2022-10-05

Application and notification of clinical investigation of medical devices

Elin Karlberg, Head of Regulatory Group

Anna Skott, Regulatory Assessor Medical Devices

Department of Clinical Trials and Special Permissions,

Swedish Medical Products Agency

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

1

European Medical Device Regulations

Trade legislation which allows free movement of products that fulfil the EU performance and safety requirements

Protects users and patients

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

2

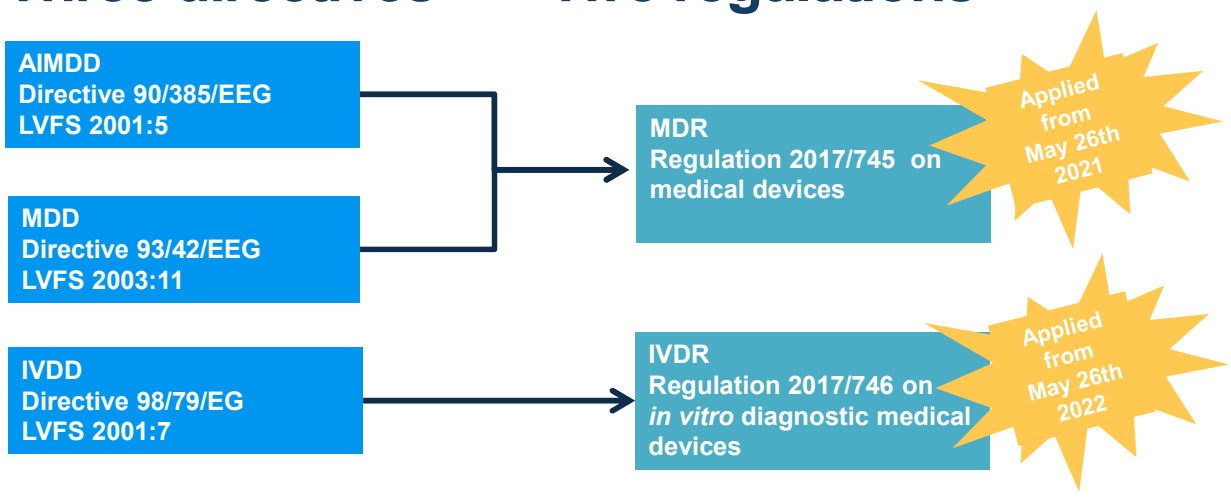
2

Why are new regulations needed?

- Technical and scientific development calls for a stronger legislation
- Diverging interpretation and implementation of directives in the EU member states
- Insatisfying traceability of medical devices
- Increase transparency and access to information

3

Three directives ⟶ Two regulations



4

Placing on the market and putting into service
(MDR Article 5)

- A device may be placed on the market or put into service only if it complies with MDR when duly supplied and properly installed, maintained and used in accordance with its intended purpose
- A device shall meet the general safety and performance requirements set out in MDR Annex I which apply to it, taking into account its intended purpose
- Demonstration of conformity with the general safety and performance requirements shall include a clinical evaluation

5

MDR Annex I
General safety and performance requirements

Chapter I: General requirements
Chapter II: Requirements regarding design and manufacture
Chapter III: Requirements regarding the information supplied with the device

6

Chapter I: General requirements

Design to prevent use error

Fit for intended purpose

Effective

Safe

Durable

Acceptable risks when weighed against benefit

Risk management system

Eliminate risks

Reduce risks as far as possible

Inform about residual risks

Chapter II: Requirements regarding design and manufacture

10. Chemical, physical and biological properties
11. Infection and microbial contamination
12. Devices incorporating a substance considered to be a medicinal product and devices that are composed of substances or of combinations of substances that are absorbed by or locally dispersed in the human body.
13. Devices incorporating materials of biological origin
14. Construction of devices and interaction with their environment
15. Devices with a diagnostic or measuring function
16. Protection against radiation

Chapter II: Requirements regarding design and manufacture (cont.)

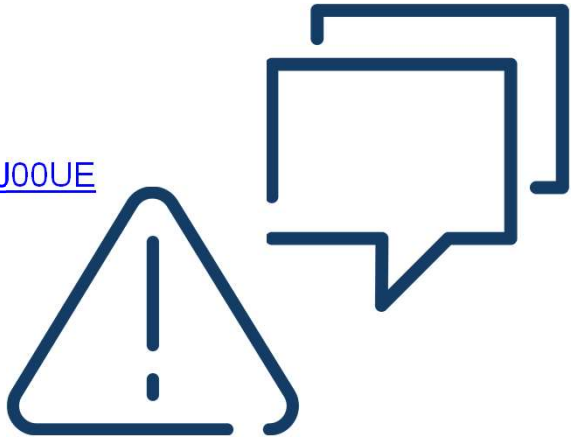
17. Electronic programmable systems — devices that incorporate electronic programmable systems and software that are devices in themselves
18. Active devices and devices connected to them
19. Particular requirements for active implantable devices
20. Protection against mechanical and thermal risks
21. Protection against the risks posed to the patient or user by devices supplying energy or substances
22. Protection against the risks posed by medical devices intended by the manufacturer for use by lay persons

9

Chapter III: Requirements regarding the information supplied with the device

Labeling and user instructions

https://www.youtube.com/watch?v=U2gQE0J00UE



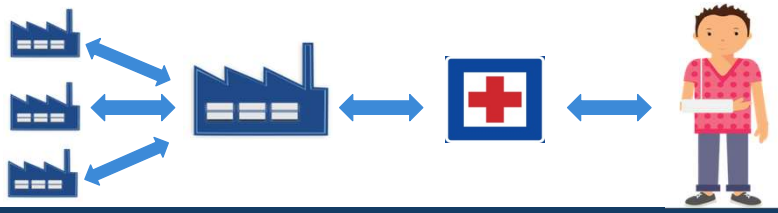
10

Traceability: Unique Device Identification

Model (UDI-DI)

Production (UDI-PI): batch,…

- Allows identification and faciltates traceability
- Helps fight falsification of devices
- To be used for incident reporting and field safety corrective actions



EUDAMED

European database on medical devices

Access to Information

- Transparency
- Patients and health care professionals can make informed decisions
- Increased coordination and flow of information between actors

Clinical Evaluation

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

13

14

Clinical evaluation – in summary

A methodologically sound ongoing procedure to

- collect
- appraise
- analyse

} clinical data pertaining to a medical device

and to evaluate whether there is sufficient clinical evidence
to confirm compliance with the relevant general requirements for

- safety and
- performance

when using the device according to the manufacturer's Instructions for Use.

15

Clinical Investigations and Performance Studies

16

Clinical investigation

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

(MDR Article 2.45)

17

Performance Study (IVD)

Performance study

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

(IVDR Article 2.42)

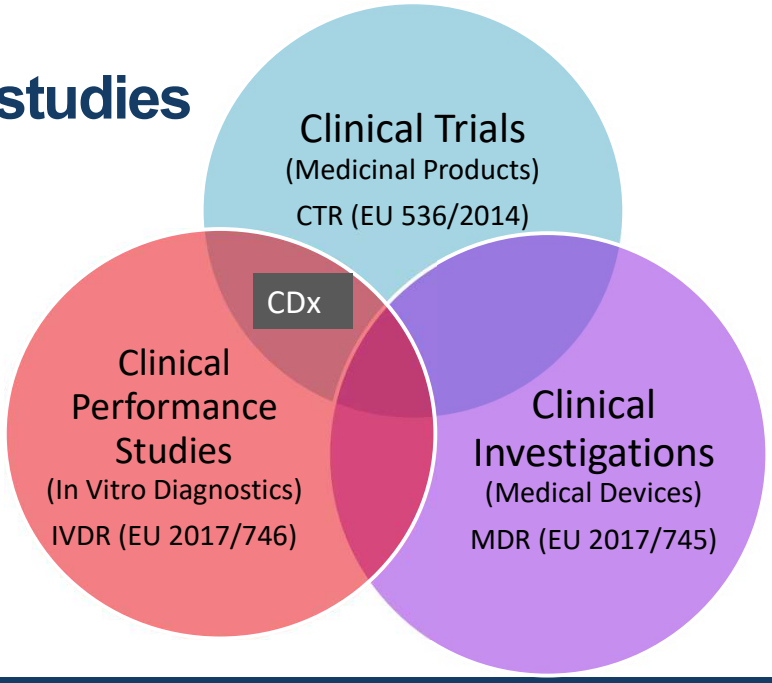
Interventional clinical performance study

A clinical performance study where the test results may influence patient management decisions and/or may be used to guide treatment

(IVDR Article 2.46)

18

Clinical studies

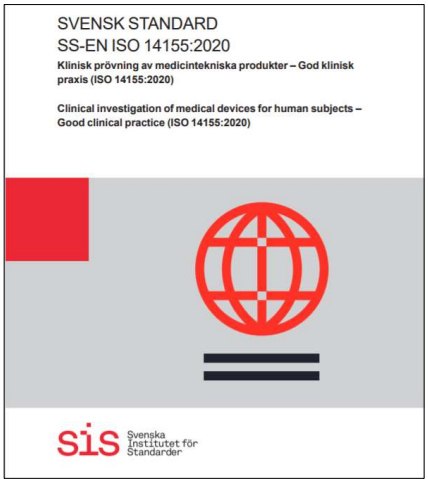


Clinical Investigation of medical devices for human subjects – Good clinical practice

SS-EN ISO 14155:2020

Quality system for the conduct, documentation and reporting etc. of clinical investigations

Similar in spirit and content to the ICH GCP, but with Medical Device particulars to be aware of



Protect the rights, safety and well-being of human subjects

Ensure the scientific conduct of the clinical investigation and the credibility of the clinical investigation results

Good Clinical Practice (GCP)

Define the responsibilities of the sponsor and principal investigator

Assist sponsors, investigators, ethics committees, regulatory authorities and other bodies involved in the conformity assessment of medical devices

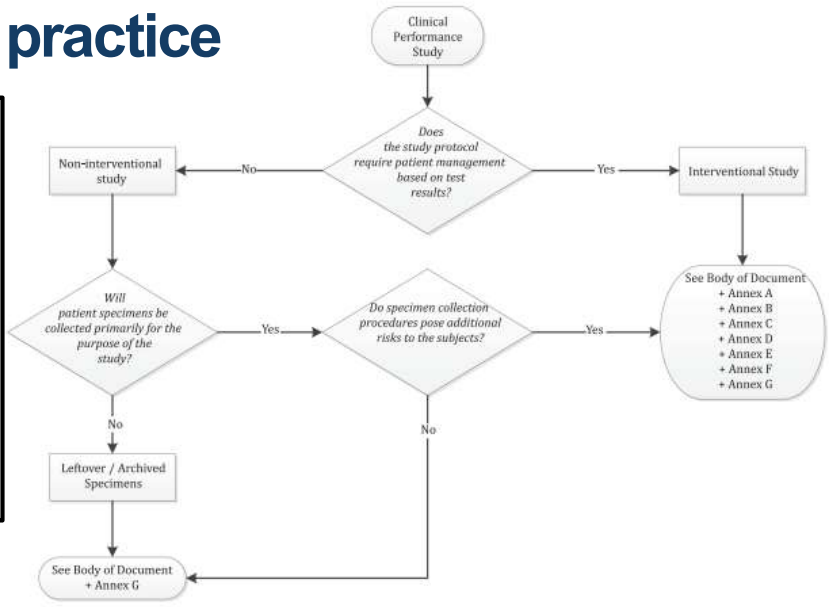
21

IVD: Good study practice

INTERNATIONAL STANDARD **ISO 20916**

First edition
2019-05

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



22

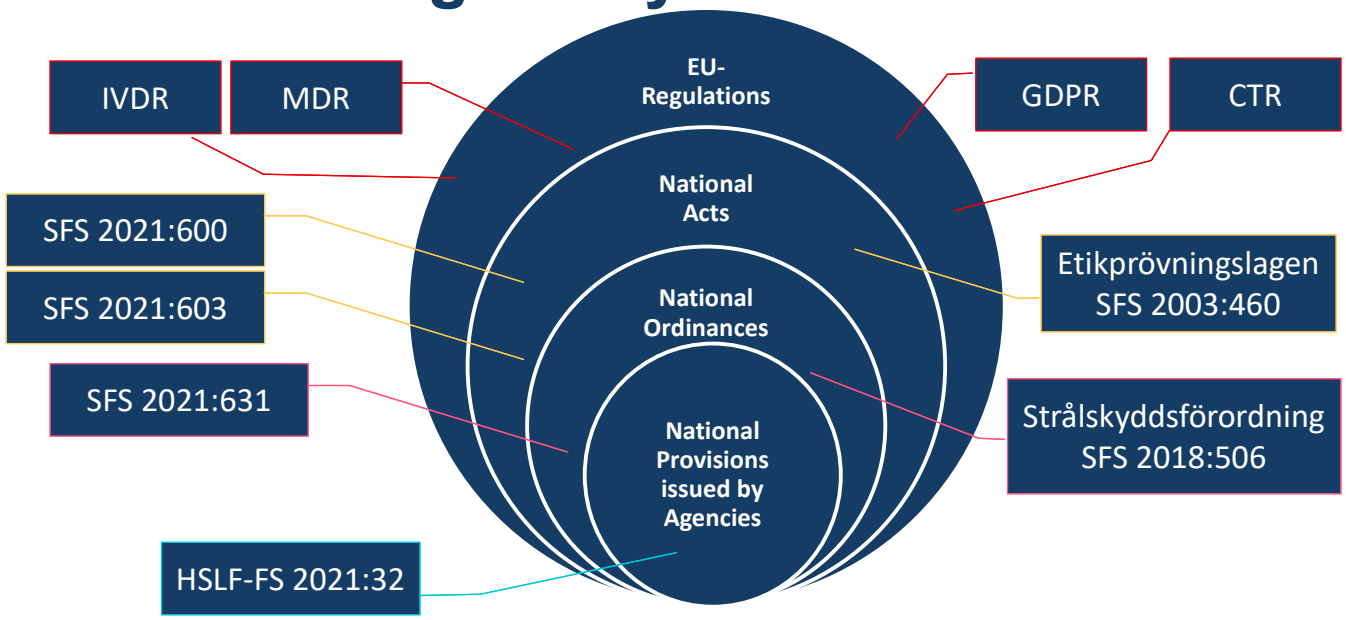
Consequences of the MDR, IVDR and adaptation of national legislation

All clinical investigations of medical devices have to be submitted to the MPA

A limited number of **performance studies** have to be submitted to the MPA:

- Surgically invasive sample-taking is done only for the purpose of the performance study
- Interventional clinical performance study
- Study involves additional invasive procedures or other risks for the subjects of the studies
- Companion Diagnostics (CDx)

Regulatory frame work



Authorisation procedures

For clinical investigations of medical devices and

some performance studies of *in vitro*-diagnostic medical devices

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

25

Coordinated procedures for authorisation

For clinical investigations of medical devices and some performance studies of *in vitro*-diagnostic medical devices

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Etikprövningsmyndigheten

Application Notification → Review by Medical Products Agency and Ethical Review Authority → Authorisation

- Sponsor is responsible for all submissions (notification and application)
- Submission to the MPA/Läkemedelsverket (later via EUDAMED)
- The MPA transmits relevant documents to the Ethical Review Authority*

**with the exceptions for some types of clinical investigations of medical devices*

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

26

26

Four different authorisation procedures – MDR

For clinical investigations of medical devices

	Medical Device	A. Applicable legislation B. Interactions with Swedish Medical Products Agency C. Ethical assessment	*When can the clinical investigation commence?*
1	**None-CE marked devices** invasive class IIa and IIb, class III	A. MDR article 62.1 or MDR article 82 + 2 chap. 6§ act SFS 2021:600 B. Apply to and await MPA's validation of the application C. Ethical assesssment is included in the approval from the MPA	*45 days after the validation date (+ time for answering questions)*
2	**None-CE marked devices** class I, non-invasive class IIa and IIb	A. MDR article 62.1 or MDR article 82 + 2 chap. 6§ act SFS 2021:600 + 6 chap. 1§ provision HSLF-FS 2021:32 B. Apply to and await MPA's validation of the application C. Await approval from the Ethical Review Authority	*40 days after the validation date*
3	**CE-marked devices** used within intended purpose BUT additional invasive or burdensome procedures comes with the investigation	A. MDR article 74.1 B. Notify the MPA at least 30 days prior to start of the investigations C. Await approval from the Ethical Review Authority	*30 days after the notification*
4	**CE-marked devices** used within intended purpose and no additional invasive or burdensome procedures comes with the investigation	A. MDR article 82 + 2 chap. 6§ act SFS 2021:600 + 6 chap. 3§ provision HSLF-FS 2021:32 B. Notify the MPA at least 30 days prior to start of the investigations C. Seperate application to the Ethical Review Authority (via Ethix)	*30 days after the notification, if ethical approval is received*

27

Three different authorisation procedures - IVDR

For some performance studies of *in vitro*-diagnostic medical devices

	Performance studies that	•Applicable legislation •Interaction with the Swedish Medical Products Agency •Ethical assessment	***When can the clinical investigation commence?***
1	• include surgically invasive sample-taking done only for the purpose of the performance study and where the sample-taking represents a major clinical risk to the subject of the study • are interventional clinical performance studies • involve additional invasive procedures or other risks for the subjects of the studies • involve companion diagnostics – *does not apply to studies using only left-over samples*	•IVDR articles 58.1 or 58.2 + 66.7b •***Apply*** to and await MPA's ***validation*** and ***authorization*** of the application •Ethical assessment is included in the approval from the MPA	*45 days after the validation date (+time for answering questions)*
2	• include surgically invasive sample-taking done only for the purpose of the performance study but where the sample-taking does not represent a major clinical risk to the subject of the study	•IVDR articles 58.1a) + 66.7a •***Apply*** to and await MPA's ***validation*** of the application •Await ***approval*** from the Ethical Review Authority	*40 days after the validation date*
3	• include a CE-marked device that is to be further assessed within the scope of its intended purpose and which involves additional procedures that are invasive or burdensome	•IVDR article 70.1 •***Notify*** the MPA at least 30 days prior to start of the study •Await ***approval*** from the Ethical Review Authority	*30 days after notification, if ethical approval is received*

28

What should be included in the application/notification?

Same documentation for both applications and notifications!

- Application and notification form
- Investigator's Brochure*
- Clinical Investigation Plan/Performance Study Plan
- A signed statement by the manufacturer that the device in question conforms to the general safety and performance requirements
- Proof of insurance cover or indemnification of subjects in case of injury
- Patient information and consent form
- Description of the arrangements to comply with the applicable rules on the protection and confidentiality of personal data
- Ethical application
- For each investigational site: CV for principal investigator + resources attestation
- Invoicing documents

** The Investigator's Brochure can be replaced by the Instructions for Use in some cases (see 6 chap. 3§ HSLF-FS 2021:32)*

Interactions with the Medical Products Agency during and after the investigation/study

- Sponsor is responsible for reporting
  - All substantial modifications during the investigation/performance study
  - Serious Adverse Events and Device Deficiencies
  - Temporary halt or early termination of the investigation/performance study
  - The end of the investigation/performance study
- Submit a clinical investigation report/performance study report accompanied by a summary that is easily understood by the intended user
  - Within 1 year after the end of the investigation
  - Within 3 months if temporary halted or early terminated
- The report and summary will be published in EUDAMED/by the EU Commission

Assessment by the regulatory authorities

- Are the risk-minimisation solutions adequate?
- Are the measures planned for the safe installation, putting into service and maintenance of the investigational device adequate?
- The safety, quality and usefulness of any components of animal or human origin or of substances, which may be considered medicinal products
- The reliability and robustness of the data generated in the clinical investigation or performance study taking account of
  - statistical approaches,
  - design of the investigation or performance study and methodological aspects
  - sample size, comparator and endpoints
- If device for sterile use, are sterilisation procedures adequate?
- Insurance, responsibilities and other formalities

Is the device ready for a study on humans?

Risks, after risk minimization, are justified…

…when weighed against the expected clinical benefits

Compliance with the safety and performance requirements has been demonstrated, apart from the aspects covered by the clinical investigation/performance study, and…

…with regard to those aspects, every precaution has been taken to protect the health and safety of the subjects.

Investigator and other personnel

Article 62.6 MDR and Article 58.7 IVDR

The **investigator** shall be a person exercising a profession which is recognised in the Member State concerned as **qualifying for the role of investigator** on account of having the **necessary scientific knowledge and experience in patient care or laboratory medicine**.

Other personnel involved in **conducting a clinical investigation/performance study** shall be suitably qualified, by education, training or experience in the relevant medical field and in clinical research methodology, to perform their tasks.

Responsibility for the patient care

Article 62.4j MDR
Article 58.5j IVDR

Qualified medical doctor, qualified dental practitioner or any other person entitled by national law to provide the relevant patient care

Common findings during the assessment

- Clinical Investigation Plan
  - Deviation management
  - Management of substantial modifications
  - Safety reporting
- Patient Information/Consent Form
  - Minimal requirements in the GCP standard not fulfilled
- Device details
  - Product description too superficial
  - Applied standards
  - Preclinical data
  - Expected clinical risks
- Need to justify/adapt the study design
  - Patient selection criteria
  - Statistical methods
  - Patient safety aspects
- Consent procedure and possible inclusion of incapacitated subjects
- Version management of documents
- Inconsistencies within and between documents

Teamwork

Visit our website for more information
https://www.lakemedelsverket.se/en/permission-approval-and-control/clinical-trials/medical-devices

Contact us

E-mail registrator@lakemedelsverket.se
Telephone +46 (0)18-17 46 00

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

37

38