Notified Bodies' Roles and Perspectives on IVDR Clinical Performance Studies

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Executive summary

- This document has been developed by the **GUIDE.MRD** consortium - see information on Annex 1.
- Watch the Webinar Recording.

The document focused on the regulatory framework for in vitro diagnostic (IVD) devices in the EU, with discussions on harmonization, interactions between notified bodies and manufacturers, and challenges in the current system. A panel of experts shared their perspectives on the role and expectations of Notify Bodies (NB), emphasizing the importance of competency evaluation and harmonization, while also addressing challenges with breakthrough medical devices and innovative products. The discussion concluded with insights on clinical evidence requirements, classification of in vitro diagnostic assays, and the need for clear communication and collaboration with stakeholders during product development and regulatory compliance processes.

Why this resource?

- Bringing an innovative diagnostic assay to market is an exciting yet complex journey.
- Compliance with the **In Vitro Diagnostics Regulation (IVDR)** is one of the key steps to ensure the safety, performance, and reliability of IVDs.
- Novelty and complexity of the IVDR deserve a discussion to help understand the regulatory landscape and path to adoption in clinical practice.

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Assessment of the clinical validity and clinical utility

Bringing an innovative diagnostic assay to market is an exciting yet complex journey.

- **Two steps** are to be considered:
  - CE mark of the test after positive Notified Body Conformity assessment (mandatory)
  - Reimbursement by payers within the healthcare system (not mandatory from regulatory perspective)

- **Notified Bodies** run the **Conformity Assessment** in accordance with Regulation 2017/746 (IVDR) on in vitro diagnostic medical devices (IVDs), which includes the assessment of the **clinical evidence including clinical performance (see slide 6)**.

- **Health Technology Assessment (HTA) bodies or equivalent national payer organizations** may evaluate the **clinical utility of the test**. This assessment is based on **measurable health outcomes and the test's ability to improve health system performance**.

- Accordingly, both **assessments are carried out by different bodies independently** and not linked to each other.

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Notified Bodies – Procedural Key Facts IVDR

Notified Bodies are **private, third-party conformity assessment bodies** designated and monitored by the **European Commision** and **Competent Authorities of EU Member States**

The Notified Body system is **harmonized across the EU.** Regardless of the Notified Body's location, **certificates issued are valid throughout the EU** and allow the manufacturer to **affix the CE mark and market the product** in all EU Member States.

NB Conformity Assessment Process
(e.g. Annex IX IVDR)

QMS

Quality Management System (QMS) based on:

- EN ISO 13485
- IVDR QMS requirements "beyond" EN ISO 13485, e.g. concerning vigilance or PMS (Post-Market Surveillance)

- Initial Certification Audit (Stage 1 / Stage 2)
- Annual Surveillance Audits
- Unannounced Audits

Techn. Doc.

Product specific **Technical Documentation** containing, e.g.:

- General product description and design information
- Risk Management, Labelling and instruction for use
- **Clinical Evidence**

- Review by NB Product Experts

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Clinical Evidence is Composed of Three Main Elements

Clinical Evidence

=

State Of The Art (SOTA)

Performance Evaluation

Scientific Validity

Evidence that an analyte is associated with a physiological or pathological state, predisposition, prognosis/trend, or safe/effective treatment

+

Analytical Performance

Evidence that the product can reliably detect/quantify the analyte.

+

Clinical Performance

Evidence that the product fulfills its intended purpose in the clinical environment, linking the product to patient benefit.

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Clinical Evidence: Characteristics to be established

Analyte(s) associated with a

- Physiological or pathological state
- Predisposition
- Prognosis/trend
- Safe or effective treatment

→ **Clinical Picture**

- Analytical sensitivity & specificity
- Accuracy (trueness & precision)
- Precision (repeatability & reproducibility)
- Limit of detection and quantitation
- Measuring range, linearity, cut-off
- Interferences (endogenous & exogenous), cross-reactions

→ **Analyte**

- Diagnostic sensitivity & specificity
- positive predictive value (PPV)
- negative predictive value (NPV)
- likelihood ratio
- expected values in normal and affected populations

→ **Patient**

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Clinical Performance Studies: Key points

Close cooperation between legal manufacturer and Sponsor is essential

IVDR Article 57 to 76	• **Legal manufacturer** (LM) responsible for **product compliance with Annex I** IVDR, apart from Clinical Performance aspects
	• **Sponsor with defined obligations** , e.g. concerning:
	  ◦ Study application submitted to Member States (if required)
	  ◦ Adherence to study plans
	  ◦ Adverse event reporting during performance studies

IVDR Annex XIII and XIV	• Detailed **Clinical Performance Study Plan (CPSP)** to be established, embedded into Performance Evaluation Plan (PEP) • **Analytical performance** compliant with IVDR needs to be evident for the assay(s) in question **prior** starting the clinical study • **Intended Purpose** needs to be defined **prior** starting the clinical study • More specific requirements defined for **interventional studies** (Annex XIV)
National laws Article 58 IVDR	• **Type of study** (observational, interventional, surgically invasive sample-taking?) defines obligation to apply to or notify **competent authority** and consultation of or assessment by **European Commission**

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Selecting a Notified Body

How does the initial process of selecting the appropriate, notified body look like?

- Notified Bodies(NBs) are private organizations performing the conformity assessment (CA) against regulations; manufacturers are responsible for compliance.
- All Notified Bodies are theoretically equal, aiming for harmonized conformity assessment outcomes.
- Considerations for selection include: ability to offer services for non-EU markets (e.g., UK, MDSAP- Medical Device Single Audit Program), technical competency in the device area, and future support.
- Currently, 17 IVDR NBs exist and are listed on the NANDO (New Approach Notified and Designated Organisations) website.
- IVD Notified Bodies work together under the Medical Device Coordination Group (MBCG) and Team-NB (The European Association of Medical Devices Notified Bodies) to harmonize approaches and engage with the European Commission and Competent Authorities.

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Dialogue between NB and Manufacturers

How does the dialogue between the NBs and the manufacturer look like?

- NBs cannot consult or provide scientific advice, but they can clarify regulatory requirements. Their role is to assess conformity against the regulation, not to advise on how to achieve it.
- Structured dialogue between NB and manufacturers is a mechanism of interaction to clarify general procedural aspects (e.g., pre-submission meetings).
- For complex products like companion diagnostics (CDx), additional stakeholders are involved: medicine manufacturers, medicine authorities, (EMA, National Competent Authorities). NB must consult EMA or the National Competent Authority for a scientific opinion. This is a mandatory step within the Conformity Assessment procedure for CDx.
- Notified Body organizations (Team-NB, NBCG) publish white papers and position papers to educate and support manufacturers.

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Challenges in the Current IVDR Framework

Which are the main challenges in the current framework?

- The IVDR, in force since 2017 with application in 2022, is still evolving, as evidenced by multiple amendments (4) and delays in transition periods. Two amendments have delayed the transition periods, thus have been a significant challenge for IVDR implementation. The latest extensions are in place to allow more time for manufacturers to transition their devices.
- The current framework is still evolving and not fully established.
- The current system may not be fully fit for purpose for innovative or orphan devices, unlike FDA's breakthrough pathways. However, working groups are addressing this.
- A key challenge is that Notified Bodies review end results – after development and evidence generation are complete. This can be a "gap" compared to Medicines Regulatory framework that allow for early scientific advice.
- The regulatory system doesn't foresee clear direct interactions between Notified Bodies and external stakeholders like payers, patients, and clinicians.

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Envisioning Potential Collaborations with Stakeholders

Which are the potential collaborations between the NBs and the the stakeholders outside of manufacturers?

- The IVDR does not foresee clear direct interactions between Notified Bodies and stakeholders outside manufacturers (payers, patients, clinicians). Per IVDR, NB are mandated to only communicate with the legal manufacturers.
- Notified Bodies cannot give scientific advice, but there are structured dialogue pathway with allows for early interactions.
- Discussions are ongoing at the European Commission level to establish processes for orphan and breakthrough devices, potentially involving Notified Bodies in innovation meetings.
- Health Technology Assessment (HTA) processes offer an opportunity for manufacturers, payers, patients, and clinicians to present their case for novel devices.
- Policy-level discussions involving industry, patient organizations (e.g., MedTech Alliance), and Notified Bodies are shaping future policy.

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Common Pitfalls in Clinical Evidence

Which are the typical pitfalls in clinical evidence and clinical performance studies found during the review?

- Intended Use Alignment: clinical studies must fully cover all claims made in the intended use. Inconsistencies between the Instructions for Use (IFU) and clinical studies (e.g., pre-analytical specifications) are pitfalls.
- Missing Data: all necessary data must be included and properly documented.
- State of the Art: refers to currently accepted clinical practice, not necessarily the most innovative. Justification for how the device meets or exceeds this is needed.
- For novel devices without existing standards, manufacturers are in charge of setting the standard rights. The approach must be justified and alternatives for standardization considered.
- Scientific Validity is crucial for novel devices, demonstrating that the measured analyte truly represents the clinical condition.
- Clinical Performance Requirements can be challenging for innovative devices due to limited patient or sample availability.
- Overall Benefit-Risk Acceptability: the IVDR allows for justification of unmet requirements if the overall clinical benefit outweighs the defined risks, requiring clear and proper documentation.

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Key messages from the experts

Make the right assumptions

Notified Bodies cannot make assumptions about missing information. Seek good advice and be well-informed about the Notified Body process. Provide a clear application letter explaining the background and setup of the application.

Plan exceptionally well and challenge your plan

For innovative devices, develop a robust product development plan and seek input from diverse stakeholders (scientific, regulatory, clinicians) to identify potential issues early, saving time and money.

Communication and collaboration are key

Start communicating with all relevant stakeholders as early as possible, ensuring a shared understanding of terminology and regulatory frameworks.

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Challenges and Recommendations

Challenges:

- IVDR is still evolving with ongoing amendments and delayed transitions
- Framework lacks clear pathways for orphan/innovative/precision diagnostics but always indicate the IVDR requirements not met and the justification. Ongoing efforts exist at the EU Commission level to discuss breakthrough device processes
- NB are involved at the end of the data generation process with no scientific advice allowed. Structured dialogs exist to discuss strategies as opposed to a clinical study design.

Recommendations:

- Engage early with NBs when possible.
- Use published guidance, Team-NB and NBCG publications and NB white papers to understand expectations.
- Attend technical meetings for clarification.
- Be proactive in regulatory meetings and scientific events.
- Be exact and consistent between the clinical evidence and claimed intended use.
- Understand and address the state of the art, especially when dealing with novel devices lacking standardization.
- Plan clinical performance studies carefully, aligning with regulatory expectations and clinical realities.

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Frequently Asked Questions

For the Clinical performance study, does the assay Provider need to validate the entire workflow (preanalytical and analytical part) or can they only validate one part (i.e. start from DNA instead or FFPE or Plasma)?

As part of the analytical performance, manufacturers have to take into account the pre-analytical part and its impact on the downstream product performance. Typically manufacturers specify pre-analytical specifications (sample drawing, sample prep, sample storage) in the IFU.

How should assay developers and reference material developers approach analytical validation (e.g. numbers of samples tested, how to achieve LOD, demonstrate reproducibility etc.) when tumor informed assays are reviewed and each assay has "unique mutation profile for each patient"?

This question could be considered as scientific advice. Therefore Notified Bodies will not provide an answer to this question.

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Frequently Asked Questions

In light of the evolving IVDR and the GUIDE.MRD focus on ctDNA-based MRD assays, how are Notified Bodies assessing state-of-the-art and clinical performance especially for assays with multiple intended (prognostic, monitoring, stratification) uses and ultra-low detection thresholds? What steps are being taken to ensure scientific rigor and EU-wide harmonization despite fragmented pre-submission processes?

For an innovative device, there is no state of the art, IVDR framework is open for the assay manufacturer to justify that some requirements could not be met such as no specimen enough to run the clinical studies. Key is to demonstrate the overall Benefit/Risk ratio, with a very robust proof of concept study, analytical studies and clinical performance studies. This advice is to look at the whole picture, and not each and every IVDR requirement, keeping the clinical benefit in mind by meeting clinical evidence.

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Frequently Asked Questions

How do you classify an assay that actually provides the evidence for many of the intended uses could be quite complex?

We need to follow rules. The IVDR has a specific annex about classification. In practice we look at the entire set of intended purposes and make decision trees where the intended purpose pulls in, in what kind of class. The highest rule counts. I.e., if intended purpose classifies the assay as class B, and another one into class C, or even class D, then the entire device would be classified as a class D.
If we want to claim these multiple intended purposes, then we definitely need to see evidence for all of these. If there is no evidence for one intended purpose, need to reduce an intended purpose or specific limitation.

Companion Diagnostics (CDx):

A test is only considered a CDx if the drug explicitly requires the test for its use.

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Glossary

CA: Conformity Assessment
CDx: Companion Diagnostics
CPSP: Clinical Performance Study Plan
ctDNA: Circulating Tumor DNA
EMA: European Medicines Agency
EU: European Union
FAQs: Frequently Asked Questions
FDA: Food and Drug Administration
FFPE: Formalin-Fixed Paraffin-Embedded
GUIDE.MRD: GUIding multi-moDal thErapies against MRD by liquid biopsies
HTA: Health Technology Assessment
IFU: Instructions For Use
IVD: In Vitro Diagnostic
IVDR: In Vitro Diagnostics Regulation
LM: Legal Manufacturer
LOD: Limit of Detection
MBCG: Medical Device Coordination Group
MDSAP: Medical Device Single Audit Program
MRD: Minimal Residual Disease
NBs: Notified Bodies
NBCG: Notified Body Competent Authorities Group
NANDO: New Approach Notified and Designated Organisations
NPV: Negative Predictive Value
PEP: Performance Evaluation Plan
PMS: Post-Market Surveillance
PPV: Positive Predictive Value
QMS: Quality Management System
SOTA: State Of The Art
TEAM-NB: The European Association of Medical Devices Notified Bodies

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Annex 1: GUIding multi-moDal thErapies against MRD by liquid biopsies

GUIDE.MRD (GUIding multi-moDal thErapies against MRD by liquid biopsies), an Innovative Health Initiative (IHI)-funded consortium focused on advancing cancer care by validating and adopting circulating tumor DNA (ctDNA) as a biomarker for minimal residual disease (MRD) in solid tumors.

The consortium is based on a multi-stakeholder collaboration working for the future of cancer care, led by Luigi Ravagnan, project leader and Dr. Klaus Pantel, scientific coordinator.

A diverse consortium made by representatives of the academic world, patient organizations, small medium enterprises, Med Tech and pharmaceutical companies.

Find out more

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A patient centric approach to personalized medicine

What GUIDE.MRD will do to support better decision making:

Identify, compare and rank best tests available for ctDNA diagnostics for MRD in the laboratory using reference standard

Analyze the best test in practice to learn more real-world applications against patient outcomes

Multi-stakeholder engagement to identify barriers and opportunities for clinical use of ctDNA, with reference standards to guide treatment choices

THE HOW: patient engagement. robust research. collaborative leadership.

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Annex 3.1: Resources - Regulatory

Medical Device Coordination Groups MDCG	MDCG deals with key issues from NB oversight to market surveillance. There are 13 divisions which provide advice and draft guidance. EU Commission chairs their meetings. They regularly publish guidance documents, e.g., https://health.ec.europa.eu/publications/step-step-guide-manufacturers-vitro-diagnostic-medical-devices_en	Medical Device Coordination Group Working Groups - European Commission
Team-NB	TEAM -NB is the EU Association of Medical devices Notified Bodies. It has 44 members, representing 20 different countries. It promotes high standards and works to harmonise practices among the Notified Bodies. They regularly publish position papers.	Home - team-nb
EU Commission site for IVDs	It includes the IVDR regulation text , transitional provisions, IVD expert panel, EU reference laboratories (EURLs), Guidance	Medical Devices - In Vitro Diagnostics - European Commission
MedTech	The Trade Association of medical technoligy industries is the EU voice of that industry to facilitate access to medical technologies for people, patients, healthcare professionals and healthcare systems.	MedTech Europe, from diagnosis to cure - Homepage
NB sites (e.g., TÜV SÜD, BSI, DEKRA)	These sites offer Application checklists, Gap analysis tools, FAQs on transitioning from IVDD to IVDR	

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Annex 3.2: Resources - HTA

EU Commission site for HTA	The Regulation (EU) 2021/2282 on health technology assessment (HTAR) entered into force on 11 January 2022 and applies from 12 January 2025. This webpage aims at informing national authorities, health technology developers and stakeholders about the implementation of the Regulation.	Implementation of the Regulation on health technology assessment - European Commission
Member State Coordination Group on HTA (HTACG)	It is composed of Member States' representatives, mainly from HTA authorities and bodies. The HTACG issues guidance for the joint work, which includes joint clinical assessments and joint scientific consultations.	Coordination Group on Health Technology Assessment (the 'HTACG')
EUnetHTA21	It supports the EU cooperation on HTA under the new regulation.	EUnetHTA21 service contract - European Commission
HTAi	Health Technology Assessment international is a collaboration of HTA professionals who are dedicated to shaping the future of health systems and improving health outcomes for all people.	HTAi – Shaping the future of HTA
Country HTA (e.g., HAS, NICE, ZIN, G-BA)	Most of the agencies provide evaluation templates, submission guidelines and list of reimbursed or evaliuated technologies.	

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