Medical devices and IVD medical devices

What are they and how do you ensure compliance?

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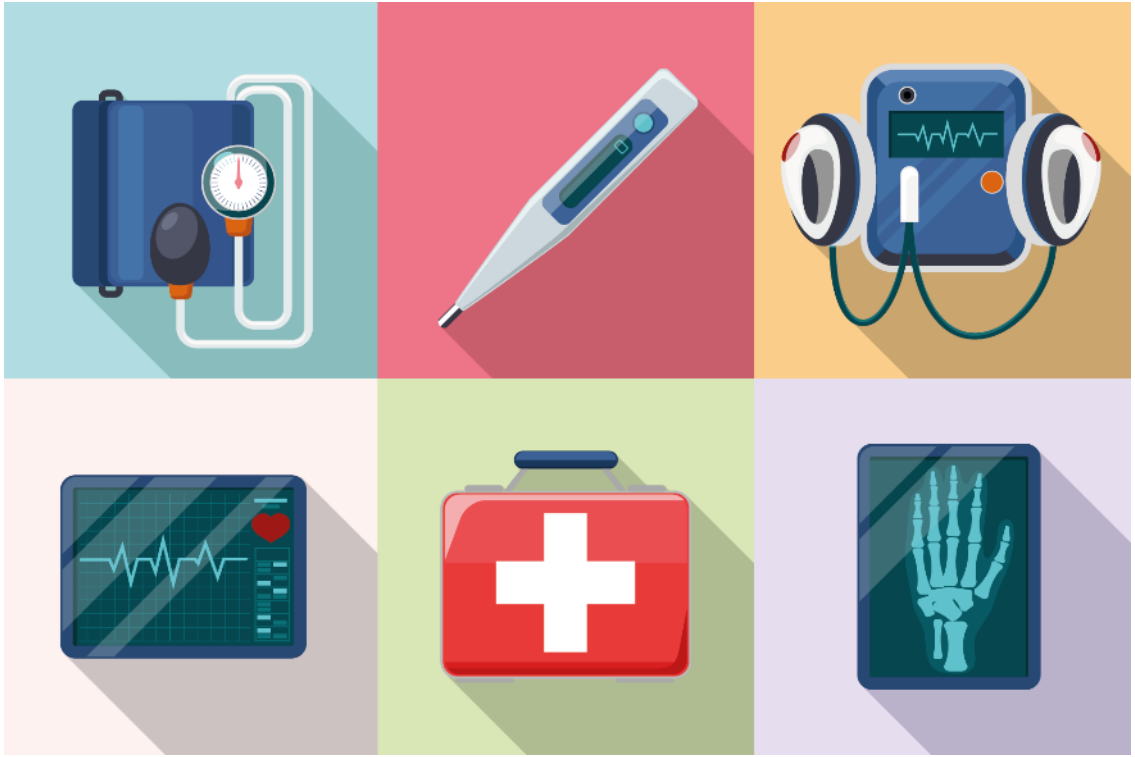
Medicines Agency

What is a medical device?



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Medicines Agency

A medical device has a medical purpose

(1) 'medical device' means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human

…any device intended by its manufacturer to be used for a medical purpose

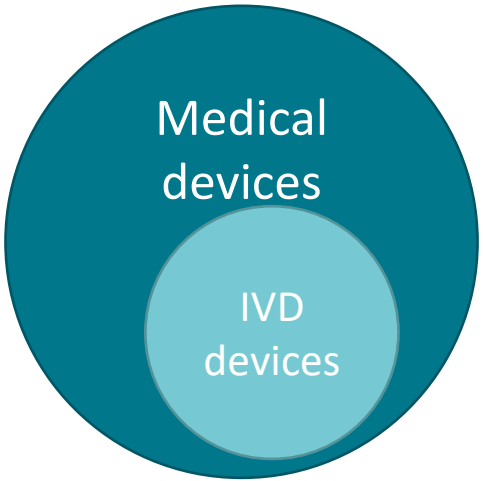
Medical purpose: Diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease

— providing information by means of *in vitro* examination of specimens derived from the human body, including organ, blood and tissue donations,

Article 2(1), MDR

An in vitro diagnostic device is also a medical device

…Any medical device intended to be used *in vitro* for the examination of specimens derived from the human body for the purpose of providing information



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Article 2(2), IVDR

The intended purpose defines whether the device is a medical device or not

Manufacturer's claims?
= Intended purpose

Medical purpose
= medical device

Exercise/life style
= not a medical device

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A medical device is not approved, it is CE marked after conformity assessment

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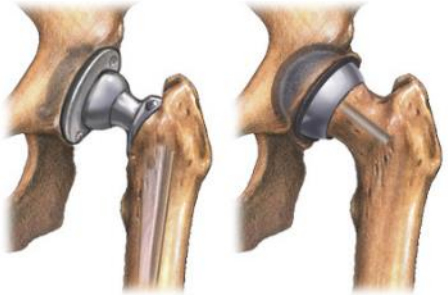
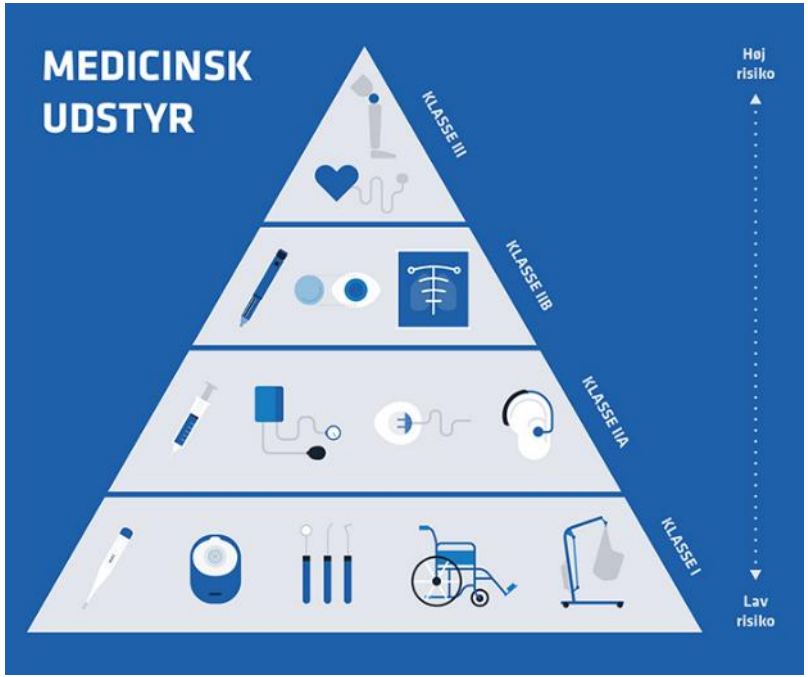
New regulations in 2021 and 2022: MDR and IVDR

- Strengthen existing regulatory system for medical devices in Europe
- Regulation, rather than a Directive → greater legal certainty and prevent variation
- Original Directives have been in place for over 25 years



Medical devices are classified according to risk



Picture from: https://laegemiddelstyrelsen.dk/da/udstyr/udvikling-af-medicinsk-udstyr/

In vitro diagnostic devices

High individual and public risk

Low individual and public risk

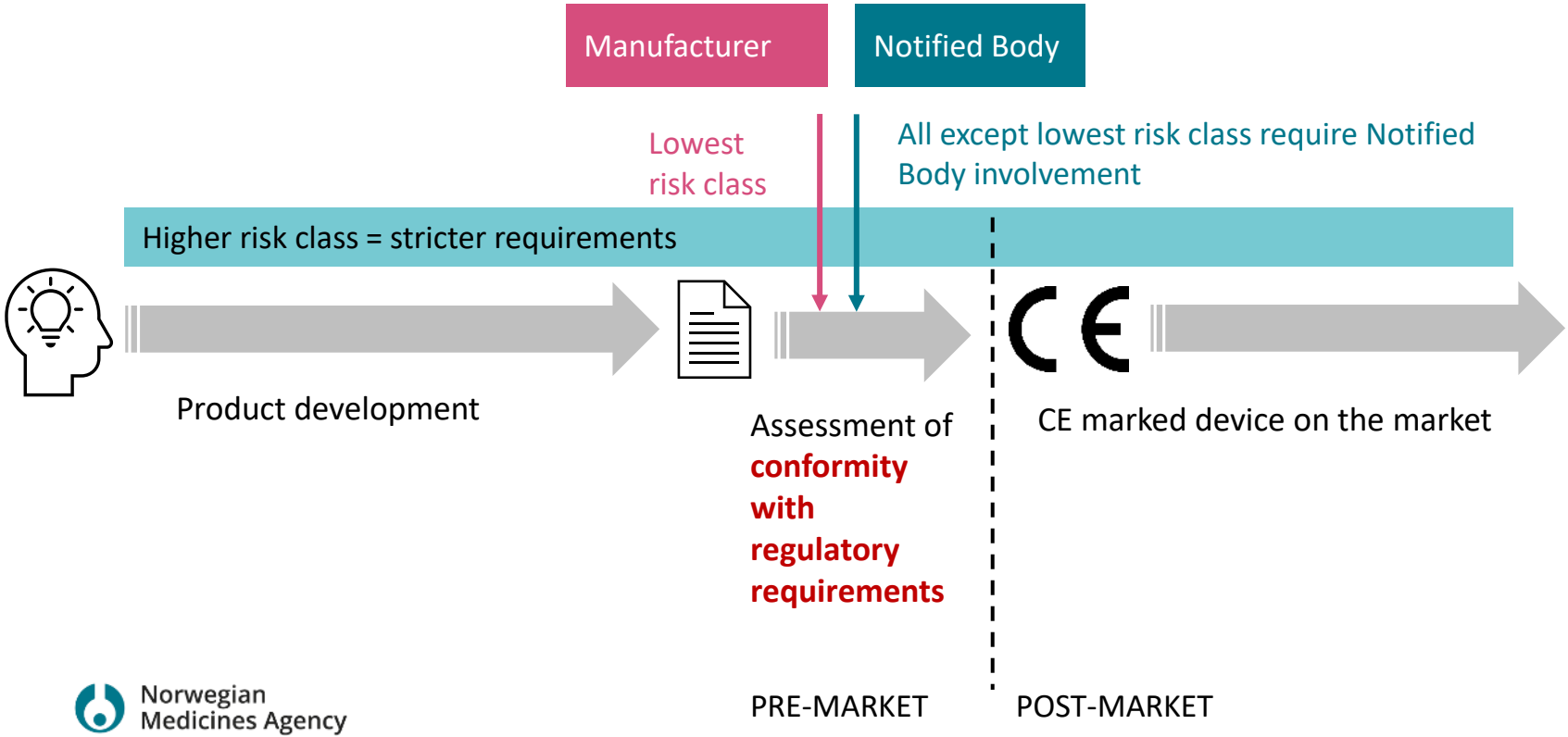
D: blood grouping, HIV, SARS CoV

C: STIs, cancer screening, genetic testing

B: CRP, pregnancy (FSH)

A: Buffers, instruments, culture media

Risk classification determines route to CE marking



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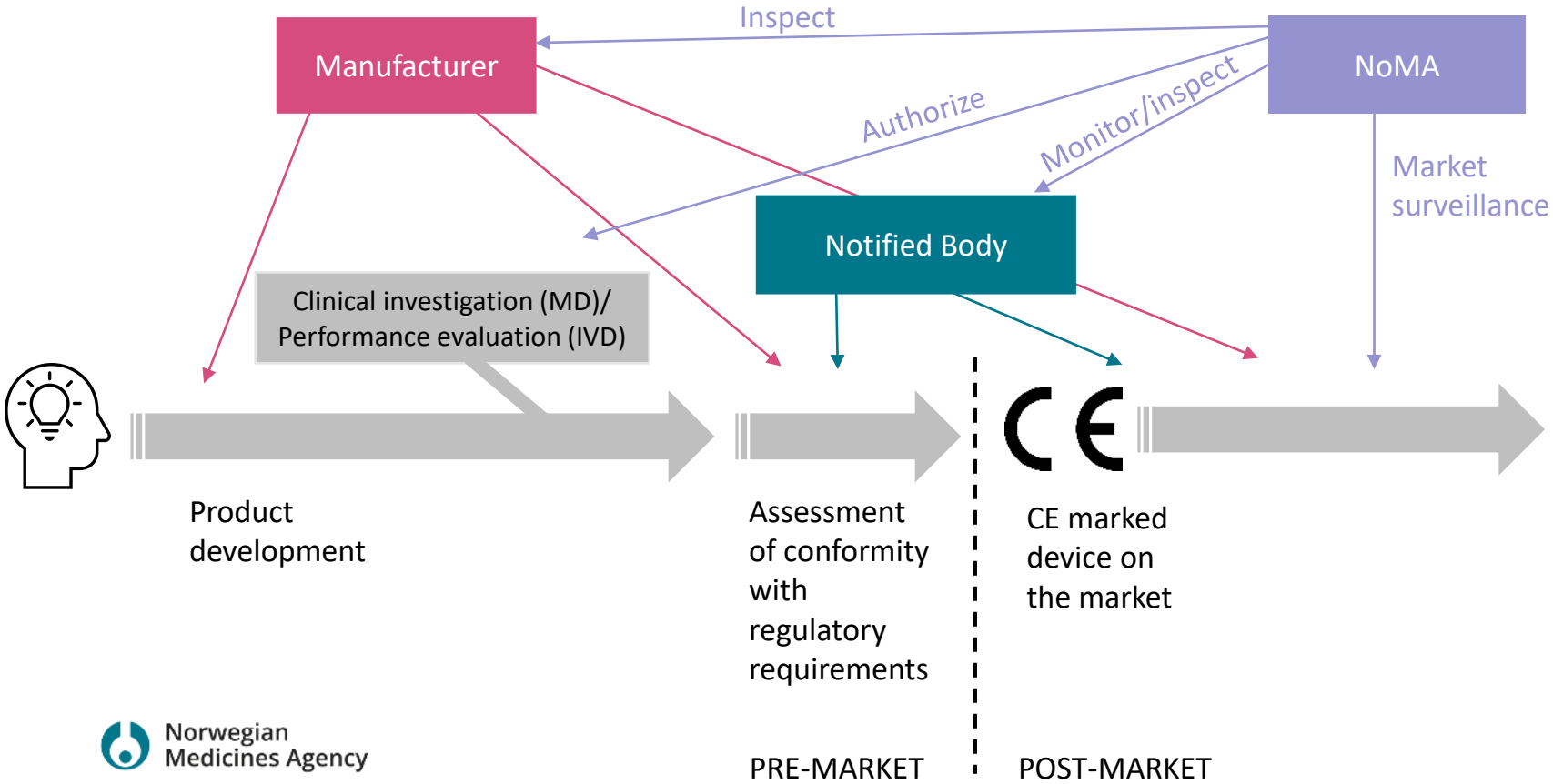
Different actors have different roles and responsibilities



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The technical documentation for conformity assessment is defined in Annex II and III of the MDR and IVDR

Annex I General safety and performance requirements (GSPR)	Annex II Technical documentation (TD)	Annex III TD on post-market surveillance
• General requirements (incl. risk management) • Requirements regarding design and manufacture (and performance for IVD) • Requirements regarding information supplied with the device	• Device description and specification • Label and instructions for use • Design and manufacturing information • GSPRs • Benefit-risk analysis and risk management • Product verification and validation	• Post-market surveillance plan • Class I (MD) and A/B (IVD): post-market surveillance report • Class IIa/IIb/III (MD) and C/D (IVD): periodic safety update report (PSUR)

Annex II covers six main areas

Device description and specification

- Intended purpose and intended users
- Principle of operation (MD) / Assay principle (IVD

General safety and performance requirements

- Annex I
- Harmonised standards

Information to be supplied by manufacturer

- Instructions for use
- Labels

Benefit-risk analysis and risk management

- Risk management plan
- Risk control

Design and manufacturing information

- Information on design stages applied (incl eg critical ingredients, algorithms, operating principle of an instrument)
- Manufacturing information (manufacturing process, assembly, final product testing)

Product verification and validation

- Pre-clinical and clinical data (MD) / analytical and clinical performance (IVD)
- IVD: stability data
- IVD: software verification and validation

… some key words for each area – YOU must familiarise yourself with the regulation

Annex II covers six main areas

Device description and specification

- Intended purpose and intended users
- Principle of operation (MD)/Assay principle (IVD

General safety and performance requirements

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- IVD: stability data
- IVD: software verification and validation

… some key words for each area – YOU must familiarise yourself with the regulation

3 tips to get you started

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Start by describing your device

- Is your device a medical device?
- What type of medical device is it? (some «special» types of medical devices, eg custom-made devices)
- What risk class does it belong to?

Establish systems for QMS and risk management

Quality management system

Governs methods used in, and facilities/controls used for

- Design
- Manufacturing
- Packaging
- Labelling
- Storage
- Installation
- Servicing
- …

Risk management

- **Risk**: combination of the probability of occurrence of harm and the severity of that harm
- **Risk management**: Systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk

Standards can be a help in establishing systems for QMS and risk management

Quality management system

Art 10 MDR/Art 10 IVDR

EN ISO 13485 is **harmonised** and covers f.ex.

- Management responsibility
- Resource management
- Product realization (e.g. **Design and development**, Purchasing, …)
- **Measurement, analysis and improvement**

Risk management

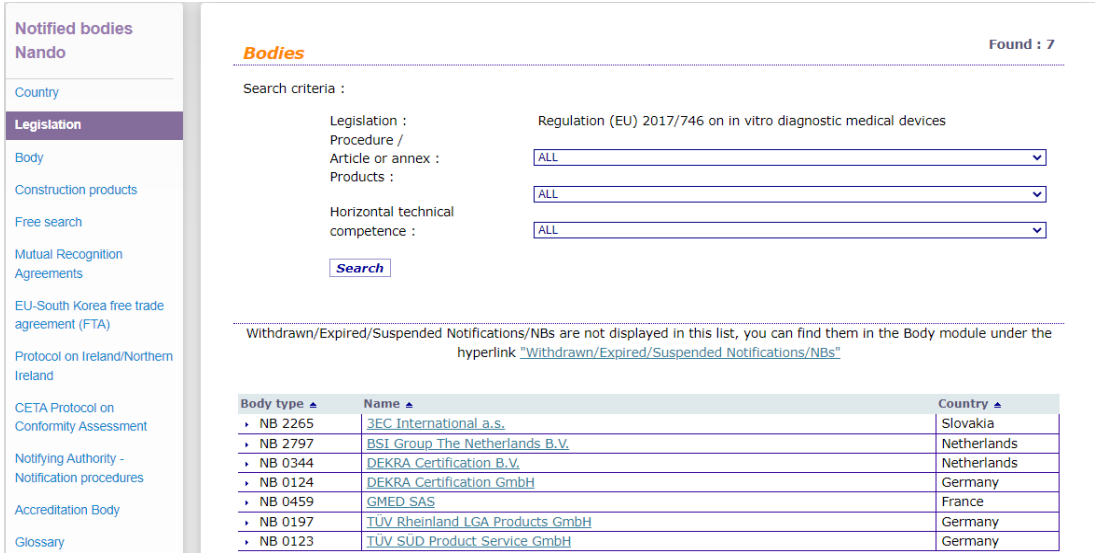
Annex I MDR/Annex I IVDR

EN ISO 14971 (not harmonised!) covers f.ex.

- Risk management
- Risk analysis, risk evaluation, risk control
- Benefit-risk analysis
- Production and post-production activities

A standard is a formula that describes the best way of doing something

Find a designated notified body in NANDO



Notified bodies Nando

- Country
- **Legislation**
- Body
- Construction products
- Free search
- Mutual Recognition Agreements
- EU-South Korea free trade agreement (FTA)
- Protocol on Ireland/Northern Ireland
- CETA Protocol on Conformity Assessment
- Notifying Authority - Notification procedures
- Accreditation Body
- Glossary

Bodies

Found : 7

Search criteria :

Legislation : Regulation (EU) 2017/746 on in vitro diagnostic medical devices

Procedure / Article or annex : ALL

Products : ALL

Horizontal technical competence : ALL

Search

Withdrawn/Expired/Suspended Notifications/NBs are not displayed in this list, you can find them in the Body module under the hyperlink "Withdrawn/Expired/Suspended Notifications/NBs"

Body type	Name	Country
NB 2265	3EC International a.s.	Slovakia
NB 2797	BSI Group The Netherlands B.V.	Netherlands
NB 0344	DEKRA Certification B.V.	Netherlands
NB 0124	DEKRA Certification GmbH	Germany
NB 0459	GMED SAS	France
NB 0197	TÜV Rheinland LGA Products GmbH	Germany
NB 0123	TÜV SÜD Product Service GmbH	Germany

Guidance is available both from the EU commission and the national authorities

Clinical evidence for medical devices and IVD medical devices

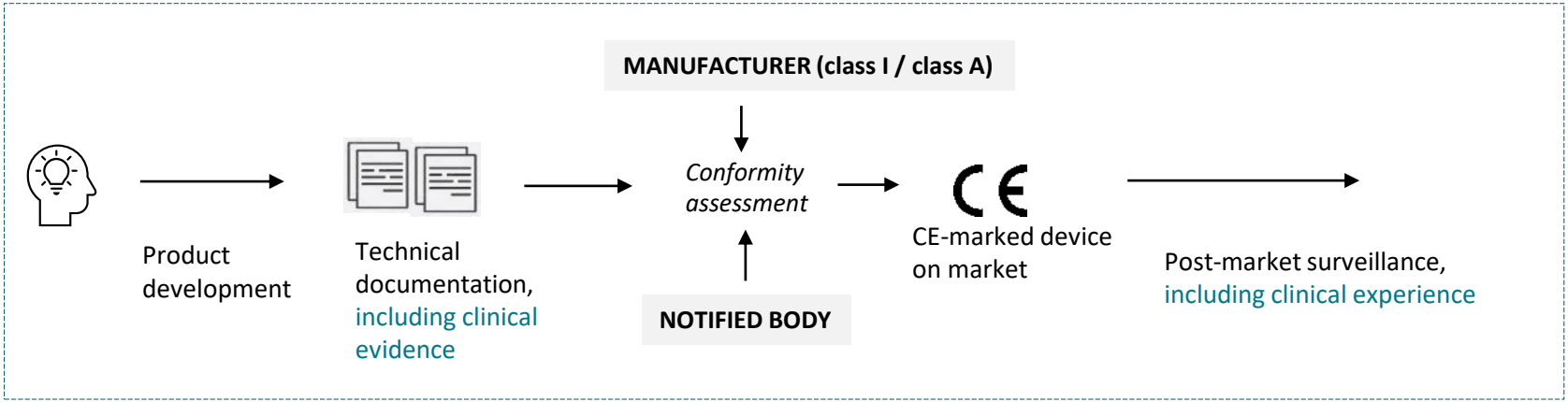
Including clinical investigations and performance studies

Anne-Mari Håkelien, Norwegian Medicines Agency (NoMA)

Norwegian Medicines Agency

Clinical evidence for medical devices

General principles



→ Clinical evidence is necessary for all medical devices

→ The manufacturer shall specify and justify the level of clinical evidence needed

→ Align risk management with evaluation of clinical data

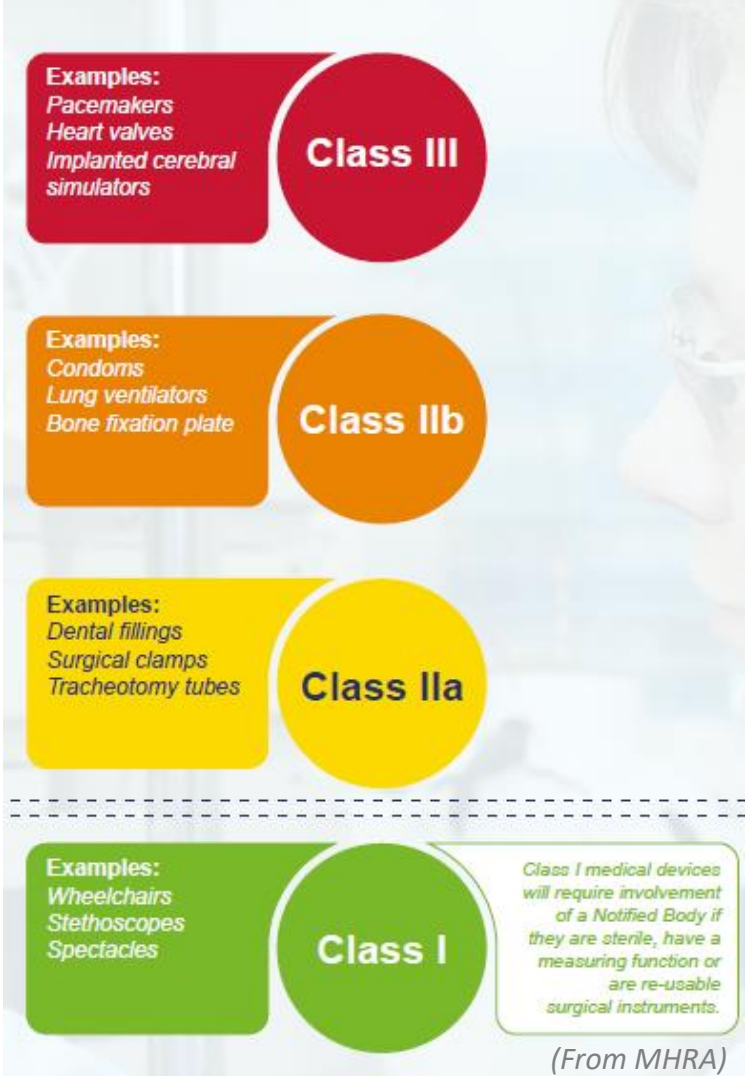
→ Requirements for methodology, planning, generating/collecting and documenting clinical evidence at both pre- and post-market stage

Medical Device Regulation (MDR)

In vitro Diagnostic Medical Device Regulation (IVDR)

Clinical evidence for medical devices

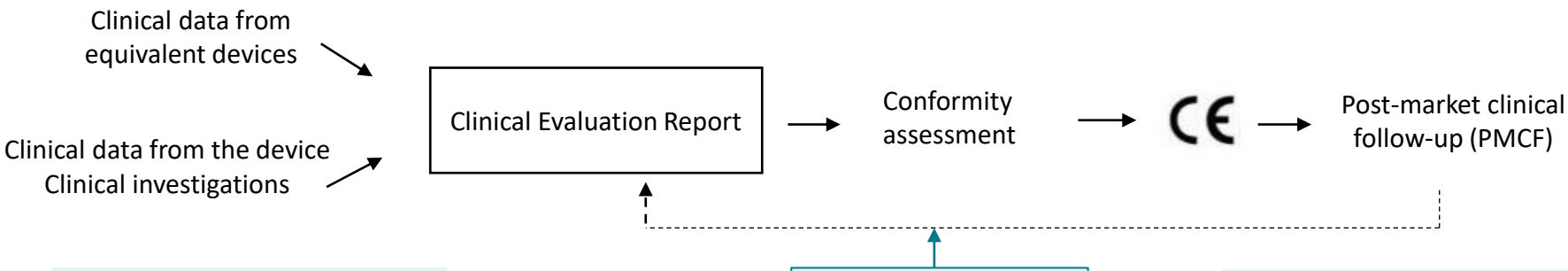
Medical Device Regulation (MDR)
Chapter VI, Annex XIV and XV



(From MHRA)

Clinical Evaluation

The manufacturer must do a clinical evaluation of the device → the clinical evidence for the device



Clinical evaluation
- Plan
- Conduct
- Document

Clinical evaluation is a continous process

Device in conformity throughout life cycle

Post-market clinical follow-up
- Proactively collect and evaluate clinical data
- Update clinical evaluation with new data

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Medical Device Regulation (MDR), Article 61 and Annex XIV

Clinical data from equivalent devices

- In order to use clinical data from an equivalent device, equivalence must be demonstrated
- The equivalent device must be technically, biologically and clinically equivalent
- Criteria for equivalence are specified in Annex XIV (& EU guidance)

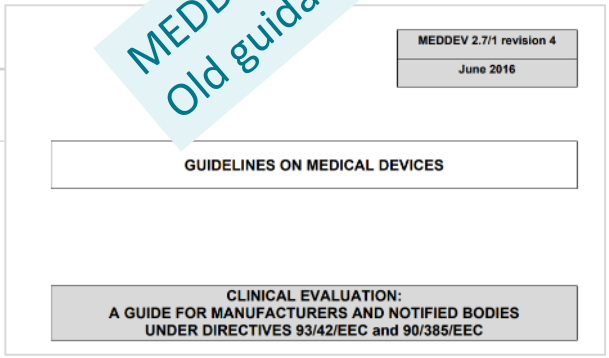
- For devices in class III or implantable devices clinical investigations shall be carried out

Medical Device Regulation (MDR), Article 61 and Annex XIV

EU guidance on clinical evaluation

MDCG 2020-6 EN •••	Guidance on sufficient **clinical evidence for legacy devices**	April 2020
MDCG 2020-5 EN •••	Guidance on **clinical evaluation – Equivalence**	April 2020
MDCG 2020-1 EN •••	Guidance on **clinical evaluation** (MDR) / **Performance evaluation** (IVDR) of medical device software	March 2020
MDCG 2020-13 EN ••• - Word version EN •••	**Clinical evaluation assessment report template**	July 2020
MDCG 2020-8 EN •••	Guidance on **PMCF evaluation report** template	April 2020
MDCG 2020-7 EN •••	Guidance on **PMCF plan** template	April 2020

MEDDEV 2.7/1
Old guidance!


MEDDEV 2.7/1 revision 4
June 2016
GUIDELINES ON MEDICAL DEVICES
CLINICAL EVALUATION:
A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES
UNDER DIRECTIVES 93/42/EEC and 90/385/EEC

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https://ec.europa.eu/health/medical-devices-sector/new-regulations/guidance-mdcg-endorsed-documents-and-other-guidance_en

Clinical investigation of medical devices

Clinical investigation of a medical device

Definition

‘any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device’

Includes pilot, early phase, confirmatory studies, ..

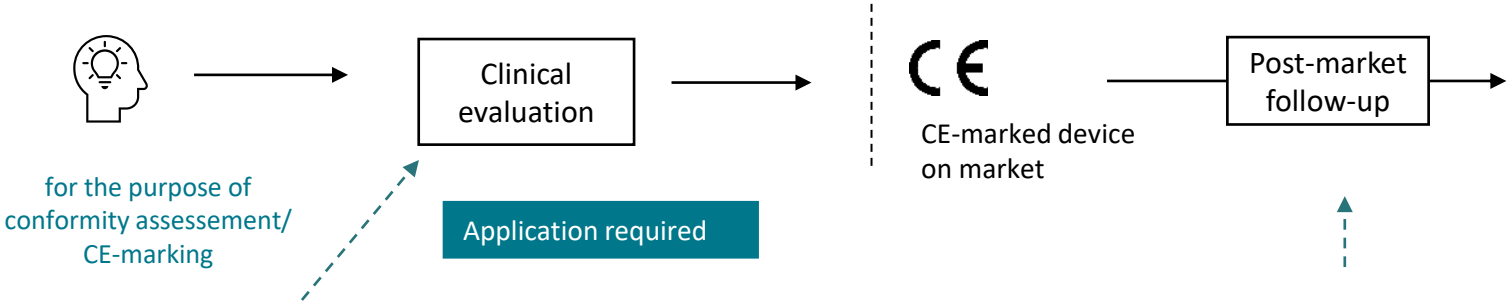
Medical Device Regulation (MDR), Article 2 (45)

Planning a clinical investigation of a medical device?

- You may need to submit an application or a notification to the relevant authority in the country where the clinical investigation will be conducted (Norway: NoMA)
- As well as submit an application to an Ethics Committee

Procedures presented are valid for NoMA (based on MDR). National variations may apply in some cases. If you plan to conduct a clinical investigation, the relevant authority in country where clinical investigation is to be conducted should be consulted-

Different types of clinical investigations



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Medical Device Regulation (MDR), Articles 62, 74 and 82

Documents to be submitted in application for a clinical investigation (MDR)

- **Application form**
- **Investigator's Brochure (IB):** Clinical and non-clinical information about the medical device under investigation that is available at the time of application (MDR Annex XV, Chapter II, Section 2). See also Annex B ISO 14155.
- **Clinical Investigation Plan (CIP)**
  Shall fulfil the requirements of MDR, Annex XV, chapter II, Section. See also Annex A ISO 14155.
- **Statement of Conformity:** signed statement that device conforms to the requirements, except for the aspects to be investigated
- Confirmation on the **suitability of the investigational site(s) and investigation team**
- **Proof of insurance** cover of the subjects
- **Patient information** documents and informed consent form
- Description measures implemented for the **protection and confidentiality of personal data**

ISO 14155:2020
Clinical investigation of medical devices for human subjects — Good clinical practice

Norway: submit by e-mail to meddev-no@noma.no

Other countries: consult authority

When European database EUDAMED becomes available, applications shall be submitted there

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Investigator's Brochure (elements to be described, not complete), from Annex XV

2.1. Identification and description of the device, including information on the intended purpose, the risk classification and applicable classification rule pursuant to Annex VIII, design and manufacturing of the device and reference to previous and similar generations of the device.

2.2. Manufacturer's instructions for installation, maintenance, maintaining hygiene standards and for use, including storage and handling requirements, as well as, to the extent that such information is available, information to be placed on the label, and instructions for use to be provided with the device when placed on the market. In addition, information relating to any relevant training required.

2.3. Pre-clinical evaluation based on relevant pre-clinical testing and experimental data, in particular regarding in-design calculations, *in vitro* tests, *ex vivo* tests, animal tests, mechanical or electrical tests, reliability tests, sterilisation validation, software verification and validation, performance tests, evaluation of biocompatibility and biological safety, as applicable.

2.4. Existing clinical data, in particular:

— from relevant scientific literature available relating to the safety, performance, clinical benefits to patients, design characteristics and intended purpose of the device and/or of equivalent or similar devices;

— other relevant clinical data available relating to the safety, performance, clinical benefits to patients, design characteristics and intended purpose of equivalent or similar devices of the same manufacturer, including length of time on the market and a review of performance, clinical benefit and safety-related issues and any corrective actions taken.

2.5. Summary of the benefit-risk analysis and the risk management, including information regarding known or foreseeable risks, any undesirable side-effects, contraindications and warnings.

Clinical Investigation Plan (elements to be described, not complete), from Annex XV

3.4. Description of the relevance of the clinical investigation in the context of the state of the art of clinical practice.

3.5. Objectives and hypotheses of the clinical investigation.

3.6. Design of the clinical investigation with evidence of its scientific robustness and validity.

3.6.1. General information such as type of investigation with rationale for choosing it, for its endpoints and for its variables as set out in the clinical evaluation plan.

3.6.2. Information on the investigational device, on any comparator and on any other device or medication to be used in the clinical investigation.

3.6.3. Information on subjects, selection criteria, size of investigation population, representativeness of investigation population in relation to target population and, if applicable, information on vulnerable subjects involved such as children, pregnant women, immuno-compromised or, elderly subjects.

3.6.4. Details of measures to be taken to minimise bias, such as randomisation, and management of potential confounding factors.

3.6.5. Description of the clinical procedures and diagnostic methods relating to the clinical investigation and in particular highlighting any deviation from normal clinical practice.

3.6.6. Monitoring plan.

3.7. Statistical considerations, with justification, including a power calculation for the sample size, if applicable.

3.8. Data management.

3.9. Information about any amendments to the CIP.

Processing of applications

Risk-based approach

- Investigational device is class I, or non-invasive IIa or IIb devices → Validation: check whether application is complete and within scope of MDR)

- Investigational device is invasive or class III → Assessment (article 71 MDR)
  - Whether device conforms to requirements
  - Risk minimization solutions
  - Reliability and robustness of data to be generated
  - (…)

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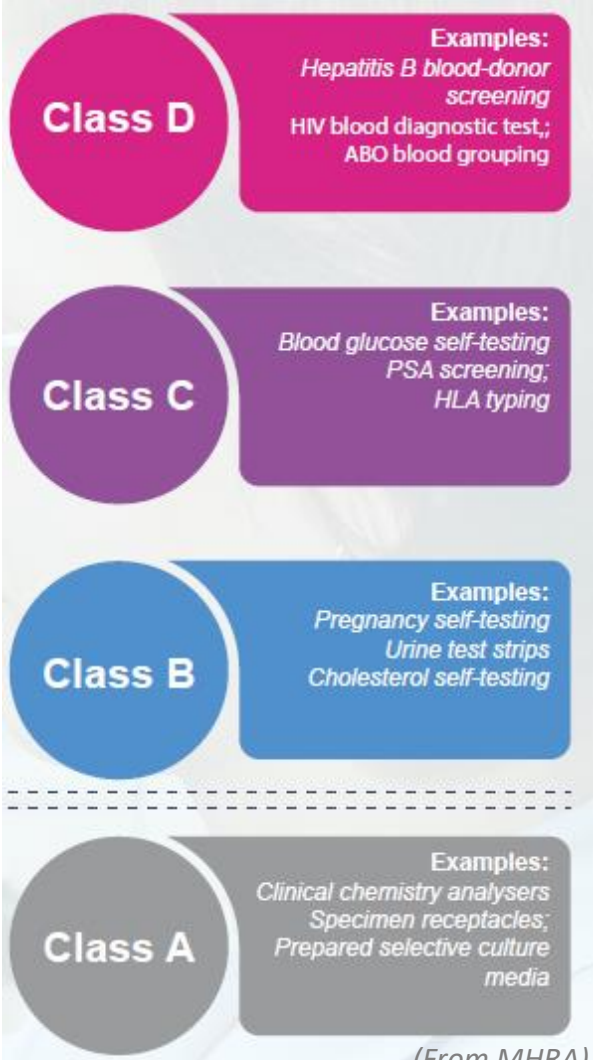
(National variations may occur, consult relevant authority in country where clinical investigation is to be conducted).

EU guidance/standards – Clinical investigation

MDCG 2021-6 EN •••	Regulation (EU) 2017/745 – **Questions & Answers** regarding **clinical investigation**	April 2021
MDCG 2021-28 EN •••	**Substantial modification** of clinical investigation under Medical Device Regulation	December 2021
MDCG 2020-10/2 EN ••• MDCG 2020-10/1 EN •••	Guidance on **safety reporting** in clinical investigations Appendix: Clinical investigation summary safety report form	May 2020 May 2020

Clinical evidence for IVD medical devices

In vitro diagnostic medical device regulation (IVDR)
Chapter VI, Annexes XIII and XIV



(From MHRA)

Performance evaluation
Clinical evidence for an IVD

Consists of three essential elements

- Scientific validity of the analyte
- Analytical performance of the device
- Clinical performance of the device

In vitro diagnostic medical device regulation (IVDR)
Article 56, Annex XIII

Scientific validity of an analyte

- the extent to which the analyte, or marker to be determined by the IVD is associated with the targeted physiological state or clinical condition.
- Sources
  - appraised literature data
  - peer-reviewed data
  - published clinical data
  - relevant information on the scientific validity of devices measuring the same analyte or marker
  - proof of concept studies

Analytical performance of a IVD

demonstration of the IVD's ability to correctly detect or measure a particular analyte

Examples of analytical performance indicators include:

- analytical sensitivity,
- Linearity
- measuring interval/range: LoQ as the lower limit and linearity as the upper limit,
- analytical specificity
- accuracy
- instrument comparison,
- cut-off value(s),
- stability.

→ shall be demonstrated based on analytical performance studies

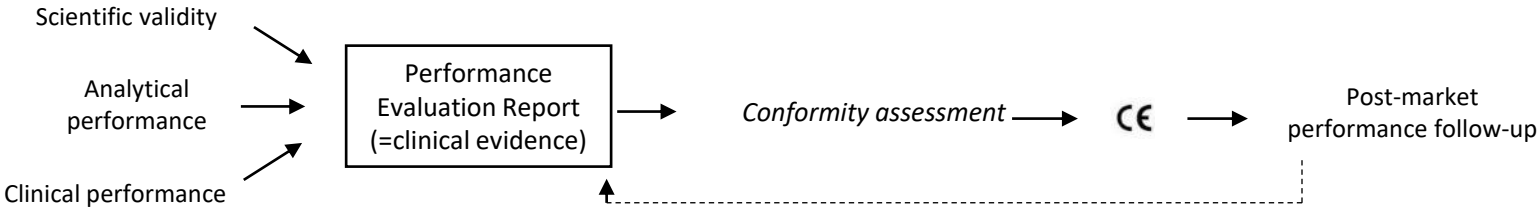
Clinical performance of an IVD

demonstration of an IVD's ability to yield results that are correlated with a particular clinical condition or a physiological/pathological process or state in accordance with the target population and intended user.

Sources of clinical data

- Clinical performance study → shall be performed unless duly justified
- Published experience from routine diagnostic testing
- Scientific peer-reviewed literature
- other sources of clinical performance data

Performance Evaluation



Performance evaluation
- Plan
- Conduct
- Document

Performance evaluation is a continous process

Device in conformity throughout life cycle

Post-market performance follow-up
- Proactively collect and evaluate performance data
- Update performance evaluation with new data, for class C and D yearly

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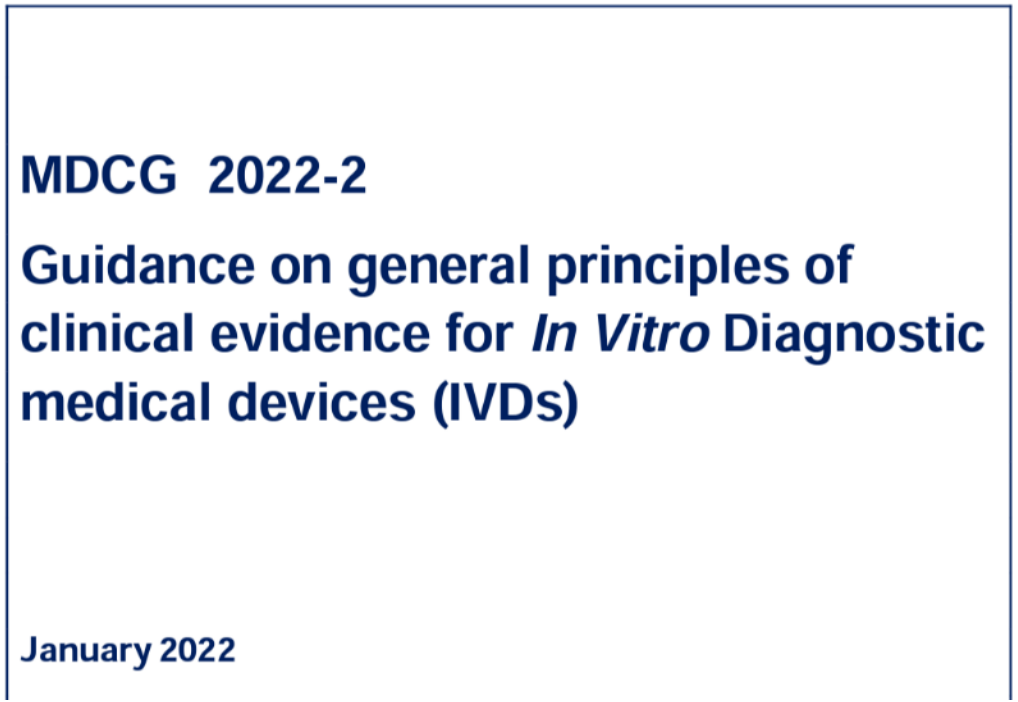
In vitro diagnostic medical device regulation (IVDR)
Article 56, Annex XIII

EU Guidance Performance Evaluation



Performance studies of IVDs

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In vitro diagnostic medical device regulation (IVDR)
Articles 57-76, Annex XIII and XIV

Performance study

Definition

‘a study undertaken to establish or confirm the analytical or clinical performance of a device’

Two categories

Analytical performance study
establish ability of a device to correctly detect or measure a particular analyte/marker

Clinical performance study
Determine clinical performance (relevance for target population, clinical condition, ..)

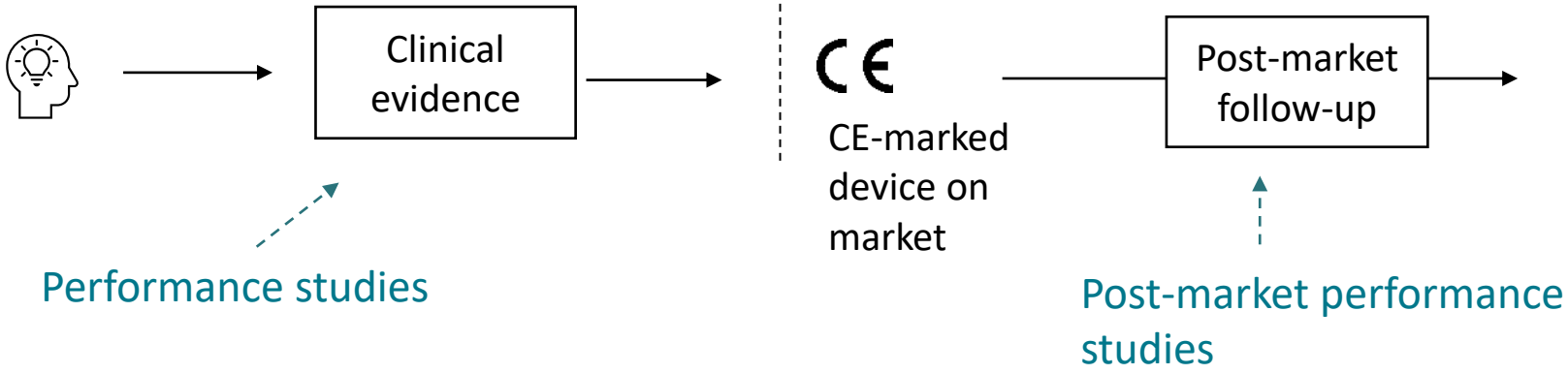
Planning a performance study of an IVD?

- You may need to submit an application or a notification to the relevant authority in the country where the performance study will be conducted (Norway: NoMA)

- As well as submit an application to an Ethics Committee

Procedures presented here are valid for NoMA and are based on IVDR. National variations may apply in some cases. If you plan to conduct a performance study, the relevant authority in country where study is to be conducted should be consulted.

Performance studies of IVD medical devices



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(IVDR)

IVD performance studies

An application to the authority is needed for

Any performance study:

- in which surgically invasive sample-taking is done only for the purpose of the performance study
- that is an interventional clinical performance study
- study involves additional invasive procedures or other risks for the subjects of the studies
- Involves a companion diagnostic (except use of left-over samples → notification to authority)

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**the relevant authority in country where the study is to conducted (Norway: NoMA)*

IVD performance studies

An application to the authority is needed for

Any performance study:

- in which surgically invasive
  the purpose of the performa
- that is an interventional clini
- study involves additional inv
  for the subjects of the studie
- Involves a companion diagn
  left-over samples → notificat

'companion diagnostic' is 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
- 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))

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**the relevant authority in country where the study is to conducted (Norway: NoMA)*

(IVDR)

Documents to be submitted in an application for a performance study

- **Application form**
- **Investigator's Brochure (IB):** Documentation on the device (Annex XIV)
- **Performance study plan**
  Shall fulfil the requirements of Annex XIV
- **Statement of Conformity:** signed statement that device conforms to the requirements, except for the aspects to be investigated
- Confirmation on the **suitability of the investigational site(s) and investigation team**
- **Proof of insurance** cover of the subjects
- **Patient information** documents and informed consent form
- Description measures implemented for the **protection and confidentiality of personal data**

ISO 20916:2019
In vitro diagnostic medical devices — Clinical performance studies using specimens from human subjects — Good study practice

Norway: submit by e-mail to meddev-no@noma.no

Other countries: consult authority

When European database EUDAMED becomes available, applications shall be submitted there

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Processing of applications

Risk-based approach

- Performance studies in which surgically invasive sample-taking is done only for the purpose of the performance study → Validation: check whether application is complete and within scope of IVDR)

Sample taking involves major clinical risk

- that is an interventional clinical performance study
- study involves additional invasive procedures or other risks for the subjects of the studies
- Involves a companion diagnostic (except for studies with left-over samples → notification to authority) →

Assessment (article 67)
- Whether device conforms to requirements
- Risk minimization solutions
- Reliability and robustness of data to be generated
- ….

** National variations in procedures may occur. Consult relevant authority.*

Notification of post-market performance study

Required for studies where

- a CE-marked IVD is investigated within its intended purpose

  and

- Subjects are submitted to procedures additional to those performed under the normal conditions of use of the device and those additional procedures are invasive or burdensome

Same documents to be submitted as for applications, however, no assessment by NoMA.

**the relevant authority in country where the study is to conducted (Norway: NoMA)*

More information

European Commission web site
https://ec.europa.eu/health/medical-devices-sector/new-regulations_en

Norwegian Medicines Agency (NoMA)
https://legemiddelverket.no/medisinsk-utstyr
https://legemiddelverket.no/english/medical-devices

E-mail: meddev-no@noma.no

Norwegian Medicines Agency

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