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The impact of the EU IVDR on clinical trials

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The EU In Vitro Diagnostic Medical Devices Regulation (EU IVDR) applies to all in vitro diagnostic devices (IVDs) used within the EU. The regulation became applicable in the EU on 26 May 2022 and has changed the landscape for the laboratory testing component of clinical trials. Laboratories and clinical trial sponsors are now discovering firsthand the consequences of using IVDs off-label, relying on in-house developed IVDs, and working with central testing facilities outside of the EU. It is becoming increasingly clear that laboratories and clinical trial sponsors must collaborate closely to reach compliance with the EU IVDR.

Keywords – clinical trials, companion diagnostic, IVD regulation, in-house developed device, laboratory-developed test

Introduction

Diagnostic laboratory testing is essential in clinical trials for human medicines, and laboratory tests are carried out during all phases of clinical trials. It is therefore no surprise that the EU IVDR, also known as Regulation (EU) 2017/746, has significantly impacted clinical trials conducted in the EU.[1] However, not all laboratory tests performed during clinical trials are affected by the regulation; the key question is whether the test is an in vitro diagnostic medical device (IVD) in the context of the clinical trial.[2] If the answer is yes, then the IVD must be further categorized to understand the implications of the EU MDR. This article explores the regulation's effects on the following three scenarios:

- IVDs bearing the Conformité Européenne (CE) mark used outside of their intended purpose,
- In-house developed IVDs within the EU, and
- IVDs that are used outside of the EU and that do not bear the CE mark.

The staggered transitioning period for IVD manufacturers to comply with the EU IVDR can heighten complexity for long-running clinical trials. This article outlines the different challenges and options involved in establishing an EU IVDR–compliant laboratory testing component of clinical trials in the EU. CE-marked IVDs (CE-IVDs) must be used when available, but two options remain for IVDs that are not CE marked. Certain IVDs that have been developed in-house can obtain partial exemption from the regulation requirements if the laboratory is established within the EU. The other option is to use the IVD in the clinical trial as a device for performance evaluation, which implies that the performance of the IVD is evaluated during the clinical trial. These IVD performance studies require separate applications and approvals in the EU countries where the clinical trial takes place.

Definitions for the terms *companion diagnostic, health institution, in vitro diagnostic medical device, intended purpose,* and *leftover specimen/leftover sample* are provided in the **Glossary** at the end of this article.

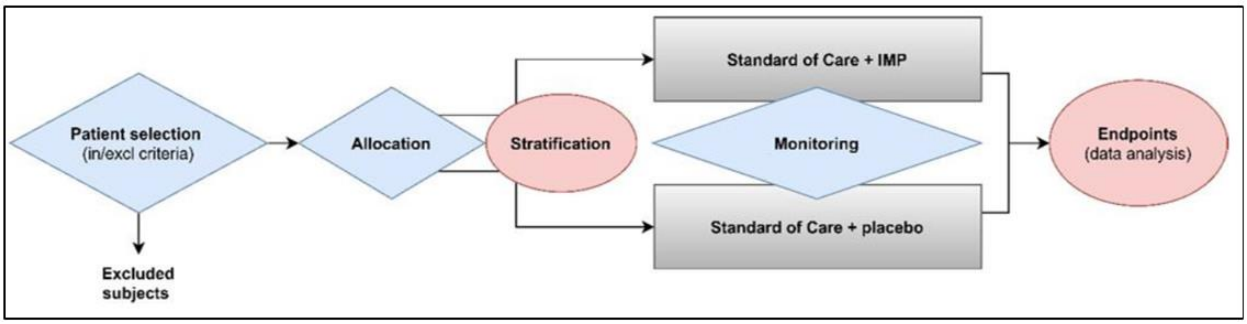
Not all laboratory tests for clinical trials are IVDs

In the EU, any product or a combination of products that meets the definition of an IVD must comply with the EU IVDR, whether that IVD is used for routine diagnostic purposes or in the specific context of a clinical trial conducted within the EU. The regulation applies to both commercially available IVDs (identifiable in the EU by their CE mark) as well as those that are made in-house by laboratories. Moreover, IVDs used outside of the EU are also in scope of the regulation if these tests are done on samples shipped from within the EU. However, not all laboratory tests meet the definition of an IVD in the context of clinical trials. This has been clarified in a 2022 guidance from the Medical Device Coordination Group (MDCG) on the interface between the EU Clinical Trials Regulation and EU IVDR, which says that laboratory tests are considered to be IVDs in the context of a clinical trial if they are used in processes for medical management decisions of trial participants.[2] The guidance, referred to as MDCG 2022-10, also provides a simplified example to clarify this (**Figure 1**, p. 3). As an example, laboratory tests that are not IVDs and are therefore not subject to EU IVDR–specific requirements may include tests that are performed for exploratory end points (except when it is predictable or foreseeable that the test will be used for patient management in the future). Laboratory tests that are subject to the regulation (i.e., IVDs) include tests used for inclusion and exclusion of participants, treatment allocation, and monitoring the safety and efficacy of the treatment during the trial. It should be noted that such tests are considered IVDs regardless of their regulatory status.

Uncertainties for CE-marked IVDs in the transition period

The most straightforward way of working is using a CE-IVD in full accordance with its intended purpose. The intended purpose, which is found in the CE-IVD's instructions for use, provides specific information about the device's medical

Figure 1. Simplified example of a blinded trial with two treatment arms[a,b]



IMP, investigational medicinal product

[a]This figure is a simplified depiction in which stratification is a method used in randomization to ensure equal distribution of chosen variables between treatment arms. [b]**Blue** = processes used for medical management decisions of trial participants and subject to the EU IVDR; **Pink** = processes likely not to have an impact on the medical management of the trial participants and not subject to the EU IVDR.

Source: MDCG 2022-10[2]

purpose (e.g., diagnosis, prognosis, prediction), target patient groups, and compatible sample types (e.g., blood, bone marrow, and tissue) and instruments.

Generally, IVDs used by a European laboratory for monitoring the safety of clinical trial participants will be CE marked and used according to their intended purpose. However, sponsors of long-running clinical trials have to factor in that not all of these IVDs are already CE marked under the EU IVDR, and some tests will never be placed on the market in compliance with the regulation; a survey published in 2023 revealed that 17% of IVDs are expected to be discontinued.[3] IVD manufacturers currently benefit from a staggered transitioning period to become compliant with the regulation.[4] They can still place IVDs on the EU market in compliance with the IVD Directive[5] – the EU IVDR's predecessor – until May 2025 for Class D devices (the highest EU IVDR risk class), May 2026 for Class C devices, and May 2027 for Class B or Class A sterile devices.

While obtaining compliance with the EU IVDR, many manufacturers are refining the intended purpose of their tests. A changed intended purpose introduces risk for long-running clinical trials because any deviation from the intended purpose would be considered off-label or "abnormal" use and would invalidate the CE mark, as the IVD manufacturer did not provide evidence that such use is safe and effective. When using a CE-IVD in a way that deviates from its intended purpose or use, the laboratory deciding this deviation would assume the role of legal manufacturer under the EU IVDR and must comply with all associated obligations.

Two pathways for using IVDs without CE marking

Several publications and surveys have demonstrated that medical laboratories in the EU have a significant portfolio of IVDs that are not CE marked for routine diagnostic purposes.[6-8] It is not documented what fraction of IVDs used for

clinical trials are CE marked, but there are clear clinical trial needs today for IVDs that are not yet CE marked, or CE marked but used outside of their intended purpose. A common example is a companion diagnostic under development, but there are others. For instance, the clinical trial may require examination of a specimen type different from the intended-purpose specimen; the laboratory developed the test specifically for use in the clinical trial; or the test is performed in a laboratory in the US. The EU IVDR provides two options for the laboratory to keep using these tests without having to go through the CE-marking process – the IVD is considered an in-house developed device, or it is an IVD for performance evaluation.

In-house developed devices and Article 5(5)

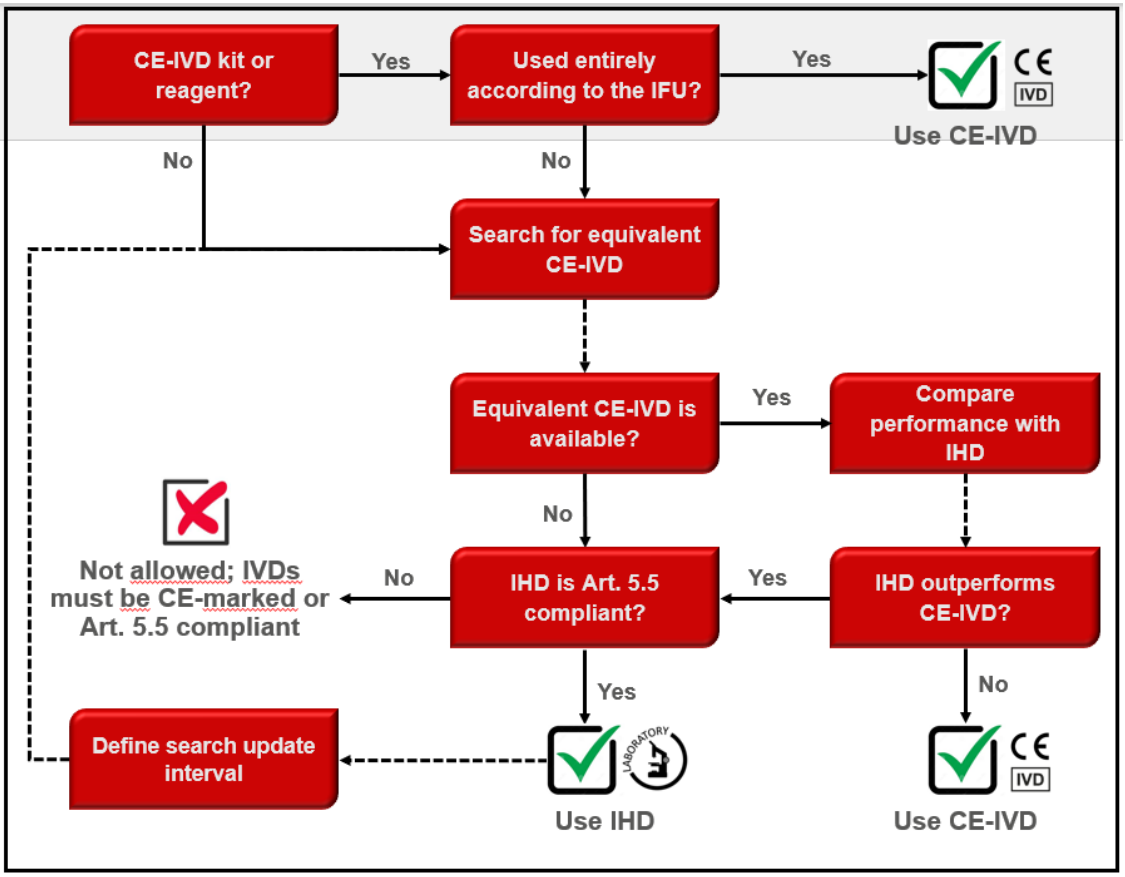
EU IVDR Article 5(5) spells out the requirements for in-house developed devices. It is important not to confuse the European term *in-house developed device* (IHD) with the American concept of laboratory-developed test (LDT). Even if they seem to refer to the same kind of laboratory tests that are designed, manufactured, and used within a single laboratory, they have a completely different regulatory status. In the US, LDTs are mostly regarded as laboratory services that are subject to the Clinical Laboratory Improvement Amendments (CLIA) and thus exempt from US Food and Drug Administration (FDA) regulation, although the FDA continues to attempt to assert authority over certain LDTs.[9-11]

Article 5(5) partially exempts IHDs from EU IVDR requirements but also imposes strict limitations on IVDs that are used in a laboratory when the test is not CE marked or used in a way that is not compliant with the intended purpose covered by the CE mark. A crucial limitation is that this partial exemption can only apply to health institutions that are established within the EU. This means that IHDs used in laboratories outside of the EU cannot make use of the partial EU IVDR exemption under Article 5(5). Compliance with Article 5(5) is to be monitored and enforced by the designated competent authority of each EU member state, potentially resulting in different interpretations of Article 5(5) compliance. An example of this is the current uncertainty on the use of IHDs by contract research organizations (CROs) that support clinical trials. At least one competent authority has explicitly stated that a CRO does not meet the definition of a health institution and that therefore a CRO cannot leverage the Article 5(5) exemption.[12]

EU-based laboratories that want to apply Article 5(5) must be compliant with EN ISO 15189, with the additional complexity that the manufacturing of IHDs must occur under an appropriate quality management system. Laboratories that produce and use IHDs must also demonstrate compliance with Annex I of the EU IVDR (General Safety and Performance Requirements) by carrying out product-specific risk management in accordance with regulation, ensuring stringent control over constant performance of the test over time, taking corrective actions in cases of performance or safety issues, and strengthening the

traceability of the components used to make up the test as well as the traceability of the test itself. Another crucial Article 5(5) requirement that becomes mandatory from May 2028 onward is that there cannot be an alternative CE-IVD product on the market with the same level of performance for the intended target patient groups. If there is such an alternative, the CE-IVD must be used. This is probably of lesser importance for tests specifically developed for a clinical trial or a clinical trial sponsor, but it is an important factor for certain esoteric tests that are not uniquely related to the drug mechanism of action. Laboratories must actively search for CE-IVDs with the same purpose as their IHDs. If there is a potentially equivalent CE-IVD on the market, then the laboratory must compare the performance of its IHD with the performance claims found in the Instructions for Use of the CE-IVD. **Figure 2** can be used to check if a certain laboratory-developed IVD can claim partial EU IVDR exemption under Article 5(5).

Figure 2. Decision tree to check compliance with Article 5(5) for in-house developed devices



CE, Conformité Européenne; **CE-IVD,** CE-marked in vitro diagnostic medical device; **IFU,** instructions for use; **IHD,** in-house developed device; **IVD,** in vitro diagnostic medical device.

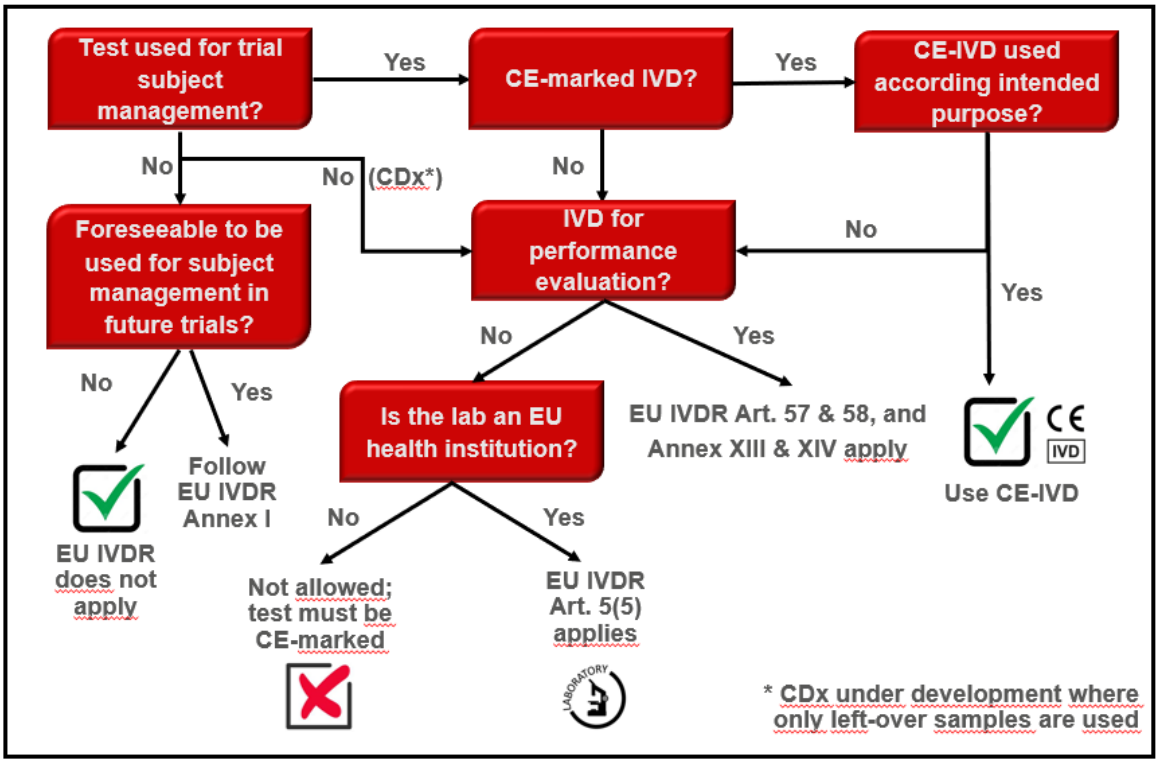
Created by Bogaert and Paulussen. Adapted from Spitzenberger F, et al.[7]

A challenge for Article 5(5) compliance is that the IHD must be fully validated. Often, laboratory validation is limited to the test's analytical performance and focuses on how good the test is in correctly detecting or measuring the analyte of interest. When IHDs are developed specifically by the laboratory for a given clinical trial, it may be difficult to establish the test's clinical performance – that is, how good the test is in providing results on the clinical condition of the patient before the start of the clinical trial. Typical clinical performance indicators include diagnostic sensitivity and specificity, positive and negative predictive value, and expected values. When such clinical performance data have yet to be generated at the start of the clinical trial, then the IHD is not in compliance with Article 5(5), the partial EU IVDR exemption does not apply, and the only option is to use the IHD as a device for performance evaluation.

IVD for performance evaluation and performance studies

The remaining option for IVDs that are not CE-IVDs and that cannot utilize Article 5(5) is to apply the regulatory solution that was constructed to facilitate the development of new IVDs. The laboratory must conduct a performance evaluation study in accordance with EU IVDR Articles 57 and 58 as well as EU IVDR Annexes XIII and XIV (**Figure 3**).

Figure 3. Decision tree for clinical trial laboratory tests to check need for compliance with EU IVDR[1,2]



CDx, companion diagnostic; **CE,** Conformité Européenne; **CE-IVD,** CE-marked in vitro diagnostic medical device; **IHD,** in-house developed device; **IVD,** in vitro diagnostic medical device; **EU IVDR,** EU In Vitro Diagnostic Medical Devices Regulation.

Created by Bogaert and Paulussen

In other words, the results generated by the IVD during the clinical trial will be used to evaluate the test's performance. This is the only option for IVDs used for EU clinical trials when the test is conducted outside of the EU or if the test has not yet proven to generate correct diagnostic results in relation to the patient's clinical condition (i.e., clinical performance). Because the results of the laboratory test will also be used for patient management decisions (or it would not be an IVD in the context of the clinical trial), the performance evaluation is conducted as an interventional performance evaluation study. Such studies are carefully reviewed by the competent authorities and ethics committee in each EU member state before receiving approval to begin.

This framework seems similar to the US process in which investigational device exemptions allow diagnostic tests that have not received marketing authorization to be used in a clinical study in order to collect safety and effectiveness data.[13] In many ways, it is indeed a similar situation, but there are crucial differences as well. In the EU, there are no exemptions from the performance evaluation study application process; neither are there any abbreviated requirements or mere study notification procedures, because the IVD must have generated enough data at the end of the clinical trial to evaluate its performance during the clinical trial. Several EU competent authorities do not accept the argument that the laboratory test is a clinical trial assay solely intended for use within a specific clinical trial and that therefore only the clinical trial – and not the performance evaluation study – has planned endpoints.

Interventional performance evaluation studies always require formal application for authorization by the competent authority of each EU member state where the clinical trial (and therefore also the performance evaluation study) is planned to be conducted. This means that both a clinical trial application and a performance evaluation study application must be submitted to the competent authority. If the sponsor of a performance evaluation study is established outside of the EU, an EU-based legal representative must be appointed before a performance evaluation study application can even be considered. Such performance study applications are now frequently referred to as Annex XIV submissions because the EU IVDR's Annex XIV is dedicated to such studies. The time needed for authorization of a performance evaluation study application must be calculated into the schedule of the clinical trial, as authorization is needed before the study can start.

In cases where competent authorities have additional questions or remarks, the lead time for authorization can range between 60 and 120 days (or more) after submission of the application. Even if the requirements for such studies and the application process are prescribed by the EU IVDR, each member state has some freedom to interpret these requirements and/or to add extra requirements. At this point in time, there is also no option to submit a single application for a coordinated assessment; an application must be made to every member state

where the study is to be conducted. For clinical trials conducted in many EU countries, this leads to a patchwork of performance evaluation study applications. The option of a coordinated assessment procedure will apply beginning in May 2029, which will likely improve the predictability of whether a performance evaluation study is authorized. Because clinical trial sponsors, laboratories, and competent authorities are still new to the process, it is recommended that clinical trial sponsors work closely with their laboratories to submit study applications and calculate extra time for questions and remarks in the application process.

The specific case of companion diagnostics

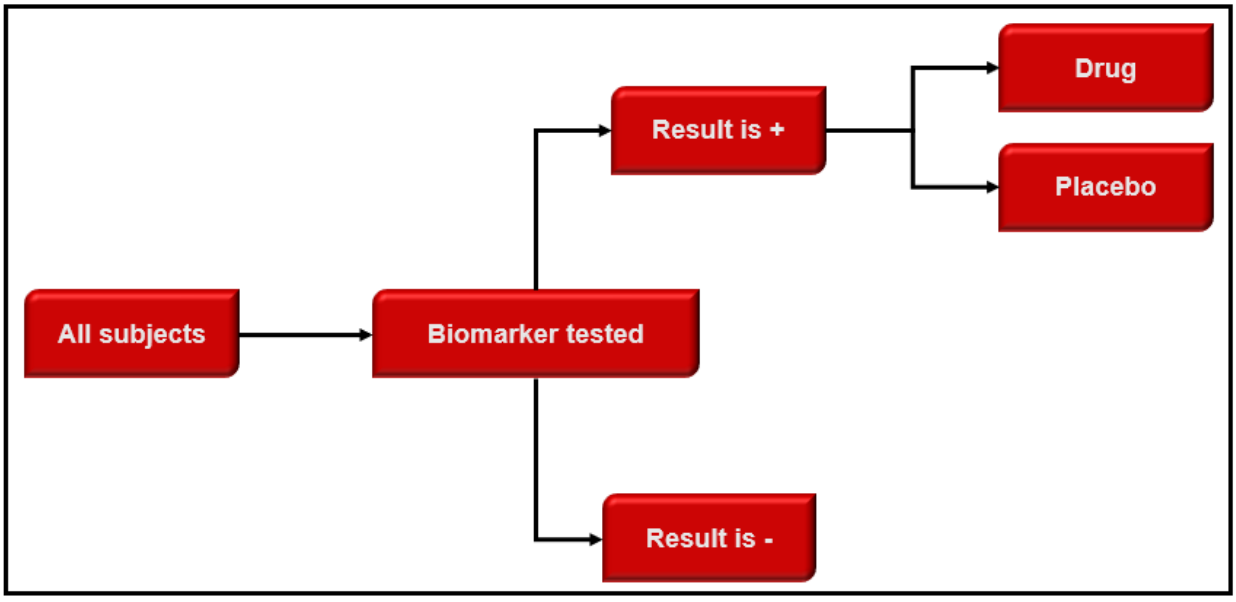
When a companion diagnostic (CDx) is codeveloped with the medicinal product, clinical trials make use of a prototype CDx, or a CDx in more advanced stages of development. In early phase clinical trials, a prototype CDx is likely to be used only for exploratory end points and to therefore not be considered an IVD within the context of the clinical trial. It becomes an IVD from the moment clinical trial patient management decisions are made based on the result of the CDx – that is, to include or exclude patients from clinical trial enrollment. In that case, where the CDx is used to provide information on the safe and effective use of a corresponding medicinal product, an interventional performance evaluation study application must be submitted.

Companion diagnostics and biomarker-driven development represent a specific case within the EU IVDR.[14] The EU IVDR requires performance evaluation study authorization for any performance study that involves a CDx, except when the study uses only leftover samples to evaluate the performance of the CDx (Figure 3). In the latter case, such studies must still be notified to (but not authorized by) the competent authority. This EU IVDR requirement raises the question about when clinical trials would use CDx in a noninterventional way. It has been argued that if the test result does not lead to any treatment decision or is used in the context of enrichment and/or exploratory studies, such tests are not CDx according to the EU IVDR's definition.[15] (*Enrichment* entails the prospective use of any patient characteristic to select a study population in which detection of a drug effect – if one is in fact present – is more likely than it would be in an unselected population).[16] It is unclear if competent authorities can come to a unified approach to such a challenge, but the consequences are significant. According to MDCG 2022-10, tests that are not IVDs in the context of clinical trials but for which development toward an IVD application is predictable should (the guidance did not use the word *shall*) be developed and validated in compliance with Annex I of the EU IVDR from the beginning but are otherwise not affected by the EU IVDR.[2]

It is therefore important to match this patient enrichment strategy with the EU IVDR and the MDCG 2022-10 guidance. **Figure 4** (p. 9) shows a predictive patient enrichment strategy where no positive drug effect is expected in the biomarker-

negative group. The test is, however, used for trial participant inclusion/exclusion and must therefore be regarded as an IVD in the context of a clinical trial, and an interventional performance evaluation study application is expected for the test. **Figure 5** (p. 10) shows a predictive patient enrichment strategy where both biomarker-positive and -negative patients are randomized, either because the result is not available at the time of randomization or because a positive drug effect is deemed possible in biomarker-negative participants. This scenario includes – but is not limited to – CDx where leftover samples are tested. If the test's intended purpose is use as a CDx and it is performed on leftover samples, a (noninterventional) performance evaluation study must be notified to the competent authorities. If the test is not performed on leftover samples (but instead samples are taken for the purpose of the test) and the test's intended purpose is use as a CDx (albeit a CDx still in development), the EU IVDR states that a performance evaluation study application must be authorized before the test can be used in a clinical trial. The situation appears to be different when the manufacturer/laboratory does not provide a test intended for use as a CDx but as a test for clinical trial participant enrichment. The test development is not considered to be at a pivotal stage for performance as a CDx, and no patient management decisions are made in the trial based on the test result. In this case, it is arguable that the test is not considered an IVD in the context of the clinical trial.[15]

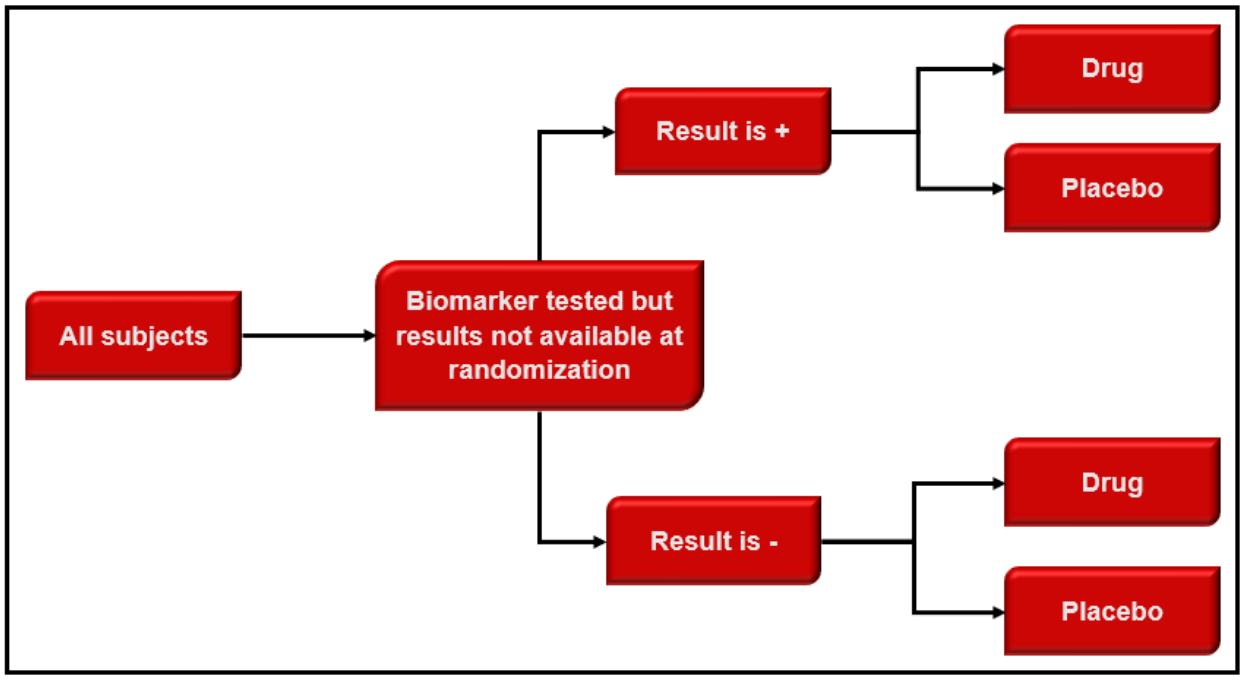
Figure 4. Test used for inclusion/exclusion[a]



[a]Even if all biomarker-positive participants are randomized, the effect of biomarker-negative patients being excluded from the clinical trial is a patient management decision.

Created by Bogaert and Paulussen. Adapted from FDA[16]

Figure 5. Test performed on leftover samples[a]



[a]Performed after trial participant randomization, or before trial participant randomization but without influencing participant randomization and therefore not affecting any patient management decisions.

Created by Bogaert and Paulussen. Adapted from FDA[16]

Conclusion

The impact of the EU IVDR on clinical trials is supposedly minimal when it comes to CE-IVDs used entirely within their intended purpose. They can be used as such by the laboratory. For long-running clinical trials, it is nonetheless advised to check whether the test was already CE marked under the EU IVDR. If the test is not CE marked but performed by an EU-based laboratory that qualifies as a health institution, the laboratory may seek partial exemption from the EU IVDR under Article 5(5) – although from May 2028 onward, this option will only apply if there are no alternative CE-marked tests available. This partial exemption may be a viable option for esoteric tests that are used for multiple clinical trials. When using IHDs, the laboratory must be fully compliant with EU IVDR Article 5(5) and ready to meet inspection from competent authorities.

If the test is not CE marked and not performed within an EU-based health institution or the test's clinical performance is not yet established, the only remaining option is to conduct an interventional performance evaluation study with a so-called Annex XIV study submission. Both performance study and clinical trial applications must be approved before the laboratory can begin testing with the IVD under investigation. Interventional performance evaluation

studies are expected to focus on the diagnostic capabilities of the test and cannot rely solely on the intent to use the laboratory test within the clinical trial.

A CDx under development is, per EU IVDR requirement, subject to performance evaluation studies with corresponding Annex XIV study authorization when this test is used for patient management decisions during the clinical trial. When a CDx performance evaluation study is conducted using only leftover samples, only notification of the study is required. When the test has not yet reached its pivotal performance stage as a CDx and no patient management decisions are made in the trial (based on the test result), the test is potentially not subject to the EU IVDR if it is clear that the biomarker test in this particular clinical trial will not be used as a CDx.

The EU IVDR has changed the landscape of the laboratory testing component of clinical trials, when these tests are carried out for medical management decisions on EU clinical trial participants. In their pursuit of achieving compliance, laboratories as well as clinical trial sponsors are currently navigating the best ways to interact with EU member state competent authorities. While it may seem that it is the laboratory's duty to ensure compliance with the EU IVDR when performing diagnostic testing for clinical trials conducted in the EU, the clinical trial sponsor bears the final responsibility. The EU Clinical Trials Regulation clearly conveys that the clinical trial sponsor is responsible for the initiation and management of the clinical trial, including the selection and use of IVDs in the trial and their overall compliance with this regulation and other legislation, such as the EU IVDR.[17] Further, the International Council for Harmonisation's Good Clinical Practice guideline also confirms that clinical trial sponsors are obliged to document the laboratory's competence in performing a certain test to support the reliability of results (in the Trial Master File and, if applicable, at the investigator site).[18]

Abbreviations

CDx, companion diagnostic; **CE,** Conformité Européenne; **CE-IVD,** CE-marked in vitro diagnostic medical device; **CLIA,** Clinical Laboratory Improvement Amendments; **CRO,** contract research organization; **EU IVDR,** EU In Vitro Diagnostic Medical Devices Regulation; **FDA,** Food and Drug Administration [US]; **ICH,** International Council for Harmonisation; **IHD,** in-house developed device; **IVD,** in vitro diagnostic medical device; **LDT,** laboratory-developed test; **MDCG,** Medical Device Coordination Group

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Glossary of terms

Companion diagnostic. A device which is essential for the safe and effective use of a corresponding medicinal product to:

- Identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or
- 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. (IVDR Article 2(7))[1]

Health institution. An organisation the primary purpose of which is the care or treatment of patients or the promotion of public health. (IVDR Article 2(29))[1]

In vitro diagnostic medical device. Any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software, or system,

whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following:

- Concerning a physiological or pathological process or state;
- Concerning congenital physical or mental impairments;
- Concerning the predisposition to a medical condition or a disease;
- To determine the safety and compatibility with potential recipients;
- To predict treatment response or reactions; and/or
- To define or monitoring therapeutic measures.

Specimen receptacles are also deemed to be in vitro diagnostic medical devices. (IVDR Article 2(2))[1]

Intended purpose. The use for which a device is intended according to the data supplied by the manufacturer on the label, in the instructions for use or in promotional or sales materials or statements or as specified by the manufacturer in the performance evaluation. (IVDR Article 2(12))[1]

Leftover specimen/leftover sample. The unadulterated remnants of human derived specimens collected as part of routine clinical practice and after all standard analysis has been performed. It should be noted that such specimens/samples would be otherwise discarded as there is no remaining clinical need for them. (EN ISO 20916:2019, 3.25)[19]