

Conclusions

General requirements for PE studies under the EU IVDD have been in place since 2002 through the EN 13612 and ISO 14155 standards and through national EU country legislations, but IVD manufacturers might not have adequately identified or considered this mixture of regulations when designing, planning and performing their CP studies.

With the establishment of ISO 20916 in 2019 and the IVDR, clear definitions of different types of clinical performance studies as well as roles and responsibilities of all involved parties (e.g., sponsor, study site, ethical committees, etc.) are now available. In addition, they provide detailed guidance for the compliant conduct of respective CP studies.

This allows manufacturers to plan the compliant conduct of respective CP studies more efficiently. NCAs and Notified Bodies obtained direction for their assessment as to whether setup, conduct and evaluation of the CP study are or were compliant. For this reason, all IVD manufacturers conducting CP studies should consider ISO 20916 requirements for their study design and conduct, even if the IVDR will only come into force in May 2022.

The number of tasks to consider for CP studies is immense. It is crucial that experienced and trained personnel with a proficient understanding of their roles and responsibilities are involved in the planning and conduct of these CP studies. In addition, manufacturers and sponsors must budget adequately for CP studies. Manufacturers might consider ISO 20916-compliant conduct of CP studies an extra burden, but following this standard will result in robust clinical performance data, easier demonstration of clinical evidence and potentially faster approval processes under the IVDR.

There is a significant risk that clinical performance data obtained in recent years without adequately respecting ISO 20916 (or EN 13612) may not be accepted by Notified Bodies to support clinical performance requirements under IVDD and IVDR. The expected “up-classification” of many IVDs through the rule-based classification system under the IVDR and the associated Notified Body involvement could result in CE certificates not being granted or even CE certificates being suspended, which ultimately could lead to manufacturers having to redo their clinical performance testing.

Regarding studies with CDx, we have recently seen increased scrutiny by the involved ECs and NCAs on the described CP study elements. CDx studies might have received approval with the medicinal product in the past and the “CP study part” might not have been controlled to the necessary level. Consequently, clinical evidence collected in current and previous noncompliant studies will likely not be accepted for the required demonstration of clinical performance under IVDR (CE Marking) and potentially for the marketing authorization application for the involved medicinal product. Complete redos of the CDx studies for recertification under IVDR for the CDx and the medicinal product, as well as field safety corrective actions (FSCA) or even recalls, are realistic scenarios.

Thus, it is advisable for IVD manufacturers to proactively review study data collected in older CP studies and assess whether these studies have met general CP study criteria. Identified gaps should carefully be discussed in the context of available scientific validity and analytical performance data. Further studies, like post-market performance follow-up (PMPF), might need to be initiated to support current clinical claims and to prepare supportive information and adequate evidence for the demonstration of clinical performance. Sometimes a redo of CP studies might also be necessary. Proactive planning of CP studies or PMPFs usually leaves significantly more flexibility for the design and scope of the respective study when compared to CP studies, which need to be initiated to remedy deficiencies identified by Notified Bodies. Adequate documentation is key, and even a well-structured PMPF plan laying out planned PMPF activities might reduce the risk of a CE suspension.

Endnotes

1. https://ec.europa.eu/docsroom/documents/31202
2. A list of potentially applicable EU harmonized standards was published and regularly updated in the Official Journal of the European Union (OJEU) until 2017. Many manufacturers used this as their source of information over years to identify the best applicable standards to demonstrate conformity to EU Directives.
3. EN 13612 section 4.1 Preconditions: Before starting a PE study it shall be ensured by the coordinator that:
   a) the performance claims of the IVDMD which are the subject of the study are specified;
   b) the IVD has been manufactured under controlled production processes and conditions;
   c) the IVD MD to be evaluated meets the quality control release specifications;
   d) a sufficient number of samples of the IVD MD can be provided during the entire period of the performance evaluation study;
   e) all legal requirements for performance evaluation studies are met;
   f) the investigator(s) is (are) adequately skilled and trained to conduct the study and the necessary resources are available.
4. ISO 20916 requires written procedures for all CP study processes, which need to be part of the Quality Management System (QMS) of the involved parties.
5. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
6. National legislation and the risk the study is posing to study participants/subjects will further define the level of EC communication needed, and whether national Competent Authority (NCA) study notification or approval is required.
7. Much of the required information can be documented in stand-alone documents separate from the CPSP (e.g., information on study sites or SAE reporting), but should be very carefully addressed. Often these documents need to be included in respective country submissions or notifications to ECs and NCAs.
8. Additional factors, such as the current coronavirus pandemic, and their potential impacts need to be considered when planning and conducting CP studies.
9. The US FDA provides a similar definition.
10. IVDR recitals 10 to 12 provide further information about which IVDs are considered to be CDx and which aren't and the role of CDx.
11. The applicability of ISO 20916 requirements needs to be checked for all studies with CDx, as well as those considered to be non-interventional.
12. Involved study personnel might need to obtain medicinal product study and medical device study requirements training in some EU countries.

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