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Curriculum Development of Human Clinical Trials for the Next Generation of PhD Students and Early Career Researchers in the Medical, Science, Pharmacy and Health Professions

CHAPTER 9

CLINICAL EVALUATION AND CLINICAL INVESTIGATIONS OF MEDICAL DEVICES

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1 Introduction

When we speak of clinical trials, we mainly refer to clinical trials of medicines, so called investigational medical products (IMPs). However, medical devices (MDs) play an equal important part in the treatment and care of patients. In Europe alone, there are more than 34,000 medical technology companies responsible for over 500 000 types of medical devices and in vitro diagnostics on the EU market.[1]

The Regulation (EU) 2017/745 of European Parliament and of the Council ("MDR"[2]) that became applicable from 26 May 2021 made medical device developments more regulated and rigorous. Compared to the previous Directives, the MDR places more emphasis for example on a life-cycle approach; on clinical investigations, on post-market follow up, etc. The key areas of the MDR are the followings:

1. New product classification: This has caused many devices to be reclassified into higher-risk classes. The product classification is expanded with new, as well as revised terms and rules. E.g. stand-alone software falls under Class IIa or higher according to the MDR, which was classified as Class I according to the MDD. For more information on this please look at CONSCIOUS Chapter 11, Medical Devices and Advanced Therapies[3].
2. Clinical Evaluation Process: Manufacturers should conduct a clinical evaluation process, and clinical evidence needs to be up-to-date, clear, convincing, and publicly available. For Class III and implantable devices, the post-market clinical follow-up evaluation report, the summary of safety and clinical performance shall be updated at least annually. And if a medical device is a high-risk product, clinical data should be collected and evaluated from medical device use. If competitor device data is used for clinical evaluation activities, it should be justified, including why and how they are similar.
3. PMS (Post-Market Surveillance) System: Manufacturers should implement a post-market surveillance system with continuous reviews and an annual update of a public summary of safety and performance, as well as clinical evaluation. The PMS plan and corresponding report are required for Class I devices whereas a PSUR (periodic safety update report) is also required for Classes IIa, IIb, and III.
4. Quality management system: Manufacturers of devices shall establish, document, implement, maintain, keep up to date, and continually improve a quality management system. E.g. ISO 13485, as a GMP in pharmaceutical industry
5. Responsible Person for Regulatory Compliance: Manufacturers should have a responsible person available within the organization who is responsible for the EU MDR compliance of their organization and ensures that the declaration of conformity of every device are prepared and updated regularly.
6. Notified bodies: The major change introduced by MDR and IVDR relates to the supervision of notified bodies, because of this change, a substantial number of the

[1] The European Medical Technology Industry in Figures 2022: https://www.medtecheurope.org/wp-content/uploads/2022/09/the-european-medical-technology-industry-in-figures-2022.pdf
[2] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02017R0745-20230320
[3] CONSCIOUS: Chapter 11, Medical Devices and Advanced Therapies, http://conscious.novaims.unl.pt/my/

previous notified bodies may potentially lose their designation or see changes in the scope of their authority.

7. Stakeholders' duties: MDR clarifies the definitions, duties and responsibilities among suppliers, importers, subcontractors, assemblers, and EU-authorized representatives.
8. EUDAMED obligations: European Union's database for medical devices that stores all relevant regulatory information for medical devices. The registration and data provide is mandatory for all of the stakeholders.
9. UDI (Unique Device Identification) System: Each medical device should have a UDI-DI (UDI-Device Identifier) and UDI-PI (UDI-Production Identifier) and each UDI should be submitted to the UDI database. This system offers a lot of benefits e.g. fast reporting serious safety incident, or help identifying counterfeit medical devices.

As you can see in the following figure, the European Parliament on 15 March 2023 delayed the implementation of the mandatory requirements of the regulation, because the lack of number of Notified Bodies and lack of preparedness of manufacturers. Therefore, manufacturers and other stakeholders now will have more time for their readiness.

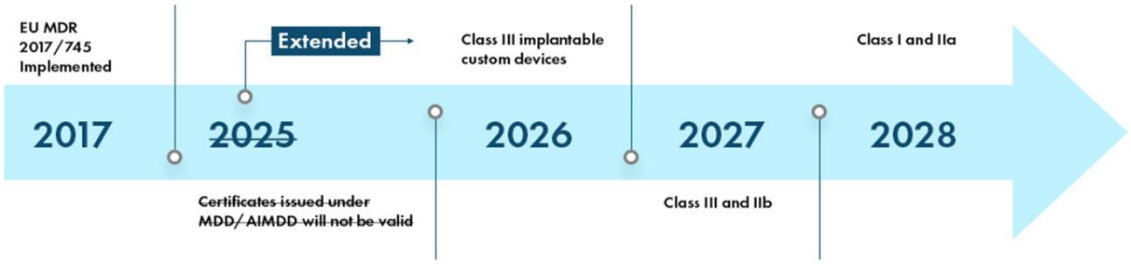

Figure 1: Recent MDR transition extensions

The aim of this chapter is to provide a comprehensive picture on medical device developments with special focus on new MDR rules. By the end of the chapter, students shall understand the basic steps and know the stakeholders, as well as difficulties of medical device developments.

2 MD development pathway

In this chapter we discuss the basic process of MD development. First, we take a look at the stakeholders of this process and their tasks, then we detail the fundamental steps of the development process.

2.1 Stakeholders in MD development

MDR identifies four economic operators: manufacturer, authorized representative, importer and distributor. When there is a European manufacturer, there is no need for an authorised representative or importer and the manufacturer can distribute itself the device. In a more complex case, a non-EU manufacturer is responsible for assigning an authorized representative who acts on behalf of the manufacturer for European regulatory tasks.

According to MDR, **manufacturer** means "*a natural or legal person who manufactures or fully refurbishes a device or has a device designed, manufactured or fully refurbished, and markets that device under its name or trademark*". Note that the manufacturer does not necessarily manufacture the device: manufacturing and also design can be subcontracted. However, it is the manufacturer who has the most responsibility concerning the device.

According to Article 10, manufacturers shall have systems for risk management (paragraph 2) and quality management (paragraph 9); conduct clinical evaluations (paragraph 3); compile technical documentation (paragraph 4); and apply a conformity assessment procedure (paragraph 6). Manufacturers are also responsible for their devices once they are on the market (paragraphs 12, 13, 14). They must have systems in place to cover their financial responsibility for harm caused by defective devices (paragraph 16). Moreover, every manufacturer shall have a named person responsible for regulatory compliance (Article 15). Manufacturers of some implantable devices will have to provide an implant card for the patient (Article 18). Once they have completed all these obligations, manufacturers shall draw up a declaration of conformity (Article 19) and apply CE marking to their devices (Article 20).

Manufacturers outside the EU/EEA shall have a contract with an **authorised representative** inside the EU/EEA (Article 11). MDR defines in Article 11 the basic tasks and responsibilities that the manufacturer has to require from the authorised representative:

- Verifying the CE marking: verify that the EU declaration of conformity and technical documentation have been drawn up as necessary.
- Keep documentation available to authorities: provide the authority with all the information and documentation necessary to demonstrate the conformity of a device.
- Cooperate with competent authorities on any preventive or corrective action taken to eliminate or mitigate the risks posed by the device.
- Terminate the mandate if the manufacturer fails to meet its obligations defined in MDR.

When there is a manufacturer outside the EU/EEA, then an **importer** who places the device on the EU market and a **distributor**, who makes the device available to the user are also often needed. The importer is often the authorised representative and/or distributor as well. A distributor can be any legal or natural person in the supply chain: a medical equipment stores, pharmacies, online sales sites, supermarkets, sports stores, etc.

The obligations of importers (Article 13) and distributors (Article 14) are also clearly described in the regulation. As MDR states importers and even distributors shall verify for example that:

a) the device has been CE marked and that the EU declaration of conformity of the device has been drawn up;
b) a manufacturer is identified and that an authorised representative in accordance with Article 11 has been designated by the manufacturer;
c) the device is labelled in accordance with the Regulation and accompanied by the required instructions for use;
d) where applicable, a UDI has been assigned by the manufacturer.

They also have to make sure that they do not jeopardise the compliance of the device with general safety and performance requirements, and they need to register complaints, non-conforming devices, etc. and report to manufacturers and authorities if necessary.

Moreover, for imported devices, distributers also have to verify that the importer has complied with the relating requirements, just like importers have to make sure that manufacturers comply with MDR.

Quiz 1

Decide which economic operator is responsible for the following tasks. In some cases, more options can be correct. If you are not sure about your answers, check MDR Article 10-14.

1. Giving details about themselves in the device registration electronic system
   a) Manufacturer
   b) Authorized representative
   c) Importer
   d) Distributor

2. Responsible for the design, development and and manufactoring of the device
   a) Manufacturer
   b) Authorized representative
   c) Importer
   d) Distributor

3. Providing information for competent authorities
   a) Manufacturer
   b) Authorized representative
   c) Importer
   d) Distributor

4. Ensuring that storage or transport conditions do not jeopardize general safety and performance requirements
   a) Manufacturer
   b) Authorized representative
   c) Importer
   d) Distributor

5. Legally liable for defective devices on the same basis as the manufacturer.
   a) Manufacturer
   b) Authorized representative
   c) Importer
   d) Distributor

Notified Bodies are responsible for assessing and certifying all Class IIa, IIb and III devices, as well as some specific Class I devices. They can apply to be designated from 26 November 2017. The process of designation, which might take 12 months or more, involves assessors from different national and European authorities. The database of Notified Bodies (NANDO)

can be found on the homepage of European Commission.[4] Note that the MDR brings more stringent requirements for the designation of Notified Bodies, with increased control and monitoring by the national competent authorities and the Commission. Since there are only a few notified bodies operating per member state, it is important to find a proper notified body for manufacturers on time. But when do notified bodies need to get involved and what are their responsibilities? To answer these questions, we should examine the product development steps in more detail.

2.2 Development steps

In the followings you can examine the steps of medical device development. Keep in mind, these steps and stages are not set in stone. This is meant purely as a general overview of what obstacles and opportunities that may lie ahead for medical device developers.

1. Idea and planning

In this phase manufacturers have to think about their own capacities and the work ahead, plan what participants they need to involve. They need to do a thorough market analysis to get information on whether there are equivalent devices on the market. They also have to plan their quality management systems and look for funding opportunities for their product.

2. Conceptualization and feasibility

This phase is about developing concept: manufacturers should identify the planned purpose of the device and also the planned users and their demands. Manufacturers should also analyse the regulation requirements that apply for their device and do a preliminary risk analysis. Once the manufacturer has a proof of concept and is convinced that the device has a market position and financially feasible, only then they should seek funding for prototyping and trial runs on the device.

3. Formulation

The aim of this phase is to define the specific requirements and necessary documents for the development phase. Concept is further elaborated and validated and all data and documents are prepared for the development phase.

4. Development

This phase is about the development of the product followed by the verification and validation through preclinical investigations. During this period the technical documentation of the device is prepared and a strategy for clinical investigations developed. Manufacturers also have to document their risk management practices. At the end of the development phase the prototype of the device is ready for further validation.

5. Validation

After development comes a profound validation phase of the device before its launch. It can include the validation of processes as well as clinical investigations. In this phase the final version of label and instructions for use have to be prepared and the conformity assessment application is completed.

[4] http://ec.europa.eu/growth/tools-databases/nando/

6. Product launch and post-market surveillance

After approval from a competent authority or a notified body (depending on the classification of your product), manufacturers launch the product. Note that there are strict requirements in MDR concerning post-market clinical follow up or post market performance follow-up. After the device is placed on the market, manufacturers are responsible for quality management system maintenance, maintenance of technical documentation and monitoring of changes in legislation and standards.

In the following Figure 2 you can see the basic steps of device development.

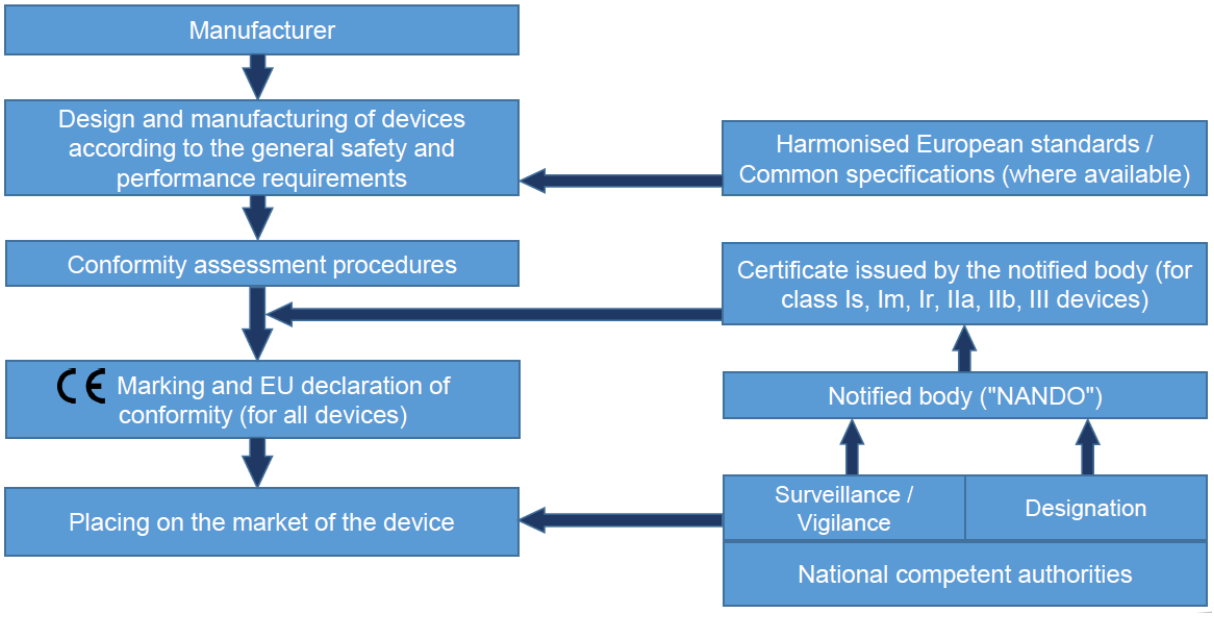

Figure 2: Basic operational scheme of the MDR[5]

The figure emphasises that manufacturers need to understand all relevant guidelines, standards etc. to design and manufacture their device and fulfil requirements of MDR. Note that Annex I (general safety and performance requirements) and Annexes II (technical documentation) and III (technical documentation on post-market surveillance) apply to all devices regardless of class. As the figure shows, after the development phase for most device classes the conformity needs to be assessed by a notified body. The role of national competent authorities is also presented in the figure: they are responsible for designation of notified bodies and also for supervision of safety issues.

As you can see from the above chapter medical device development is a long and diversified process, during which its stakeholders need to have exhaustive knowledge on the applicable regulations, standards, guidelines and also special rules related to the device in question. The latter chapters focus on some of the most important areas of medical device developments (clinical evaluation, registration requirements and vigilance), however, several other important topics (e.g. post-market duties) cannot be part of this Lesson due to the complexity of the MD development process.

[5] Source: Mario Gabrielli Cossellu: „*Impact of the new Medical Device Regulations on patients and society*" Opportunities and challenges conference 2023.02.02., Budapest, Hungary.

3 Clinical evaluation and clinical investigation

Clinical evaluation starts during the development phase and is an ongoing process throughout the life cycle of a medical device. According to MDR, clinical evaluation means "*a systematic and planned process to continuously generate, collect, analyse and assess the clinical data pertaining to a device in order to verify the safety and performance, including clinical benefits, of the device when used as intended by the manufacturer*". Therefore, clinical evaluation includes the collection of clinical data already available in the literature as well as the setting up of any necessary clinical investigations.

The manufacturer shall specify and justify the level of clinical evidence necessary to demonstrate conformity with the relevant general safety and performance requirements. The evaluation must be appropriate to the nature, classification, intended purpose and risks of the device in question, as well as to the manufacturer's claims in respect of the device. Moreover, the clinical evaluation shall be thorough and objective, and take into account both favourable and unfavourable data. In the pre-market phase, clinical evaluation identifies clinical safety and performance data that need to be generated before the device is marketed.

There are three different ways to go through the clinical evaluation process:

1. **Without clinical data**: In this case demonstration of conformity is based on the results of non-clinical testing methods alone, including performance evaluation, bench testing and preclinical evaluation. MDR Article 61 (10) states that manufacturers shall specify why they consider this method adequate for their medical device.
2. **Literature review with proof of equivalence:** When manufacturers can prove that there are enough clinical data available and can determine equivalence (see next subchapter).
3. **Literature review and clinical investigation**: When manufacturers find out that data still needs to be generated with the device under evaluation, or it is compulsory to perform clinical investigations due to the device category (see next subchapter on clinical investigations).

Beyond MDR regulation requirements, MEDDEV 2.7/1 revision 4[6] gives detailed information on clinical evaluation in practice, including guidance on how to do literature review, what to include in the clinical evaluation report, etc. However, note that MDR sometimes have stricter rules then MEDDEV guidelines, therefore, the knowledge of recent changes is crucial. The next subchapters focus on the basic requirements of MDR for the proof of equivalence and the specialities of clinical investigations.

3.1 Proof of equivalence

It is without any doubt that carrying out a clinical investigation is the most direct way to generate clinical data for the purpose of CE marking of a medical device. However, it is also the most expensive and time-consuming way, therefore, most developers try to find another path if it is

[6] https://ec.europa.eu/docsroom/documents/17522/attachments/1/translations/

not necessary to conduct clinical investigations with the device (Article 62 and Annex XV set out the new and more precise requirements for clinical investigations).

Clinical data can also be sourced from:

- clinical investigation(s) or other studies reported in scientific literature, of a device for which **equivalence to the device in question can be demonstrated**,
- reports published in peer reviewed scientific literature on other clinical experience of either the device in question or a device for which **equivalence to the device in question can be demonstrated**

As indicated, it is the **demonstration of equivalence** that allows the manufacturer to let clinical data from an equivalent device enter the clinical evaluation process of the device in question. If this path is used, equivalence to the other device shall be fully investigated, described and demonstrated in the clinical evaluation report. However, the concept of equivalence can be applied only in a limited number of situations (MDR Article 61 paragraphs 4, 5, 6).

A manufacturer of **implantable devices and class III devices** (for classification of devices see CONSCIOUS Chapter 11, Medical Devices and Advanced Therapies[7]) shall perform clinical investigations except if the device has been designed by modifications of a device already marketed by the same manufacturer and equivalence can be demonstrated according to the MDR.

For a manufacturer of implantable devices and class III devices claiming equivalence to an already marketed device not manufactured by him is also possible path if:

- the modified device has been demonstrated by the manufacturer to be equivalent to the marketed device and this demonstration has been endorsed by the notified body, and
- the clinical evaluation of the marketed device is sufficient to demonstrate conformity of the modified device, and
- the two manufacturers must have a contract in place that allows the manufacturer of the second device full access to the technical documentation on an ongoing basis.

When claiming equivalence, the MDR requires that all **technical, biological and clinical characteristics** are considered. There are a number of prerequisites that shall be fulfilled for the demonstration of equivalence. Below you can find some of the most important considerations based on the **MDCG 2020-5 guidance document:**[8]

- The overall considerations of equivalence shall conclude whether the listed technical, biological and clinical characteristics in the MDR are similar to the extent that there would be no clinically significant difference in the safety and clinical performance of the device. Note that some of the listed characteristics in the MDR shall be the same, not only similar (for more, see Quiz 2).

[7] CONSCIOUS: Chapter 11, Medical Devices and Advancesd Therapies, http://conscious.novaims.unl.pt/my/
[8] https://health.ec.europa.eu/system/files/2020-09/md_mdcg_2020_5_guidance_clinical_evaluation_equivalence_en_0.pdf

- Manufacturers may identify more than one equivalent device
  to the device under evaluation, but each device shall be equivalent to the device under evaluation in all the listed technical, biological and clinical characteristics. This means that manufacturers shall not use different parts of different devices to claim equivalence to the device under evaluation. In exceptional cases, a deviation from this principle may be considered: when device systems comprised of several more or less “stand alone” devices, where it may be justified to consider equivalence of a device in the system (for further information look at MDCG 2020-5).
- The manufacturer is expected to fully identify and disclose any differences between the two devices. The assessment of whether any differences in characteristics would result in clinically significant difference in safety and clinical performance shall also be duly substantiated and based on proper scientific justification.

Quiz 2

Take a look at Equivalence table of MDCG 2020-5. Decide whether the following technical, biological and clinical characteristics need to be the same OR just similar between Device 1 (under clinical evaluation) and Device 2 (marketed device) when an equivalence is to be proven.

1. Similar/the same design of the device.
2. Similar/the same physiochemical properties of the device.
3. Uses similar/the same materials or substances in contact with similar/the same human tissues or body fluids.
4. Similar/the same kind and duration of contact with human tissues or body fluids.
5. Similar/same kind of user.
6. Similar/the same severity and stage of similar/the same disease.

3.2 Clinical investigations

As you could see, proof of equivalence needs a thorough and systematic examination of the devices, however it is much more time- and cost-effective way than clinical investigations. In the following paragraphs we discuss what the types of clinical investigations are, and how conformity of devices can be proven through clinical investigations.

As for clinical investigations MDR differentiates between three categories:

A. **Clinical investigations conducted to demonstrate conformity of devices** (MDR Article 62(1))

   These investigations are carried out as part of the clinical evaluation for conformity assessment purposes. They are designed, authorised, conducted, recorded and reported in accordance with the provisions of Articles 62 to 80, the acts adopted pursuant to Article 81, and Annex XV.

   Where a clinical investigation is to be conducted to assess, outside the scope of its intended purpose, a device which already bears the CE marking Articles 62 to 81 also apply.

B. **Clinical investigations conducted to further assess, within the scope of its intended purpose, medical devices bearing the CE marking** (MDR Article 74(1))

These investigations, also called post-market clinical follow up, or PMCF investigations involve submitting subjects to procedures additional to those performed under the normal conditions of use of the device and those additional procedures are invasive or burdensome. For starting such investigations, the sponsor shall notify the Member States concerned at least 30 days prior to its commencement by means of the electronic system.

C. **Other clinical investigations** (MDR Article 74(1))

Those investigations that are not performed for any of the purposes listed in Article 62(1), comply with the provisions of Article 62 (2) and (3), points (b), (c), (d), (f), (h), and (l) of Article 62(4) and Article 62(6).

For these clinical investigations a national regulatory pathway can be applied for in the Member State where the clinical investigation would be conducted.

Note that it is the sponsor's responsibility to determine the correct regulatory pathway for their clinical investigations. If the sponsor is uncertain about which route to apply for a particular clinical investigation, the National Competent Authority may be consulted.

Another classification of clinical investigations with medical devices is pilot, pivotal and post-market trials. Main differences of these stages can be seen on Figure 3.

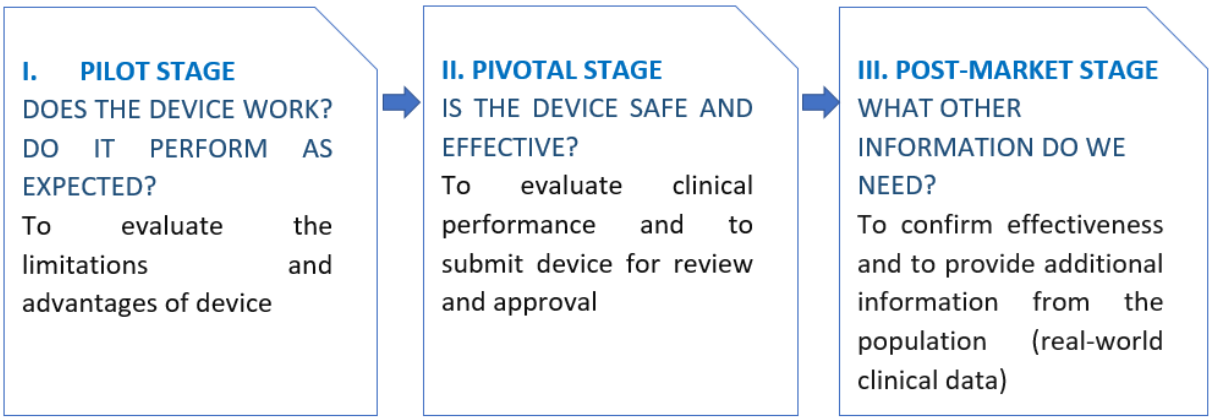

Figure 3: Stages of medical device investigations

In academia, pilot clinical investigations are also common since they are less expensive. Pilot clinical investigation is typically an early-stage clinical investigation, which includes the following types:

- First in human clinical investigation
- Early feasibility clinical investigation
- Traditional feasibility clinical investigation

These clinical investigation designs are further described in the standard ISO 14155:2020.

Practical exercise 1

In the following table you can see some differences between medical device clinical investigations and clinical trials with IMPs. Examine the differences.

	Clinical investigations on investigational **medical devices**	Clinical trials on investigational **medical products**
Clinical trial needed?	Not always required, depends on risk assessment.	Yes, required in every case.
Regulatory requirements	• Regulation (EU) 2017/745 (MDR) • ISO standard 14155:2020 • MDCG guidance documents • Declaration of Helsinki • member states requirements	• Regulation (EU) No 536/2014 • Directive 2005/28/EC on GCP • ICH guidelines • Declaration of Helsinki • member states requirements
Stages of clinical trials	Pilot stage, Pivotal stage, Post-market stage	Phase I, Phase II, Phase III, Phase IV
Healthy subject recruitment	In most cases it is not possible to apply the device into healthy subjects.	Drug trials usually start with phase I trials on a small number of healthy volunteers.
Total number of participants needed	Usually around one or two hundreds.	Usually thousands.
Use of placebo	For many devices it would be unethical or impossible.	For many drug trials the control is placebo.
Blinding	Blind investigations with devices are Pilot stage, Pivotal stage, Post-market stage are.	Double blind trials are commonly used.

Regarding medical device investigations try to answer the following questions. If you need help look at the recommended literature.

1. Which of the stages of MD clinical investigations concentrates mostly on safety and efficacy of device? (See e.g.: Figure 3)
2. In which of the stages of MD clinical investigations do healthy volunteers could take part? Name same medical devices which cannot be applied to healthy volunteers.
3. In case of medical device investigations what can be the comparator beyond placebo? (See e.g.: Clinical investigation – application form[9])
4. If blinding is difficult what other techniques can be applied to avoid bias in the clinical investigation? (See e.g.: MHRA: Clinical investigations of medical devices – statistical considerations[10])

[9] https://health.ec.europa.eu/system/files/2021-05/mdcg_2021-8_annex1_0.pdf
[10] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1097800/Statistical_considerations_clinical_investigations_-_May_2021.pdf

3.3 Specialities of pre-market clinical investigations

In the followings we concentrate on the first type (3.2. subchapter A category): **clinical investigations conducted to demonstrate conformity of devices**. CONSCIOUS Chapter 11[11] introduces some of the main requirements needed for such clinical investigations, however, we give you more detailed guidance in this lesson to help you understand the whole process of planning such an investigation.

As clinical data resulting from trials need to be robust and reliable, the MDR sets high standards for quality and safety requirements for medical device clinical investigations, similar to investigations with pharmaceutical agents. Since these requirements are similar to drug trials (those are presented in other lessons of CONSCIOUS II program), we do not want to go into detail into all steps, however, it is important to highlight some new requirements for medical device investigations.

1. The MDR has introduced the term '**sponsor**' as "any individual, company, institution *or organisation* which takes responsibility for the initiation, for the management and setting up of the financing of the clinical investigation". This is important, because under the Directives, only the manufacturer or authorized representative is identified as the responsible party for the conduct of a clinical investigation. However, according to MDR sponsor is responsible for meeting MDR clinical study-related requirements.

2. Where the sponsor of a clinical investigation is not established in the Union, that sponsor shall ensure that a natural or legal person is established in the Union as its **legal representative**. Such legal representative shall be responsible for ensuring compliance with the sponsor's obligations regarding MDR.

3. Sponsors of clinical investigations need to develop clinical investigation-related **SOPs** to ensure compliance with the MDR, guidelines and other relevant documents. The specific SOPs that a sponsor develops will depend upon the responsibilities of the sponsor in the development and management of the clinical investigation and whether any activities are outsourced. In the latter case, the sponsor should ensure that the selected vendor is sufficiently qualified to provide the needed service.

4. Commission sets up a module in the **electronic database system** (EUDAMED) for medical devices for the submission of all applications or notifications for clinical investigations. This system must be used for all applications, modifications, SAE and device deficiency reporting, and final reporting. However, not all modules of this system are working now, which means that until further notice, national authorities still accept applications, modifications, etc.

5. MDR Article 78, "**Coordinated assessment procedure for clinical investigations**", introduces a new process for submitting a clinical investigation application where the investigation is planned to be conducted in more than one Member State. The sponsor may submit a single application, transmitted by means of the EUDAMED to all Member States in which the investigation is to be conducted. The sponsor must propose that one of the Member States acts as the coordinating Member State.

[11]CONSCIOUS: Chapter 11, Medical Devices and Advancesd Therapies, http://conscious.novaims.unl.pt/my/

6. MDR states that there should be a **Union-wide unique single identification number** (the 'CIV-ID') of clinical investigations. The purpose of generating a CIV-ID is to create a European tracking number which can be used to identify a specific clinical investigation. As there is no possibility for sponsors to generate this number before EUDAMED is fully functional, sponsors can currently obtain this number from national Competent Authorities.[12]

7. In the absence of the EUDAMED, a series of **clinical investigation application/notification documents** have been created to support clinical investigation procedures with respect to MDR. These templates are available in MDCG 2021-08 document.[13] Sponsors are encouraged to use these templates. However, it is important to check with the individual Member States in which the clinical investigation is planned to be conducted as to any specific national requirements.

Review the templates of MDCG 2021-08 document. If you take a look at *"Clinical investigation – application form under Medical Device Regulation"* document you can see what information need to be included in the application form. For example, if you read 3.1 Investigational medical device chapter, it can be seen that it is the task and responsibility of the applicant to determine the purpose, the type, the classification of the investigational medical device.

8. Under MDR Article 80, there are new requirements on recording and reporting of **adverse events** that occur during clinical investigations. These requirements are detailed in next chapters of this lesson. However, it is important to note that MDR also states that the sponsor shall establish a procedure for **emergency situations** which enables the immediate identification and, where necessary, an immediate recall of the devices used in the investigation. It is expected that this procedure will be managed within the manufacturer's QMS.

9. The sponsor shall ensure adequate **monitoring** of the conduct of a clinical investigation. The extent and nature of the monitoring shall be determined by the sponsor taking into account the objective and methodology of the clinical investigation; and the degree of deviation of the intervention from normal clinical practice.

3.4 Supporting documents for application

This chapter does not focus on listing all supporting documents that are part of the application form since it is listed in CONSCIOUS Chapter 11[14] and can be found in MDR Annex XV Chapter II, however, we would like to emphasise some requirements that are new or unique for clinical investigations with medical devices.

Clinical investigation plan: The clinical investigation plan (CIP) shall set out the rationale, objectives, design methodology, monitoring, conduct, record-keeping and the method of analysis for the clinical investigation in similar depth as clinical trial protocols of drug trials. This

[12] https://health.ec.europa.eu/system/files/2021-07/mdcg_2021-20_en_0.pdf
[13] https://health.ec.europa.eu/system/files/2021-05/mdcg_2021-8_en_0.pdf
[14] CONSCIOUS: Chapter 11, Medical Devices and Advancesd Therapies, http://conscious.novaims.unl.pt/my/

document also includes statistical considerations with justification,
data management, criteria and procedures for follow-up of subjects, defined in Annex XV of MDR.

Monitoring plan: Usually, the **monitoring plan** is part of the CIP, but it is important to emphasise that according to MDR monitoring is a must, and the sponsor shall appoint a **monitor that is independent** from the investigational site.

Conformity statement: A signed statement by the natural or legal person responsible for the manufacture of the investigational device that the device in question conforms to the general safety and performance requirements apart from the aspects covered by the clinical investigation and that, with regard to those aspects, every precaution has been taken to protect the health and safety of the subject.

Technical documentation: Its parts are defined in MDR ANNEX II. Among many others, it contains design and manufacturing information including data on all design stages, manufacturing processes and their validation applied to the device; demonstration of conformity with the general safety and performance requirements set out in Annex I of MDR; detailed risk analysis/management documentation; all pre-clinical and clinical data. Technical documentation must be submitted to the competent authority upon request (similarly to the Investigators' Brochure of medicinal products).

Ethical opinion: Depending on the national law, copy of the opinion or opinions of the ethics committee or committees should be acquired prior to the application. In those member states where this is not required at the time of the submission of the application, a copy of the opinion or opinions shall be submitted as soon as available.

As it can be seen, the MDR brings more stringent requirements for clinical investigations then MDD, while the scope of the MDR has also broadened. Therefore, many guidance documents can help manufacturers and sponsors of clinical investigations,[15] as well as scientific advice services[16] are also available from authorities.

4 Registration requirements

EUDAMED is a database of medical devices available on the EU Market to improve transparency and coordination of information. The EUDAMED database is organized in modules, which can be seen in the next figure. These modules will be implemented over time and according to the implementation dates of the MDR and IVDR (Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices), as the European Commission promised.

[15] https://www.medical-device-regulation.eu/mdr-guidance-documents/
[16] https://www.ema.europa.eu/en/news/ema-pilots-scientific-advice-certain-high-risk-medical-devices

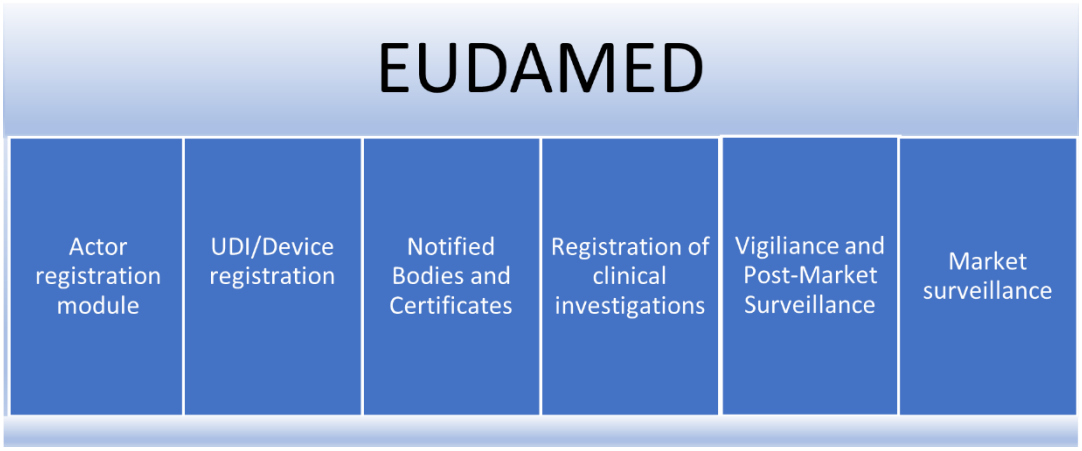

Figure 4: EUDAMED modules

The individual modules will store the data crucial to identify the product, its stakeholders, certificates granted and assigned to it as well as safety and performance data over time. Under the MDR and IVDR, the data upload to EUDAMED becomes a requirement. Some of the data need to be uploaded prior marketing of the product (data required under module 1 to 4) and others need to be curated over time (data required under modules 5 and 6).

The implementation of the EUDAMED has been delayed. The Actor registration module, the UDI/Device Registration Module and the Notified Bodies Module are currently available to the public. Since December 2020, it is possible for companies to register, the two others were released in October 2021. The three remaining modules will most likely be made available at the same time. As of January 2023, they and with that the entirety of the EUDAMED are scheduled to be operational in the second quarter of 2024.

4.1 The Actor registration

It is the first of the six EUDAMED modules and available since December 2020, the Actor Module requires all players who collaborate with it in any way to register with EUDAMED. The actors belong to two groups: Supervising Entities and Economic Operators. Traders are not required to register with EUDAMED.

Supervising Entities are: European Commission (EC), Competent Authority (CA), Designated Authority (DA), Notified Bodies (NB). Economic Operators are: Manufacturer (MF), Authorised Representative (AR), System & Procedure Pack Producer (PR), Importer (IM).

All operators get a Single Registration Number (SRN) with the registration in EUDAMED. The SRN is used to identify all Economic Operators. It consists of the Country ISO2 Code, the Actor Role Abbreviation, and a nine-digit number. For each role, a unique number is assigned. If an economic operator holds several roles, they receive a separate SRN for each. Accordingly, the operators must register separately for each role. For non-EU companies, the registration process runs through their Authorized Representative (AR).

If you are more interested in this topic, take a look at the European Commission guideline on Actor registration request process **here**.[17]

4.2 UDI/Medical Devices Registration

The UDI Module is planned to register all medical devices, because the system should allow the identification and traceability of medical devices (excluding custom-made and clinical trial devices) and IVDs. All medical devices must have a UDI-DI on the UDI carrier, on the label. However, not all information related to a device can added to a label, but EUDAMED contains all data and information about the device. The Commission designated UDI issuing to agencies, these are: GS1 AISBL, Health Industry Business Communications Council (HIBCC), International Council for Commonality in Blood Banking Automation (ICCBBA) and Informationsstelle für Arzneispezialitäten (IFA) GmbH.

If a manufacturer gets an SRN from the actor registration module, they can start to register devices in the EUDAMED, in the UDI module. The first thing to do is to assign a Basic UDI-DI to the device or devices. The Basic UDI-DI code shall follow the nomenclature of the issuing entity (code supplier). There is specific data that needs to be included in the Basic UDI-DI. This Basic UDI-DI will cover one or many UDI-DIs. This must be kept track of in the QMS as well. Only the UDI-DI part of the UDI is to form input into EUDAMED. You need to enter all the relevant device data corresponding to the specific UDI-DI you are registering in the device registration module.

The mandatory data that needs to be put into EUDAMED for each UDI-DI is:

- UDI-DI value,
- UDI-DI Issuing Entity,
- Reference, Article or Catalogue number,
- Device with Direct marking,
- Quantity of device(s),
- Type of UDI-PI,
- Labelled as single use,
- Device labelled as sterile,
- Need for sterilisation,
- Containing latex,
- Medical device nomenclature code,
- Device Status,
- Reprocessed single-use,
- Member State of the Placing on the EU Market of the Device.

The use of this module is not obligatory until the whole EUDAMED is fully functional, and not mandatory for devices in clinical investigations.

[17] https://health.ec.europa.eu/system/files/2021-07/md_actor_registration_request_process_en_0.pdf

Figure 5: UDI encoding sample for Medical Devices from GS1

Using a Unique Device Identification (UDI) system **based on international guidance** should significantly enhance the post-market safety of medical devices by better targeting of recalls, easier monitoring by competent authorities, reducing medical errors and can help by fighting against counterfeit devices. UDI system is the key for the traceability of medical devices, and the post-market safety-related activities for devices (and help to fight against falsified devices, new in Europe, but it exists in USA).

Figure 6: Sample for UDI

This bar code contains a lot of information. **Basic UDI-DI** identifies the group of product (intended purpose, risk class, essential design, manufacturing characteristics, only visible on certificates). The **UDI-DI is the device identifier**. It identifies a specific device from a manufacturer. This is the **static part** of the UDI number. The **UDI-PI is the production identifier**. It is the **dynamic part** of the UDI. It tells you about lot number, serial number, manufacturing date, expiration date, etc. An UDI is complicated, it contains a lot of data about the device, meanwhile. 25 characters is the maximum length of the UDI-DI.

If you are more interested in this topic, take a look at the following video ("The EUDAMED database and EUDAMED logins").[18]

Because this learning material concentrate on clinical investigations, we have to emphasise that UDI-DI codes are not necessary for devices used in clinical investigations. In that case, the manufacturer should generate **CIV-ID for MDR Clinical Investigations.** The purpose of

[18] https://www.youtube.com/watch?v=JY7R7ZYE7qo&t=24s

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generating a CIV-ID is to create a European tracking number which can be used to identify a specific clinical investigation. A CIV-ID facilitates communication between sponsors and competent authorities, as well as between competent authorities in different member states. For clinical investigations under MDR the competent authorities use EUDAMED to obtain a Union-wide unique single identification number (the 'CIV-ID'), upon submission of the required information to EUDAMED.

Sponsors are encouraged to obtain a CIV-ID from a competent authority before the first submission of application/notification, because Single Identification Number (SIN) cannot be generated till the EUDAMED is fully functional. Hence, the CIV-ID can be used throughout their clinical investigation documentation wherever the SIN would have been used if EUDAMED was available. However, the CIV-ID may also be generated by the competent authority upon receipt of a first submission.

4.3 Notified Bodies and Certificates Module

Certificates issued by Notified Bodies are stored in this module. That means the QMS certificates and conformity assessment certificates, too. The module is used to enable communication between the Notified Bodies, for example, if a manufacturer withdraws an application. In addition, the status of the consultation procedures for clinical evaluations is visible here. The Summaries of Safety and Clinical Performance (SSCP) and the corresponding reports of the Notified Bodies will be publicly accessible. A notified body that refuses a manufacturer a certificate must report this information to this part of EUDAMED so that other notified bodies are aware of the situation. This is also true if a manufacturer has terminated the conformity assessment for some reason.

4.4 Vigilance and PMS Module

Some reports will have to be submitted via the Vigilance Module. It is used to report the followings:

- Submission of Periodic Safety Update Report (PSUR)
- Submission of Periodic Summary Reports (PSR)
- Reporting of Serious Incidents and Field Safety Corrective Actions (FSCAs) and Field Safety Notices (FSNs).

FSCAs are automatically distributed to the appropriate authorities after they are reported in the Vigilance Module. FSNs are published. There will also be a function in the module to generate summary reports.

4.5 Registration of Clinical Investigations Module

The Clinical Investigations Module is used to manage clinical investigation and performance evaluation data. In addition, applications for clinical performance studies and trials can be submitted, as well as clinical follow-ups and post-market product changes, reports, etc.

When the module will be ready, and the mandatory use starts, the module will be the international registration site for MD clinical investigation: the sponsor will need to do the application procedure through it. If a multicentre trial is planned, the sponsor uses the module for the application, and also chooses the coordination authority for the process: similarly, as it

works now in clinical studies with IMPs which applications need to be initiated at the EMA CTIS (Clinical Trial Information System) portal.

4.6 Market Surveillance Module

This module is designed to facilitate cooperation and coordination between individual EU member states. For example, market surveillance results can be exchanged between the authorities and Notified Bodies. In addition, the reports in this module will also be made available to the public.[19]

As a part of market surveillance, the responsible authorities will regularly check the functionality and safety of medical devices that are already on the market. Document reviews, physical inspections, and laboratory tests are conducted for this purpose. Counterfeit and unsafe products are thus removed from the market to ensure the safety of their users.

Quiz 3
Answer the following questions.

1. What is the EUDAMED?
   a) European database for medicines
   b) European database for medical devices
   c) European Development Agency for Medical Devices
   d) European Development Agency for Medicines

2. Which are not the modules of EUDAMED?
   a) Actors (economic operators) registration
   b) Customer Information
   c) UDI/Devices registration
   d) Notified Bodies and Certificates
   e) Clinical Investigations and performance studies
   f) Vigilance and post-market surveillance
   g) Traders authorization
   h) Market Surveillance

3. Which is the identification code in clinical investigations?
   a) Basic UDI
   b) UDI-D
   c) UDI-PI
   d) CIV-ID

4. Does EUDAMED contain publicly available information?
   a) no, the modules are for Economic Operators only
   b) no, the modules are for Supervising Entities and Economic Operators
   c) yes, there are some publicly available information
   d) yes, every information is publicly available

[19] https://ec.europa.eu/tools/eudamed/#/screen/home

5 Safety reporting

Safety reporting for medical devices also became stricter with the MDR, and it is important to note that safety reporting categories and reporting timelines differ from traditional clinical trials with IMPs. The following chapter gives a summary on safety reporting requirements of medical device clinical investigations.

In MDR there is a clear distinction made between “Vigilance” and “Post Market Surveillance”. Vigilance is the identification, reporting and trending of **serious incidents** and **the conduct of safety related corrective actions**. The “Post Market Surveillance” (PMS) is the monitoring of information from various sources and **periodically reconfirm** that the benefits of the device continue to outweigh its risks.

For safety reporting it is recommended to keep in mind the MDCG 2020-10/1 Rev 1[20] which document was first created in 2020, but reviewed in 2022 and it clearly and thoroughly outlines the procedures for safety reporting in clinical investigations of medical devices under the EU MDR.

5.1 Method of reporting

MDR provides specific rules for pre-market clinical investigations and post-market clinical follow-up investigations as well. It does not make a difference whether the device has a CE mark. However, requirements for safety reporting will depend on whether you are using the investigated medical device within its intended purpose:

- If the investigated medical device is CE marked and will be used within its intended purpose, the provisions on vigilance laid down in Article 80(6) and Articles 87 to 90 of the MDR and the acts adopted pursuant to Article 91 of the MDR shall apply for PMCF clinical investigations.
- If the investigated medical device is not CE marked, or is CE marked but will be used outside its intended purpose, the provisions on safety reporting laid down in Article 80 of the MDR shall apply.

In the following section we concentrate on MDR requirements for the latter type of clinical investigations.

In safety reporting the **following definitions** are crucial. Some of them can be familiar from other lessons, however, it is important to see that medical devices have more categories of adverse events.

Adverse Event (AE)
Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device. (MDR Article 2(57)).

[20] https://health.ec.europa.eu/system/files/2022-11/md_mdcg_2020-10-1_guidance_safety_reporting_en.pdf

Note that this definition includes anticipated and unanticipated events as will, and also those events that are related to the comparator or the procedures involved, not just the tested medical device.

Serious Adverse Event (SAE)

Any adverse event that led to any of the following:

a) death,
b) serious deterioration in the health of the subject, that resulted in any of the following:
   i. life-threatening illness or injury,
   ii. permanent impairment of a body structure or a body function,
   iii. hospitalisation or prolongation of patient hospitalisation,
   iv. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
   v. chronic disease,
c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect

(MDR Article 2(58))

Adverse device effect (ADE)

Any adverse event related to the use of an investigational medical device or a comparator. For example, a low SpO2 level, because of an inadequate use of a ventilator needs to be reported as ADE.

Serious adverse device effect (SADE)

Any adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Anticipated serious adverse device effect (ASADE)

Any serious adverse device effect which by its nature, incidence, severity or outcome has been identified in the last risk assessment document upon serious adverse device effect occurred.

Unanticipated serious adverse device effect (USADE)

Any serious adverse device effect, the nature, severity or outcome of which is not consistent with the reference safety information.

<table>
<tr><th>Adverse events</th><th>Non-device related</th><th colspan="2">Device or Procedure related</th></tr>
<tr><td>Non-serious</td><td>Adverse event (AE)</td><td colspan="2">Adverse Device Effect (ADE)</td></tr>
<tr><td rowspan="3">Serious</td><td rowspan="3">Serious Adverse event (SAE)</td><td colspan="2">Serious Adverse Device Effect (SADE)</td></tr>
<tr><td>Anticipated</td><td>Unanticipated</td></tr>
<tr><td>Anticipated Serious Adverse Device Effect (ASADE)</td><td>Unanticipated Serious Adverse Device Effect (USADE)</td></tr>
</table>

Figure 7: Categorization of Adverse events[21]

[21] Based on European Standard ISO 14155:2020.

Incident

Any malfunction or deterioration in the characteristics or performance of **a device made available on the market**, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect. (MDR Article 2(64))

Serious incident

Any incident that directly or indirectly led, might have led or might lead to any of the following:

a) the death of a patient, user or other person,
b) the temporary or permanent serious deterioration of a patient's, user's or other person's state of health,
c) a serious public health threat.

(MDR Article 2(65))

Device deficiency

Any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

Examples of such problems are for example the followings:

- faulty brakes on a wheelchair,
- a faulty ear thermometer giving a low reading,
- a faulty batch of test strips for a blood glucose meter giving wrong readings,
- labelling or instructions on the device are not clear,
- unsafe design,
- quality issues that impact safety.

5.2 Reportable events

Based on the definitions above, the following events are considered reportable events to authorities of Member States in accordance with MDR Article 80(2):

a) any **serious adverse event** that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible;

b) any **device deficiency** that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;

c) any new findings in relation to any event referred to in points a) and b)

The period for reporting shall take account of the severity of the event. Where necessary to ensure timely reporting, the sponsor may submit an initial report that is incomplete followed up by a complete report.

Quiz 4
Decide which of the following events are AE/SAE/ADE/SADE.

1. The subject was transported to a hospital, and treated due high blood pressure value during the clinical investigation.
   a) it is an AE
   b) it is a SAE
   c) it is an ADE
   d) it is a SADE

2. The subject measured high blood pressure level at home once
   a) it is an AE
   b) it is a SAE
   c) it is an ADE
   d) it is a SADE

3. The subject has dizziness, nausea and sweating several times a day.
   a) it is an AE
   b) it is a SAE
   c) it is an ADE
   d) it is a SADE

4. The subject had to be transported to the hospital due the high blood pressure, and got hospital care for two days, because the investigated device, a new wrist band, measures low blood pressure every morning, but the subject feels nausea and headache.
   a) it is an AE
   b) it is a SAE
   c) it is an ADE
   d) it is a SADE

5. The subject does not take the pills for high blood pressure, because the investigated device, a new wrist band, measures low blood pressure every morning, but the subject feels nausea and headache.
   a) it is an AE
   b) it is a SAE
   c) it is an ADE
   d) it is a SADE

5.3 Reporting timelines

This guidance document states that for all reportable events as described above which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: Immediately, but not later than **2 calendar days** after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.

This includes events that are of significant and unexpected nature such that they become alarming as a potential public health hazard. It also includes the possibility of multiple deaths occurring at short intervals. These concerns may be identified by either the National Competent Authorities or the manufacturer.

Any other reportable events as described above or a new finding/update to it: Immediately, **but not later than 7 calendar days** following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

The sponsor shall implement and maintain a system to ensure that the reporting of the reportable events will be provided by the investigator to the sponsor immediately, but **not later than 3 calendar days** after investigation site study personnel's awareness of the event.

Did the MDR changed the rules for reporting timeframes? The 2-day reporting deadline for serious public health threats remains unchanged from the MDD, as does the 10-day deadline for reporting a death or a serious health deterioration. However, it is important to know, that a 15-day reporting deadline for reporting all other serious incidents replaces the MDD's 30-day for reporting all other reportable incidents.

Safety reports should be done on EUDAMED, but until the vigilance module of EUDAMED is available, the national vigilance reporting procedures will remain in place: most member states except these report via emails. Incident report sample form and its help text can be found at the website of European Commission:
Manufacturer incident report 2020[22]
Manufacturer incident report Helptext 2020[23]

5.4 Vigilance similarities to IMPs

According to the MDR, medicinal products and medical devices are only approved for the market if manufacturers can guarantee the safety of their products, because patient safety has to be a very important concern in the healthcare sector. If adverse events occur after the products have been placed on the market, the vigilance procedures of the competent industries must be activated.

When we talk about differences between medical devices and drugs, we have to mention that there is a difference in the nomenclature. The task of **pharmacovigilance** is to monitor the product safety in the pharma industry. In the new MDR regulation the vigilance that we knew from the pharma industry is divided into two phases: **post-market surveillance** is the continuous monitoring and evaluation of the safety and performance of approved medical devices, while **vigilance** refers to medical devices under clinical investigations.

With MDR, the aim was to establish a vigilance system that is as strict as the one for medicinal products mandatory for the pharmaceutical industry. Medical device manufacturers are now obliged to designate a responsible person for vigilance tasks; to set up a system for monitoring potential risks (including malfunctions, performance deficiencies, or adverse events), to maintain updated post-market surveillance plans. The new framework was established to improve patient safety and strengthen surveillance mechanisms.

[22] https://ec.europa.eu/docsroom/documents/41681
[23] https://ec.europa.eu/docsroom/documents/37350

6 Conclusion

In this chapter, we studied the steps of MD development process with a focus on clinical evaluation and clinical investigation for the purpose of CE marking. We also tried to demonstrate the new challenges due to registration requirements and vigilance of MDs. We concentrated mainly on the duties of manufacturers and sponsors of medical devices that could be useful for the future MD developers of the academia, as well as for industry.

It is important to emphasise that when you plan to develop a medical device, you should consult a specialist at the very beginning of the process. This can help you find the correct path: to categorise the device correctly; to keep adequate and proper documentation, to establish the necessary quality management system, etc.

We hope that this lesson gave you an idea of the long and complex processes of MD development and helps you among the rules, guidelines and several stakeholders of this area.

End of chapter quiz

1. Which is not the responsibility of a manufacturer?
   a) establishing a risk management system
   b) application for CE marking
   c) compiling technical documentation
   d) registering their importers in EUDAMED

2. During a proof of equivalence what characteristics of the devices are needed to be compared?
   a) biological
   b) technical
   c) clinical
   d) all of the above

3. What does coordinated assessment procedure refer to?
   a) cooperation between economic operators during MD development
   b) single application of the clinical investigation for more member states
   c) simultaneous evaluation of several medical devices
   d) none of the above

4. Which statement is false regarding clinical investigations of MDs?
   a) MDR details post-market clinical investigation regulations as well.
   b) Sponsor is responsible for the choice of regulatory pathway of a clinical investigation.
   c) Clinical investigations are usually necessary for Class III devices.
   d) Sponsor should be established in the EU to conduct a clinical investigation in any member state.

5. Which statement is false regarding monitoring of clinical investigations of MDs?
   a) The frequency of monitoring is defined in the monitoring plan.
   b) Monitoring is compulsory.
   c) The appointed monitor can be the employee of the trial site.
   d) Monitoring plan can be part of the protocol or a separate document.

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6. Which of these modules of the EUDAMED is not working yet?
   a) Actor Registration
   b) UDI Registration
   c) Registration of clinical studies
   d) Notified Bodies Registration

7. What is UDI-PI?
   a) device identifier
   b) production identifier
   c) expiration date identifier
   d) risk class identifier

8. Which guidance document is about safety reporting of MD investigations?
   a) MDCG 2020-10
   b) MDCG 2020-5
   c) MDCG 2021-6
   d) MDCG 2022-5

9. Which statement is false?
   a) An AE can be related or not related to the investigational device.
   b) AEs cannot be anticipated, just unanticipated.
   c) An AE can be e.g. an abnormal laboratory finding.
   d) An AE can be related to the comparator.

10. What is the term in MDR for the continuous monitoring and evaluation of the safety and performance of approved medical devices?
    a) post market surveillance
    b) post launch surveillance
    c) post market vigilance
    d) none of the above

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