Addressing the European Union (EU) In Vitro Diagnostic Regulation (IVDR) Challenge in Targeted Oncology Trials

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01. Introduction

The European Union (EU) In Vitro Diagnostic Regulation (IVDR 2017/746) went into effect May 2022, dramatically changing the regulatory requirements for oncology clinical trials using an in vitro diagnostic (IVD) for patient enrollment. Sponsors developing experimental targeted oncology drugs are grappling with the new regulatory framework, which lacks alignment between drug and device regulations. This means sponsors may have to manage two parallel submissions and processes: a clinical trial for the drug and a separate performance study for the IVD or device used for patient selection, adding significant complexity and coordination between device and drug sponsors.

**Health Institution per EU IVDR Article 5(5)*

- Scope: Applies to devices manufactured and used entirely within health institutions (e.g., hospitals, labs).
- Non-Transferability: The devices must not be transferred to any other legal entity.
- No Commercialization: Devices cannot be manufactured on an industrial scale for general marketing.
- QMS Requirement: The institution must maintain a Quality Management System (compliant with ISO 15189 or national provisions).
- Technical Documentation: Laboratories must create and update documentation demonstrating compliance with IVDR Annex I (General Safety and Performance Requirements).
- Performance Evaluation: Laboratories must perform a self-evaluation to justify that the device meets performance needs.
- Public Declaration: Institutions must make a declaration public, which can be checked by national authorities.

02. Options to avoid IVDR Annex XIV Device Performance Study Authorization

- Enroll patients with a CE-marked test used within intended use
- Enroll patients with a test validated in-house at a qualified Health Intitution*
- Enroll patients with prior local test results (preferably CE-marked tests)
- Test patients retrospectively, which may require a Notification

03. Device Performance Study Evaluation is Required in Parallel to Drug Performance Study

Two Protocols, Two Potential Sponsors
Establishing which entity is the sponsor of the device performance study is the first important decision that needs to be clarified in the contract between the drug and device sponsors.

- 'Sponsor' means any individual, company, institution or organisation which takes responsibility for the initiation, for the management and setting up of the financing of the performance study (Article 2(57) IVDR).
- Either the device or the drug company can be the sponsor of the Device Performance Study.
- The Device Sponsor or a contracted CRO on their behalf assumes responsibility for:
  - Submission and approval of the Device Study to the Ethics Committees and National Competent Authorities
  - Study monitoring
  - Data management
  - Adverse Event reporting
  - Study closeout
- The Roles & Responsibilities of each identity should ideally be clarified at the contracting stage.

04. Integrated Oversight: Parallel Device Performance Study and Drug Performance Study

The two studies run parallel to each other with significant overlap and required coordination between the drug and device sponsors.

Informed Consent Documents

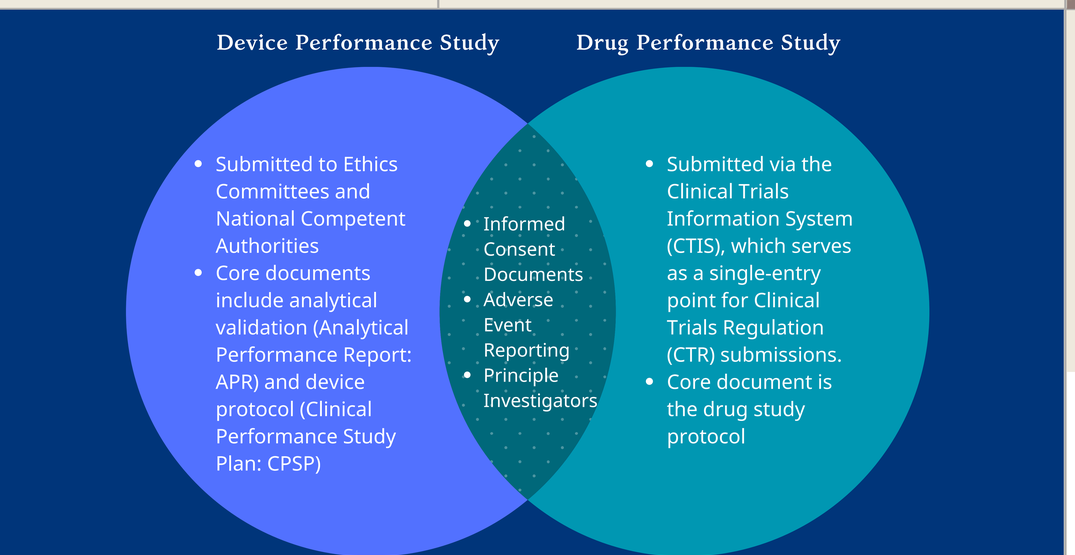
- Consent must mention the device used to enroll patients, and if missing, is a substantial modification to the submission.
- Some countries require separate consent for the device screening, while other countries require a combined consent.

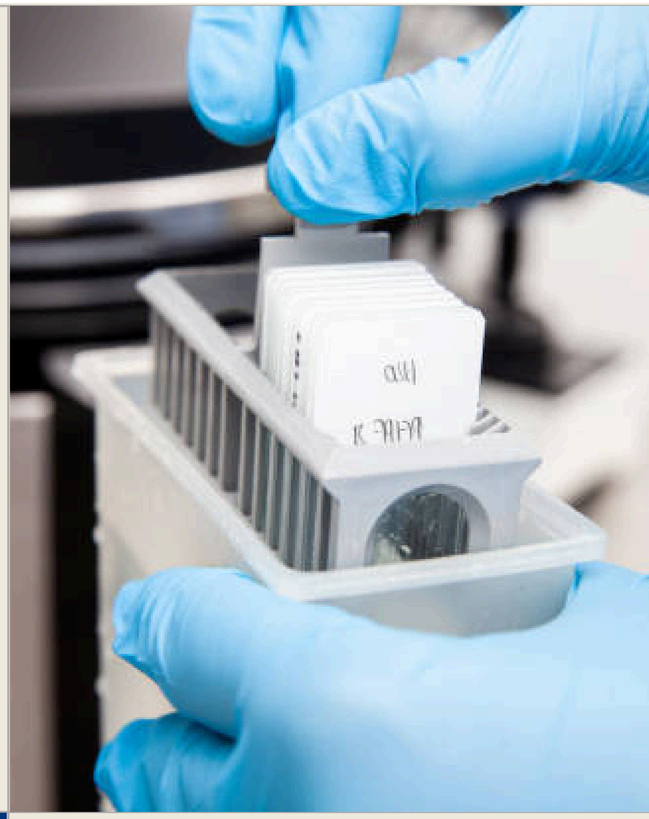
Adverse Event Reporting

- On the device side false positive and negative test results could lead to an AE and must be shared with the drug sponsor for evaluation.
- Laboratory sites performing the test must train personnel to understand device deficiencies and deviations.
- On the drug side, AEs related to sample collection for testing must be shared with the device sponsor for evaluation.
- Drug site Principle Investigators (PIs) must be trained on device-related AEs and reporting.

Principle Investigators

- PIs of the drug study also serve as PIs of the device study.
- There may be country-specific device trainings for the PIs.
- Recommend training PIs on parallel structure of device and drug performance studies.





05. Practical Considerations

If a separate Device Performance Study Evaluation is required for use of a test to prospectively enroll patients into an oncology study:

- Immediately establish device sponsorship and clarify roles and responsibilities during contracting.
- Plan far in advance (6-12 months) to allow sufficient time to create Annex XIV submission documentation and allow for variable approval times from the National Competent Authorities.