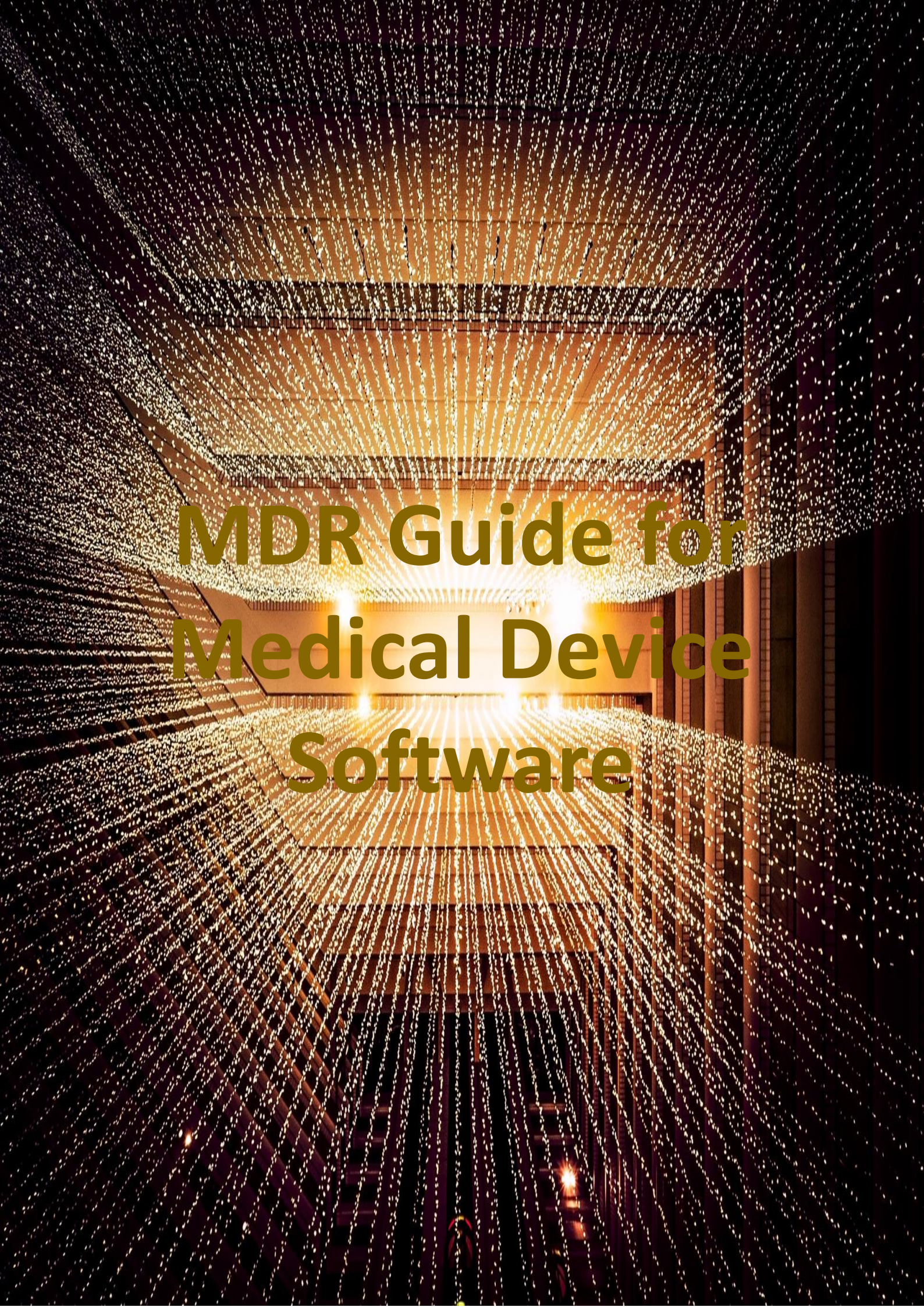

MDR Guide for
Medical Device
Software

Motivation

The Dutch authority VWS organised stakeholder meetings for the implementation of the MDR in the Netherlands. In 2018 VWS organised special stakeholder meetings for software under the MDR. The Dutch parliament raised questions since there was a concern that the MDR was a roadblock for Start-ups and manufacturers of Apps. Therefore, a VWS taskforce for Medical Device Software (MDSW) was initiated to create a "simplified" MDR Guide for Medical Device Software.

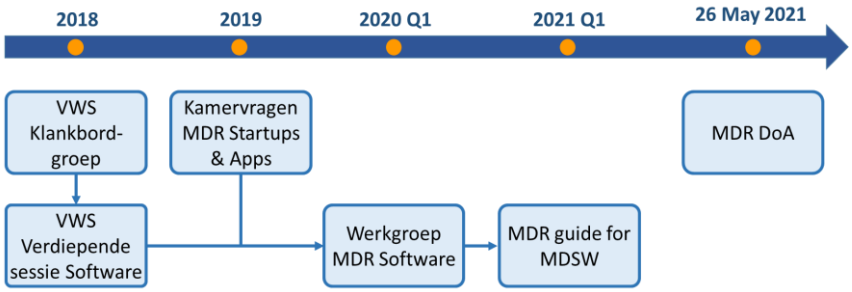


Figure 1 MDR Guide for MDSW timelines

The focus of this MDR Guide for Medical Device Software is:

- To cover MDSW, including related hardware aspects.
- To explain aspects of the MDR, which are needed to get CE certified.
- To identify additional aspects needed for MDSW, such as privacy and cybersecurity.
- To provide a workflow to implement the MDR and give insight in the implementation costs. So, a realistic project plan can be created.
- To give insight to Start-ups what expertise has to be acquired.

The purpose of this Guide is not:

- Guidance, since this would have put limits on what could have been explained.
- Translating the MDR in Dutch. The English terminology is most used, and many users only can read English.
- Covering the IVDR, Custom Made Software and In-House Developed Software.

This MDR Guide for Medical Device Software was created under considerable time pressure to be ready before the implementation of the MDR, limiting how far certain subjects could be worked out. Therefore, a maintenance update on a later date is planned for:

- 5.4 Software Development Life Cycle: Agile Development.
- 5.5 Risk Management: Software Risk Management techniques.
- Interoperability: Health Apps.
- 5.9 Clinical Evaluation: Artificial Intelligence.

Guide overview

- EU: Implementation Model for medical devices Regulation Step by Step Guide

The setup of the Guide follows a process flow. See chapters on the left side of the image. The chapters are linked to areas in the MDR, see the right side of the image. Per chapter or paragraph, the relevant MDR articles or Annexes are given. In addition, also the guidance is mentioned and other useful documentation.

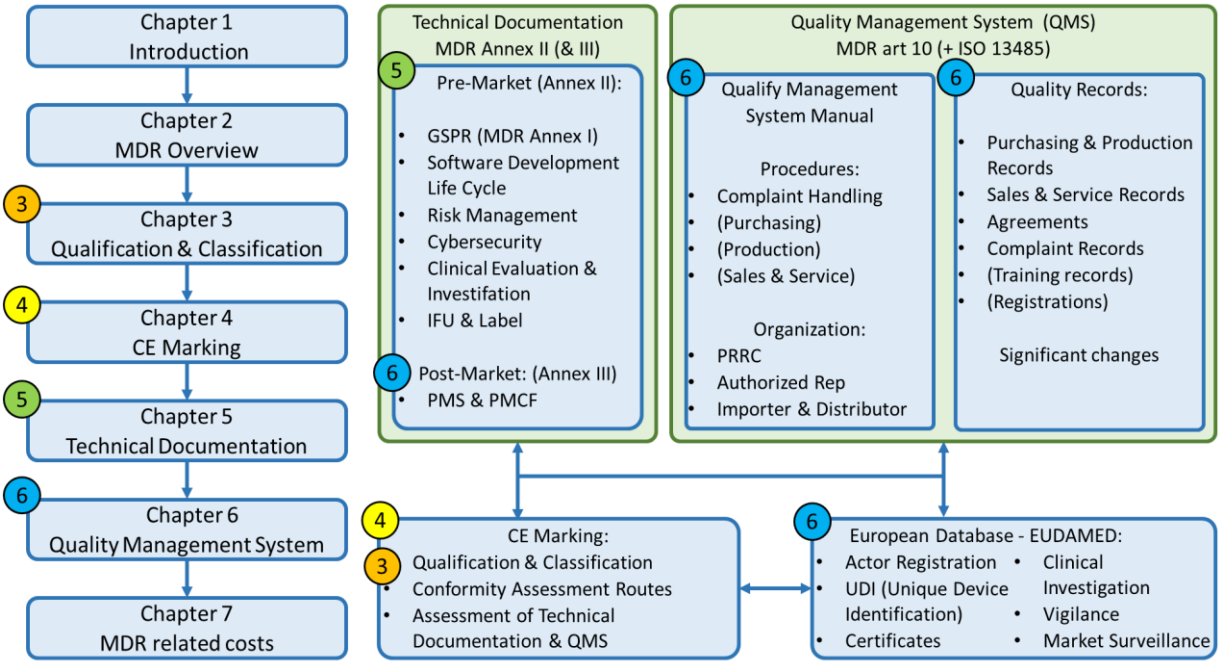


Figure 2 MDR Guide overview for MDSW

The guide has the following structure:

1. Chapter 1 Introduces the MDR guide for MDSW.
2. Chapter 2 Introduces the MDR and gives an overview of its contents.
3. Chapter 3 Explains Qualification. During qualification it is investigated if the software is within the scope of the MDR and therefore has to follow the regulations within the MDR. Qualification is a comparison of the intended use of the software and the definition of the Medical Device. If it matches, then the software is called MDSW. Chapter 3 Explains Classification. Classification determines the risk class of the Medical Device. The higher the risk class the stricter the MDR requirements are. Classification is comparing the intended use of the Medical Device with the classification rules.
4. Chapter 4 Explains the CE marking. The CE mark is a symbol on MDSW that shows that the product is allowed according the MDR on be sold on the market. In most cases for MDSW a Notified Body reviews the technical documentation and audits the quality management system (QMS) before the CE can be applied. A Notified Body is a technical competent organisation appointed by the Competent Authority (the national government) and the European Commission. When the Notified Body review and audit are successful, then the MDSW is CE certified and is the Manufacturer allowed to sell the product. The risk class determines the detailed certification steps, which is called a conformity assessment route.
5. Chapter 5 Describes the contents of the Technical Documentation. The Technical Documentation contains the evidence that is created during the development process, so that the Notified Body can review the quality of the MDSW and if all related MDR requirements are fulfilled. The Manufacturer uses a GSPR checklist, to show where the evidence for the Software Development (Life Cycle), Risk Management, Clinical Evaluation and other processes can be found in the Technical Documentation.
6. Chapter 6 Describes the QMS. ISO 13485 contains the requirements for a QMS of Medical Devices. The QMS contains the procedures which describe the activities needed to develop, purchase, produce, sell and service a MDSW. The QMS also describes the organisation of the Manufacturer and its external relations with amongst other suppliers, importers, and distributor. Evidence for the execution of the QMS activities have to be documented in so called Quality Records. In most cases the Notified Body audits the QMS to review if the related MDR requirements are fulfilled.
7. Chapter 7 Describes the MDR related costs. This chapter describes the resources needed to implement the MDR. Without management support, a decent project plan, dedicated project manager and allocation of

resources, most MDR project will be a struggle. The chapter also gives a Start-up insight in what resources and activities need to be financed.

Document references

- MDR Guide for Medical Device Software, version 0.6 – 26 April 2021
  https://fme.nl/mdr-guide-medical-device-software

Disclaimer: Information and interpretation presented within this guide is based on the current understanding of the Medical Device Regulation and is intended for information purposes only and not intended to give advice. Please check the information before use, with the official publications. Please check the interpretations before use, with the responsible authorities. The author shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of this guide. The author shares his personal view and experience and the information provided in this guide was created independently. This guide was peer reviewed, however this guide should not be used to base conclusions on.

MDR Guide for Medical Device Software team:

- Claire de Monte (VWS)
- Laurine Keulemans (VWS)
- Jan-Jaap Baalbergen (NFU)
- Robert van Wijk (OIZorg / FarMedvisie)
- Luc Knaven (FHI)
- René Drost (NAMCO)
- Roel Barelds (Tenzinger)
- Corine Böhmers (Health Innovation Park)
- Leo Hovestadt (FME / Elekta)

And of course, thanks to all the reviewers.

Contact: Inaccuracies and suggestions for improvement of this document can be send to Leo Hovestadt via the contact form where this guide is published.

Table of Contents

1. Introduction

The Medical Device Regulations (MDR) is applicable from 26 May 2021 for all Medical Devices in Europe. The MDR has a huge impact on App developers and MDSW manufacturers. The MDR brings many new requirements and often also more stricter requirements because of up-classifications. The MDR introduces an extension of the definition of software as a medical device. Software devices that fall under the scope of this definition is MDSW as a module of a software solution or as an accessory to a Medical Device.

The translation of the MDR requirements into practical actions is complex and resource heavy. Therefore a work group of experts with affiliations within the national Branch Organisations Nederlandse Federatie van Universitair Medische Centra (NFU), Federatie van Technologiebranches (FHI), Ondernemersorganisatie voor de Technologische Industrie (FME) and Organisatie ICT-Leveranciers in de Zorg (OIZorg) in coordination with the Dutch Ministry of Health (VWS) developed a Guide in response to the many questions coming from Software manufacturers including start-ups.

The Guide intends to:

1. Provide an explanation of the steps and challenges for a (start-up) software manufacturer to successfully place MDSW on the market under the MDR. A companion document for in house-made software is made separately by the NFU but is not publicly available.

2. Explain the key concepts of the MDR.

3. Provide an overview of the qualification and classification steps of the MDR. Qualification is the process of determining if software is a medical device according to the MDR and should therefore follow the requirements of the MDR. This software is then called MDSW.

Note: MDSW can also be delivered in combination with hardware, therefore also hardware aspects are discussed in this guide.

Note: Out of scope of this Guide is In Vitro Diagnostic Software, ”Custom Made Software” and ”In-House Developed Software” such as In-House-Developed Radio Therapy Software.

Note: It is expected from the reader to have at least some understanding of the r consequences of the Medical Device Regulation. This Guide will offer an overview of the MDR. For the translation of the MDR to your business and product development process you might still need an expert or consultant, with in depth knowledge of the MDR and an understanding of your business and your software products. The content of this Guide is strictly informative and has no legal status.

2. MDR Overview

2.1. MDR background

The MDR is applicable for placing a medical device on the market in the EU. After many years of discussion, the European Parliament and Council adopted the Medical Device Regulation (MDR) in May 2017. The MDR regulates the required steps until a medical device for human use can be placed on the European market as well as the resulting post-market actions. It will be applicable from 26 May 2021 onwards and will replace the current Medical Device Directive (MDD – 93/42/EEC) and Active Implantable Medical Device Directive (AIMDD – 90/385/EEC). The MDR is applicable for the EEA (EU and Iceland, Liechtenstein and Norway) and other countries that have an agreement with the EU to follow the MDR (think of Switzerland, Australia, etc.).

2.2. MDR key concepts

- EU: Medical Device Regulation (MDR) 2017/745
- EU: Factsheet for Manufacturers of medical devices
- Medtech Europe: Medical Devices Regulation – Flowchart

To place a Medical Device in the EU, the device and the Organisation selling the Medical Device need to conform to the applicable legislation. This legislation is called the Medical Device Regulation. For higher risk class Medical Devices both the Product and the Organisation need to be certified. Certification is checking that the requirements specified in the MDR are fulfilled and this is then followed by certification (officially approval). When the Organisation is certified, this is called a Quality Management System (QMS) Certification.

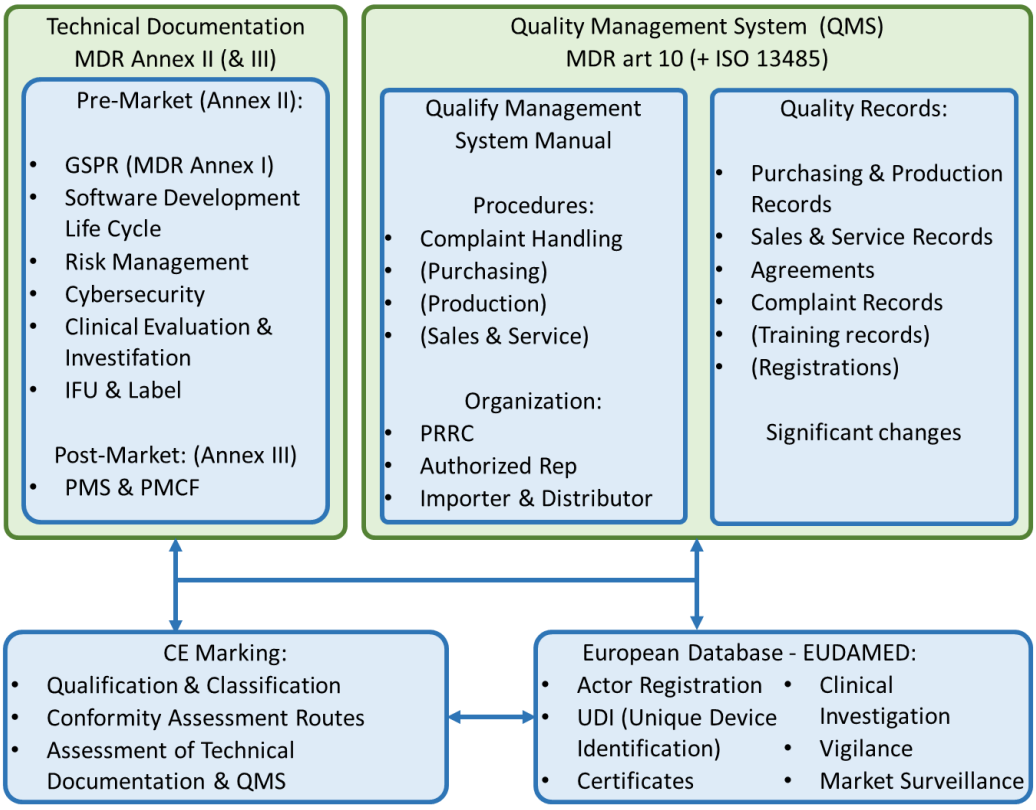


Figure 3 Overview of MDR key concepts

The product certification is done by a Notified Body. A Notified Body is an organisation which can certify and is notified (appointed) by the European Commission. The product certification is done based on the documents in the Technical documentation. For risk class I products (excluding products with a measurement function, Im, sterile products, Is, and re-usable surgical instruments, Ir) the Manufacturer can self-certify its products. The Technical documentation can be requested by the Competent Authority who might check its contents.

The QMS certification is normally certified by the Notified Body. The QMS certification is done based on the procedures in the QMS manual and on the Quality Records which contain evidence that the procedures of the QMS Manual are followed. For risk class I products, a certification by a Notified Body is not necessary, however it is possible that the Competent Authority will perform an inspection.

In the European database the Manufacturer, the Notified Body and the Competent Authority have to upload data related to the Certification process of the Manufacturers Organisation and Products. EUDAMED is not yet ready, so now there are transition provisions in place.

2.3. MDR structure

The MDR has the following sections:

- Preamble. The pre-amble is used as background information and consideration for the development of the MDR. In general, this section is not used by manufacturers, but can help in the interpretation.
- Chapters with Articles. The chapters are used to divide the MDR in logical sections Every chapter has several articles with requirements.
- Annexes. The Articles sometimes refer to Annexes where further detail about an article is given.

The following table shows the major sections of the MDR:

Table 1 MDR Preamble, Chapters and Annexes

Preamble			
Chapters			
I	Scope & definitions	VI	Clinical evaluation and clinical investigations
II	Making available of devices, obligations of economic operators, reprocessing, CE marking, free movement	VII	Vigilance and market surveillance
III	Identification and registration of devices and economic operators, summary of safety and clinical performance, EU medical device databank	VIII	Cooperation between Member States, Medical Device Coordination Group, EU reference laboratories, device registries
IV	Notified bodies	IX	Confidentiality, funding, penalties
V	Classification and conformity assessment	X	Final provisions
Annexes			
I	General Safety & Performance Requirements	IX	Full QA Plus technical documentation Examination
II	Technical Documentation	X	Type Examination
III	Technical Documentation on Post Market Surveillance	XI	Product Conformity Verification
IV	EC Declaration of Conformity	XII	Conformity Assessment for Custom-Made Devices
V	CE Marking of Conformity	XIII	Content of Certificates Issued by a Notified Body
VI	Information for Registration of Devices & Economic Operators & Data Elements UDI	XIV	Clinical Evaluation and Post Market Clinical Follow-up
VII	Notified Body Requirements	XV	Clinical Investigations
VIII	Classification Criteria Conformity Assessment Annexes	XVI	List of Non-Medical Products Included in the MDR

When the MDR was created, several parts could be more detailed by additional legislation. Therefore, it was possible to create extensions for the European Commission, called Implementing Acts and for the Competent Authorities called Delegated Acts. These acts also required as the MDR itself. To correct small mistakes in the MDR corrigenda are published.

To help with the interpretation of the MDR there are guidance documents provided by the MDCG, called MDCG guidances. The old Meddev guidance is still used often, however the Meddev guidance is officially no longer applicable after 26 May 2021. In addition to the MDR guidance documents, the following documents from the European Commission or Competent Authorities are available:

- “Blue guide” on the implementation of EU product legislation.
- Exhaustive list of requirements for manufacturers of medical devices.
- Implementation Model for Medical Devices Regulation - Step by Step Guide.
- CAMD - FAQ – MDR Transitional provisions. Note this guidance should have been updated for the new transition dates.

For specific products or activities there are Common Specifications or Harmonised Standards. A Common Specification has to be fulfilled and a Harmonised Standard contains guidance for which alternatives may be used.

EC countries have legislations and regulations supporting the implementation of the MDR. These typically contain regulations for what needs to be locally arranged. Think of translation requirements or which department performs which task for the MDR within the national government.

2.4. MDR and other regulations

The MDR also is s implementations in local legislation which have impact. The major elements in the Netherlands are:

- Medical Devices Law (Wet Medische Hulpmiddelen), specifying requirements for:
  - Code of Conduct (Gedragsregels).
  - Fees and Fines (Vergoedingen en boetes).
  - Competencies Dutch Authority (Bevoegdheden NL overheid).
  - Clinical Investigations (Klinisch Onderzoek).
- Medical Devices Decree (Besluit medische hulpmiddelen), specifying requirements for:
  - Implant card and National Register of Implants (Landelijke Implantaten Register (LIR)).
  - Reprocessing of single use products.
- Medical Devices Rule (Regeling Medische Hulpmiddelen), specifying requirements for:
  - Language requirements.
  - Certificate of Free Sales.
  - Custom-Made Devices.

2.5. In-house developed software

- MDR art 5(5) Definition (1) Medical Device
- IEC 62304 MDSW development process

A companion document for in house-made software to the MDR guide is made separately by the NFU but is not publicly available. MDR art 5(5) makes it possible for health institutions to develop, manufacture and use medical devices in their own house, provided that the following conditions are met:

- The devices fulfil the General Safety and Performance Requirements (GSPR) as described in MDR Annex I.
- The devices are not transferred to another legal entity.
- The devices are manufactured and used under an appropriate quality management system.
- An equivalent device is not available on the market.
- The health institution provides information upon request on the use of such devices to its competent authority.
- The health institution draws up a public declaration on the use and justification of the devices.
- The health institution draws up documentation describing the design, manufacturing facility and process and the performance of the device, showing the device to follow the relevant GSPR.
- The health institution reviews experience gained from clinical use of the devices and takes all necessary corrective actions.

MDR art 5(5) makes clear that the performance and safety requirements for in-house developed medical devices are the same compared to a MDR CE marked medical devices. Under MDR art 5(5) there is no obligation for health institutions for CE marking In-house developed software and certify the quality management system, unless these devices are transferred to another entity. In that case the health institution becomes a manufacturer and has to act like a manufacturer. To comply to the state-of-the-art software development, the IEC 62304 MDSW development process is recommended.

3. Qualification and Classification

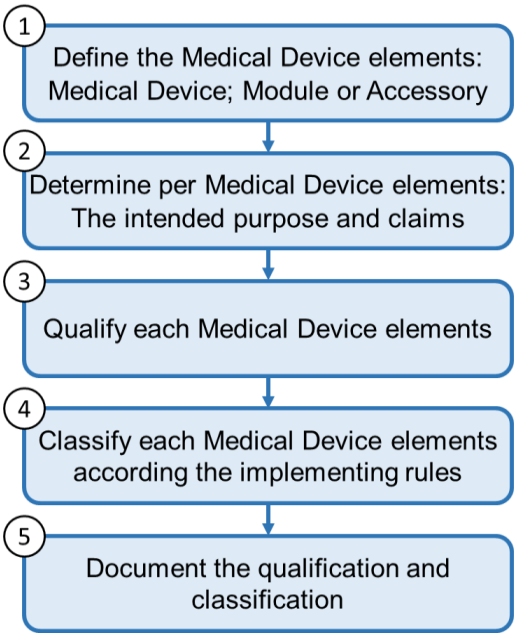
3.1. Introduction

- This chapter explains Qualification. During qualification it is investigated if the software is within the scope of the MDR and therefore has to follow the regulations within the MDR. Qualification is a comparison of the intended use of the software and the definition of the Medical Device. If it matches, then the software is called MDSW.

  Outside the EU MDSW is often called Software as a Medical Device (SaMD). That definition should not be used since it can lead to incorrect qualification and classification of the MDSW. Software "Qualifies" according to the MDR if it meets the definition for "Medical Device" MDR art 2(1). Note that software that is qualified according to the IVD, IVD MDSW has to follow the requirements of the IVDR. These requirements are closely related to the MDR requirements, however there are quite a few differences. The IVDR requirements are not described in this guide.

- This chapter also explains Classification. Classification determines the risk class of the Medical Device. The higher the risk class the stricter the MDR requirements are. Classification is comparing the intended use of the Medical Device with the classification rules. The classification rules are mentioned in the MDR Annex VIII.

- To help with the Qualification & Classification there is guidance MDCG 2019-11 Qualification and Classification of software. Classification is considered to be very complex, and it is very normal to use external expertise for correct Qualification and Classification purposes. It is considered good practice to document the argumentation for both the Qualification and Classification. The qualification and classification steps are:

Step	Remarks
 *Figure 4 Qualification and classification steps*	1. Elements (Device, Module or Accessory) with a CE mark need to be qualified separately (in its own right). Elements without a CE mark do not need to be qualified. Further explanation about modules can be found in MDCG 2019-11 chapter 7 Modules. 2. For each element the intended purpose needs to be determined. Claims about safety, performance, risks and benefits also need to be considered. 3. The qualification is performed and based on the definitions of a Medical device and MDSW and the intended purpose and claims. The result is the qualification as a Medical Device or MDSW, or not. 4. The classification is performed based upon the intended purpose and claims according to the classification rules and implementing rules (how to perform the classification). The result is a risk class of the device. 5. Documenting the rationale for the qualification and classification is important, as it is the basis for the certification process to be followed.

3.2. Intended purpose and claims

- MDR art 2 Definition (1) Medical Device
- MDR art 2 Definition (12) Intended Purpose
- MDR art 7 Claims
- IMDRF SaMD WG/N12 "Software as a Medical Device": Possible Framework for Risk Categorization and Corresponding Considerations

The intended purpose and the claims about safety, performance, risks and benefits determine the qualification and classification of the medical device. In general, it is best to describe them in a technical way. For example, the device performs a specific therapy, instead of the device cures the patient from a specific disease. The technical claims are easier to prove, and curing patients, often requires clinical evidence from a clinical investigation. When creating an intended purpose, it is advised to use the language of MDR art 2 (1) of the definition of a Medical Device, to avoid qualification problems. Moreover, it is advised to use the language of IMDRF SaMD WG/N12 chapter 5 to avoid classification problems, since the MDCG 2019-11 guidance is based on this section.

For devices with general indications for use that do not specify a disease, condition, or population (or an anatomical site from which a disease state or population may be inferred), the indications for use and intended purpose are the same. Such indications for use are referred to as “tool type” indications for use. Examples of devices with “tool type” indications for use include devices such as scalpels, which are often indicated for cutting tissue, or imaging devices, which are often indicated for taking images of the body.

Claims on safety, performance, risks and benefits need evidence see MDR art 7. It is advised to make a claim matrix, containing the claim, where it is made and where the evidence is. The Claim Matrix can be placed in the Clinical Evaluation Report. A claim matrix could look like this:

Table 2 Claim matrix

Claim	Where made	Evidence
• Treatment plan calculated in 2 minutes	• Brochure • Document identification number and revision	• Validation report with analysis of treatment plan calculated within 2 minutes. • Document identification number and revision
• Device uses state of the art algorithms	• Website • Document identification number and revision	• See Clinical evaluation report evidence for this claim (which contains analysed scientifically published articles)

3.3. Qualification

- MDCG 2019-11 Guidance on Qualification and Classification of Software
- MDCG 2021-xx Borderline and Classification manual (to be published)
- Infographic Is your software a Medical Device?

Qualification is an important step and should always be done before classification. The guidance MDCG 2019-11 Qualification and classification of software contains a decision tree to be followed (see figure below), to determine if your software is MDSW.

Medical Devices include devices with the specific medical purpose of prediction and prognosis of a disease. The MDR introduces an extension of the definition of software as a medical device. Software devices that might fall under the scope of this definition is MDSW as a module of a software solution or as an accessory to a Medical Device.

Table 3 MDCG 2019-11 Figure 1: Qualification Steps

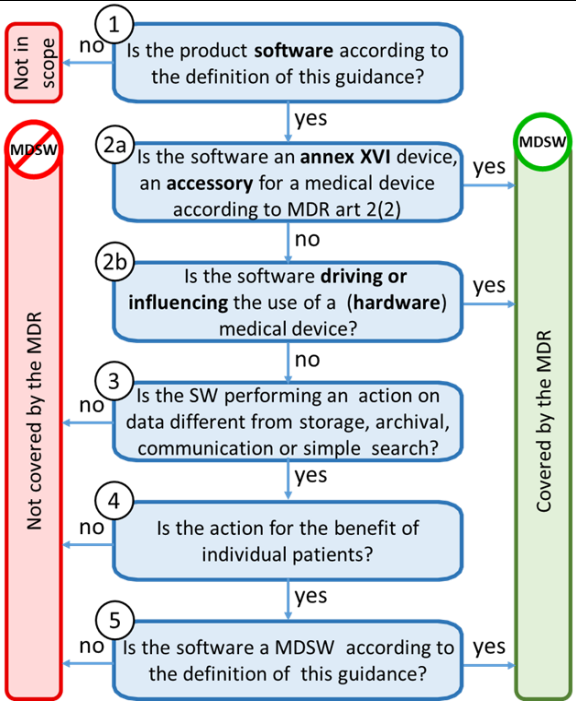


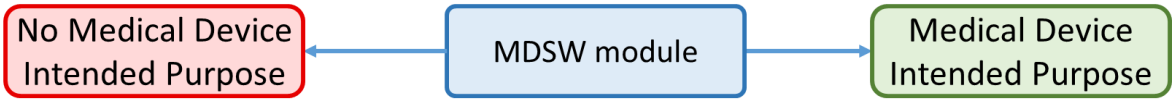
Figure 5 MDCG 2019-11 Qualification Steps

1. Look if the Software matches the Software definition: A set of instructions that processes input data and creates output data.
2. a) Look if the Software matches the Accessory definition (MDR art 2(2)): *An article which, whilst not being itself a medical device, is intended by its manufacturer to be used together with one or several particular medical device(s) to specifically enable the medical device(s) to be used in accordance with its/their intended purpose(s) or to specifically and directly assist the medical functionality of the medical device(s) in terms of its/their intended purpose(s).* The part or the accessory can be individually CE marked.
   b) Look if the Software is driving or influencing hardware. If the software is part of hardware, then classification rule 11 does not apply as it then falls within the same risk class as the device (MDR Annex VIII implementing rule 3.2).
3. Look if the Software matches 3.
4. Look if the Software matches 4:
   *) Software for population and epidemiological studies is not in scope.
   *) Software for educational purposes is not in scope, provided it is not directed at individual patients, i.e. doesn't use patient input data to provide patient specific decision support.
5. Look if the Software matches the MDSW definition. Software that is intended to be used, alone or in combination, for a purpose as specified in the definition of a "medical device" in the Medical Devices Regulation.

   In other words: does the software create information for a medical purpose?
   *) regardless of its location: e.g. operating in the cloud, on a computer, on a mobile phone, or as an additional functionality on a hardware medical device.
   *) regardless of whether the software, in addition, also drives or influences the use of a (hardware) device.

Examples for the Qualification can be found in MDCG 2019-11 and the Borderline and Classification manual.

The following figure shows Software Modules which have or have not a Medical Device intended purpose:



• Patient information transfer or storage	Electronic Patient Record System	• Image viewer with diagnostic functionality • Medication module
• Patient identification • Patient scheduling	Hospital Information System	• Indicating high blood pressure
• Showing and saving pictures	Picture Archive Communication System	• Compare pictures to identify disease progression
• Measuring skin tone to prevent sunburn	Health app	• Measuring skin tone to prevent cancer

Figure 6 Examples of software modules with intended purpose

3.4. Classification

- MDR art 2 Definition (4) Active Device
- MDR art 51 Classification of devices
- MDR Annex VIII Classification rules
- MDCG 2019-11 Guidance on Qualification and Classification of Software
- MDCG 2021-xx Borderline and Classification manual (to be published)

3.4.1. Implementing rules

The implementing rules have a huge impact on how a Medical Device needs to be divided in Modules with or without a Medical Device intended purpose, how to define accessories and if the CE marking need to take place on the Medical Device level or on the Module and Accessory level.

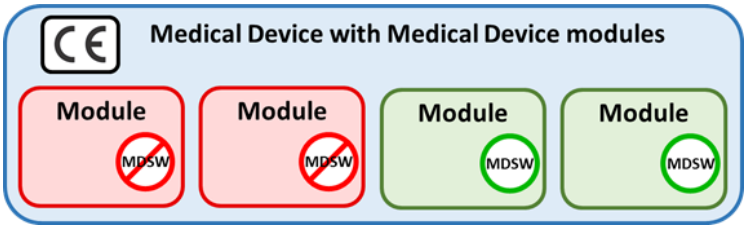
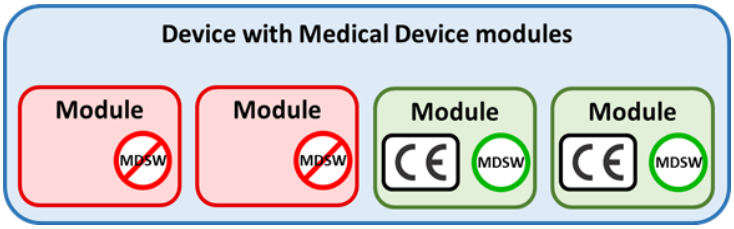
Table 4 Implementing rules

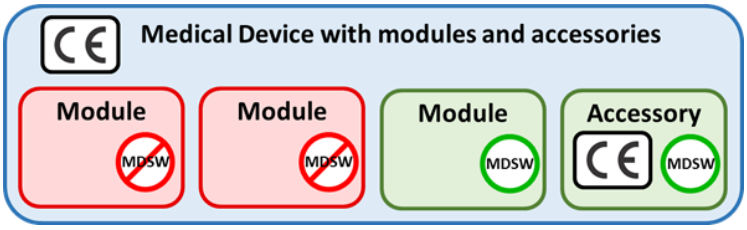
Implementing rule	Remarks
3.1. Application of the **classification rules** shall be governed by the **intended purpose** of the devices.	The intended purpose of the Medical Device, Module or Accessory determines the classification. It deserves recommendation to do the classification both on Medical Device and on Module / Accessory level, since rule 11 can cause up classification of the hardware, when the MDSW is classified in its own right.
3.2a. If the device in question is intended to be used in combination with another device, the classification rules shall apply separately to each of the devices.	This rule also applies to a Medical Device, which is classified on a Module level.
3.2b. Accessories for a medical device and for a product listed in Annex XVI shall be classified in their own right separately from the device with which they are used.	Consider the consequences of implementing rule 3.1
3.3a. Software, which drives a device or influences the	Consider the consequences of implementing rule 3.1

Implementing rule	Remarks
use of a device, shall fall within the same class as the device.	
3.4. If the device is not intended to be used solely or principally in a specific part of the body, it shall be considered and classified on the basis of the most critical specified use.	If there are several classifications possible, the highest classification applies.
3.5. If several rules, or if, within the same rule, several sub-rules, apply to the same device based on the device's intended purpose, the strictest rule and sub-rule resulting in the higher classification shall apply.	If there are several classifications possible, the highest classification applies.
3.7. A device is considered to allow direct diagnosis when it provides the diagnosis of the disease or condition in question by itself or when it provides decisive information for the diagnosis.	The MDCG guidance gives the following example: Active devices, such as electronic thermometers and stethoscopes, which include MDSW intended for direct diagnosis may be classified as class IIa per Rule 10, third indent since body temperature and heart rate are considered decisive information for diagnosis (implementing rule 3.7), where the nature of the variations of these parameters would not result in immediate danger to the patient.

Applying implementing rules 3.1, 3.2 and 3.3 allow three main variations, how MDSW can be part of a Medical Device. Further explanation about modules can be found in MDCG 2019-11 chapter 7 Modules. The variations and their consequences can be seen in the following table:

Table 5 CE marking of MDSW with modules

Variation	Consequences
	CE marked Medical Device • Must meet MDR requirements. • Must be qualified and classified. Medical Device Modules: • Are driving or influencing the Medical Device.
	CE marked Medical Device modules • Must be within the intended purpose. • Must meet MDR requirements. • Must be qualified and classified. Non-CE-marked modules: • Must be outside intended use. • Must be safe and performing when used in combination with CE marked modules.

Variation	Consequences
	CE marked Medical Device • Must meet MDR requirements. • Must be qualified and classified. Medical Device Accessory: • Is intended to be used together with one or more Medical Device(s). • Must meet MDR requirements. • Must be qualified and classified in its own right.

3.4.2. Classification rules

The classification rules determine the risk class of a Medical Device or Accessory. Classification has to be done very accurately, since an incorrect classification has huge consequences. Too low, might lead to huge fines and force products to be removed from the market. Too high might lead to additional work, the need for additional clinical investigations and therefor higher costs.

Classification is based on the intended purpose and the claims of the Medical Device, Module or Accessory. The intended purpose is compared with the classification rule text. It is best practice, to do this with all the rules, since there are some hidden surprises. For example: Rule 8: All implantable devices and long-term surgically invasive devices are classified as class IIb unless they are active implantable devices or their accessories, in which cases they are classified as class III. An accessory of an implantable device can also be MDSW, which is not implanted. By means of rule 8, it can become class III, needing a clinical investigation. So, the intended purpose should be carefully described, if this could be the case.

MDD or AIMDD compliant Medical Devices can be placed on the market as long as they have a valid CE certificate (MDR art 120 (3) even if they are up classified under the MDR, however the QMS need to conform to MDR art 10 after 26 May 2021. In addition, no significant changes can be made to the Medical Device after 26 May 2021, as this would then require CE-marking under the MDR.

It deserves recommendation to do the classification both on Medical Device and on Module / Accessory level, since rule 11 can cause up-classification of the hardware, when the MDSW is classified in its own right.

Table 6 Classification rules

Rule	**Remarks**
Rule 1 – 4 Non-invasive devices	These rules are in general for non-invasive hardware devices. These rules have to be considered if the MDSW is part of the hardware, driving or influencing the hardware or an accessory to the hardware.
Rule 5-8: Invasive devices	These rules are in general for invasive hardware devices. These rules have to be considered if the MDSW is part of the hardware, driving or influencing the hardware or an accessory to the hardware.
Rule 9-13: Active (including software)	These rules are for software and hardware devices. Software is defined as an active device.
• Rule 10: Diagnosis or monitoring	This rule is about diagnosis or monitoring. These two terms should not be confused. In most cases the physician is doing the diagnosis, and the software only provides the information, which is monitoring.
• Rule 11: Software	See paragraph 3.4.3 for an extensive explanation.
Rule 14-22 Special rules	These rules describe specific situations, for which additional classification rules are made. These rules are in general not applicable for MDSW. These rules

Rule	Remarks
	have to be considered if the MDSW is part of the hardware, driving or influencing the hardware or an accessory to the hardware.

3.4.3. Classification rule 11

MDR annex VIII, rule 11 will often lead to the highest classification for MDSW. Not applying the MDCG 2019-11 guidance, however, comes at a high price, as shown in Table 1. The text of rule 11 is repeated in this table. For example, according to rule 11, all MDSW treating or diagnosing cancer (which is critical) is class III. However, under the MDD, in general, this is class IIb or lower, and sometimes even class I.

To obtain a correct classification, the guidance document MDCG 2019-11 and MDR annex VIII implementation rule 3.3 should be used. The MDCG 2019-11 guidance is based on the IMDRF/SaMD WG/N125 guidance, which is the source for the table. The IMDRF guidance recognizes that most software has an indirect influence on treatment or diagnosis and that therefore, the classification should be lower. So, software that drives clinical management (middle column in the table) or software that informs clinical management (right column), should have a lower risk class. An example coming from the IMDRF guidance is radiation therapy treatment planning. This software is driving clinical management of radiation treatment delivery for cancer, which is critical. Applying MDCG 2019-11 puts this software in the middle column in the top row, and thus the classification is class IIb. It should be noted that IMDRF/SaMD WG/N12 contains a mistake, which is explained in the note from MDCG 2019-11 Annex III. The N12 document mistakes are in 7.3 Criteria for Category II for i and iii, 7.4 Category III for i and ii examples.

The software in the left column is often part of treating and diagnosing hardware. Here, implementing rule 3.3a is important, which says software driving a medical device or influencing the use of a medical device, should fall within the same class as the medical device, avoiding the problem of rule 11 for hardware containing software.

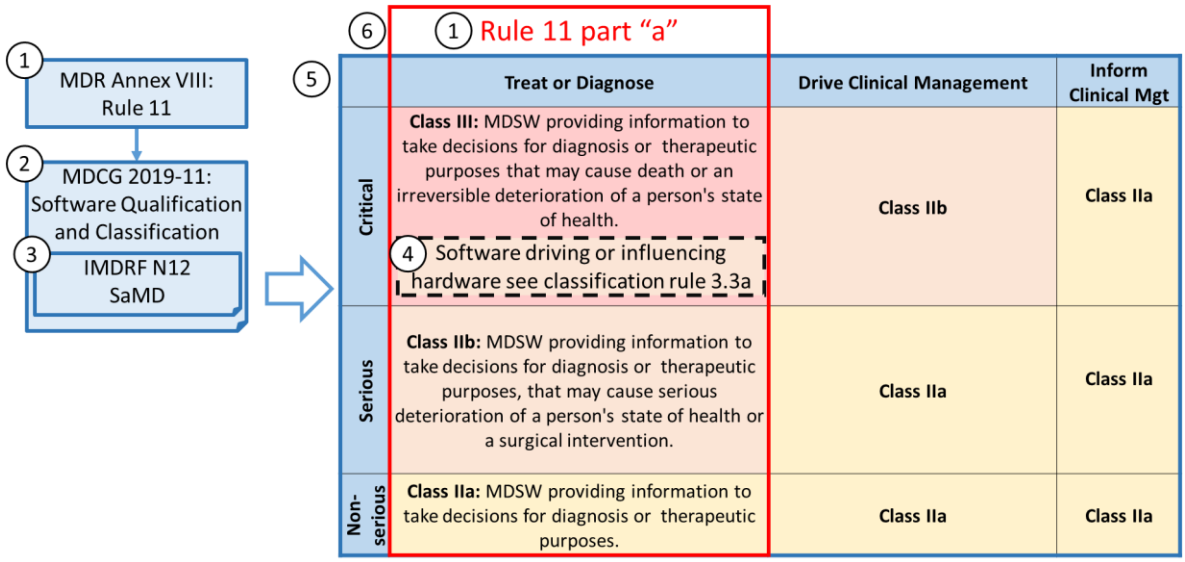


Figure 7 Classification rule 11

3.5. Requirements related to risk class

The risk class of a device has consequences for the obligations of a Manufacturer. The major consequences are shown in the table below:

Table 7 Requirements related to risk class

Major obligations	**Class I**	**Class Is, Im, Ir**	**Class IIa**	**Class IIb**	**Class III & Implantables**
Quality Management System:	Art. 10		Art. 10 & ISO 13485		
• Assessment of the QMS by the Notified Body	-	Annex IX: section 1	Annex IX: section 2, 3		
Technical Documentation:	Annex II, III				
• General Safety and Performance Requirements checklist	Annex I				
• Risk Management	Annex I part section 3				
• Clinical Evaluation Plan / Report	Annex XIV part A				
• PMCF Plan	Annex XIV part B				
• Clinical Development Plan	Annex XIV part A section 1				
• Clinical Investigation (file)	(The need for a clinical investigation is determined in the clinical evaluation)				Annex XV
• Summary of Safety and Clinical Performance	-				Art 32
• PMS Plan	Art. 84				
• PMS Report	Art. 84		-		
• Periodic Safety Update Report	-		Art. 86		
• Assessment of Technical Documentation by the Notified Body	-	Annex IX: section 4, only for Sterile, Measurement or Reusable part	Annex IX: section 4		
Specific additional procedures	-				Annex IX: section 5
Declaration of Conformity	Annex IV				
CE marking of Medical Device	Annex V				

Note 1: the requirements for the conformity assessments routes for product conformity verification and type examination are not shown, because of their limited practical use.

4. CE Marking

4.1. Introduction

This chapter explains the CE marking. The CE mark is a symbol on MDSW that shows that the product is allowed according the MDR on be sold on the market. In most cases for MDSW a Notified Body reviews the technical documentation and audits the QMS before the CE can be applied. A Notified Body is a technical competent organisation appointed by the Competent Authority (the national government) and the European Commission. When the Notified Body review and audit are successful, then the MDSW is CE certified and is the Manufacturer allowed to sell the product. The risk class determines the detailed certification steps, which is called a conformity assessment route.

4.2. Conformity Assessment route

Depending on the risk class of a Medical Device you can determine what is required to obtain your CE Mark, this is called Conformity Assessment route. There are multiple Conformity Assessment routes, but most are not practical for MDSW. Only the most important Conformity Assessment Route per risk class are given below:

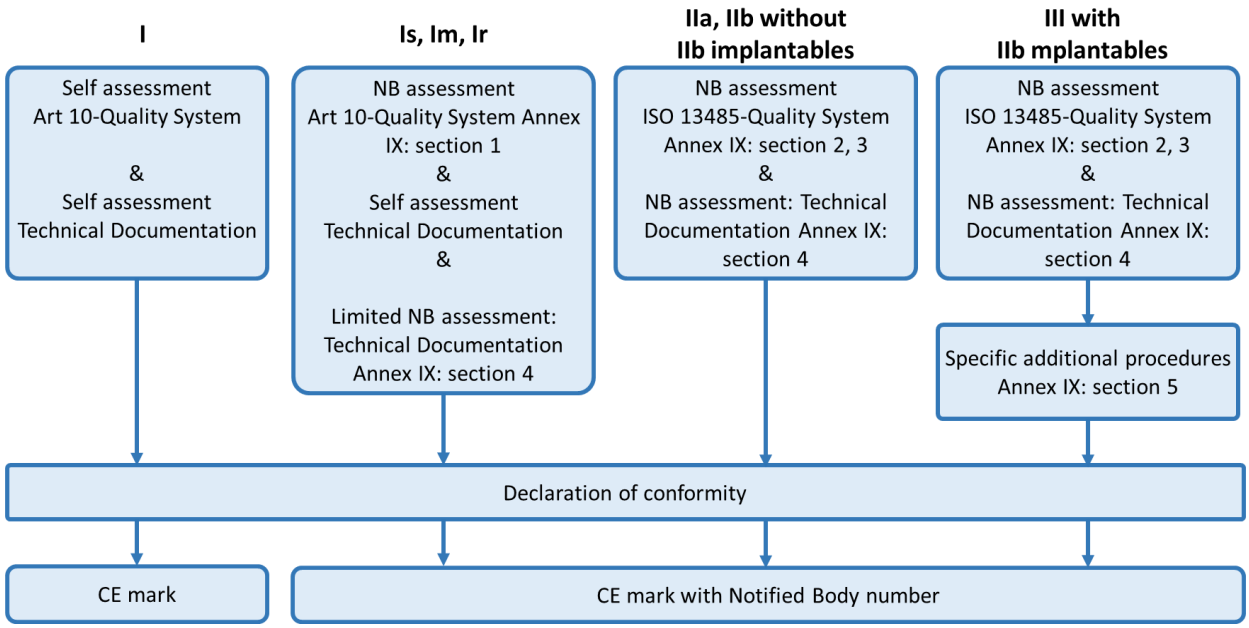


Figure 8 Conformity Assessment routes

Risk Class I, the manufacturer has to do the following:

- Self-assessment of Technical Documentation (Annex I) and QMS (Art. 10 and Annex II & III).
- Draw up a Declaration of conformity (MDR art 19 and Annex IV).
- Perform a registration at Farmatec (also called CIBG and NOTIS).
  - Submit the product information showing the intended use and the risk classification of the Medical Device.
  - Provide a Declaration of Conformity (MDR art 19 and Annex IV).

Risk Class Is (sterile device), Im (measurement device), Ir (reusable device): These risk classes are not likely applicable for MDSW, with the exception of Class Im. In addition to the activities mentioned under risk class I, also a Notified Body is needed who performs the following activities:

- Assessment of Technical Documentation concerning measurement function, sterility or reusability (Annex I).
- Provide CE certificate for the Medical Device fort the measurement function, sterility or reusability.

Risk Class IIa, IIb without IIb implantables: The difference between risk class IIa and IIb is not that large. However, for risk class IIb, the Notified Body oversight is more intense. The Notified Body has to do the following:

- Assessment of QMS (Annex IX).
- Assessment of Technical Documentation of a representative device for each category of devices (for Class IIa: MDR art 52 Para 6).
- Assessment of Technical Documentation of a representative device of each generic device group (for Class IIb: MDR art 52 Para 4).
- Provide CE certificate for the Medical Device.
- The manufacturer has to draw up a Declaration of conformity (MDR art 19 and Annex IV).

Risk Class III and IIb implantables: This risk class has two phases. A Clinical Investigation phase with oversight of the Competent Authority and a Pre-Market phase, with oversight from the Notified Body. This split in responsibilities causes a major problem. According to Annex VII, a Notified Body is not allowed to give consultancy to a

manufacturer. The Notified Body reviews if there is sufficient Clinical Evidence, however currently the Notified Body is not allowed to do that review before the Clinical Investigation phase. Class III MDSW manufacturers are strongly advised to discuss this issue at the start of the developing of a new MDSW, both with the Competent Authority and Notified Body (what their position is, and how that can be solved).

- **In the clinical phase, the Competent Authority has to do the following:**
  - Review Clinical Investigation Safety & Ethics.
  - Review Clinical Development Plan / Strategy.
- **In the clinical phase, the European Commission has to do the following:**
  - Send selected product group dossiers to expert panel for scrutiny procedure (Note the Notified Body sent the file to the European Commission).

- **In the clinical phase, the Expert Panel has to do the following:**
  - Review Clinical Investigation.
  - Review Clinical Development Plan / Strategy.
  - Give binding advise to the notified body.
- **In the pre-market phase, the Notified Body has to do the following:**
  - Assess QMS (Annex IX).
  - Assess Technical Documentation and QMS (Annex II & III).
  - Assessment of Technical Documentation (MDR art 52 (3)).
  - Provide CE certificate for the Medical Device.
  - The manufacturer has to draw up a Declaration of Conformity (MDR art 19 and Annex IV).

4.3. Competent Authority and MDCG

The Competent Authority are the departments of the Ministry of Health (VWS in The Netherlands) that execute the MDR. In the Netherlands it is arranged in the following manner:

- The ministry of VWS is responsible for implementing the MDR in Dutch legislation and represents the Netherlands in the MDCG. VWS also designates the Dutch notified bodies.
- The Health and Youth Care Inspectorate (Inspectie Gezondheidszorg en Jeugd (IGJ)) is responsible for the medical devices on the Dutch market and inspects manufacturers and oversees the vigilance reporting and field corrective actions called Market Surveillance (this is not the same as Post Market Surveillance). The IGJ also supervises the Dutch notified bodies.
- CCMO coordinates the clinical investigations in The Netherlands.
- RIVM provides scientific support to the above-mentioned authorities in The Netherlands.

The MDCG is a council with representatives from all the Member States of the European Union. Swiss and some other countries have also a seat in the MDCG, but do not have a vote. The MDCG together with the European Commission develop the MDCG guidance and execute oversight on the implementation of the MDR. An example of the oversight is the Joint Assessment Teams that accredit the Notified Bodies.

4.4. Notified Body

The Notified Bodies perform the CE marking audits for the QMS and the Technical documentation reviews, depending on the requirements of the Conformity Assessment routes. The audit and review activities do follow strict requirements, checked by the Competent Authorities. The Notified Body assessment has the following elements:

- ISO 13485 stage 1 audit (only class IIa, IIb and III)
  - To verify the readiness of the organization’s QMS for a stage 2 audit including:

    - A review of the QMS documentation.
    - A review of the status and understanding regarding requirements of the standard.
    - Determination of the QMS scope.
    - Evaluation of the planning and performance of internal audits and the management review process
- ISO 13485 stage 2 (certification) (only class IIa, IIb and III)
    - To evaluate the implementation and effectiveness of the QMS. Typically, there are 3 months between stage 1 and 2, allowing to gather evidence of implementation and effectiveness of the QMS processes. The Notified Body will review all processes and determines how the manufacturer has implemented the MDR and ISO 13485 requirements.
- Technical documentation review (class Im, Is, Ir, IIa, IIb and III)
    - Prior to the ISO 13485 stage 2 certification audits, all relevant technical documentations are assessed by a team of experts, involving at least product, clinical and biocompatibility experts when applicable. They will evaluate, if requirements according MDR annex I, II and III including clinical evaluation and related documents and activities, such as PMS, PMCF and if applicable PSUR and SSCP have been fulfilled.
    - For class Im only the measurement aspect, Is only the sterilisation aspect and , Ir only the reusable aspect of the technical documentation is reviewed.
- Nonconformities.
- In general, some nonconformities will be raised during each audit and technical documentation review. These nonconformities need to be resolved and closed before the certification process can finalized.

Notified Bodies perform other MDR activities like reviewing System Security Certified Practitioners (SSCPs) and registering information in EUDAMED.

Obtaining a Notified Body is not easy. The search should start early in the development process. Notified Bodies can be found in the NANDO database at the European Commission website from DG SANTE. The NANDO database shows the accredited scope of a Notified Body, which indicates if the Notified Body is allowed to accept the Medical Device for certification.

The Notified Bodies are overloaded and do a strict customer pre-selection. They only accept good quality customers. A good well-resourced MDR project plan and a good setup of the Technical documentation provides evidence of being a good customer.

4.5. Declaration of Conformity and CE Marking

- MDR art 5 Placing on the market
- MDR art 19 Declaration of Conformity
- MDR art 20 CE marking of conformity
- MDR annex IV Declaration of Conformity
- MDR annex V CE Marking of conformity

When the conformity assessment is ready, the manufacturer can make a Declaration of Conformation. This is a document that the manufacturer declares that its device and quality systmen meets the requirements of the MDR. For class I devices the manufacturer does the conformity assessment on his own, which is called a self-assessment. For class IIa and higher Medical Devices, the Notified Body makes this assessment and provides a CE certificate as results of this assessment. After the Declaration of Conformity the Manufacturer can place the CE mark on the Medical Device and then the Medical Device can be sold in the EU, which is called placing on the Market.

Where software is submitted on a media it should be properly CE marked. Where the identification of the software is displayed in the GUI, place the CE mark close to the device identification.

4.6. Free sales certificates

- MDR art 60 Certificate of free sale
- Medtech Europe Impact of changes under the new EU Medical Devices Regulation (EU) 2017/745 to international registrations

To export a Medical Devices outside of the European Union in general a Free Sales Certificate and related paperwork is needed as required by the country of destination. Most manufacturers outsource this to a professional service organisation, which often saves a lot of money, time and frustration. A typical list of those documents looks like this:

- Certificate of free sales, this can be obtained via Farmatec.
  - Declaration of Conformance.
  - CE certificate of a Notified Body for Class I measurement, sterile and reusable, Class IIa/b and Class III.
- Certificate of Origin.
- Digital or physical stamp Chamber of Commerce.
- Translation by a Sworn Translator.
- Notarization of documents.
- Apostille or legalization of signatures.
- Legalization of documents at the Ministry of Foreign Affairs.
- Embassy of country of destination approval.

5. Technical Documentation

5.1. Introduction

Chapter 5 describes the contents of the Technical Documentation. The Technical Documentation contains the evidence that is created during the development process, so that the Notified Body can review the quality of the MDSW and if all related MDR requirements are fulfilled. The Manufacturer uses a GSPR checklist, to show where the evidence for the Software Development (Life Cycle), Risk Management, Clinical Evaluation and other processes can be found in the Technical Documentation.

5.2. Technical Documentation (on Post-Market Surveillance)

- MDR Annex II: Technical Documentation
- MDR Annex III: Technical Documentation on Post-Market Surveillance
- Recommendation NB-MED/2.5.1/Rec5: Technical Documentation
- GHTF-SG1-N011R17 Summary Technical Documentation for Demonstrating Conformity to the Essential Princples of Safety and Performance of Medical Devices (STED)

The term Technical Documentation (or technical file) refers to all the documents that a medical device manufacturer has to retain. The requirements for those documents are given in MDR annex II and III. The Technical Documentation of MDR Annex II. NB-MED/2.5.1/Rec5: Technical Documentation and GHTF-SG1-N011R17 Summary Technical Documentation (STED) give guidance how to setup the Technical Documentation, however this guidance has aged significantly.

The Technical Documentation for a device has to be created and maintained (MDR art 10 (4)). The Technical Documentation has to be supplied to the Competent Authorities when requested. A copy has to be kept by the Authorised Representatives (MDR art 11 (3)). The Person responsible for regulatory compliance has to ensure the Technical Documentation is kept up to date (MDR art 15(3)). The Notified Body reviews the Technical Documentation (MDR annex IX chapter II). To facilitate all these uses that the technical documentation is structured well as described in MDR annex II and III. Strict traceability is expected between the Technical Documentation, the GSPR checklist and the related documents. The related documents has to be immediately available, so either in hardcopy or in electronic file format, such as a pdf. Strict requirement traceability is also expected between safety, performance requirements and claim, user requirements, system requirements, software / functional requirements, risk analysis, risk controls and tests.

For the MDR annex II documents the GSPR checklist of annex I have to be used, to check if all the (General) Safety and Performance Requirements are met and the evidence is in a corresponding document. For the Technical Documentation on Post-Market Surveillance, such a checklist does not exist. It is good practice, to create the Technical Documentation at the start of a development project and make empty references for the documents needed. Otherwise completing the documentation at the end of a development project can be a huge task.

The technical documentation (MDR annex II) gives the details what has to be documented. In addition, technical documentation for the Software Development Life Cycle, Cybersecurity and Interoperability have to be added. The technical documentation consists of the following elements:

- Device description and specification, including variants and accessories
  - Device description:

        - Name.
        - UDI.
        - Patient population and their medical condition.
        - Principle of operation.
        - Qualification of the medical device.
        - Classification. of the medical device.
        - Explanation of innovations.
        - Description of accessories and, if applicable, system modules / components.
        - Configurations and variants.
        - Parts and components.
        - Raw materials and elements with human body contact.
        - Technical specifications.
    - Reference to previous and similar generations of the device.
- Information to be supplied by the manufacturer:
    - Device and packaging label and instructions for use.
- Design and manufacturing information:
    - Description of the development process.
    - Description of manufacturing processes.
    - Software Validation of development tools.
    - Manufacturing validations, monitoring and final device testing.
    - Identification of all suppliers and subcontractors used for development, manufacturing, hosting, installation and service activities.
- General safety and performance requirements (annex I):
    - Identification of applicable GSPRs in MDR annex I.
    - Evidence of conformity with the GSPRs, including:
        - Methods used to demonstrate conformity.
        - Applicable standards, Common Specifications and other requirements.
        - Links to documents demonstrating conformity.
- Benefit-risk analysis and risk management:
    - Benefit-risk analysis MDR Annex I (1,8), where benefits outweigh the risks and the benefit - risk ratio meets the State of the Art and the risks are reduced as far as possible and acceptable.
    - Risk Management MDR Annex I (3), as required in ISO 14791.
- Device verification and validation:
    - Pre-clinical data:
        - System requirements test plan and report.
    - Clinical data:
        - Clinical evaluation plan and report.
        - PMCF plan and report.
    - Description of combination/configuration with connected devices.

The technical documentation on post-market surveillance (annex III) consists of the following elements:

- Post-market surveillance plan.
- Post-market surveillance report (class I).
- Periodic safety update report (PSUR) (class IIa, IIb, III).

5.3. General Safety and Performance Requirements (GSPR)

5.3.1. GSPR checklist

- MDR Annex I: General Safety and Performance Requirements
- MDCG 2021-5 Guidance on standardisation for medical devices
- COCIR Recommendation Applicability of EHSR of the Machinery Directive (2006/42/EC) to Medical Devices
- Medtech Europe: The use of state-of-the-art standards in the absence of harmonised standards under the IVD and Medical Devices Regulations (IVDR/MDR)

The GSPR in MDR Annex I stands for General Safety and Performance Requirements. These requirements should be met by your MDSW if they are applicable. It is good practice to put the GSPR requirements in a checklist, as can be seen below. In this example for clarity, not the complete text under requirement is shown. In the second column it is shown if the requirements are applicable (A) or not applicable (NA). If it is applicable, then in the last column the evidence has to be given. For instance, the risk management report. Normally the reference to this report is given, which is part of the technical documentation as mentioned in MDR Annex II. If the requirement is not applicable, then in this column a justification has to be given, why the requirement is not applicable. In the middle column common specifications, (harmonized) standards or guidance should be given, for which the evidence in the last column is shown. The evidence is part of the Technical Documentation see MDR Annex II.

Table 8 GSPR checklist

#	Requirement	A N/A	Common specification, standard, sub clause or ref.	Reference or Justification for not applicable {additional notes}
1	Performance and safety {Include the full text here from the annex.}	A	• ISO 14971 • MEDDEV 2.7.1 rev 4 • IEC 82304-1 • ISO 60601-1-6 • {MDCG SSCP}	• Risk management report • Clinical evaluation report • Verification & Validation report • Summary of safety and clinical performance
2	Reduction of risks	A	• ISO 14971	• Risk management report
3	Risk management system	A	• ISO 14971	• Risk management report
4	Risk control measures and residual risks	A	• ISO 14971	• Risk management report
5	Risks related to use	A	• ISO 14971 • IEC 62366-1 Application of usability engineering to medical devices In case of medical electrical equipment also: - IEC 60601-1-6 Medical electrical equipment: Usability	• Usability specifications • Usability verification (formative evaluation) • Usability validation (summative evaluation)
6	Device lifetime	A		
7	Packaging, transport, storage	?	• ISO 11607-1 • ISO 11607-2	{Not always applicable for MDSW}

#	Requirement	A N/A	Common specification, standard, sub clause or ref.	Reference or Justification for not applicable {additional notes}
			• EN 868-5	
8	Positive benefit - risk ratio	A		
9	Devices without a medical purpose	N/A		
10	Chemical, physical and biological properties	N/A		
11	Infection and microbial contamination	N/A		
11.7	Packaging systems for non-sterile devices	A		• System Requirements Specification • Verification Report
12	Devices incorporating a medicinal product, substances absorbed or locally dispersed	N/A		
13	Devices incorporating materials of biological origin	N/A		
14	Construction of devices and interaction with their environment	A	• MDCG 2019-16 Guidance on Cybersecurity for medical devices	
14.2d	Software and IT environment interaction risks	A	• IEC 60601-1 Requirements for medical electrical equipment • IEC/ISO 80001 Risk management for IT networks incorporating medical devices • IEC 82304-1 Health software	{This clause is explicitly addressing risks for software at the system and network level. This includes consideration of cybersecurity and network potential risks and information to the user for IT networks that cannot be validated by the manufacturer.}
15	Devices with a diagnostic or measuring function	?		
16	Protection against radiation	N/A		
17	Electronic programmable systems and software	A		
18	Active devices and devices connected to them	A		{Software is active}
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 for use by lay			

#	Requirement	A N/A	Common specification, standard, sub clause or ref.	Reference or Justification for not applicable {additional notes}
	persons			
23	Label and instructions for use	A	• EN 1041: Information supplied by the manufacturer of medical devices • ISO 15223-1: Medical devices – Symbols to be used with medical labels, labelling and • information to be supplied – Part 1: General requirements	• Labels • Instructions for use (clinician and patient) • Service manuals • Installation manuals, • Marketing material • Website

5.3.2. Applicable Standards

In preparation of the GSPR checklist a search is performed which Regulations, (Harmonized) Standards, Common Specifications and other Guidance is applicable for developing the MDSW. These are often called the Applicable Standards. In the GSPR checklist, the Applicable Standards are placed in the column “Common specification, standard, sub clause or ref.”

When a harmonized standard is followed, then compliance with the MDR is assumed for the scope of the harmonized standard. Following a Harmonized Standard is “voluntary”, however in practice they are almost always followed. A Common Specification is comparable to a harmonized standard. However, it is required to follow a Common Specification. Often it is recommended to follow a standard, but it is not required.

If the MDSW is part of a hardware device, then also the Machine Directive is applicable. The COCIR Recommendation Applicability of EHSR of the Machinery Directive (2006/42/EC) to Medical Devices, explains how to fill out the EHSR requirements of the Machinery Directive.

Software that contains hardware also leads to additional requirements. Some important examples are:

- Machine Directive which contains requirements if your software is embedded in hardware.
- REACH, ROSH, and others which contain environmental regulations.
- Ecodesign Directive for design and energy saving, which contain environmental regulations.
- Batteries Directive which contains regulations for batteries.
- Packaging Directive which contains packaging regulations.

MDSW always functions in an environment, the interaction with the environment often leads to additional requirements. Some important examples are:

- General Data Protection Regulation (GDPR) containing privacy requirements if you gather Personal Data.
- Radio Equipment Directive (RED) (new release under development) containing requirements for Cybersecurity.
- IVDR contains requirements if your device is also an In Vitro Diagnostic device according to the IVDR.

Software often needs to communicate and share data with its environment (interoperability), think of standards, such as:

- HL-7 standards contain requirements for transfer of clinical and administrative data.
- DICOM standard contains requirements for the communication and management of medical imaging information.
- HCIM (Health and Care Information models) in Dutch called ZIB’s (ZorgInformatieBouwstenen). A ZIB defines the structure of care information in a certain situation, to facilitate that care providers can share information. Nictiz

coordinates the development and usage of the ZIB's. Nictiz is the national competence centre for electronic exchange of health and care information.
- Certification of certain elements of interoperability, like sharing information about minors is implemented in Dutch legislation.

5.4. Software development life cycle

- MDR Annex I: 17.1 Repeatability, Reliability and Performance
- MDR Annex I: 17.2 State of the Art, Software Development Life Cycle, Risk Management, (Cyber)security and Verification and Validation
- MDR Annex I: 17.3 Mobile platforms
- MDR Annex I: 17.4 Hardware, IT networks, (Cyber)security
- IEC 62304 MDSW development process
- IEC 82304-1 Health software requirements for product safety
- IEC 60601-1 Medical electrical equipment requirements for safety and performance
- HL7 Consumer Mobile Health Application Functional Framework

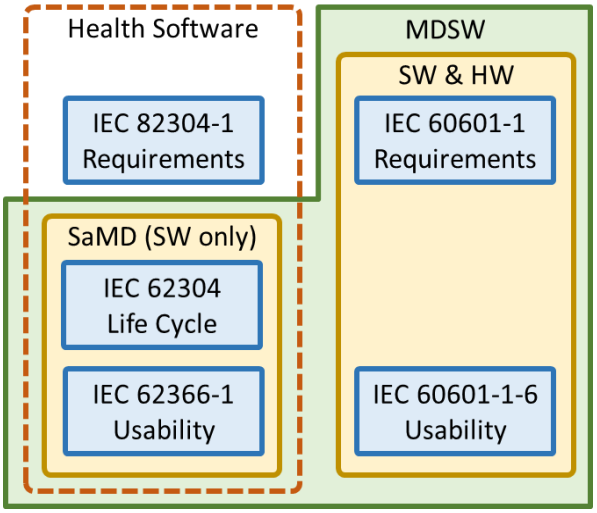


Figure 9 Software development life cycle standards

A software development process has to be implemented for the development of MDSW independent of the methodology followed like Agile or Waterfall. The standards describe the development process and the deliverables. The following standards are to be considered for the software development life cycle and for usability:

- IEC 62304 MDSW – Software Life Cycle Processes: This standard is expected to be followed for all software development in addition to ISO 13485 for the QMS. Note: According to ISO 14971 risks should be reduced as far as possible which is more restricting than IEC 62304 Amendment 1, so here ISO 14971 should be applied.
- IEC 82304-1 Health software – General requirements for product safety: This standard is for stand-alone health apps or clinical information systems and can be used in addition to IEC 62304 for MDSW if applicable. The standard also describes higher-level requirements such as security aspects.
- IEC 60601-1 Medical electrical equipment – Part 1: General requirements for safety, including essential performance: This standard is for MDSW integrated in electronic equipment and can be used in addition to IEC 62304 for MDSW if applicable.
- IEC 62366-1 is usability for software and IEC 60601-1-6 is for MDSW integrated in electronic equipment and can be used in addition to IEC 62366-1 if applicable.

Full documentation and traceability of the deliverables is expected, to pass the CE marking process. Therefore, the development process should be in place from the start of the project, which requires a high level of discipline. To help with this it is common to use specialized software development software, despite the high cost.

5.5. Risk management

5.5.1. Introduction

- MDR Annex I (1) Acceptable risk
- MDR Annex I (2) Risk reduction
- MDR Annex I (3) Risk Management
- MDR Annex I (4) Risk Controls
- ISO 14971 Application of risk management to medical devices
- IEC/TR 80002-1 Guidance for applying ISO 14971 to software
- NPR 5326 Risk management during development and maintenance of custom software (Dutch)

ISO 14971 describes a systematic approach to risk management for medical devices. IEC/TR 80002-1 gives guidance for applying ISO 14971 to software. The goal of ISO 14971 is to obtain a safe medical device, therefore:

- There are no unacceptable risks.
- There is a positive benefit - risk ratio, which is analyzed in the clinical evaluation.

Please note ISO 14971 is for risks related to safety and performance. Security risks are discussed in the paragraph about cyber security.

5.5.2. Risk Management Plan

ISO 14971 requires a risk management process for the entire product life cycle. This includes planning and execution of all relevant tasks, activities, procedures, and responsibilities both during product development and when the product is placed on the market. This also includes design changes, new risks, changes in the benefit - risk ratio, etc. To obtain such information, a pos-market surveillance system is needed.

The risk management process is described in the risk management plan:

- Risk analysis.
- Risk assessment.
- Risk control.

A risk management plan defines the acceptance criteria: a device is sufficiently safe when the benefits outweigh the risks. The risk - benefit ratio is evaluated in the clinical evaluation report. However, the risk - benefit ratio can change over time. Risks that were acceptable in the past do not have to be acceptable in the future.

Risk Management contains the mitigations for safety risks found in literature, vigilance and regulatory (e.g. MAUDE) databases for own or similar/benchmark devices. The risk management plan derives an acceptable benefit - risk ratio from the clinical evaluation, based on:

- Consideration of the state of the art.
- Consideration of product-relevant safety standards or common specifications.
- Comparison with similar / benchmark devices.
- Analysis of data from clinical evaluations.

The risk management plan is related to the clinical evaluation, PMS and PMCF:

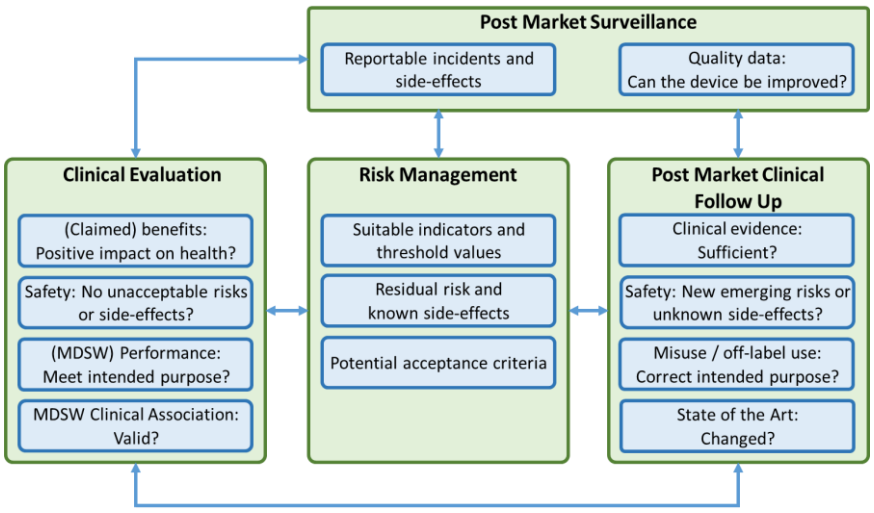


Figure 10 Risk management plan relation to Clinical Evaluation, PMS and PMCF

5.5.3. Risk analysis, evaluation and control

Risk analysis and evaluation contain the following steps:

- Define risk acceptance criteria.
- Determine the hazards of a product, i.e. those related to the intended use of the product.
- Estimate risks as a combination of severity and probability.
- Decide whether risks are acceptable.
- Checking and implementing risk control measures.
- Identify new risks and decide whether they are acceptable.
- Determine residual risk and decide whether this appears justifiable.

5.5.4. Risk control

Risk control measures can reduce risks. These are:

- Integrated safety through design.
- Protective measures in the medical device itself or in the manufacturing process.
- Safety information, however in general, this is considered not to reduce risk.

The implemented risk control measures need to be verified and the residual risk assessed. The individual and overall residual risk needs to be acceptable.

5.5.5. Risk management report

Prior to release for commercial distribution of a medical device, the manufacturer shall carry out a review of the risk management process. This review shall at least ensure that:

- The risk management plan has been appropriately implemented.
- The overall residual risk is acceptable.
- Appropriate methods are in place to obtain relevant production and post-production information.

5.6. Clinical Evidence

5.6.1. Introduction

Clinical Evaluation:
- MDR art 61 Clinical Evaluation
- MDR Annex XIV part A Clinical Evaluation
- MDCG 2020-13 Clinical evaluation assessment report template
- MDCG 2020-6 Guidance on sufficient clinical evidence for legacy devices
- MDCG 2020-5 Guidance on clinical evaluation – Equivalence
- MDCG 2019-9 Summary of safety and clinical performance
- (Meddev 2.7. rev 4 Clinical evaluation according the MDD; this document still contains valuable information)

MDSW Clinical Evaluation:
- MDCG 2020-1 Guidance on clinical evaluation of MDSW
- IMDRF SaMD WG/N41 Software as a Medical Device (SaMD): Clinical Evaluation
- IMDRF SaMD WG (PD1)/N41R3 Software as a Medical Device (SaMD): Clinical Evaluation (Proposed Document)

Clinical Investigation:
- MDR art 61 (4-6) Clinical Investigation
- MDR art 62 - 82 Clinical Investigation
- MDR Annex XV Clinical Investigations
- MDCG 2020-10 Guidance on safety reporting in clinical investigations
- MDCG 2021-6 Questions & Answers regarding clinical investigation
- ISO 14155 Clinical investigation of medical devices for human subjects – Good Clinical Practice

Every Medical Device must have sufficient clinical evidence and is therefore seen as the most important element to get market access. The clinical evaluation is a scientific approach to create that evidence and has a long list of detailed requirements in the MDR and the applicable guidance's. The clinical evaluation is strictly reviewed if it meets the requirements. For this the MDCG guidance for Clinical Evaluation Assessment Report is used.

To bring a Medical Device on the market, there must be evidence that the device is safe, and that the device is doing, what it should do. For this evidence is needed, which consist of two parts. Technical Evidence, coming for instance from testing and clinical evidence, which is coming from the Clinical Evaluation Report.

The clinical evaluation is a systematic and scientific analysis process. How to do this process is described in the MDR Annex XIV part A and in the guidance Meddev 2.7. rev 4. For the clinical evaluation clinical data is gathered for the own device or for look-a-likes which are called equivalent devices. Clinical data can come from clinical investigations and post-market clinical follow up studies or post market surveillance studies. When the clinical data is analysed, the conclusions are called clinical evidence. When possible, clinical evidence maybe replaced by technical evidence, for class IIb devices or lower (see MDR art 61(10)). For implantables and class III devices always clinical evidence need to be available, and often clinical investigations according to MDR art 61 (4-6).

The clinical evaluation aims to examine and evaluate clinical data to verify the clinical safety and performance of the medical device. The results of the clinical evaluation are used to assess whether the risks associated with the use of the medical device are acceptable in relation to the expected benefit. The manufacturer must keep the clinical

evaluation up to date throughout the entire life cycle of the product, by repeating the literature study, and doing post market surveillance. He must update the PMCF assessment report for Class III and implantable medical devices annually. For lower class devices there must be at a minimum a plan for PMCF studies Art. 61 (11) and Annex XIV Part B).

In the clinical evaluation it is assessed whether there is sufficient clinical evidence for the safety and the performance of the device. At a minimum a literature study for the Medical Device in clinical practice has to be performed. If there is still insufficient Clinical Evidence or the device is risk class III, then a Clinical Investigation needs to happen. The Clinical Evidence is put in the Technical documentation.

The results of the clinical investigation needs to be reported in EUDAMED for implantables and class III devices in a Summary of Safety and Clinical Performance. And for Class IIa and higher devices also in a Periodic Safety Update Report.

5.6.2. Clinical Evidence documentation

The overall documentation related to the clinical evaluation is getting more complex according to EU MDR. It requires the following documents:

- Clinical Evaluation Plan (CEP, Annex XIV, Part A, 1.) describing the procedure for clinical evaluation to demonstrate the benefit - risk ratio based on the state of the art.
- Clinical Evaluation Report (CER, Art. 61 (12)).
- Clinical Development Plan (CDP, Annex XIV Part A 1a & 1d).
- Clinical Investigation Plan (CIP, Annex XV 3).
- Post-Market Clinical Follow-up (PMCF) plan (Annex XIV, Part B) or a justification as to why a PMCF is not applicable (outlined in the PMS plan).
- PCMF evaluation report (annual update) for class III and implantable devices (Art. 61(11), Annex XIV).
- Summary of Safety and Clinical Performance (SSCP) for class III and implantable devices (Art. 32 and 61).
- Periodic Safety Update Report (PSUR) for classes IIa (biannually update), IIb (annual update) and class III (annual update) devices (Art. 86).
- Clinical Evaluation Assessment Report (CEAR, Annex VII section 4.6, to be compiled by the notified body).

Table 9 Clinical Evaluation related documentation

MDR risk class	Clinical Evaluation	Clinical Develop-ment Plan	Clinical Investi-gation	Post Market Clinical Follow-Up plan	Post Market Clinical Follow-Up report	Summary of Safety and Clinical Performance
Class I	√	√	Justification or Clinical Investigation required	√	Justification or PMCF report required	-
Class IIa	√	√	Justification or Clinical Investigation required	√	Justification or PMCF report required	-
Class IIb - implantables	√	√	Justification or Clinical Investigation required	√	Justification or PMCF report required	-
Class III + implantables	√	√	√	√	Justification or PMCF report required	√

The clinical evaluation report (CER) compiles the conclusions of the clinical evaluation. In addition, the manufacturer must provide a publicly available “Summary of safety and clinical performance” (Art. 32) for certain high-risk devices. The notified body in turn documents the results of the clinical evaluation assessment in the clinical evaluation assessment report (CEAR). In the case of certain high-risk devices, the expert panel, the competent authorities, the authority responsible for notified bodies and the EU Commission have these documents at their disposal. The manufacturer commits himself to the collection of post-market surveillance data in the PMS plan. The periodic safety update report (PSUR) summarizes this data and contain among others also the main findings of the post-market

clinical follow-up (PMCF). Notably, the EU MDR does not say something about the frequency of clinical evaluation updates. MEDDEV 2.7/1 Rev. 4 includes such information.

5.6.3. Pre-Clinical, Clinical Data and MDR art 61(10)

Clinical data is any "information concerning safety or performance that is generated from the use of a device" (Art. 2 (48)). It can come from the following sources:

- Clinical investigation of the device concerned or of an equivalent device.
- Clinical experience with the device concerned or an equivalent device.
- PMCF.

Manufacturers can use clinical data from post-market surveillance (e.g. vigilance data) as well as results from PMCF studies as additional sources for clinical evaluation. For this reason, some manufacturers have already started to collect data for their devices from other markets such as the US. This includes data from Investigator Initiated Studies (IIS). Whether these data are sufficient to demonstrate the performance, clinical safety and clinical benefit of a device depends on the quality and significance of the data. The manufacturer must conduct clinical studies (e.g. PMCF studies) if the available clinical data is insufficient. Manufacturers should link and keep up to date risk management data, quality management system and clinical evaluation procedures on a regular basis.

Note that pre-clinical and clinical data must be part of the technical documentation (Annex II (6.1.)) including:

- Test results.
- Test design and protocols (in the case of software the verification and validation.
- Clinical evaluation report / plan.
- PMCF plan / evaluation report.

Where possible clinical performance study data should be obtained to complement the clinical evidence. If non-clinical testing method data is used instead of clinical evidence this should be adequately justified according to MDR art 61 (10). This is also applicable for MDR high risk devices, however the requirement for Clinical Investigation in MDR art 61 (4) remains.

5.6.4. Clinical Evidence

- **Clinical Evidence introduction**
  - The key concept of the MDR is "sufficient clinical evidence" related to MDR art 2 definition (51) about "clinical evidence" and MDR art 61.1 about "clinical evaluation". Using these two references, the key concept can be interpreted in the following way:
    - Clinical evidence is based on clinical data, which is analyzed in a clinical evaluation.
    - Sufficient (level of clinical evidence) is determined by the manufacturer so that a qualified assessment (MDR art 2 definition (51)) can determine that a device is safe and performing and can achieve its intended benefits based on the intended purpose.
    - The accessor of the manufacturer must be qualified (MDR art 2(51)). In addition, also the Notified Body needs to have a qualified accessor (MDR Annex VII 3.2.4) to analyze whether the presented evidence is sufficient.
  - The accessor of the Manufacturer plays an important role. Therefore, it is preferred that the accessor is an experienced and practicing physician if possible. This avoids a difficult discussion with the Notified Body or the Competent Authority if the accessor is qualified enough.

- **Clinical Evidence acceptance criteria**

- The following table gives an overview of the acceptance criteria for clinical evidence:

Clinical Evidence Element	Acceptance criteria (justify the level of clinical evidence)
State of the Art MDR art 61(3c)	• A literature search towards (treatment) alternatives including an identification of side-effects for each of the alternatives and common device related issues also from similar benchmark devices.
Clinical data MDR art 61(1)	• Need to be of sufficient quality. o A literature search for clinical data obtained with one's own device or with equivalent devices, based on a systematic search strategy (often PICO). o The equivalency needs to be justified. o Covering indications (clinical condition, physiological state). o Clinical data appraised (quality criteria including intended purpose). o Clinical data analysed.
	• Need to be of sufficient amount, for example: o Statistical sample size to uncover undesirable side effects. o Cut-of date for literature search.
Safety MDR Annex I-1	• Acceptable when free from unacceptable risk.
Undesirable Side effects MDR Annex I-8	• Acceptable when weighed against the benefits see benefit - risk ratio.
(Clinical) Performance MDR Annex I-1	• Acceptable when the intended performance can be achieved.
Benefit - risk ratio MDR Annex I-1	• Acceptable when: o Benefits outweigh the risks and undesirable side-effects. o Benefit – risk ratio has a positive impact on health. o Benefit – risk ratio is comparable or better than the state of the art. o Benefits must be measurable outcomes or indirectly measurable outputs with a clinical impact.
Clinical Investigation MDR art 61(4-6)	• Perform Clinical Investigation if required.
Claims MDR art 7, GSPR 23.4.c	• Acceptable when the claim can be achieved.
Identify gaps in the GSPR where additional clinical data is needed.	• This should include an identification of the residual risk originating from risk management reports for which also additional clinical data is needed.
Identify set of instructions / algorithms which need SW clinical evaluation	• The MDSW set of instructions or algorithms which generates clinically relevant output or benefits, need clinical evidence. • Justified based on MDR art 61(10) which set of instructions / algorithms do not need clinical evidence
Valid clinical association MDCG 2020-1	• Acceptable when the output associates with an indication (clinical condition or physiological state).
Technical Performance MDCG 2020-1	• Acceptable when the MDSW output is accurate and reliable for the input.
Clinical Performance MDCG 2020-1	• Acceptable when the MDSW generates clinically relevant output or benefits when used as intended.
PMCF plan MDR art 61(11)	Consider gathering clinical data for the following situations: • Clinical data gaps between MDD vs MDR requirements if any • Equivalent device clinical data is used instead of own clinical data • Technical data is used for clinical data where 61(10) is used

- **Clinical Evidence per development stage**

- The MDR and the Meddev guidance for Clinical Evaluation are very brief about what clinical evidence to gather during which phase of the device life cycle.
- In principle 4 critical steps during the life cycle of a medical device can be identified where clinical evidence plays an important role:
  - Development phase: Gather (voluntary) clinical evidence to determine the State of the Art as input for development. The development phase is out of scope of the MDR, and currently there are no harmonized standards covering the development phase under the MDR. Manufacturers are advised already to determine the State of the Art in this phase.
  - Clinical investigation phase: Create clinical evidence to fill the gaps and prepare for market approval. Therefore, it is useful to identify gaps in the clinical evidence where new clinical data is needed. (Note: the term clinical investigation is used in the MDR, however in other jurisdictions this is called clinical study or clinical trial). A clinical investigation is needed for MDR class IIb implantables and class III devices (MDR high risk devices) according to MDR art 61(4), unless exempted under MDR art 61(5 or 6). It is remarkable that the Notified Body only comes into scope at the Pre-Market phase. It would be beneficial to have an earlier review by a Notified Body, such as the review if an investigational device is safe and sufficiently performing to begin a clinical investigation and if the investigation aims to collect the right clinical data to support a later CE mark. It is argued that such a review would be "advising by the Notified Body", and therefore this review should not take place. However, everybody is helped by an early Notified Body review: the patient who knows the investigational device is as safe as possible and performing. The manufacturer who has more certainty that the investigational device will eventually be CE marked.
  - Pre-Market phase: Evaluate if the level of clinical evidence is sufficient to demonstrate conformity with the General Safety and Performance Requirements (GSPR) and to obtain CE mark.
  - Post-Market phase: Evaluate if there is new clinical evidence obtained during use of the device which necessitates corrective action. In addition, review if the medical device is still state of the art.

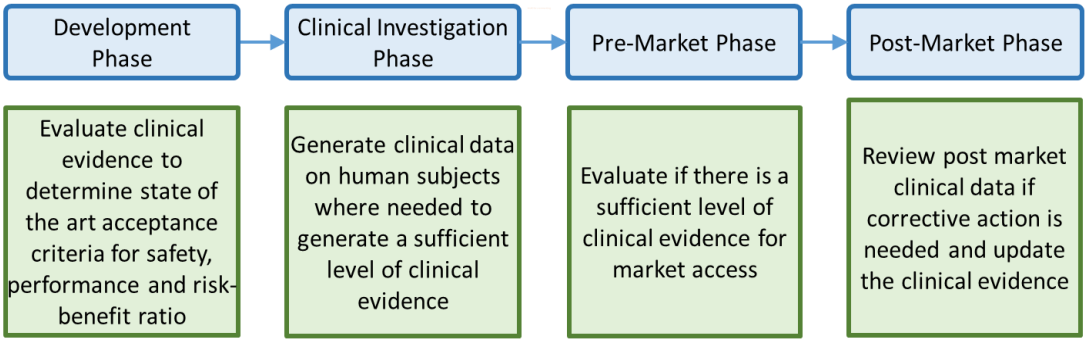


Figure 1. Clinical evidence requirements per life cycle phase according to the MDR and the CE Meddev.

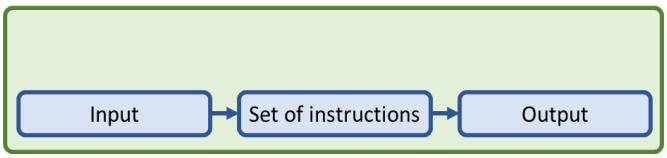
- **Clinical Evidence for MDD or AIMDD legacy devices**
  - Devices that are already legally on the market under the MDD or AIMDD (the directives) are called legacy devices. The legacy devices form a special subgroup. Under the MDR grandfathering is not defined. Grandfathering is a mechanism which regulates the acceptability under the MDR of a CE marked device under the directives. Therefore, devices that are safe and performing as intended under the MDD or AIMDD lose their CE-mark after their MDD or AIMDD certificate expires.
  - For that reason, the clinical evidence required for market access under the MDR for legacy devices should preferably be created when the device still has a valid certificate under the MDD or AIMDD as referenced by MDR art 120 (2) and (3). This newly created clinical evidence should also be endorsed by a Notified Body with a valid MDR certificate. In practice there is ample time to do this since there is a severe limitation of MDR Notified Body capacity. A solution is not in sight for this unless MDR art 120 is amended.
  - When MDR Notified Body capacity is not available for a manufacturer, it is likely that any amendment to the MDR if ever created, requires that a manufacturer has a complete technical documentation, a valid clinical evaluation and has performed documented effort to obtain in time a MDR Notified Body.
  - What is expected from a manufacturer of legacy devices?

        - Conduct a gap analysis to determine if there is a lack of technical data to meet the MDR GSPR requirements.
        - Conduct a gap analysis to determine if the existing clinical data provides sufficient clinical evidence with respect to the MDR requirements. Please note that the definition of clinical data has changed from the directives towards the MDR, so existing clinical evidence might no longer be valid or sufficient. Also note that MDR art 61 (4) requires clinical investigations for MDR high risk devices, unless exempted by MDR art 61 (4, 5, 6). When exempted the notified body shall check if the PMCF plan is appropriate and includes post market investigations to demonstrate the safety and performance of the device.
    - If clinical data gaps have been identified, there are several possibilities to bridge those gaps, such as:
        - A (PMCF) clinical investigation.
        - A PMCF investigation based on a scientifically sound questionnaires or registries.
        - Narrow the intended purpose of the device to those indications only for which sufficient clinical data is available.
    - A PMS plan to gather other clinical experience data is always required.

- **Clinical Evidence for MDSW**
    - **Valid Clinical Association:**
        - First, there must be a valid clinical association between the output of the software and the clinical condition, disease, injury, or disability. Therefore, the manufacturer must carry out a comprehensive literature study by searching the relevant databases (e. g. PubMed) for systematic and non-systematic reviews as well as meta-analyses. Moreover, he can use guidelines of medical societies as a source. Here the key questions are:
            - Does the output of the medical software correspond to the current state of science and technology regarding its intended purpose?
            - Is the functionality of the software of clinical relevance in medical practice?
        - All results of the valid clinical association examination belong to the section “state-of-the-art in science and technology as well as clinical background” of the clinical evaluation report.

Valid clinical association:
The MDSW **output** should **associate** with an **indication** (clinical condition or physiological state).

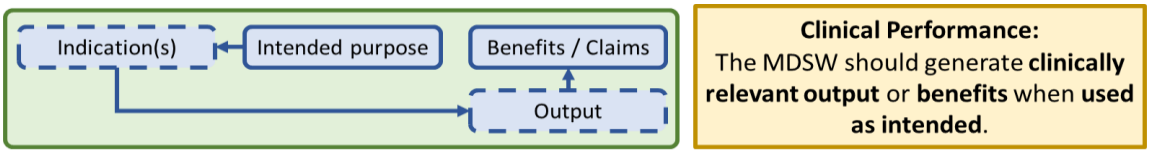
    - **Technical Performance**
        - Second, the manufacturer must validate his device analytically or technically by carrying out validation and verification tests as well as comparative tests in the case of device equivalence. In addition, the device must comply with the relevant standards. Finally, the manufacturer has to demonstrate the risk-based approach in the clinical evaluation by addressing software risks, e. g. caused by incorrect data input, insufficient precision of output, inadequate upper/lower limits, technical failure of e.g. mobile devices or the software environment, missing operability, and compatibility. Here the key questions are:
            - Is the software algorithm working correctly and reliably?
            - Are all specifications fulfilled regarding the intended purpose?
        - Standard IEC 82304-1 should be harmonized under the EU MDR in the future and can be used for validation of stand-alone software. The results belong to the section “route of clinical evaluation/device under evaluation” of the clinical evaluation report.



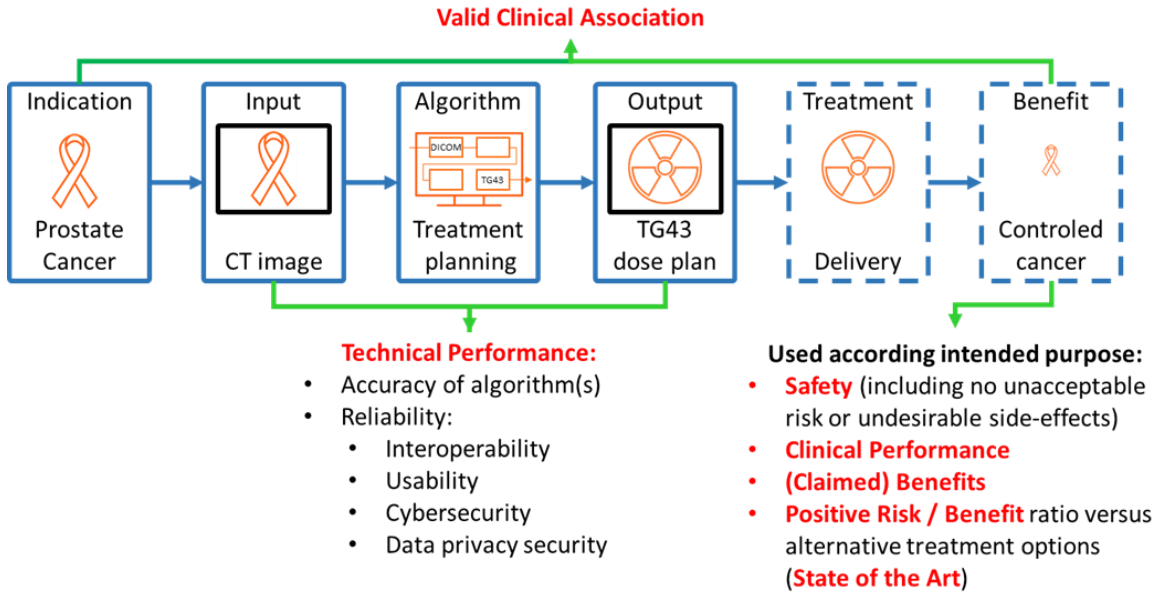
Technical Performance:
The MDSW **output** should be **accurate** and **reliable** for the input

    - **Clinical Validation**

- Third, the manufacturer must measure the ability of the software to yield a clinically meaningful output. Clinical investigations conducted with the own medical device or an equivalent one, validation and verification, post-market surveillance and usability studies are possible. Here, the key questions are:
  - Does the desired (precise and reliable) output of the medical software meets the intended purpose in the target population?
  - Does the output have the desired clinical significance for the corresponding patient population?
  - Is the result of the algorithm relevant to the diagnosis, treatment or prevention of a disease in a patient?
- All results of the clinical validation belong to the section "route of clinical evaluation/device under evaluation" of the clinical evaluation report. Consider that the corresponding IMDRF guidance introduces a risk categorization for stand-alone software. These categories are different from the medical device risk classes of the EU MDR and the software safety classification of standard EN 62304. However, the EU MDR and the harmonized standards are finally relevant for placing medical devices on the market in the EU.



- **Clinical Evidence for MDSW example:**
  - How to perform the MDSW Clinical Evaluation is not easy in practice. Good examples can in IMDRF SaMD WG (PD1)/N41R3 Software as a Medical Device (SaMD): Clinical Evaluation (Proposed Document). In the back of this document there are several examples. These examples never made it in the final guidance document but are very useful.
  - Radiation Treatment Planning Software is intended for use by a trained physician in radiation therapy to create a radiation treatment plan for the treatment of tumors after approval by that physician. The radiation treatment plan is used to drive a radiation treatment device, which executes the plan to radiate the tumor.
  - Below is an example from Radiation Therapy.



5.6.5. Clinical Evaluation

The following table gives the Clinical Evaluation Stages and its contents.

Clinical Evaluation Plan / Report contents MDR Annex XIV part A and the guidance Meddev 2.7. rev 4

Stage 0: Definition of the scope of the clinical evaluation

Device Description and scope (7 & A3):

- Names & Codes
- Legal Manufacturer
- Regulatory status / Classification
- Intended purpose, (Contra)Indications & Claims
- Detailed description
- Technical File references
- Overview of changes

Clinical background, current knowledge, state of the art (8-10 & A4 & 5; MDCG 2020-6):

- Literature search:
  - Acceptable Risk / Benefit ratio vs clinical alternatives
  - Acceptable undesirable side-effects vs clinical alternatives
- Compliance Common Spec./ (Harmonized) Standards
- Risk mitigation of risks from vigilance reports, MAUDE, etc

Stage 1: Identification of pertinent data held by the manufacturer (8.1)

Premarket data

- Risk Management
- Bench testing
- Usability Study (6.1)
- Animal Testing
- Pre-Market Clinical Investigations

Post market data

- Previous clinical evaluations
- Post Market Clinical Follow-up (&IIR)
- Post Market Surveillance
- New risk from PMS / PMCF
- New claims
- Design changes
- Review State of the Art
- Update literature search and analyses

Stage 1: Identification of pertinent data from literature (8.2)

Demonstration of Equivalence (A1; MDCG 2020-5):

- Based on Clinical, Technical, Biological aspects.
- Access to Technical File
- Equivalent device(s) conform to MDD / MDR?
- Justify issues.

Literature Search (A4 & 5):

- Identification (search)
  - PICO
  - Own / equivalent device
  - Risks (unacceptable)
  - Claims
- Screening duplicates
- Screening relevance

Stage 2: Appraisal of pertinent data (A6)

- On full text article
- On degree of quality, relevance and contribution

Stage 3: Analysis of the clinical data (A7)

Compliance to specific GSPR requirements (MDCG 2020-6):

- Safety (10 & A7.41 & MDR GSPR 1)
- Acceptability of side-effects (10 & A7.4 & MDR GSPR 8)
- Performance (10 & A7.3 & MDR GSPR 1)
- Acceptable benefit/risk profile (10 & A7.2 & MDR GSPR 1):
  - Benefits:
    - Improved clinical outcome
    - Improved Quality of Life
    - Improved diagnosis
    - Improved public health impact
  - Risks:
    - Residual risks
    - Side-effects

GSPR requirements for software / diagnostics (MDCG 2020-1):

- Valid clinical association
- Technical performance
- Clinical performance

Stage 3: Analysis of the clinical data (Meddev A7)

Supporting labelling & promotional material (6.1):

- Intended use (6.1)
- Claims (6.1; MDR art 7)
- Indications (6.1)
- Contra-Indications (6.1)
- Precautions & warnings

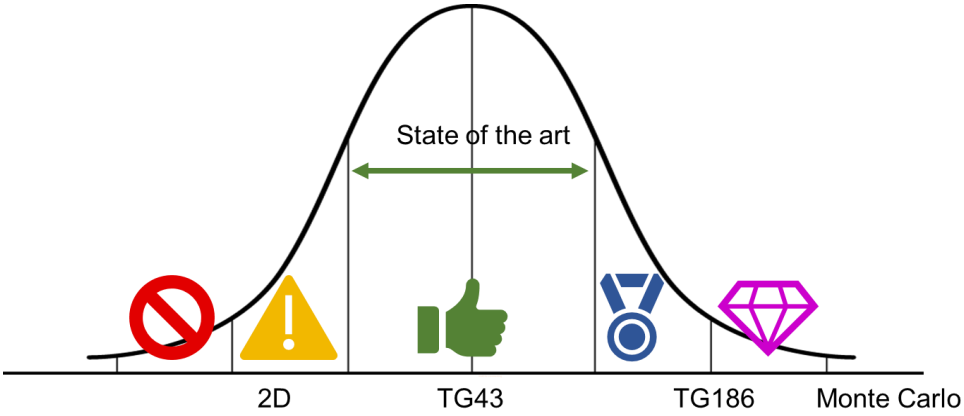
Stage 4: Clinical Evaluation Justifications and Conclusions

- Conclusion Clinical Evaluation Report (11)
- Clinical Investigation justification (10.2c, 10.3 & A2)
- PMCF Justification (10.2d, 10.3 & Meddev 2.12)
- Clinical Development Plan (MDR A14-A1a)
- Update frequency Clinical Evaluation (6.2.3)

Evaluators

C.V.
Check qualifications (6.4)
Declaration of interests (A11)

- **State of the Art**
  - Demonstration of the State of the Art has several interpretations:
    - Demonstration of State of the Art based on a literature review as outlined in Meddev 2.71 rev 4 art 8.2 and Meddev 2.71 rev 4 annex 5.1:
      - Demonstration of an acceptable benefit - risk ratio when taking into consideration the medical alternatives (MDR recital (49)).
      - Demonstration of acceptable undesirable side effects when taking into consideration the medical alternatives. Medical alternatives can be alternative therapeutic interventions, benchmark devices, measures for the management of diseases, or others.
      - Demonstration of State of the Art based on existing medical guidelines from, for example, professional societies.
    - Demonstration of State of the Art (Meddev 2.71 rev 4 annex 7.1) through the application of (harmonised) standards or common specifications. Under the MDR a justification is needed about that the use of these standards is justified. The most up to date list of standards can be found at the FDA website called the recognized standards.



- **Benchmark / similar devices**
  - A similar device is a device for which the intended use, the biological, technical and clinical characteristics are similar (comparable) to your own device. A benchmark device is a similar device to which the safety and performance of your own device can be compared.
  - In cases where equivalence cannot be demonstrated under the MDR, the clinical data of benchmark / similar devices may be useful for a variety of other purposes, such as:
    - Ensuring that risk management is comprehensive by identifying relevant hazards and clinical risk.
    - Understanding the state of the art, the natural course of a disease and alternative available treatment options.
    - Helping to define the scope of the clinical evaluation, by identifying any design features in similar devices that pose special safety or performance concerns.
    - Helping to create clinical investigation plans or post-market clinical follow-up (PMCF) plans, and PMS plans.
- **Equivalent devices (see MDR Annex XIV (3)**
  - An equivalent device is a device for which the biological, technical or clinical characteristics match your own device as required by the MDR Annex XIV (3).
  - The manufacturer can demonstrate equivalence to already marketed medical devices. Annex XIV (3) of EU MDR specifies 3 characteristics, that manufacturers must consider when demonstrating equivalence:
    - Technical (e.g. conditions of use, properties, and algorithms).
    - Biological (not applicable for software).
    - Clinical (e.g. clinical condition or purpose, population and performance).

- If equivalence can be demonstrated according MDR annex XIV section 3, then clinical data of the equivalent device can be used for the device under evaluation to support the conformity assessment. The clinical data of an equivalent device may be used to generate clinical evidence for acquiring market approval.
- The equivalency assessment must be based on the relevant aspects of technical, biological and clinical characteristics of both devices. A gap analysis should be conducted by the manufacturer to assess any clinically significant difference between the device under evaluation and the device to which equivalence is claimed. The demonstration of equivalence can be based on multiple devices, although this is often challenged by regulators or Notified Bodies. The use of multiple equivalent devices is particular important for software, where often the features of multiple devices are combined.
- For class I devices and class IIa and IIb devices considerations of equivalency shall be based on proper scientific justification. The manufacturer must have sufficient levels of access to the data relating to the equivalent devices, such as brochures with technical characteristics, an instruction for use, measurements of performance characteristics, etc.
- For MDR class III devices in practice equivalency can only be accomplished for an own equivalent device, since it is very difficult to meet the additional requirement from MDR art 61-5, which says that the manufacturer of the device under evaluation should have a contract in place with the manufacturer of the equivalent device which should explicitly allow full access to the technical documentation on an ongoing basis.
- To demonstrate equivalence, the characteristics of the compared devices must match. It is therefore important that the demonstration is based on adequate scientific justification. Additionally, the manufacturer must clearly show that he has sufficient access to the comparator data.
  - It is not reasonable to demand that equivalence is demonstrated for the software code, provided …
  - The principles outlined in ISO 10993 series of standards for the biological evaluation of medical devices can be adopted.
  - 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. Note: all is a problem for software.
  - Pre-clinical data for the consideration of equivalence can be used.

- **Qualified assessment**
  - The clinical evaluation report must receive a qualified assessment from the manufacturer and from the Notified Body for MDR class IIa/b devices (MDR medium risk devices) and MDR high risk devices. This assessment includes an evaluation if there is a sufficient level of clinical evidence to claim that the device has a beneficial benefit - risk ratio and can be considered State of the Art.

5.6.6. Clinical Development Plan

A Clinical Development Plan (also called strategy) is required for every Medical Device. An example is shown for a hardware product, so that it is clear what is expected from such a plan. MDSW often does not deliver directly patients benefits / outcomes or endpoints, therefore for each MDSW it should be seen how to create the Clinical Development Plan.

Typical MDSW activities which fit in such a plan are:

- Valid Clinical Association study. Objective: Proof of concepts. Endpoint: a valid clinical association.
- Usability study. Objective: Safe and easy to use. Potential endpoint: usability.

Milestones	Study design (examples)	Potential acceptance criteria
Development stage	• *Formative and summative usability study per ISO 63266*	*Objective: Safety, easy to use, easy to learn* *Potential endpoints: Usability*
Pilot stage	• Structured case report(s) / first in man	Objective: Proof of concept Potential endpoint(s): Correctly treat subjects, meet intended purpose
	• Prospective uninterrupted case series.	Objective: Safety & Performance Potential Endpoint(s): Toxicity; tumor response; local control
Pivotal stage	• Prospective study with matched (historical) controls. • Randomized clinical trial. • Registry based trial.	Objective: Effectiveness compared to standard treatment Potential Endpoint(s): (disease-free) survival; local control; acute toxicity
Postmarket stage	PMCF based on real world data: • Retrospective registries	Objectives see Annex XIV part B 6.1: • confirming the safety and performance of the device throughout its expected lifetime • identifying previously unknown side-effects and monitoring the identified side-effects and contraindications • identifying and analyzing emergent risks on the basis of factual evidence • ensuring the continued acceptability of the benefit-risk ratio • identifying possible systematic misuse or off-label use of the device Endpoint(s): Long-term toxicity, (disease-free) survival, Rare side effects, Patient-Reported Outcomes
	PMCF based on real world data: • Physician questionnaire • Patient questionnaire	Objectives see Annex XIV part B 6.1. Endpoint(s): Usability Endpoint(s): Quality of Life

5.6.7. Clinical Investigation

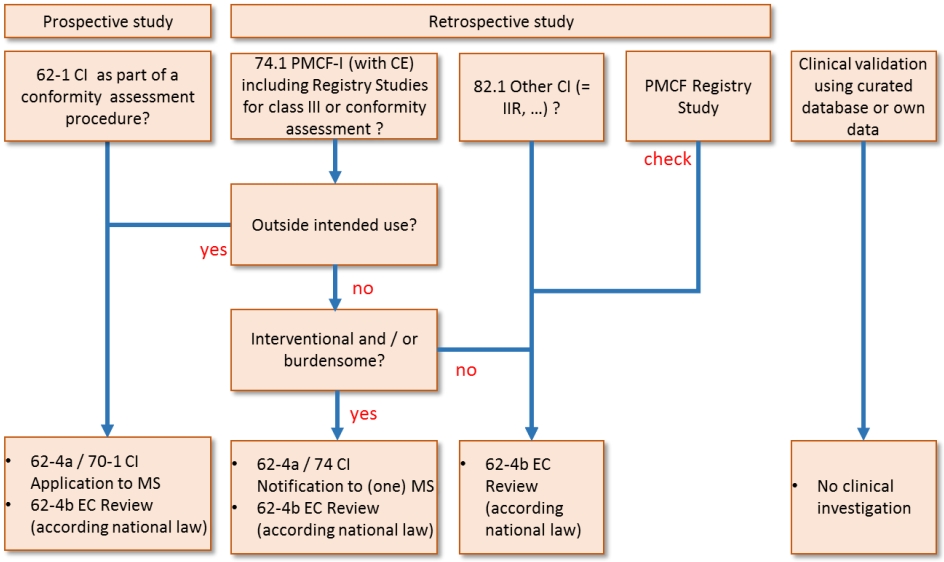
Clinical Investigations are often called clinical trials or clinical studies. The manufacturer must consider a clinical Investigation if he:

- Launches completely new software with new features and functionality.
- Modifies existing software in such a way that clinical safety and performance may be affected.
- Uses existing software for a new medical purpose.

In general, manufacturers must conduct a Clinical Investigation when it comes to high risk medical devices like class III and implantable devices (MDR art 61 (4)). Furthermore, the manufacturer may consult an expert panel (Art. 106) in case of class III and class IIb active devices intended to administer or remove a medicinal product (Art. 61 (2)). The expert panels give advice in product development and assist the EU Commission in the preparation of guidelines and common specifications. There is one exception concerning the high-risk devices mentioned above. If the clinical evaluation of a medical device marketed under the EU MDD is based on “sufficient clinical data”, no clinical study is required (Art. 61 para. 6). However, there is currently no general definition of “sufficient clinical data”, as their kind and extent are highly dependent on the type of medical device. In the future there will probably be EU-wide evaluation criteria. Respective guidelines or common specifications should be device specific.

The patient data collected is also regulated by the GDPR, and the patient should give a specific consent for this, which by default does not cover secondary use of the patient data. Therefore, also future use of the patient data should be considered, so that the patient consent also includes this.

The figure below shows the notification and review requirements for prospective and retrospective Clinical Investigations. A PMCF study is a Retrospective Investigation.



5.7. Usability

- MDR art 83 (3f) Identification of PMS data to improve usability
- MDR Annex I (5) Reduce risks use error
- MDR Annex I (14.2) Reduce risk design
- MDR Annex I (14.6) Ergonomic principles
- MDR Annex I (23) (23): Information supplied with the product.
- IEC 62366-1 Application of usability engineering to medical devices
- IEC 62366-2 Section 15.3 Design software user interfaces
- ISO 9241 series ergonomics of human-computer interaction
- ANSI/AAMI HE75 section 21 Software-user interfaces
- BSI The growing role of human factors and usability engineering for medical devices

IEC 62366-1 is usability for software and IEC 60601-1-6 is for MDSW integrated in electronic equipment and can be used in addition to IEC 62366-1 if applicable. IEC 62366-1 has to be used in together with ISO 14971 risk management. IEC 62366-1 describes the usability engineering process aimed at ensuring an acceptable risk for a MDSW. IEC TR 62366-2 explains in more detail how usability engineering can be designed, and can be next to IEC 62366-1.

The MDR has to following sections that are applicable for usability:

- MDR art 83 (3f): When the MDSW has been placed on the market the manufacturer has to record incidents and report them as part of Post Market Surveillance and consider the need to improve the usability of the MDSW.
- MDR, Annex I (1) MDSW has to be suitable for their intended purpose and the environment in which the device is used. IEC 62366-1 calls this the use specification.
- MDR Annex I (3): MDSW has to prevent foreseeable misuse. The following is expected:
  - Analyse foreseeable misuse of similar devices from literature, vigilance databases and post market surveillance data.
  - Define use scenarios with subsequent task analysis
  - Monitoring of users during formative and summative evaluations
- MDR Annex I (5): MDSW has to be designed to eliminate or reduce risks related to use error:
  - Reduce risks related to the ergonomic features of the MDSW and the use environment (design for patient safety).
  - Consider technical knowledge, experience, and health condition of the user (design for type of user).

    - The following is expected:
        - Inherent safety: a switch that does not exist cannot be pressed by accident.
        - Protective measure: a switch that has a flip cannot be pressed by accident.
        - Information for safety: for instance, a warning in the manual for pressing a switch by mistake.
- MDR Annex I (14.1): MDSW has to be designed to eliminate or reduce risks from use in combination with other devices including interoperability. These combinations have to be included in usability requirements and inherent safety against faulty connections has to be implemented as far as possible.
- MDR Annex I (14.2): MDSW has to be designed to remove or reduce as far as possible the risk of injury, by implementing ergonomic features.
- MDR Annex I (14.6): Any measurement, monitoring or display scale shall be designed and manufactured in line with ergonomic principles, taking account of the intended purpose, users, and the environmental conditions in which the devices are intended to be used.
- MDR Annex I (21.3): Displays have to be understandable.
- MDR Annex I (22): The MDSW has to be safe for use by lay persons.
- MDR Annex I (23): The instructions for use and labels for the DSW have to be usable.

The usability engineering process has the following elements:

- **Usability engineering plan**
    - The usability engineering plan shall describe the project and provisions for implementing the usability engineering process.
- **Usability input data**
    - The project starts with gathering the design input data for usability, such as:
        - MDR and other Regulatory requirements, like for the instruction for use or the labelling.
        - User requirements form product managers, application specialists, service, sales, etc.
        - Data from previous projects.
        - Feedback from users on previous versions of medical devices.
        - Analysis of similar medical devices.
- **Use specification**
    - The use specification contains information about:
        - Intended purpose.
        - Indications and patient groups.
        - User profiles.
        - Use environment.
        - Operating principles.
- **Identifying characteristics for safety**
    - The usability analysis process is performed in parallel to the ISO 14971 risk management process. This step identifies:
        - The primary operating functions in the device.
        - The use scenarios.
        - The possible use errors.
- **Identifying hazardous situations**
    - This step identifies:
        - The use specification.
        - Data from comparable devices or previous generations of the device.
        - User errors identified in the previous step.
- **Identifying hazard-related use scenarios**
    - This step identifies sequence of events and the related hazards.
- **Selecting hazards-related scenarios for summative evaluation**
    - This step identifies hazard-related scenarios for the summative evaluation based on objective criteria. Usually the scenarios that have most impact on the benefit risk ratio.
- **Identifying mitigations and user interface specification**

- The risks related to the use scenarios are evaluated on severity, frequency, and possibly detectability. Mitigation actions are identified. The mitigation actions are documented in the user interface specification (see ISO 14971 (6.2):
    - Changes in user-interface design, including warnings like message boxes.
    - Training of users.
    - Information in the instruction for use and labelling.

- **Formative Evaluation**
    - The formative evaluation is performed during the design phase. The formative evaluation can be started with internal employees and is usually also performed in later stages with users. The methods of evaluation depend on the context: questionnaires, interviews, presentations of mock-ups, observation of use of prototypes.
- **Summative evaluation**
    - The summative evaluation is performed at the end of the design phase. It can be done after the verification, or during the validation of the MDSW. The summative evaluation has to be done with users. FDA guidance provides samples sizes for each user group. The evaluation has to be done in a (simulated) use environment.

5.8. Cyber security

5.8.1. Introduction

General:
- MDR Annex I (14.2.(d)) MDSW and IT networks interaction risks
- MDR Annex I (17.2) State of the Art, Software Development Life Cycle, Risk Management, (Cyber)security and Verification and Validation
- MDR Annex I (17.3) Mobile platforms
- MDR Annex I (17.4) Hardware, IT networks, (Cyber)security
- MDR Annex I (18.8) Unauthorised access
- MDCG 2019-16 Medical Devices: Cybersecurity
- IMDRF/CYBER WG/N60 Principles and Practices for Medical Device Cybersecurity
- ENISA NIS directive All devices: Network and Information Security
- RED directive (Cybersecurity part under construction)
- GDPR (General Data Protection Regulation)

Requirements:
- BSI-CS 132 Network-Connected Medical Devices: Cyber Security Requirements
- ISO/IEC 15408 IT products and systems: security techniques
- IEC 62443 industrial automation and control systems: processes, functional requirements, security

Security risk management:
- AAMI TIR 57 Security risk management for medical devices
- IEC 60601-1: Appendix H.7 Medical electrical equipment: Causes of hazardous situations of medical devices in IT networks.

Verification and validation testing:
- UL 2900-1 Network-connectable products: verification and validation testing
- UL 2900-2-1 Network-connected components of healthcare systems: verification and validation testing

Manufacturer Disclosure Statement and implementation:

- HIMSS/NEMA HN1-2013 (MDS2) MDSW and IT networks: Manufacturer Disclosure Statement on Medical Device Security Note: The MDS2 statement is related to the requirements in EN 80001-1 section 3.5.
- IEC 80001 Healthcare IT networks: risk management, IT networks
- IEC 80001-1 Healthcare IT networks
- IEC/TR 80001-2-2-2 Healthcare IT networks
- ISO 27799 Healthcare IT networks: information security, management

Hackers have found medical devices and hospitals vulnerable for cyber-attacks, such as the crippling of hospitals with the "WannaCry" ransomware. Although medical devices are often not the primary target of ransomware, medical devices in a network are often indirectly affected. DoS attacks disrupt services of a health IT network and, make devices or network resources unavailable to its user.

Therefore, the MDR requires manufacturers to establish, implement, document, and maintain a risk management system, including for security and cybersecurity risks. This system must be a continuous iterative process throughout the lifecycle of a device. The regulation requires manufacturers to control the risks related to the IT environment and single fault conditions. The manufacturers have to mitigate the impact of security vulnerabilities in the host platform, in the operating system or in the network and to ensure their devices are resilient against attacks and manipulation. Build-in cyber security is now a must, however which regulations, and standards to meet is not clear, since this area is quickly evolving.

Cyber security is also very complex, since several stakeholders need to cooperate with each other. The hospital asset owner is responsible for secure operation of the Medical Device. The hospital system integrator is responsible for implementing a secure IT environment. The Medical Device manufacturer is responsible for developing a secure solution, including security requirements for the asset owner and system integrator to protect the Medical Device.

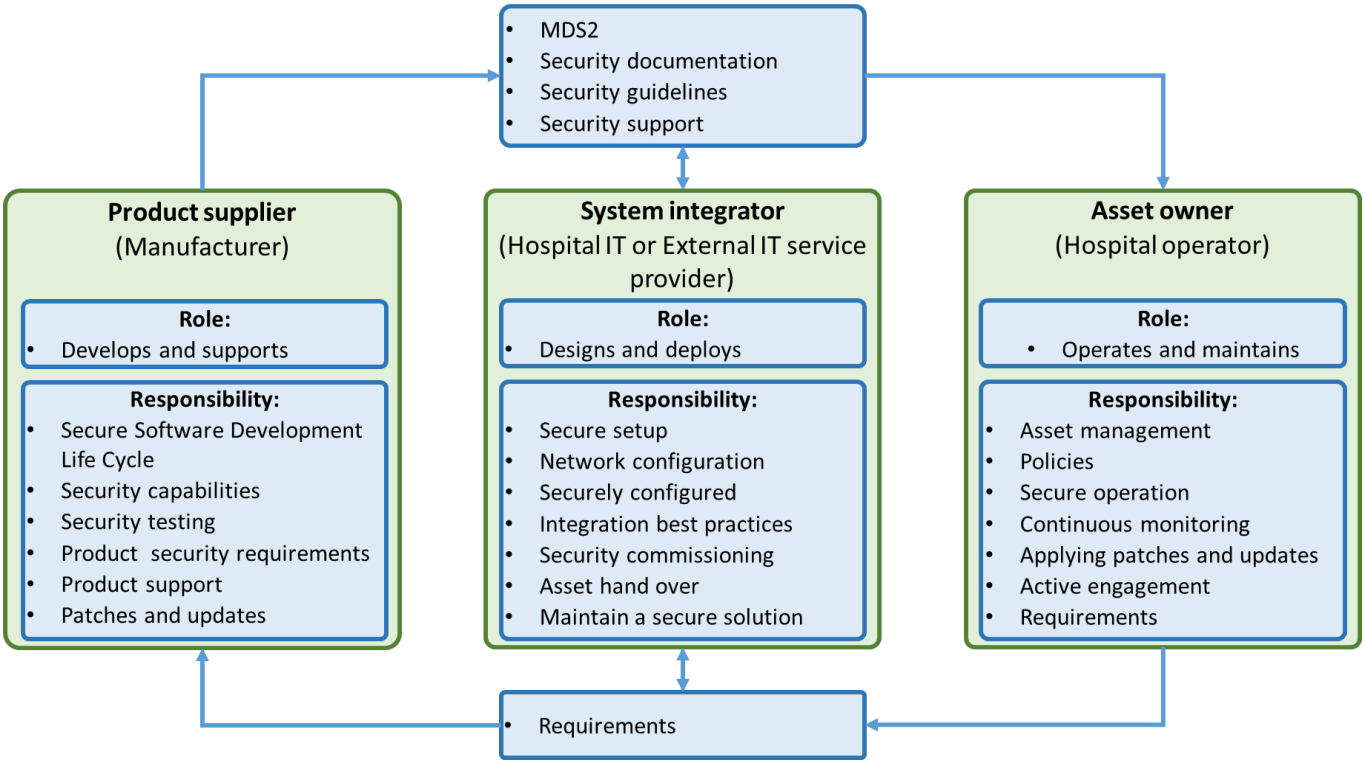


Figure 11 Overview of cybersecurity roles

The MDR requires the implementation of cyber security in their products and also define requirements for the IT environment, so that the devices can operate securely. These requirements are defined in Annex I in paragraph

14.2d, 17.1, 2 and 4. The expectation is that Medical Devices are secure by design and address by default cyber security threats.

The UL standards UL 2900-1 and UL 2900-2-1 describe verification and validation of security risk control measures against design requirements for vulnerabilities, exploits and software weaknesses. IEC 60601-1 Appendix H.7 describes possible causes of hazardous situations of medical devices in IT networks.

The usage of mobile devices is described in the DTS (Diabetes Technology Society) “Guidance for Use of Mobile Devices in Diabetes Control Contexts” and wireless diabetes devices are described in the DTSec standard.

The IEC 80001-1 and related standards are for asset owners of Healthcare IT Networks. Another family of standards covering this is the ISO/IEC 27000 series. The IEC 62443 Standard Series are helpful for defining cyber security requirements for critical infrastructures and are also very applicable for system integrators.

5.8.2. Cyber security risk management

In addition to risk management according to ISO 14971, risk management for cyber security has to be performed. The security of a device can negatively impact the safety of the device. For instance, when the operation of ventilators on an IC unit have a password protection (secure). In an emergency situation, this can be unsafe when the operator does not have the password. So, when doing risk management for security, always the trade-off for the safety and performance of the device needs to be assessed.

For the security risk management AAMI TIR 57 can be used, which complements the safety risk management activities of ISO 14971. Alternatively, the risk management method of ISO/IEC 15408 standards can be used.

5.8.3. Secure Development Life Cycle (SDLC)

The process to design and develop, maintain and decommission medical devices while considering their associated cybersecurity risks is the best way to build security into devices. A secure SDLC involves integrating security testing and other activities into an existing development process, such as writing security requirements alongside functional requirements and performing an architecture risk analysis during the design phase of the SDLC.

5.8.4. (Self)-certification

Owners of Healthcare IT networks regular request Medical Device Manufacturers that they certify that they comply with cyber security requirements, mostly with a MDS2 statement. The MDS2 is defined in HIMSS/NEMA HN1-2013 “Manufacturer Disclosure Statement on Medical Device Security”. This statement is based on the implementation of the requirement in IEC 80001-1 Section 3.5 and the requirements in IEC/TR 80001-2-2-2.

The EC has adopted the NIS Network and Information Security directive and is also working on integrating Cyber security in the RED directive. The NIS directive requires health care providers to take cyber security measures. Which can include Medical Device manufacturer audits and certifications. In addition is the EC working on certification requirements through ENISA (European Union Agency for Cybersecurity).

5.9. GDPR (Privacy)

If the MDSW handles patient data, then the General Data Protection Regulation (GDPR) applies to the processing of personal data. Exceptions apply e.g. to certain authorities and private persons. An important part of the GDPR principles concerns the territorial scope. Accordingly, the GDPR applies to companies which have customers in the EU, track customers by means of data profiling or offer goods or services in the EU in general. The fact whether such

a company has its own branch in the EU is not relevant. The GDPR is valid in every case. A further aspect of GDPR principles affects the way how data are processed in general. These principles are:

- Transparency.
- Purpose limitation.
- Data minimization.
- Accuracy.
- Storage limitation.
- Integrity.
- Confidentiality.

5.9.1. Personal Data

GDPR only applies for personal data. Personal data means any information relating to an identified or identifiable natural person which is called a “data subject”. Processing of personal data is generally prohibited and is only allowed if a legitimation exists (in the GDPR). However, there are special categories of personal data whose processing has to meet stricter requirements. This applies for data revealing racial or ethnic origin, political opinions, religious or philosophical beliefs, or trade union membership. Also, genetic data, biometric data, data concerning health or data concerning sexual orientation are considered to be special categories. When we talk about medical devices and medical software, of course “data concerning health” is of particular interest. Unfortunately, as shown above, the GDPR apparently prohibits their processing. However, there are some exceptions whose precise understanding is important for a manufacturer or operator of medical software.

There are four relevant situations in which manufacturers or operators of medical devices (or software) can lawfully process health:

- The data subject has explicitly given consent.
- The processing is necessary for the purpose of medical treatment.
- For reasons of public interest in the area of public health.
- For assuring high quality standards of the product.

However, the GDPR restricts the processing of health data as part of the medical treatment because only specialized personnel are permitted to do that. In addition, the GDPR explicitly allows the EU member states to introduce additional regulations at this point.

5.9.2. Roles and Responsibilities

The GDPR principles include certain roles with the processing of personal data, the controller, the joint controller, the processor, or the third party. The controller is the responsible body and determines the purposes and means of the processing of personal data. Two or more controllers are joint controllers when they determine the purposes and means of data processing together.

The processor is an external party and processes the controller’s data on behalf of him. A processor is thus a kind of an external “employee” of the controller which has to process the data to the requirements of the controller. Hence, it is very important to evaluate who plays which role in order to find out what obligations each party has in each individual case. If you are a processor, you are responsible for meeting the legal requirements of the GDPR.

The manufacturer has then also take the necessary technical and organizational measures as part of the risk management. It is often difficult for medical device manufacturers to judge whether they are actually “responsible” for the data processing of their product. Not only the contractual aspects but also the technical and organizational conditions are important. The medical device design and the way how it transfers and processes data also play an important role. If, for example, a manufacturer gets access to patient data for remote maintenance, he is a processor. In this case the controller has to make an agreement with the processor. If the processor processes the data independently (for other purposes on his own behalf), he becomes the controller.

5.9.3. Access, Rectification and Erasure

The data subject therefore has the right to obtain confirmation from the controller as to whether the controller has processed data relating to him or her. In this case, he or she has the right to access these personal data, i.e. also to a copy of all data stored by the controller. In addition, the data subject may also request information on a range of supplementary information, such as the purpose of the processing, the duration of the storage or any recipients of the data. Moreover, the data subject has the right to request that the controller rectify inaccurate personal data without delay. The same applies to the deletion of personal data, e.g. if the data subject withdraws its consent, if data has been unlawfully processed or if the data is no longer required for the respective purpose. It follows that the more networked medical technology is and the more players are involved in the application of medical software, the more costly it should be to implement the above-mentioned legal requirements consistently. However, it becomes even more complex if personal data is published in any way in the use of a medical product or medical software. In this case, the controller has to take reasonable steps, including technical measures, to cause deletion of the respective data. This also includes search engines or public directories. Fortunately, this case shouldn't be the rule.

5.9.4. Profiling

Another issue of the GDPR principles regarding the rights of the individual are his rights in the case of profiling. Profiling is any form of automated processing of personal data in order to evaluate personal aspects relating to a natural person, including health. Therefore, profiling is a relevant component of many medical devices including medical software. Examples are a patient monitoring system or a device to continuously measure a metabolic component. It is therefore important to know that the data subject has the right not to be subject to a decision concerning him or her or similarly significantly affects him or her. However, there are restrictions to this rule, especially if the data subject has explicitly consented or if a contract has to be fulfilled. Nevertheless, the GDPR principles mentioned above, transparency, access, rectification, and erasure apply as well in the case of profiling. For example, the data subject has the right to know whether and how profiling is carried out. The controller has to provide meaningful information about the logic involved as well as the scope and desired effects of such processing. The data subject has the possibility to revoke his consent at any time.

5.9.5. Data Portability

What happens to my data when I change a provider? Also, here the GDPR strengthens the rights of the data subjects. For the first time there is a right on data portability. Accordingly, the data subject can receive the personal data concerning him or her, which he or she has provided to a controller. Then, the controller has to provide the data in a structured, commonly used and machine-readable format. The GDPR principles also demands that the transfer of data from one controller to another controller has not to be slowed down by any (technical) hurdles. It will become clear in the future how the controller can technically implement this demand together with the medical devices or software manufacturers. The more players are involved in a medical device, system or method, the more difficult it will be to provide consistent interfaces and processes for smooth data transfer. Here, too, privacy by design will quickly pay off.

5.9.6. Risk Management

The GDPR recognizes that data processing procedures represent high risks for the privacy of persons. The measures for the protection of the data has to be appropriate. The GDPR requires a special impact assessment for data processing that involves a particularly high risk. This could be e.g. the case when profiling is performed. The controller is responsible for this special form of risk management. In particular, he or she evaluates the cause, type, specificity and severity of the risk and takes necessary measures from this. By doing so, the controller has to prove that the processing of personal data is in compliance with the GDPR. If the controller cannot limit the risk by suitable technical measures, he or she should consult the supervisory authority before processing. The data protection assessment is therefore a kind of preliminary check.

5.9.7. Privacy by Design (GDPR)

It is part of the GDPR principles to think about data protection from the outset, to view it holistically and to implement it in all processes. Consequently, the GDPR demands that the controller establishes privacy by design in his organization and therefore in his processes. This requirement applies to all data processing systems (software and hardware) that collect and process personal data from data subjects. Therefore, it applies equally to old systems and, of course, to new systems to be purchased. The controller is obligated to privacy by design. Software manufacturers are not obliged to develop or offer data protection-friendly technology for GDPR reasons unless they are controllers themselves. However, controllers may expect to receive products with which they can implement privacy by design in their processes. This will create a corresponding market pressure. If a (medical) software manufacturer studies the GDPR in detail, he knows exactly what his customers need in order to be "compliant". If the manufacturer advertises "GDPR compliant" or "compliant to the current legislation" and the software does not meet these requirements, a civil legislation problem can arise. Therefore, the manufacturer should inform a customer if the software design is not GDPR compliant, e.g. due to a modular structure.

5.9.8. Privacy by Default (GDPR)

According to GDPR, a controller can only use software and hardware which has data protection-friendly pre-settings. Hence, data protection and data security has to be implemented routinely in devices, software and systems. Consequently, privacy by default should also become standard in medical devices and medical software. In the standard settings, software may only process as little personal data as possible and transmit as little data as possible to "outsiders". Of course, this also applies to medical software. However, this has to function perfectly as part of medical diagnosis or therapy. Here, both the software manufacturers and the controllers has to weigh the compromise between medical device performance and data protection in view of the GDPR principles. Overall, the manufacturer should transparently explain to the customer or the processor, respectively, how the software is structured and to what extent the manufacturer can influence privacy by design and privacy by default. As an appropriate measure he should create a corresponding documentation that describes in detail how the software realizes GDPR requirements.

5.10. Interoperability

MDR Annex I (14.5) Interoperability
MDR art 2 Definition (26) Interoperability
EGIZ Gedragscode Elektronische Gegevensuitwisseling in de Zorg
NEN 7510 Informatiebeveiliging voor de zorgsector
NEN 7512 Vertrouwensbasis voor gegevensuitwisseling
NEN 7513 Logging
NEN 7521 Toegang tot patiëntengegevens
ISO 13972 Zorg Informatie Bouwstenen (Health and Care Information Models (HCIM))

MDSW interoperability is quickly evolving with many institutes trying to create order. The main institutes where standards and information can be found are:

- NICTIZ (Dutch IT Institute for Healthcare - Nationaal ICT Instituut in de Zorg).
- HIMMS (Healthcare Information and Management Systems Society).
- IHE (Integrating the Healthcare Enterprise).
- HL7 (Health Level Seven).
- SNOMED (Systematized Nomenclature of Medicine).
- CDISC (Clinical Data Interchange Standards Consortium).
- ISO (International Organization for Standardization).
- NEN (Stichting Koninklijk Nederlands Normalisatie Instituut).

MDSW can share health data with information systems, devices, applications, or other entities. If this is done without any restrictions, we call this interoperability. Standards, protocols and procedures are required for interoperability of entities. There are four levels of Interoperability:

- Foundational (Level 1): Establishes the inter-connectivity requirements needed for one system or application to securely communicate data to and receive data from another.
- Structural (Level 2): Defines the format, syntax and organization of data exchange including at the data field level for interpretation.
- Semantic (Level 3): Provides for common underlying models and codification of the data including the use of data elements with standardized definitions from publicly available value sets and coding vocabularies, providing shared understanding, and meaning to the user.
- Organizational (Level 4): Includes governance, policy, social, legal and organizational considerations to facilitate the secure, seamless and timely communication and use of data both within and between organizations, entities and individuals. These components enable shared consent, trust and integrated end-user processes and work-flows.

The information model (data attributes), the functional model (role played within the interoperable system), and the architectural model (how the device is connected within the system) should be considered during the development. Design inputs have to include the desired functional and performance characteristics of the electronic interface.

Manufacturers of interoperable medical devices should perform a risk analysis and conduct appropriate testing that considers the risks associated with interoperability, the anticipated users, reasonably foreseeable misuse, and reasonably foreseeable combinations of events that can result in a hazardous situation.

If the medical device/application is meant to exchange or use data with or from other entities, then the device description should include a description of the information exchanged, how it is exchanged, which (International) standards, procedures and/or protocols are used and the impact the exchanged information has on the device or other impacted devices. This may include some or all the following elements based upon the claims of data exchange and use made for the medical device:

- Explain the purpose of the interface and the role the device plays within an interoperable system. This may be as simple as stating that the device is meant to deliver device data to a specific product, technology, or system architecture described in a particular standard.
- Specify if the interface is meant to transmit, receive, or exchange information.
- Specify any international standards, procedures and/or protocols used, including relevant version numbers and dates.
- Describe the requirements for timeliness and the integrity of the information (e.g. Sample rate, transmission rate).
- Describe the communication format, rate, and transmission method.
- Describe how updates, maintenance is handled in relation to the used standards.
- Discuss the limitations (what the user should not do), contraindications, precautions, and warnings.
- Describe the functional and performance requirements.
- List the Application Programming Interface (API) if the device is software that can be used by other software, medical device, or system.

Interoperability Standards can be divided in the following categories:

- **Vocabulary/Terminology Standards**
  - Health information systems that communicate with each other rely on structured vocabularies, terminologies, code sets and classification systems to represent health concepts.
  - RadLex (example): A unified language of radiology terms for standardized indexing and retrieval of radiology information resources, managed by the Radiological Society of North America. It unifies and supplements other lexicons and standards, such as SNOMED-Clinical Terms and DICOM.
- **Content Standards**

    - Content standards define the structure and organization of the electronic message or document's content.
    - For example, HL7's Version 2.x (V2) (example): A widely implemented messaging standard that allows the exchange of clinical data between systems. It is designed to support a central patient care system as well as a more distributed environment where data resides in departmental systems.
- **Transport Standards**
    - Transport standards address the format of messages exchanged between computer systems, document architecture, clinical templates, user interface and patient data linkage.
    - For example, Digital Imaging and Communications in Medicine (DICOM): The standard for the communication and management of medical imaging information and related data. DICOM enables the transfer of medical images across systems and facilitates the development and expansion of picture archiving and communication systems.
    - For example, Fast Healthcare Interoperability Resources (FHIR): An HL7 standard for exchanging healthcare information electronically. The basic building blocks of FHIR are "resources," which describe exchangeable health data formats and elements. HL7-FHIR resources can also be seen as content standards. FHIR also provides standardization for application programming interfaces (APIs).
- **Privacy and Security Standards**
    - Privacy standards aim to protect an individual's (or organization's) right to determine whether, what, when, by whom and for what purpose their personal health information is collected, accessed, used or disclosed. Security standards define a set of administrative, physical, and technical actions to protect the confidentiality, availability, and integrity of health information.
    - For example, the General Data Protection Regulation (GDPR), in the Netherlands called "AVG", outlines privacy and security regulations for all processing and storage of data relating to data subjects (or people) in the EU. This regulation extends to health information and any organization that may process or store data on these subjects.
- **Identifier Standards:**
    - Entities use identifier standards to uniquely identify patients or providers.
    - For example, EUDAMED which stores Unique Device Identifiers.

5.11. IFUs, labels, brochures and website

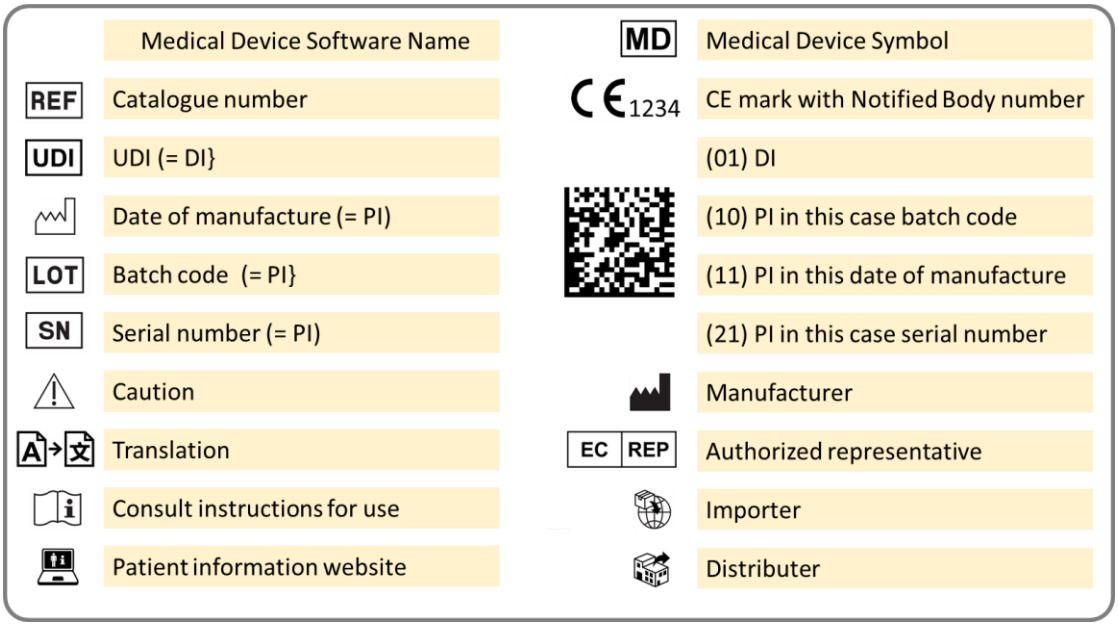
5.11.1. IFUs and labels

- MDR ANNEX I: 23 Label and instructions for use
- MDR Annex I: 23.4 f MDSW and accessories selection
- MDR Annex I: 23.4 ab MDSW minimum requirements
- MDEG 2008-12- II-6.3 Mandatory Languages Requirements for Medical Devices (aged)
- ISO 15223-1 Medical Devices — Symbols to be used with medical device labels, labelling 6 and information to be supplied — Part 1: General requirements
- EN 1041 Information supplied by the manufacturer of medical device
- ISO 20417 Information to be supplied by the manufacturer
- ISO online browsing platform (OBP) Symbols
- IEC 82304-1 Health software requirements for product safety
- Medtech Europe Use of Symbols to Indicate Compliance with the MDR

The requirements for labels, packaging and Instructions for Use (IFU) are described in MDR ANNEX 1 section 23. There are many additional requirements for labels and IFU's such as Implant Cards, but most are not applicable for MDSW. IEC 82304-1 contains additional requirements for the IFU such as:

- Start-up and shut-down instructions (§ 7.2.2.5 & 7.2.2.6).
- Disposal instructions for the software in relation to Information Security and Privacy (§ 7.2.2.9).
- IT Network specifications and risks (§7.2.3.2).

The use of symbols on the label as an alternative to written language is permitted in the MDR regulation: Annex I: 23.1. h. There are 24 official languages in Europe, which creates a necessity to translate the information provided on the labels into multiple languages. This requirement can be dealt with by using symbols. The symbols which can or should be used are described in ISO 15223-1. There is no good advice possible if these symbols can be used, since the standard is not yet harmonized, although it is intended to become a harmonized standard. As there is no similar standard, it is good practice to explain the symbols in the IFU. The symbols can be found on the ISO online browsing platform (OBP). In the figure below the most important symbols MDSW is shown.



There are two types of barcodes used, linear code 128 or 2D data matrix barcodes. Linear barcodes are more universal and can also be read by older and cheaper barcode scanners. 2D barcodes can contain much more content in much less space. 2D barcodes are the preference but check your customers base if this is the case. Barcodes should be validated for their readability at the point of use. The barcode information needs to be next to the barcode in human readable form. The different codes have a prefix, like (01) which contains the DI, and which is also shown next to the corresponding UDI symbol.

The Instructions for use and labels need to be translated in the official languages of the European Union, when that is required for a certain country (see MDEG 2008-12- II-6.3, note: this document is not maintained). The translation requirement is not always enforced for professional use. More information about that can be found on the websites of the EU member states.

5.11.2. Promotional and informational materials

The MDR does not extensively discuss promotional material (i.e. brochures and websites) and informational materials (i.e. scientific publications and training materials). Only handling of the claims is discussed in MDR art 7. There is a wide variety in promotional and informational materials, and it is wise to follow best practices. This will result in the following information on or with those materials:

- (Trade) name of the device.

- Device identification details.
- Manufacturer registered name and address.
- CE mark and Notified Body number.
- Statement of the purpose of the material and the audience since this reduces the liability. For example:" This clinical guide is to inform health care providers of the clinical performance of the device".
- The information should be relevant for the intended audience:
  - Buyer of the device.
  - Patient (as user) When applicable state that the instructions for use should always be checked prior to the application of the device.
  - Health care provider (as user). When applicable state that the instructions for use and accepted (medical) guidelines should always be checked prior to the application of the device.
  - Service engineers. When applicable state that the service instructions should always be checked prior to servicing the device.

A regulatory review on promotional materials brings regulatory and liability protection, so it is beneficial, to give as much promotional and informational materials a regulatory review. This is a popular area to ignore good advice, especially with press releases, most large internationals have learned a hard lesson and now have good procedures in place. Best practice review criteria are:

- Valid regulatory approval for specific country matching intended use and indications.
- Valid patient selection criteria if applicable.
- Valid product identification as submitted. Establishment names instead of brand names.
- No misleading product display, inks, quotes, references, or other information.
- No misleading information leading to potential patient injury (i.e. patient not seeking proper medical advice from a licensed physician).
- Proper balance is between risks and benefits. The more promotional text, the more information about risks, contra-indications, side-effects, etc.
- Valid (clinical) claims and if applicable validated or clinical evaluated (also called substantiated). Statements about intended use and indications, safety, performance, benefits and risks are seen as claims. Those close need evidence. The evidence is reviewed in the Clinical Evaluation and the promotional material is reviewed if the claims have adequate evidence.
- Common sense may be applied. A suggestion is also a claim.
- References to well recognized sources of scientific information:
  - Clinical investigation (preferably randomized clinical trials).
  - Meta-analysis of clinical investigations.
  - Standards and guidance from organisations such as ISO, IMDRF, IEC, HL-7, etc.
    - Scientific peer reviewed publications and journals from well recognized (scientific) bodies, such as WHO, IAEA, FDA, GEC/ESTRO, etc.
- No off-label use should be promoted.
- Proper division between branded (for the devices) and unbranded information (no specific device mentioned, such as a meta-analysis for certain treatment options).
- Proper audience, communication channels and methods are used.
- Proper medical advice and procedures described, if applicable and if allowed to communicate.
- Review if there is a risk for fines for (improper / unclear) claims or for off-label promotion or comparison claims.

Articles must be from bona fide peer-reviewed journals or textbooks published by a bona- fide independent publisher. Articles must be in its original state. Must contain disclosure statement for the right audience. Must disclose any relationship (including financial) between the manufacturer, the product and authors. Scientific Guides / articles must be separated from sales brochures. In general, it is good to separate branded from unbranded information.

Off-label articles must be clearly marked “This information concerns a use that has not been approved or cleared”. If the device is partially cleared, then it must include the approved labelling as well. If an off-label use of the device is described in a paper written by a clinical investigator(s), the paper may be distributed by a manufacturer only if it is provided in its entirety. The off-label articles must contain a bibliography of other articles relating to the new use. All significant risks or safety concerns known to the manufacturer concerning the unapproved use that are not discussed in the journal article or reference text.

Websites need to be reviewed as labelling. Use gateway page for location selection. For instance, USA and outside USA. Indications only approved abroad must be segregated from the USA site, with no hyperlinks between them, disclaimers are insufficient.

Do not link to off-label/ unapproved information from within the website. Observe the minimal “two clicks” rule for off-label information. Avoid hyperlinks to chat rooms or sites known to discuss off-label use of the product. Provide notice that viewer is leaving the website with a disclaimer: This hyperlink is for information purposes only, we do not control, nor accept responsibility for the content of linked website.

Not approved information, pre-approval off-label information, including study announcements, can be given, when it is in segregated in the investor or news section of a website and/or distributed to the press concurrently with a newsworthy event. Including both positive and negative results of clinical trials. An example website disclaimer is: This Web site contains information about products which may or may not be available in different countries and if applicable, may or may not have received approval or market clearance by a governmental regulatory body for different indications for use. Please consult individual country sites for approved uses and any applicable restrictions. Press releases issued by clinical institutions or investigators regarding off-label uses must not include statements or endorsements of the off-label use by anyone from the manufacturer.

Trade show best practices:

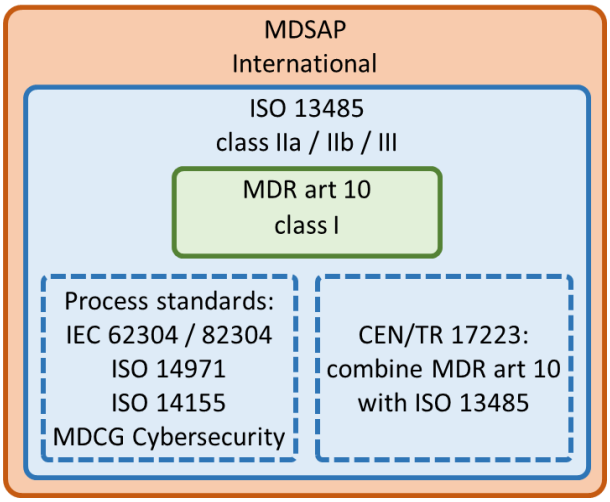
- Sales trained in communicating within the intended use and indications.
- Sales trained in making permitted announcements (disclosures).
- Trade-Show promotional materials review used, including displays, etc.
- Sales handouts reviewed. No mix-up from branded and non-braded materials.
- Consider having clinical personnel present to respond to questions that are off label.
- Consider having separated spaces for cleared vs uncleared devices / USA vs international sales.
- Uncleared devices:
  - Not cleared demo model: Prominent statement of regulatory status (i.e. 510(k) pending).
  - (USA) Cannot make safety or performance claims.
  - (USA) Cannot discuss product beyond the anticipated approval, to avoid post approval off-label issues.
  - (USA) Cannot take orders / discuss price. Can collect leads.
  - Can explain intended use and features.
  - Can discuss research or investigational use.

6. Quality Management System

6.1. Introduction

- MDR art 10 General obligations of manufacturers
- ISO 13485 Medical devices – Quality Management Systems
- CEN/TR 17223 describes how to combine ISO 13485 and MDR art 10
- IMDRF SaMD WG/N23 Software as a Medical Device (SaMD): Application of QMS
- Medical Device Single Audit Program (MDSAP)

Chapter 6 describes the QMS. ISO 13485 contains the requirements for a QMS of Medical Devices. The QMS contains the procedures which describe the activities needed to develop, purchase, produce, sell and service a MDSW. The QMS also describes the organisation of the Manufacturer and its external relations with amongst other suppliers, importers and distributor. Evidence for the execution of the QMS activities have to be documented in so called Quality Records. In most cases the Notified Body audits the QMS to review if the related MDR requirements are fulfilled.



A medical device quality management system (QMS) is a structured system of procedures and processes covering the aspects of design, manufacturing, supplier management, risk management, complaint handling, clinical data, storage, distribution, product labelling, and more. This information is put in the quality manual, procedures (often called SOPs), work instructions and templates. When the activities are performed, often an administration has to be kept in quality records, to have evidence that the Quality System was followed. The quality records are also used as input for other processes, such as risk management and quality improvement processes.

Setting up a quality system for medical devices is a considerable effort, therefore often a consultant is used. For start-ups it is recommended first to start with a minimum set of procedures covering Design Control, Risk Management and Document Control & Records Management.

The quality system must meet the requirements of MDR art 10 for all risk classes. For risk class IIa and higher the quality system in practice also needs to meet the requirements of ISO 13485. The quality system is audited according ISO 13485 by a Notified Body. For the international implementation of ISO 13485 an audit methodology is developed called MDSAP (Medical Device Single Audit Program), which contains a set of standardized audit questions. This methodology is often used by the Notified Body to certify the quality system.

6.2. ISO 13485 and MDR art 10

- MDR art 10 General obligations of manufacturers
- ISO 13485 ISO 13485 Medical devices - QMSs
- CEN/TR 17223 describes how to combine ISO 13485 and MDR art 10.
- IMDRF SaMD WG/N23 Software as a Medical Device (SaMD): Application of QMS
- Medical Device Single Audit Program (MDSAP)
- Recommendation NB-MED/2.5.2/Rec1 Subcontracting - QS related

The ISO 13485 has five sections with requirements that have to be implemented, for class IIa devices and higher. To this the requirements of MDR art 10 have to be added. CEN/TR 17223 describes how to combine ISO 13485 with MDR art 10.

The following figure gives an overview of the Quality Management System:

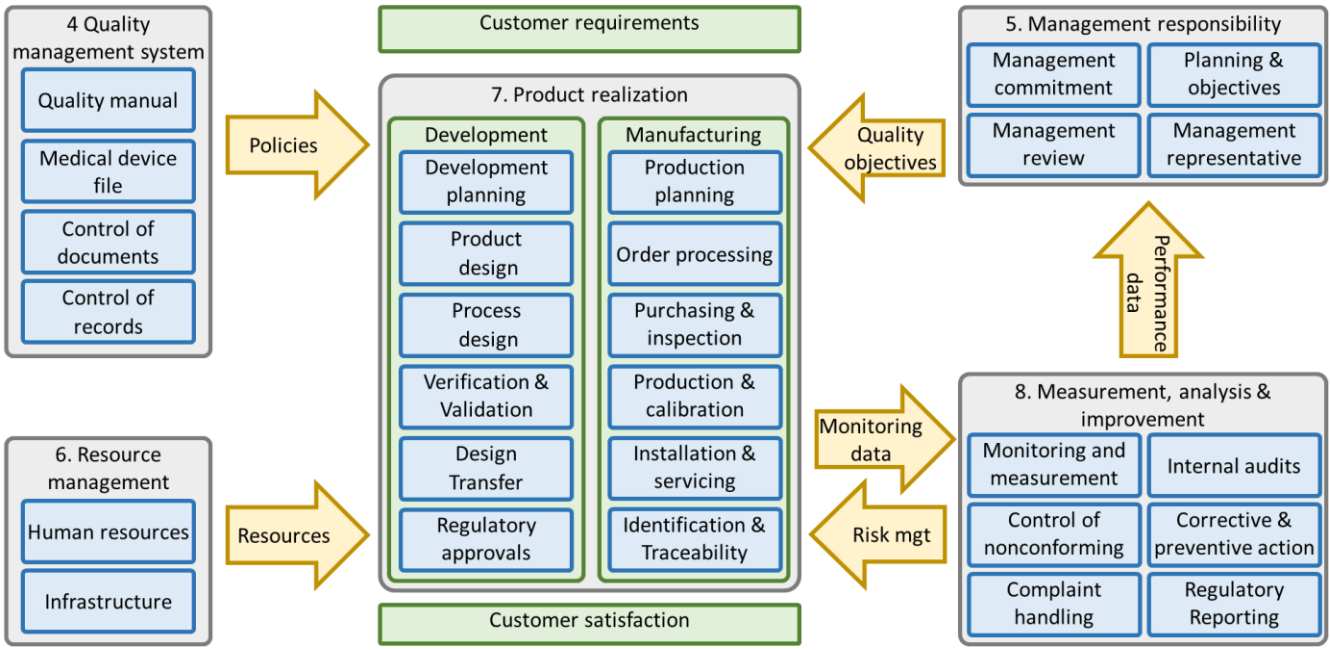


Figure 12 ISO 13485 Quality Management System

The relevant ISO 13485 sections are:

Section 4: Quality Management System – This section contains general QMS requirements, as well as the documentation requirements. It includes the requirements for the Quality Manual, Control of Documents, and Control of Records, all of which are required documents in the QMS.

Section 5: Management Responsibility – The management responsibility requirements cover the need for top management to be instrumental in the implementation and maintenance of the QMS. Along with planning for the QMS, there is a need for top management to be involved in the ongoing review of the system to ensure customer satisfaction and improvement.

Section 6: Resource Management – The section on management of resources covers the necessity to control all resources, including human resources, buildings, and infrastructure and the working environment.

Section 7: Product Realization – The product realization requirements deal with all aspects of the planning and creation of the product or service. This section includes requirements on planning, product requirements review, design, purchasing, creating the product or service, and controlling the equipment used to monitor and measure the product or service. ISO 13485 allows for requirements in the section to be excluded if they are not applicable to the manufacturer (such as a manufacturer that does not manufacture product himself).

Section 8: Measurement, Analysis, and Improvement – This last section includes the requirements needed to make sure that you can monitor whether your QMS is functioning well. It includes assessing customer satisfaction, internal audits, monitoring products and processes, dealing with non-conforming product, and corrective and preventive actions.

To complete the QMS, the requirements for a MDSW manufacturer have to be added:

- Guidance for this can be found in IMDRF SaMD WG/N23 Software as a Medical Device (SaMD): Application of QMS.
- In addition, the requirements for the process development standards have to be added for IEC 62304 / 82304 Software Development Life Cycle, IEC 62366 Usability, ISO 14971 Risk Management, MDCG 2019-16 Cybersecurity and if applicable ISO 14155 Clinical Investigation. Process development standards have to be followed from the beginning of a software development project.

6.3. Person responsible for regulatory compliance (PRRC)

- MDR art 15 Person responsible for regulatory compliance
- MDCG 2019-7 Guidance on MDR art 15 on a PRRC
- Commission Recommendation 2003/361/EC of 6 May 2003 concerning the definition of micro, small and medium-sized enterprises (OJ L 124, 20.5.2003, p. 36).

The Person Responsible for Regulatory Compliance (PRRC) is responsible for compliance with the MDR as described in MDR art 15, just like the Management Representative is responsible for the Quality System Therefore those two functions will be often combined in one person. The MDCG 2019-7 Guidance on MDR art 15 on a PRRC gives more background information how to implement the PRRC function.

The PRRC has to be registered in EUDAMED, and his contact details are visible to the general public. Therefore, it is advised to use a generic e-mail address and telephone number. The PRRC can have personal liabilities, but this is arranged in the local legislation arranging the implementation in each Member State. When there is more than one PRRC the division in responsibilities shall be described. Small and Medium Enterprises (SME's) may outsource the PRRC function. A SME has less than 50 employees and less than 10 Million Euro turnover.

The table below shows the PRRC responsibilities and to what sections of the MDR these responsibilities relate:

MDR art 15.3 PRRC responsibilities	Related MDR sections
• The conformity of the devices is appropriately checked, in accordance with the QMS under which the devices are manufactured, before a device is released	• MDR art 10(9): Establish, document, implement, maintain, keep up to date and continually improve a quality management system that has to ensure compliance with the MDRs in a manner that is proportionate to the risk class and the type of device. • Note: MDR art 10(9): describes in detail what quality management aspects has to be addressed.
• Technical documentation and is drawn up and kept up to date	• MDR arti 10(4) Draw up and keep up to date technical documentation according MDR Annex II and III. • MDR Annex II Technical Documentation • MDR Annex III: Technical Documentation on Post-Market Surveillance
• EU declaration of conformity is drawn up and kept up to date	• MDR art 10(6) Draw up an EU declaration of conformity see MDR art 19 and affix the CE mark see MDR art 20. • MDR art 19 EU declaration of conformity • MDR Annex IV: EU Declaration of Conformity (DoC)
• Note: CE marking is a consequence of drawing up the EU declaration of conformity	• MDR art 20 CE marking of conformity • MDR Annex V: CE marking of conformity
• Post-market surveillance obligations are complied with in accordance with MDR art 10 (10)	• MDR art 10.10. Post market surveillance system in accordance with MDR art 83.

MDR art 15.3 PRRC responsibilities	Related MDR sections
	• MDR art 83 Post-market surveillance system of the manufacturer
• Reporting obligations referred to in MDR art 87 to 91 are fulfilled	• Article 10(13) System for recording and reporting of incidents and field safety corrective actions see MDR art 87 and 88. • MDR art 87 Reporting of serious incidents and field safety corrective actions • MDR art 88 Trend reporting • MDR art 89 Analysis of serious incidents and field safety corrective actions • MDR art 90 Analysis of vigilance data • MDR art 91 Implementing acts
• For investigational devices, the statement referred to in MDR Annex XV chapter II (4.1) is issued.	• MDR Annex XV chapter II (4.1). A signed statement for the investigational device that the device conforms to the GSPR.

The PRRC usually needs to exercise its function:

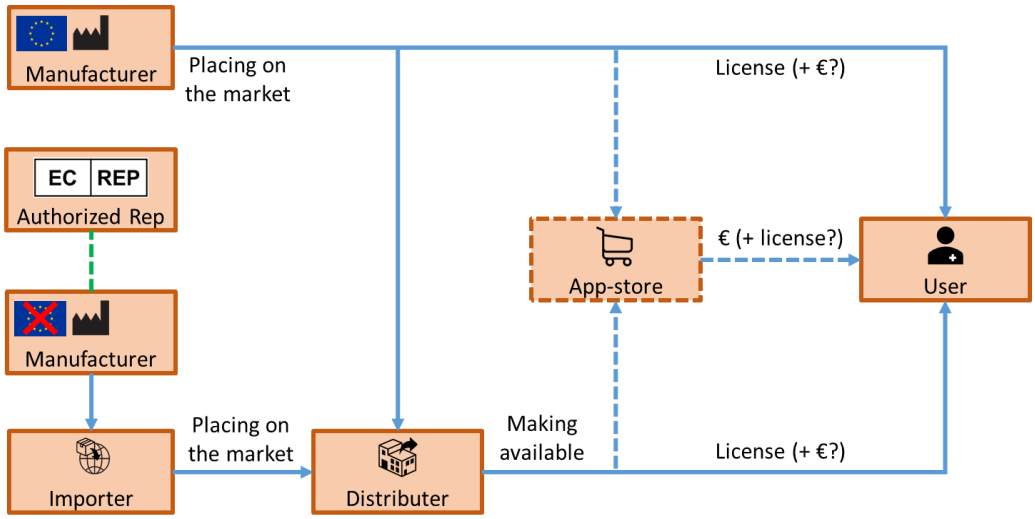
- Full access to for instance technical documentation and certificates).
- Adequate authority to initiate product hold, CAPA, quality systems changes, etc.
- An escalation process to allow a direct communication line to senior management.
- Sufficient documentation to demonstrate his/her track record is complete. This is also essential to avoid unnecessary liabilities, when the PRRC execute its job in an adequate way.

6.4. Economic Operators

- MDR art 5 Placing on the market and putting into service
- MDR art 6 Distance sales
- MDR art 11 Authorised representatives
- MDR art 12 Change of authorised representative
- MDR art 13 General obligations of importers
- MDR art 14 General obligations of distributors
- MDR art 16 Cases in which obligations of manufacturers apply to importers, distributors or other persons
- EU: Blue guide: The 'Blue Guide' on the implementation of EU products rules
- EU: Factsheet for Authorised Representatives, Importers and Distributors of Medical Devices
- EU: Factsheet for Procurement Ecosystem of medical devices
- EU: SANCO/B/2/PBE/pdw Ares(2010) 332016 interpretative document of the commission's services placing on the market of medical devices
- HPRA: Guide for Distributors of Medical Devices
- COCIR: Position Paper Economic Operators under the Medical Device Regulation
- COCIR: Template for Suspected Incident Form for Trade Partners
- MedTech Europe: Questions & Answers on Economic Operators to support IVDR/MDR implementation

Economic operators play an important role how MDSW is sold and serviced within the EU. The requirements are based on the Blue guide and further details are given in the MDR. For MDSW the requirements are not intuitive. Each Economic Operator has to meet certain MDR requirements, so identifying the Economic Operator roles is important. Economic operators are manufacturers (MDR art 10), authorized representatives (MDR art 11 and 12), importers (MDR art 13), distributors (MDR art 14), and system & procedure packers (MDR art 22). Economic operators need to register themselves (MDR art 31), except for distributors, and system & procedure packers, which

depends on the Competent Authority where the distributor and system & procedure packers is located. The COCIR Position Paper on Economic Operators under the Medical Device Regulation provides more details.



An importer, distributor or procedure packer who changes a Medical Device or it's intended use, becomes a Manufacturer (MDR art 16). Those changes include selling a Medical Device under its own name or changing to the intended use or the Safety and Performance of a Medical Device. In that case also a QMS is needed. A Manufacturer, who is outside the EU, needs an Authorized Representative and an importer.

When a manufacturer is using a distributor an agreement is needed. Below are the requirements for a ditributor and in bold what should be in an agreement:

- Check whether the medical device has a valid CE marking.
- Check that the UDI is on the label (from May 2021 for Class III, May 2023 for Class IIa / IIb and May 2025 also for Class I).
- Check whether the manual and label contain the correct information.
- Check whether the importer complies with the requirements.
- Store and retain the device according to the manufacturer's instructions.
- Inform the manufacturer (and possibly the importer and authorized representative) and if necessary, the Competent Authority if there are complaints or something is wrong with the device. COCIR has developed a Template for this: Suspected Incident Form for Trade Partners.
- Keeping a complaint register.
- Cooperate with any corrective actions (e.g. withdrawal from the market in the event of a recall).
- Cooperate with inspections (e.g. by showing documentation and providing samples).

The MDR art 6 on distant sales does not address the function of App-stores and SaaS business models. Using App-stores is a challenge:

- If App-stores operate as resellers they need to fulfil the operator roles of Importer or Distributor where necessary. App-stores as resellers can place on the market or make available the MDSW. App-stores in general do not want to operate as distributor and become an Economic Operator, since they then need to meet the requirements of the MDR.
- If App-stores operate as a marketplace, they assist in financial transactions and warehousing the MDSW app. In this role the App-store is not an Economic Operator but becomes a supplier of services. The manufacturer is then providing the license and needs an importer and distributor for this, if the Manufacturer is outside the EU. For a Manufacturer having an App-store as critical supplier is a challenge, since then a quality agreement is needed that a Notified Body can audit them.

A manufacturer can place MDSW on the market. A manufacturer outside the EU needs an Authorized Rep and Importer to place MDSW on the market. A MDSW which has not yet passed customs is not yet placed on the market. MDD / AIMDD stock placed on the market before 26 May 2024 in the supply chain at the importer or distributor can be sold or put into service (MDR art 120 (4)) until 26 May 2025.

6.5. UDI (traceability) and EUDAMED

6.5.1. UDI introduction

- MDR art 27 Unique Device Identification system
- MDR art 28 UDI database
- MDR Annex VI UDI database
- MDCG 2018-1 Guidance on Basic UDI-DI and changes to UDI-DI
- MDCG 2018-3 Guidance on UDI for systems and procedure packs
- MDCG 2018-4 Definitions/descriptions and formats of the UDI core elements for systems or procedure packs
- MDCG 2019-1 MDCG guiding principles for issuing entities rules on Basic UDI-DI
- EU UDI system frequently asked questions and answers
- MedTech Europe's Guidance on Basic UDI-DI Assignment
- HL7 ANSI/HL7 UDI, HL7 Cross Paradigm Implementation Guide: UDI Pattern

The Unique Device Identification (UDI) code is used to identify a Medical Device. Its main purpose is to identify a Medical Device uniquely. This is extremely important when a recall or warning of the product has to take place. Keeping track of Medical Device production and use is called traceability. The UDI also has many secondary uses, like managing the logistical flow or stock.

The UDI will be globally implemented, however, each regulatory country of economic area has its own implementation, which causes small differences. In this guide the European MDR implementation for UDI will be discussed, considered that the Medical Devices also can be exported. The UDI code will be publicly available through registration in the EUDAMED database.

The USA Food and Drug Administration (FDA) implemented requirements for UDI in 2013. The FDA requirements deviate slightly from the MDR requirements for UDI. When there are export plans to the USA, then it is good to study first the differences, which can be difficult to implement at a later stage.

The provisions for the European UDI system are defined in Art. 27, 28, 29 and 31 as well as in Annex VI of the EU MDR. There is further explanation of the use of UDI and EUDAMED in:

- MDCG 2018-1 v3 Guidance on Basic UDI-DI and changes to UDI-DI.
- EUDAMED database final data elements under the Basic UDI-DI:
  - MDCG 2018-3 Guidance on UDI for systems and procedure packs.
  - MDCG 2018-4 Definitions/descriptions and formats of the UDI core elements for systems or procedure packs.
  - MDCG 2019-1 MDCG guiding principles for issuing entities rules on Basic UDI-DI.
  - MDCG 2019-4 Timelines for registration of device data elements in EUDAMED.
  - MDCG 2019-9 Summary of safety and clinical performance A guide for manufacturers and notified bodies.
- European Commission: UDI system frequently asked questions and answers.
- Regulation (EU) 2017/2185 Commission Implementing Regulation (EU) 2017/2185 on the list of codes and corresponding types of devices for the purpose of specifying the scope of the designation as notified bodies in the field of medical devices.

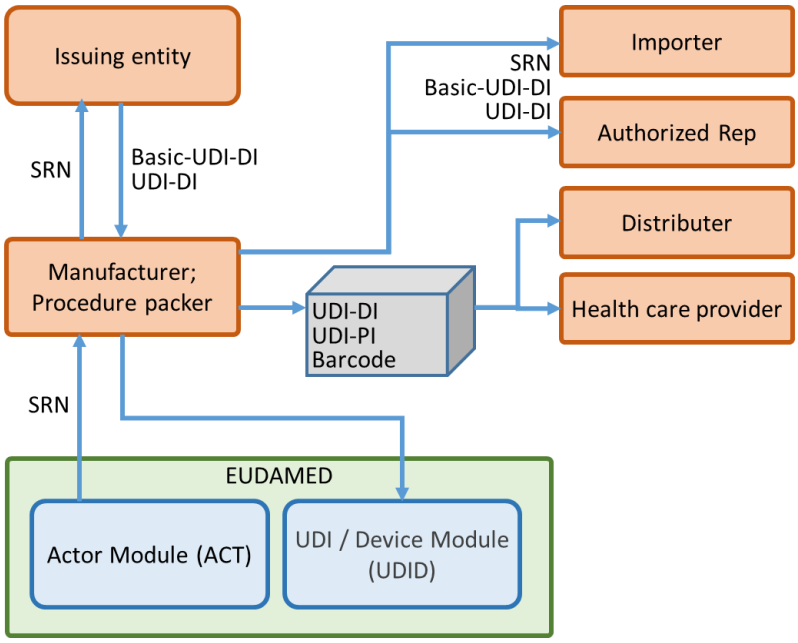
- MedTech Europe guidance for assigning Basic UDI-DI.

The issuing entities have submitted their own guidance which can be found on their websites:

- GS1 https://www.gs1.org/
- IFA https://www.ifaffm.de/en/home
- HIBC https://www.hibcc.org/
- ICCBBA https://www.iccbba.org/

6.5.2. UDI system overview

To make the UDI code work a whole system is created:



- **SRN & EUDAMED Actor Module**: The manufacturer (or procedure packer) must be uniquely identified with an SRN (Single Registration Number). The manufacturer registers via the Competent Authority in the EUDAMED Actor Module and receives the SRN. The SRN will appear for instance on each Declaration of Conformity and CE certificate.
- **Basic-UDI-DI**: Each Medical Device model of a manufacturer must be uniquely identified with a Basic-UDI-DI (Basic-UDI Device Identifier). A Basic-UDI-DI is used to group one or more Medical Devices, MDSW modules or Accessories, thus the Basic-UDI-DI is used to group one or more UDI-DI's. The manufacturer requests the Basic-UDI-DI at an issuing entity. The Basic-UDI-DI is used to connect similar Medical Devices from a certain manufacturer. The Basic-UDI-DI will appear for instance on each Declaration of Conformity and CE certificate, but it will not appear on the Medical Device product label. Note: A Basic-UDI-DI connects devices with same intended purpose, risk class and essential design and manufacturing characteristics. A change in intended purpose, risk class, essential design or manufacturing characteristics, usually results in a new Basic-UDI-DI.
- **UDI-DI**: Each commercially available System, Medical Device, Module or Accessory of a manufacturer must be uniquely identified with an UDI-DI. Any change to the data elements relating to the medical device (e.g. trade name, product version, or model) may require a new UDI-DI to be assigned. The manufacturer requests the UDI-DI at an issuing entity and receives a range of numbers for the UDI-DI. A change in the data elements relating to the medical device (e.g. trade name, product version, or model) usually results in a new UDI-DI. For software there are specific requirements, see next paragraph.

- **EUDAMED UDI / Device Module:** The manufacturer (or procedure packer) must submit the Basic-UDI-DI and UDI-DI to the UDI / Device Module into EUDAMED. In EUDAMED it's attributes are linked to the Basic-UDI-DI and UDI-DI. This data has to be added to EUDAMED and has to be maintained by the manufacturer.
- **Nomenclature code**: The nomenclature code is to identify what type of Medical Device the UDI-DI is. For instance," Radiation Treatment Planning Software". The manufacturer can determine the nomenclature when maintaining the UDI-DI in EUDAMED. Each UDI-DI has a nomenclature code.
- **UDI-PI:** The UDI-DI is created by the manufacturer for each lot number or serial number of a device. For MDSW the UDI-PI contains the software version.
- **UDI**: An UDI consists of an UDI-DI + UDI-PI. The UDI appears on the product label. Economic actors and health care providers, which get in contact with the product throughout the supply chain, register the UDI number. This registration allows for traceability.
- **Issuing entity**: The EU Commission has officially designated the following issuing entities: GS1, HIBCC, ICCBBA and IFA GmbH. These organizations have developed standards for the uniform use of machine-readable information such as identification keys, data attributes and barcodes. An example of the UDI-DI is the GS1 GTIN (Global Trade Item Number).

Below are the main attributes linked to the codes above of which most have to be maintained in EUDAMED:

Basic UDI-DI: • Notified Body • Type, number and expiry date of the certificate issued by the notified body • SRN • Name /address of manufacturer • Devices manufactured by another legal person • Member State in which the device has been placed on the market in the Union • Class IIa, class IIb or class III devices: Member States where the device is or is to be made available • Risk class of the device • Measuring function (y/n) • Implantable (y/n) • Active device (y/n) • Identification number or link to electronic system of clinical investigations • Specification as to whether the intended purpose of the device is other than a medical purpose • Class III products /implants: summary of safety and clinical performance • Status of the device	**UDI-DI:** • UDI-DI value • Quantity per package • Basic-UDI-DI • Additional UDI-DI • Reference /catalogue number • Device model • Direct marking (y/n) • Unit of use UDI-PI • Type of UDI-PI's) • Name and address of the manufacturer • SRN • Name and address of the authorised representative • Nomenclature code • Risk class • Name/trade name • Additional product description • Clinical size • Storage /handling conditions • Information labelled in accordance with Section 10.4.5 of Annex I • URL for additional information (eIFU, etc.) • Critical warnings /contra-indications • Status of the device • Systems /procedure pack: UDI-PI • Systems /procedure pack: Indication
UDI-PI: • Serial number /lot number • Expiry date • Manufacturing date, if expiry date is not applicable	**SRN:** • Type of economic operator (manufacturer, authorised representative, or importer) • Company name, address and contact details • Name address and contact details of the PRRC (person responsible for regulatory compliance)

The following table gives an overview of the main places where the SRN, Basic UDI-DI and UDI (UDI-DI + UDI-PI) are used:

Place of use	SRN	Basic UDI-DI	UDI (UDI-DI + UDI-PI)
Manufacturer	Art. 30 (1)		
Authorised Rep	Art. 30 (1)		
Importer	Art. 30 (1)		
Declaration of Conformity	Art. 27 (6)	Art 27 (6)	
Conformity assessment certificates	v	v	
Certificate of free sale		Art 60 (1)	
Technical Documentation: Product description and specification		Annex II 1.1b	
Product registration	Art 29 (1-4)	Art 29 (1-4)	
Technical documentation: information to be supplied by the manufacturer, up-to-date List			v
Reporting of serious incidents and field safety corrective actions	v		v
EU technical documentation assessment certificate		v	
EU type-examination certificate		v	
EU product verification certificates		v	
Summary of safety and clinical performance (Class III)	Art 32 (2a)	Art 32 (2a)	
Implant card for Patients			Art 18 (1)
Clinical trials documents			recommended
Vigilance reporting			recommended
Hardware product: the UDI and related information needs to be on the "UDI carrier" (barcode-label). The barcode label needs to be on the product and the product packaging. The label contains: • machine readable information (according to the barcode format received from the issuing entity) • human readable information			Part C Annex VI
Software product			• Annex VI part C 6.5 • MDCG 2018-5 UDI Assignment to MDSW

6.5.3. UDI for MDSW

For UDI used with MDSW there are specific requirements in Annex VI Part C and MDCG 2018-5:

- The UDI (UDI-DI + UDI-PI) is usually given on system level of the software if the intended use and risk class is the same.

- The software identification on the label is part of the UDI-PI.
- After certain software changes a new UDI-DI must be assigned.
- The human-readable form can be stored in software menus. If there are no user interface other ways have to be used, e.g. an application programming interface (API).

The UDI-DI changes when:

- Any change of the basic UDI-DI.
- Any changes which impact the original performance, safety, or the interpretation of data.
- A change to the name or trade name, version or model number, critical warnings or contra-indications, user interface language requires a new UDI-DI.

Minor software revisions, e.g. bugfixes without relation to safety and security, require a new UDI-PI and not a new UDI-DI.

6.5.4. EUDAMED introduction

- MDR art 29 Registration of devices
- MDR art 31 Registration of manufacturers, authorised representatives and importers
- MDCG 2019-4 Timelines for registration of device data elements in EUDAMED
- MDCG 2021-1 Guidance on harmonised administrative practices and alternative technical solutions until EUDAMED is fully functional
- EU EUDAMED database final data elements under the Basic UDI-DI
- EU Regulation 2017/2185 Commission Implementing Regulation (EU) 2017/2185 on the list of codes and corresponding types of devices for the purpose of specifying the scope of the designation as notified bodies in the field of medical devices.

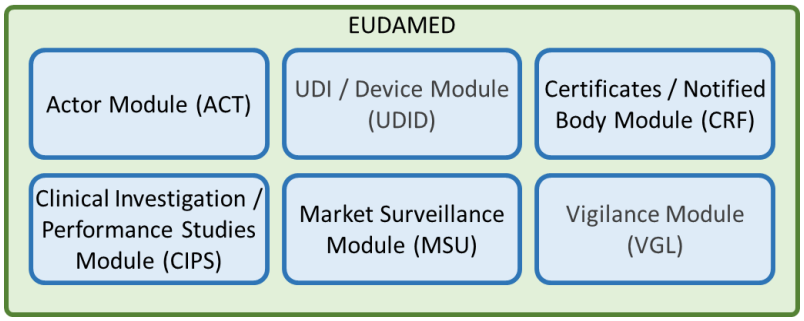
EUDAMED stands for “European Database for Medical Devices”. This database is operated by the European Commission and contains all relevant information on medical devices on the EU market.

“EUDAMED aims to improve market surveillance by giving competent authorities swift access to information about manufacturers and their authorized representatives, products and certificates, and vigilance data, it should also contribute to the exchange of information on clinical examination data and the consistent application of the above directives, in particular with regard to reporting requirements.”

The traceability of medical devices, facilitated by Eudamed, should improve the effectiveness of recalls and other field actions, incident reporting and market surveillance. Furthermore, positive impacts on the reduction of product counterfeiting, the reduction of medical malpractice and the procurement, storage and disposal of medical devices are expected.

6.5.5. EUDAMED database structure overview

The EUDAMED database consists of 6 interconnected databases. Manufacturers, other Economic Operators, Notified Bodies, Competent Authorities and each can maintain certain parts of the data contained in EUDAMED. EUDAMED contains the following modules:



- **Actor Module (ACT)**. In the Actor module, Economic Operators have to register. This registration goes via the Competent Authority who does the validation of the Economic Operator. In the Netherlands Farmatec / CIBG has that role. After validation, the Competent can give the Economic Operator the SRN (Registration Number).
  UDI / Device Module (UDID). The UDI / Device Module does contain all device-specific information and have the same functions as the comparable database of the American Health Authority (FDA) GUDID. The main difference to the GUDID is that the UDI data is divided into two areas BASIC UDI-DI and the UDI-DI. Manufacturers and other economic operators are responsible for maintaining all their Basic-UDI and UDI-DI attributes.
- **Certificates / Notified Body Module (CRF)** – Any medical device distributed in Europe and reviewed by a Notified Body requires a CE certificate. These certificates are stored and managed in this module.
- **Clinical Investigation / Performance Studies Module (CIPS)** This module contains the information from pre and post market clinical studies and is also used by the competent Authorities to share information and coordinate their activities.
- **Vigilance Module (VGL)** This module contains all information related to serious incidents. Manufacturers need to vigilance report those incidents, provide summaries thereof in PSUR's (Periodic Safety Update Reports) and provide TR's (trends reports). Follow-up actions like Field Safety Corrective Action (FSCA) and Field Safety Notifications, also need to be reported. The competent Authorities file their assessment reports of the Manufacturers actions.
- **Market Surveillance Module (MSU)**. In this module the results of the market surveillance are reported, like inspection reports of Economic Operators and yearly analysis reports on the safety of the Medical Devices on the market. Based on those reports' actions can be initiated to improve the situation.

6.6. MDR, EUDAMED and Trade Agreements in transition

MDR art 120 Transitional provisions
MDR art 123 Entry into force and date of application
MDCG 2019-4 Timelines for registration of device data elements in EUDAMED
MDCG 2020-3 Transitional provisions on significant changes of MDD or AIMDD devices
MDCG 2019-10 Transitional provisions on validity of certificates of MDD or AIMDD devices
MDCG 2020-2 Transitional provisions of class I art 120(3, 4)
MDCG 2021-?? Guidance on appropriate surveillance according to MDR art 120(3)
MDCG 2021-?? Q & A on clinical investigation

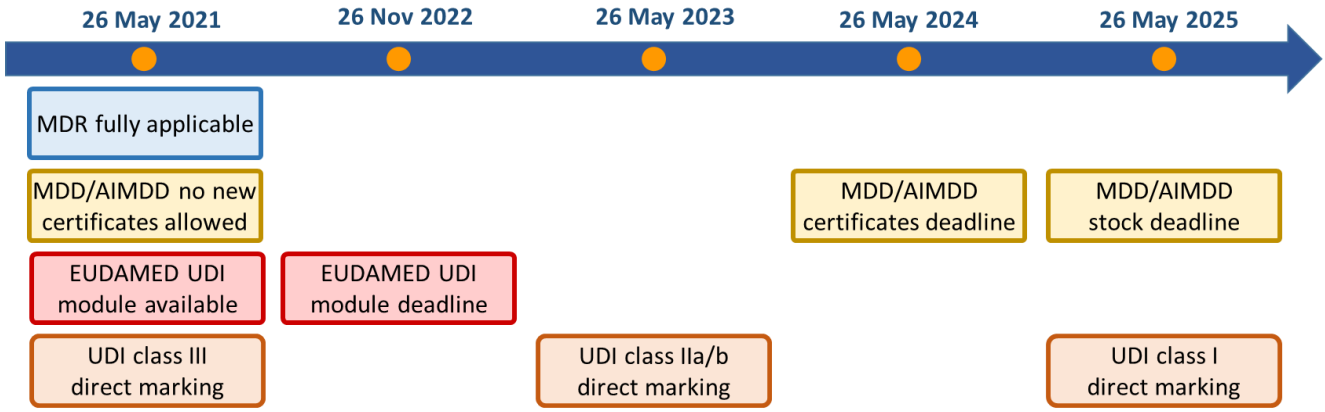
The MDR came into force on 25 May 2017. In a four-year transition period until 26 May 2021, it replaces both the MDD and the AIMDD. It is possible to have for the same device both an MDD/AIMDD and an MDR certificate. The manufacturer must register the Basic-UDI and UDI-DI including the attributes in EUDAMED. The implementation dates for direct marking with the UDI-DI and UDI-PI on the product depends on the risk class. The manufacturer cannot apply for the assignment of an UDI art. 27 (3) before EUDAMED is ready.

After 26 May 2021 making significant changes to MDD and AIMDD devices is no longer possible, causing additional problems for MDSW with its short development cycles. A significant amount of MDSW devices will be up classified

because of classification rule 11. Causing new requirements like the need for a Notified Body or Clinical Investigations.

An overview on the important implementation dates and deadlines is given below and can be seen in the figure below:

- 26 May 2017:
  - MDR has come into force MDR compliant can be placed on the market see MDR art 120 (5). This also applies to custom-made products see MDR art 2 (3) and systems and procedure packs see MDR art 2 (10-11). MDR class Is, Im, Ir, class IIa and higher need an MDR designated see MDR art 120 (6).
- 13 March 2019 Compendium I:
  - No significant changes.
- 13 November 2019 Compendium II:
  - Introduction of a transition period for class I devices.
- 26 May 2021 (Date of Application):
  - MDR: The MDR is fully applicable and the MDD / AIMDD are no longer applicable. Notified Bodies only may submit MDR CE certificates.
  - MDD / AIMDD certified devices: may still be placed on the market, with a valid CE certificate art. 120 (2). Class I devices need to have a valid Declaration of Conformity from before 26 May 2021 see Compendium II. The QMS has to meet the requirements of MDR art 10. No significant changes to the device and intended purpose can be made art. 120 (3). A significant change as result of a corrective measure, can be implemented if accepted by the competent authority.
  - MDD / AIMDD guidance like the MEDDEV's and NBOG's are no longer applicable. However not having them would lead to serious holes in the guidance. When using them, it is advised to review them on where the differences are with the MDR and give a justification, why they can be used.
  - MDD / AIMDD harmonized standards have hardly any replacements under the MDR, in addition most of them aged. It is advised in general to use the most recent standard and provide a justification, why they can be used. The FDA recognized standard database is a good starting point for finding the most applicable standards.
  - EUDAMED: Basic-UDI and UDI-DI information including their attributes can be put in EUDAMED art 123 (3e).
  - UDI: class III products need to be marked art 123 (3f).
  - Clinical Investigations that started before 26 May 2021 may continue after this date art. 120 (11). However adverse event reporting and device deficiencies need to be performed according to the MDR.
- 26 November 2022:
  - EUDAMED: Basic-UDI and UDI-DI information is required to be available MDR art 123 (3e).
- 26 May 2023:
  - UDI: class IIa / IIb products need to be UDI marked art 123 (3f).
- 26 May 2024
  - MDD / AIMDD certificates expire, and thus are no longer allowed to be sold.
- 26 May 2025:
  - UDI: class I products need to be UDI marked art 123 (3f).
  - MDD / AIMDD stock placed on the market before 26 May 2024 may no longer be sold or put into service art 120 (4).
- 26 May 2027:
  - Start coordinated assessment procedure for Clinical Investigations art 123(3h)



The transition to the MDR requires special attention for the existing trade relations, such as Mutual Recognition Agreements. The relation for the United Kingdom and Switzerland is insecure now, and it is likely they become WTO Third Countries. These changes can cause changes in the labelling, the invalidation of MDD / AIMDD certificates or the non-availability of a Notified Body. Concessions for these situations have to be given by the National Competent Authority, and in general a concession is no longer than 6 months.

6.7. Post Market obligations

6.7.1. Post Market Surveillance and Post Market Clinical Follow-Up

Post-Market Surveillance (PMS):

- MDR art 83 PMS system
- MDR art 84 PMS plan
- MDR art 85 PMS report
- MDR art 86 Periodic Safety Update Report (PSUR)
- MDR art 92 Electronic system on vigilance and on post-market surveillance
- MDR Annex III Technical documentation on PMS
- ISO/TR 20416 PMS
- Setting up PMS (original title: Vormgeven PMS voor medische hulpmiddelen onder de MDR en de IVDR)

Post-Market Clinical Follow-up (PMCF) and Registries:

- MDR art 61(11) PMCF
- MDR Annex XIV part B PMCF
- MDCG 2020-7 Guidance on PMCF plan template
- MDCG 2020-8 Guidance on PMCF evaluation report template
- IMDRF Registry WG/N46 Tools for Assessing the Usability of Registries in Support of Regulatory Decision-Making
- IMDRF Registry WG/N42 FINAL:2017 Methodological Principles in the Use of International Medical Device Registry Data

The MDR uses the terms post-market surveillance (PMS), vigilance and market surveillance. Since any of these terms are also often used for all three activities combined, this is a source of confusion. Even more confusion is caused by the significant overlap of PMS with post-market clinical follow up. And the overlap of Clinical Evaluation with Post-Market Clinical Follow-Up. And the association of Post Market Clinical Follow Studies with Clinical Investigations.

The European database Eudamed is going to contain vigilance and PMS information. The information contained in Eudamed is going to be transparent to the general public. Therefore patient and employee privicy has to be protected according to the GDPR in the vigilance and PMS process. It is also recommended that the information which will be stored in Eudamed is screened for trade secrets.

The terms can be explained as follows:

- **Post Market Surveillance (see MDR art 83 and ISO/TR 20416 Post-market surveillance)**
  - Post-market surveillance (PMS) aims to monitor the safety and performance and to improve the quality of the device once it is placed on the market. Some safety and performance risks only become apparent when the devices are used, stored, transported or cleaned. Continuous and systematic post-market surveillance is therefore crucial to prevent uncontrolled risks as a result of defects or undetected security issues.
- **Vigilance (see MDR art 87)**
  - Vigilance is the reporting of serious incidents and field safety corrective actions by manufacturers to the relevant competent authorities. The timescale for reporting depends on the severity of the serious incident. In addition, trends in expected undesirable side effects and incidents that are not classified as serious have also be reported.
- **Market Surveillance (see MDR art 93)**
  - Market surveillance is performed by the Competent Authorities to check that the devices on the market comply with the MDR and are not a health or safety threat.

The following table shows which documents are required per risk class:

Table 10 PMS related requirements per device risk class

MDR risk class	Post Market Surveillance Plan	Post Market Surveillance Report	Periodic Safety Update Report	Post Market Clinical Follow-Up Plan	Post Market Clinical Follow-Up Report
Class I	√	√	-	√	If no report, Justification required
Class IIa	√	-	≤ 2yr	√	If no report, Justification required
Class IIb - implantables	√	-	≤ 1yr	√	If no report, Justification required
Class III + implantables	√	-	≤ 1yr	√	If no report, Justification required

The following figure shows how the acceptance criteria of PMS, PMCF and Clinical Evaluation relate to each other. Unfortunately, a Clinical Evaluation and PMS has to contain all applicable information for the reviewer, which is a challenge for not duplicating to much information from the Clinical Evaluation, PMS and PMCF.

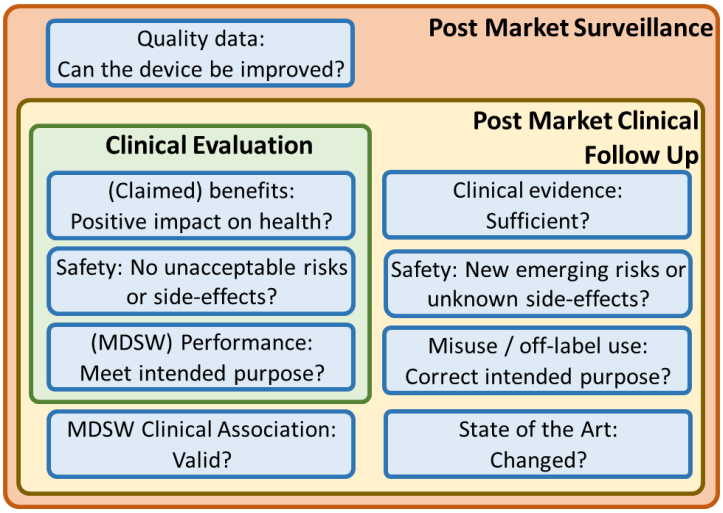


Figure 13 Acceptance criteria from Clinical Evaluation, PMS and PMCF.

- **Post-market surveillance plan (see MDR art 84 and Annex III 1.1)**
  - PMS is undertaken in accordance with a PMS plan. The PMS plan Is when applicable coordinated with authorised representatives, importers, and distributors. The contents of the PMS plan are described in MDR Annex III. The PMS plan describes which data to collect, how to analyse the data and the resulting risks, how to implement improvements and how to communicate with competent authorities, notified bodies, economic operators, and users.
  - The PMS plan has to describe the methods for data gathering and analysis. The objectives of the PMS plan have to have acceptance criteria. The post-market surveillance plan shall identify which information sources (see Annex III 1.1a) have to be used:
    - Serious incidents, and field safety corrective actions.
    - PSUR, and serious adverse events if applicable.
    - Non-serious incidents, undesirable side-effects, and information from trend reporting (see MDR art 88).
    - Feedbacks and complaints, provided by users, distributors, and importers. Feedbacks from information sources such as:
      - Non-solicited observations by healthcare providers.
      - Observations by the organization's sales and marketing teams.
      - Service reports or maintenance reports.
      - Regulatory compliance notifications.
  - The post-market surveillance plan shall also identify pro-active data collection methods. Pro-active data collection is often planned in a PMCF plan. When no PMCF is performed, a justification has to be given. The following methods are pro-active:
    - Surveys.
    - Literature searches.
    - Analyses of registries.
    - Analyses of Vigilance and Field Corrective Action information from similar (and competitor) medical devices which can be found at regulatory agencies, such as in the MAUDE database from the FDA and EUDAMED in the near future.
    - Post-market clinical follow-up studies.
  - The data analysis needs to be performed (MDR art 83 (3)):
    - To update benefit - risk ratio determination & improve risk management.
    - To update design, manufacturing, and service information, IFU and labelling.
    - To update clinical evaluation.
    - To update SSCP for class III and implantable devices.
    - To identify needs for preventive, corrective or field safety corrective action.

        - To identify improvements for usability, performance and safety of the device.
        - To contribute to the post-market surveillance of other devices if applicable.
        - To detect undesirable side effects that could be an unacceptable risk. These are reportable, unless they are:
            - Identified in the labelling.
            - Clinically well-known and predictability.
            - Documented with a risk assessment prior to the occurrence of the incident.
            - Clinically acceptable in terms of the individual patient benefit.
            - Reviewed by a qualified assessor.
    - To detect trends (see MEDDEV 2.12/1) in the defined observation period in frequency or severity of incidents that might lead to a significant negative impact on the benefit-risk analysis ratio as defined in the clinical evaluation. These trends are reportable.
    - Traceability and interfaces to other processes have to be clearly defined, such as to PMCF, risk management, vigilance reporting, clinical evaluation, corrective and preventive actions, and the implementation of improvements in the QMS, development, production, sales and service (see MDR art 83 (3).
    - The PMS plan needs to contain vigilance reporting criteria (see MDR art 83 (4), and reference to procedures to fulfil the manufacturers obligations as defined in MDR art 83, 84, 85 and 86.
- **Post-market surveillance report (see MDR art 85)**
    - A Post Market Surveillance Report is required for class I devices (incl. classes Is, Im and Ir) to summarize the results and conclusions of the data gathered as defined in the PMS plan. The report includes the justification behind and the description of preventive and corrective actions that have been taken, and it has to be updated when necessary.
- **Periodic Safety Update Report (PSUR) (see art 86)**
    - A PSUR is required for class IIa, class IIb and class III device, to summarize the results and conclusions of the data gathered as defined in the PMS plan. The PSUR has to include the conclusions of the benefit-risk determination, the main findings of the post-market clinical follow-up, and the volume of sales of the device together with information on the population using the device. The report includes the justification behind and the description of preventive and corrective actions that have been taken.
- **Post-market clinical follow-up (PMCF) (see MDR Annex XIV Part B)**
    - PMCF is part of PMS system.
    - PMCF is the active collection of safety and performance data on clinical experience when the device is use. For PMCF a wide range of scientific techniques can be used to gather and analyse the clinical data, such as a registry study, a patient or physician survey or a new clinical investigation.
- **PMCF plan**
    - PMCF is undertaken in accordance with a PMCF plan. The PMCF plan should aim to confirm safety and performance, identify unknown side-effects, identify contraindications or risks and ensure continued acceptability of the benefit-risk ratio.
    - The PMCF plan has to describe the methods for data gathering and analysis in a scientifically sound way. The objectives of the PMCF plan has to have acceptance criteria.
    - The PMCF is a continuous process that is post market part of clinical evaluation and forms a bridge from evidence collected during the premarket stage with clinical data collected when the device is in regular use.
- **PMCF Report**
    - A Post Market Surveillance Report is not always required. However, a justification has to be given in either the Clinical Evaluation Report, the PMCF plan or PMS plan.
    - The following review criteria could use a justification that no additional clinical data is needed:
        - Where CE marking was based on equivalence, MDR art 61(10) or MDD / AIMDD legacy device clinical data.
        - High risk anatomical locations.
        - High risk target populations e.g. paediatrics, elderly.
        - Severity of disease/treatment challenges.
        - Questions of ability to generalize clinical investigation results.

- Unanswered questions of long-term safety and performance.
- Results from any previous clinical investigation, including adverse events or from post-market surveillance activities.
- Risks identified from the literature or other data sources for similar marketed devices.
- Interaction with other medical products or treatments.
- Verification of safety and performance of device when exposed to a larger and more varied population of clinical users.
- Emergence of new information on safety or performance.
- Identification of previously unstudied subpopulations which may show different benefit/risk-ratio e.g. hip implants in different ethnic populations.
- Continued validation in cases of discrepancy between reasonable premarket follow-up time scales and the expected life of the product.

6.7.2. Complaint Handling and Vigilance reporting

Feedback and complaint handling:

- ISO 13485 - 8.2.1 Feedback
- ISO 13485 - 8.2.2 Complaint handling

Vigilance reporting:

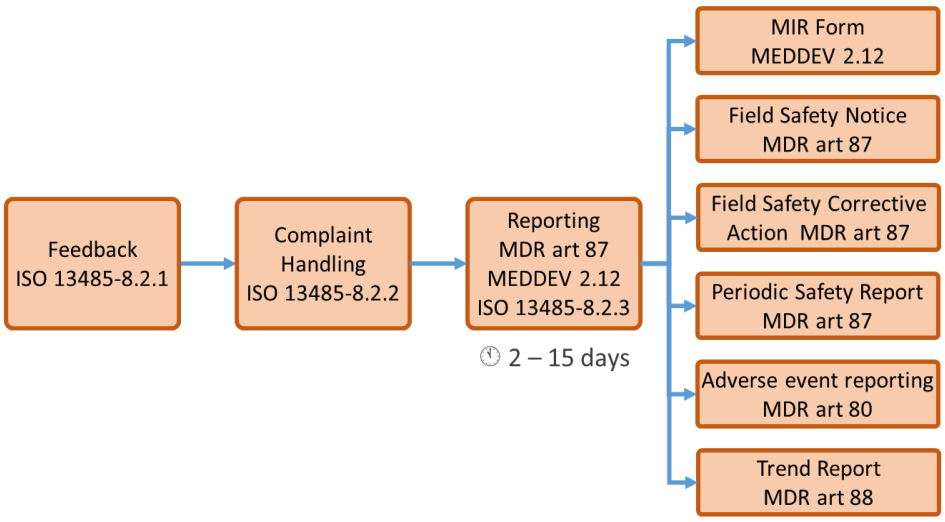
- MDR art 80 Recording and reporting of adverse events that occur during clinical investigations
- MDR art 87 Reporting of serious incidents and field safety corrective actions
- MDR art 88 Trend reporting
- MDR art 89 Analysis of serious incidents and field safety corrective actions
- MDR annex III technical documentation on Post-Market Surveillance
- MEDDEV 2.12/1 Guidelines on a medical devices vigilance system & Additional Guidance Regarding the Vigilance System as outlined in MEDDEV 2.12-1 rev. 8
- GHTF SG2 document N54 Appendix C : Global Guidance for Adverse Event Reporting for Medical Devices provides useful guidance on the trending procedure.

Market surveillance:

- MDR art 90-100 Market Surveillance
- EU regulation 2019/1020 on market surveillance and compliance of products

After the device has been placed on the market, the manufacturer and other economic operators have the obligation to monitor the quality, performance and safety of a device throughout its entire lifetime (see paragraph on PMS) , report incidents and correct those incidents. The essential part of to do this process is described in ISO 13485 – 8.2.1 Feedback (which includes Post Market Surveillance), ISO 13485 – 8.2.2 Complaint handling and MDR art 87 Vigilance Reporting. In theory Manufacturers of class I products are exempt of following the ISO 13485, however they are advised to implement this section of the ISO 13485.

The system has the following elements:



The Complaint Handling and Vigilance reporting process can be setup in multiple ways. Following are the typical elements in such a process:

- **Feedback (see ISO 13485 - 8.2.1)**
  - The manufacturer has to setup a process to (actively) receive and review feedback. There are two types of feedback:
    - Event driven feedback: For example:
      - A complaint report from a hospital that the MDSW was involved in the harm of a patient.
      - A service report that a bug did not allow the patient to be treated.
    - Review driven feedback. The activities for review driven feedback are described in the Post Market Surveillance Plan, for example:
      - A helpdesk record review showing a trend in more customer calls after the release of a software update, which qualifies as an alleged deficiency (complaint). Often these reviews are part of a PMS report, PMCF report or Clinical Evaluation Report.
      - A development audit which uncovers a certain test has not been performed correctly, which has to be reviewed if it can cause an alleged deficiency.
    - The feedback has to be checked if it classifies as a complaint. If the feedback is an alleged deficiency, it classifies as a complaint. See also the complaint definition in ISO 13485: a written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, usability, safety or performance of a medical device that has been released from the organization's control or related to a service that affects the performance of such medical devices. Please note that usability and service are included.
- **Complaint handling (see ISO 13485 - 8.2.2)**
  - The complaints handling process has to follows the following typical steps:
    - Document the complaint.
      - Whether the device failed to meet specifications;
      - Whether the device was being used for treatment or diagnosis; and
      - The relationship, if any, of the device to the reported incident or adverse event.
      - If the user has reported the complaint to the authorities, then ask for a copy of the report.
    - Investigate the complaint:
      - The name of the device.
      - The date the complaint was received.
      - Any unique device identifier (UDI), and any other device identification(s) and control number(s) used.
      - The name, address, and phone number of the complainant.
      - The nature and details of the complaint.
      - The dates and results of the investigation.

        - Any corrective action taken.
        - Any reply to the complainant.
    - Access the risk immediately (see MDR art 89) and check if the incident classifies as a serious incident, since otherwise reporting timelines cannot be met.
    - Justify if the complaint is not a serious incident and does not pose a safety or performance risk and is therefore not reportable, for example:
        - The MDSW is working as intended.
        - The alleged deficiency is not a treatment or diagnostic feature.
        - The alleged deficiency is 100% detectible prior to use.
        - The alleged deficiency causes the device not to be usable.
        - No product involved.
        - The product stopped working safely.
    - Verify if the risk analysis needs to be updated and if there are design changes needed. For serious incidents a root cause investigation has to be performed if the root cause is not yet known. (see MDR art 89 and ISO 14971).
    - Describe corrections, preventive and corrective actions if required (see ISO 13485 – 8.5). This process is often called the CAPA process (Corrective Action and Preventive Action). Create a CAPA if a Field Safety Notice (FSN) or Field Safety Corrective Action (FSCA) is initiated. The CAPA also requires the effectiveness check of the FSN and FSCA.
    - Describe the handling of complaint-related product (see ISO 13485 – 8.3). This includes products at the customer, stock in the warehouse and work in progress.
  - The complaint handling process has to be compliant with the GDPR if patient data is handled.

- **Vigilance reporting (see MDR art 87):**
  - **Vigilance reporting** and its forms are described in MEDDEV 2.12/1, since this guidance is based on the MDD / AIMDD, it is likely to be replaced in the coming years with MDCG guidance. The MEDDEV 2.12 contains requirements to which Competent Authority has to be reported until EUDAMED is ready. The **Manufacturer Incident Report form (MIR form)** is used to report the serious incident according to MDR art 87 and Meddev 2.12. The Competent Authority in the Netherlands is IGJ. Based on the reporting of the manufacturer the Competent Authority assesses the risk for the public health and starts an investigation with follow-up actions as necessary.
  - Any serious incident that occurs with a device that is not in the EEA, Turkey or Switzerland and did not lead to a Field Safety Corrective Action is not reported through vigilance in the EU.
  - **Incidents** can be divided in two types:
    - Serious incidents, which need vigilance reporting.
    - Non-serious, incidents which need trend reporting.
  - **Serious incidents** have to be reported within:
    - 2 days for serious public health threats.
    - 10 days in the event of death or an unanticipated serious deterioration in a person's state of health
    - 15 days for all other serious incidents.
  - **Field Safety Corrective Action (FSCA) and Field Safety Notice (FSN)** (MDR art 87 and 89 and MEDDEV 2.12/1)
    A Field Safety Corrective Action has to be reported immediately when identified in the CAPA process to restore the safety and performance of the Medical Device. An FSCA should be notified to the user via a Field Safety Notice.
  - **Product Summary Reports (PSR)** (MDR art 87 (9) and MEDDEV 2.12/1)
    Product Summary Reports are used for reporting similar serious incidents when agreed with the Competent Authority.
  - **Serious Adverse Events (SAE)** (MDR art 80)
    Serious Adverse Events have to be reported in addition to vigilance reports if the device is used in a Clinical Investigation.

- **Trend Report** (MDR art 88 and MEDDEV 2.12/1)
  - Trend reports contain non-serious incidents that are normally received as complaints that are not reported or expected side-effects. GHTF SG2 N54 Appendix C: provides useful guidance on the setup of trend reporting.
  - A trend report has to be submitted to the National Competent Authority (NCA) only when any statistically significant increase in the frequency or severity of incidents that are not serious incidents or that are expected undesirable side-effects that could have a significant impact on the benefit-risk analysis.
  - A trend report has to be submitted to the National Competent Authority (NCA) according MDR art 88 where the manufacturer or its authorized representative has his registered place of business.
- **Periodic Safety Update Report (PSUR)** (MDR art 86)
  - The Periodic Safety Update Report has to be made for class IIa, IIb and III devices. The PSUR summarizes analysis, results, CAPA's and conclusions.
- **Summary of Safety and Clinical Performance (SSCP)** (MDR art 32)
  - The **Summary of Safety and Clinical Performance** has to be made for class III and implantable devices. The SSCP contains safety and performance information that need to be clear for patients and users of the device.

- **Market Surveillance (see MDR art 90 - 100):**
  - The competent authorities perform market surveillance activities to ensure that medical devices meet the MDR requirements and do not endanger health and safety. Market surveillance and control of products entering the EU market are described in MDR art 90-100 and EU regulation 2019/1020. EUDAMED has a module for Market Surveillance containing inspection reports of Economic Operators and yearly analysis reports on the safety of the Medical Devices on the market. Based on those reports' actions can be initiated to improve the situation by the competent authorities. EUDAMED also gives the Competant authorities quick access to other information important for market surveillance, such as vigilance reporting and adverse event reporting.

6.7.3. Maintenance, updates, upgrades, lifetimes and warrantees

- ISO 13485 - 7.5.4 Servicing activities
- ISO 13485 - 8.2.2 Complaint handling
- COCIR Good Maintenance Services Practice Guide: Optimising the equipment life cycle

The MDR and the ISO 13485 do not give much clarity how to setup a program for maintenance, updates, upgrades and lifetimes for MDSW. Although written for capital equipment including software, the COCIR Good Maintenance Services Practice Guide describe all the elements which are needed.

The maintenance program interferes with the complaint handling, where the question arises, is corrective maintenance an alleged deficiency (see complaint definition ISO 13485) and should it therefore be handled as a complaint? When the manufacturer handles corrective maintenance as complaints, several additional administrative requirements arise, see ISO 13485 8.2.2 Complaint Handling. However, this might be a safe approach, since many auditors are of the opinion that corrective maintenance should be classified as complaints. When a manufacturer does not want to have this administrative burden, then describing the conditions which might need maintenance, like replacing a defective light bulb, should be described that these conditions are not considered a complaint.

The Terms and Conditions of Sales should contain the conditions of a warrantee. A warrantee limits the liabilities of a manufacturer since it defines when the liabilities end. The Instruction for Use should contain the lifetime of a device and the obligation for doing updates and upgrades for a user, including commissioning, maintenance, training, service contract, calibration, testing and other requirements linked to the safe use of a device.

6.7.4. Significant changes after placing the product on the market

- MDR art 83 (4) Preventive or corrective action, field safety corrective action.
- MDR art 120 (3) No significant changes to Legacy devices after Date of Application
- ANNEX VII Requirements to be met by Notified Bodies 4.9. Changes and modifications
- ANNEX IX Conformity assessment based on a QMS and on assessment of technical documentation 2.2c ”management of design or QMS changes”
- MDCG 2018-1 Guidance on basic UDI-DI and changes to UDI-DI
- MDCG 2020-3 Guidance on significant changes regarding the transitional provision under MDR art 120 of the MDR with regard to devices covered by certificates according to MDD or AIMDD
- NBOG 2014-3: Guidance for manufacturers and Notified Bodies on reporting of Design Changes and Changes of the Quality System
- NB-MED/2.5.2/Rec2 Reporting of design changes and changes of the quality system

When the device is placed on the market, changes to the device often have a regulatory impact:

- For MDD / AIMDD no significant changes are allowed after 26 May 2021 if the device remains on the market with a MDD/AIMDD certificate. Significant changes result in MDR certification of that device. What a significant change is, is described in detail in MDCG 2020-3. Design changes and changes in the intended purpose (called intended use in the MDD and AIMDD) are considered significant. A significant change as result of a corrective measure, can be implemented if accepted by the competent authority.
- For MDR devices the manufacturer shall have a procedure to manage design or QMS changes see ANNEX IX. This procedure should be aligned with the agreement with the Notified Body which defines (substantial) changes to be submitted to the Notified Body for pre-approval see ANNEX VII 4.9. Other changes are reviewed during the Notified Body audits.

Note the MDD/AIMDD and the MDR and its related guidance mix-up the terms for significant and substantial change.

It is wise and required to review the consequences of the change before making it. The MDCG 2020-3 guidance discusses several types of changes for MMM and AIMDD products, which in general considered significant:

- Intended Purpose changes:
  - Extension or change to the intended purpose.
  - New user or patient population.
  - Change of clinical use (example: anatomical site).
- Design or Performance Specification changes:
  - Requires further clinical or usability data.
  - New risks require control measures.
  - Existing risks negatively affected.
  - Change to built-in control mechanism.
  - Change to operating principles, source of energy or alarms.
- Software changes:
  - New or major change to operating system or component.
  - New/modified architecture/database structure.
  - Change of algorithm (but not software bug fixes, security updates).
  - Required user input replaced by closed loop algorithm.
  - New diagnostic or therapeutic features or new channel of interoperability.

    - New user interface or presentation of data that impacts performance.
- QMS changes see MDCG 2020-3 9.6:
    - Change in company ownership.
    - Extension to manufacturing and/or design control.
    - New facility or line modification/relocation.
    - Significant modifications to special processes.
    - Change in authority of the management representative.
    - Post-market surveillance and vigilance issues.
    - Concerns about implementation or corrective actions.

The Blue guide allows updates and repairs to software placed on the market, unless the MDR describes more specific requirements. Note: an importer or distributor who changes a Medical Device, becomes a Manufacturer, see the section about Economic Operators. The following table discusses the impact of an update / change in such cases:

Change element	Typical impact
Intended purpose change, for instance: • New user or patient population • Change of clinical use (example: new anatomical site)	• Any change in intended purpose or indication is significant. This is also true for new claims impacting safety and performance of the device. • Check risk class • New Basic-UDI-DI • New UDI-DI • MDR devices see ANNEX IX • MDD / AIMDD device need MDR certificate after 26 May 2020
Significant and substantial design and QMS change / bug / security update	• Significant changes include changes of the Basic UDI-DI. • MDCG 2020-3 guidance discusses several types of significant changes • Check risk class • New UDI-DI • Class I check if this change has to be notified to the Competent Authority • Class IIa/IIb check if this change needs to be reviewed by the Notified Body • Class III check if a Technical documentation review by the Notified Body is needed
Minor design change / bug / security update	• Minor changes in general have no impact on the safety and performance or essential security. • New UDI-PI
Other changes	• Any change to the data elements relating to the medical device (e.g. trade name, product version, or model) may require a new UDI-DI to be assigned. • Any change which impacts the original performance, safety, or the interpretation of data. • A change to the name or trade name, version or model number, critical warnings or contra-indications, user interface language requires a new UDI-DI.

7. MDR related costs

Chapter 7 describes the costs and resources needed to implement the MDR. In addition, senior management commitment, a decent project plan, a dedicated project manager and allocation of resources, are needed.

The following should be included in the MDR project plan:

- Where is the medical device going to be marketed?
- Which regulatory approvals are needed for those markets?
- Is reimbursement available in that market?
- For the MDR:
  - Is the device a medical device according to the MDR (see qualification in chapter 3)?
  - What is the product risk class (see classification in chapter 3)?
  - What is the conformity assessment route (see chapter 4)?
  - Is a suitable Notified Body available (see chapter 4)?
  - What is needed for certification (see paragraph 2.2 and 4.4)?
  - What is the intended purpose and what are the claims (see paragraph 3.2)?
  - What is the (clinical) evidence needed for the intended purpose and the claims? Is that evidence available or has that evidence to be created (see paragraph 5.6)?
  - Are clinical investigations needed to create the evidence (see paragraph 5.6)?
- For the organization:
  - Is suitable (external) expertise available (see table below)?
  - Is a suitable PRRC available (see paragraph 6.3)?
  - Is an Authorized Representative needed and available (see paragraph 6.4)?
  - Are importers or distributors needed and available (see paragraph 6.4)?
  - Are Appstore's or cloud services foreseen, and do they meet regulatory requirements (see paragraph 6.4)?
- Are there sufficient financial resources (see table below)?
- Is there a realistic timetable and can the medical device be ready in time (see table below)?

The resource needs vary per medical device and risk classification. The following table provides a rough estimation of these resources.

Activities	Required	Throughput time	Cost	Expert needed
Product related out of pocket cost	class I	> 1 year	> € 30k	
	class IIa/b		€ 250k - € 350k	
	class III		> € 350k	
• GSPR checklist	class I - III	> 2½ months	> 160 hrs	• MDR product external expert
	class IIa/b & III		> 160 hrs	• Quality Manager
• Risk Management	class I - III	> 2½ months	> 160 hrs	• MDR product external expert
	class IIa/b & III		> 160 hrs	• Quality Manager
• Technical documentation	class I	> 1 year	> 160 hrs	
	class IIa/b		> 1000 hrs	• MDR product external expert
	class III		> 2200 hrs	
	class I		> 160 hrs	

Activities	Required	Throughput time	Cost	Expert needed
	class IIa/b		> 1000 hrs	• Quality Manager
	class III		> 2200 hrs	
• Clinical Evaluation during development	class IIa/b & III	> 2½ months	> 160 hours	• Clinical evaluator • Physician reviewer
• Clinical Evaluation pre-clinical investigation	class III	> 2½ months	> 160 hours	• Clinical evaluator • Physician reviewer
• Clinical Evaluation pre-market	class I	> 2½ months	> 160 hours	• Clinical evaluator • Physician reviewer
• Product manual (and labels)	class I - III	> ½ year	p.m.	• Technical writing and label designers
• Translations	class I - III	> 2 months	Translation costs calculate per word over total of manual words per language	• Native speaking translators and reviewers with expertise in clinical application • Technical writing and label designers
• Clinical Investigation approval (CCMO and Ethical committee)	class III	> ½ year	Fees per country (posted on the Competent Authority website	• CRO • Quality Assurance
• Clinical Investigation	class III	>> 1 year	>> € 100k	• CRO • Investigators • Quality Assurance
• QMS Manual setup	class IIa/b & III	1 year	€ 25k (€ 80 – € 150 per hour)	• ISO 13485 consultant
• QMS related	class I - III	2 – 3-year total MDR preparation	5 - 10% of the time of your internal resources	• Internal resources
• Product notification	class I	1 month	Fees see Competent Authority website	• Quality Assurance
• Product certification	class IIa/b & III (and Is / m / r)	1 year	Fees as quoted per Notified Body	• Notified Body • Quality Assurance
• QMS Certification	class IIa/b & III		(€ 250 – € 400 per hour)	• Notified Body • Quality Assurance
• Vigilance reporting	class I - III	Not applicable		• Quality Assurance
• PMS and PMCF	class I	Not applicable	> 160 hrs	• PMS and PMCF not likely
	class IIa/b		> 320 hrs	• PMS and possibly PMCF

Activities	Required	Throughput time	Cost	Expert needed
	lass III		>> € 100k	• PMS and likely PMC

Appendix 1: Resources and hyperlinks

Resource	Topic	URL / Search term
	•	•
European Commission	• Medical Devices overview page	• ec.europa.eu/health/md_dialogue/overview_en
• MDR	• Medical Device Regulation	• ec.europa.eu/health/md_newregulations/overview_en
	• MDCG guidance overview	• ec.europa.eu/health/md_newregulations/guidance_en
• MDD	• Guidance MEDDEVs • Consensus statements • Informative documents • Harmonised European standards	• ec.europa.eu/health/md_sector/current_directives_en
Competent Authorities and Agencies in Europe	• CAMD • ENISA	• www.camd-europe.eu • www.enisa.europa.eu
Competent Authority Netherlands	• IGJ (Inspectie Gezondheidszorg en Jeugd) • VWS (Volksgezondheid, Welzijn en Sport) • CCMO (Centrale Commissie Mensgebonden Onderzoek) • RIVM (Rijksinstituut voor Volksgezondheid en Milieu) • CIBG (also known as Farmatec)	• www.igj.nl • www.rijksoverheid.nl/onderwerpen/medische-hulpmiddelen/nieuwe-wetgeving-medische-hulpmiddelen/meer-informatie-nieuwe-medische-hulpmiddelen • www.ccmo.nl • www.rivm.nl • www.cibg.nl
Competent Authority Belgium	• FAGG (Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten)	• www.fagg.be/nl/MENSELIJK_gebruik/gezondheidsproducten/medische_hulpmiddelen_hulpstukken •
Competent Authority (US)	• FDA	• www.fda.gov
NANDO	• Notified Bodies overview	• ec.europa.eu/growth/tools-databases/nando/
Notified Body	• Netherlands: BSI-NL, DEKRA & DARE • Belgium: SGS.	• www.bsigroup.com/nl-NL • www.dekra.nl • www.dare.nl • www.sgs.be
Notified Body guidance	• Notified Body Operations Group • Team-NB documents • NB-MED documents	• www.nbog.eu/nbog-documents/ • www.team-nb.org/team-nb-documents/ • www.team-nb.org/nb-med-documents/
Branch organisations for MDSW	• COCIR (EU) • Medtech Europe (EU) • FHI (NL) • FME (NL) • OIZorg (NL) • AGORIA (BE)	• www.cocir.org • www.medtecheurope.org • www.fhi.nl • www.fme.nl • www.oizorg.nl • www.agoria.be
Competence centre	• Nictiz (NL – data exchange) • GEC Estro	• www.nictiz.nl • www.estro.org
Standardisation	• ISO (International) • CEN-CENELEC(European) • NEN (NL) • HL-7 (NL) • DICOM • IEC • HIMSS • UL • SNOMED • WHO • ANSI	• www.iso.org • www.cencenelec.eu • www.nen.nl • www.hl7.nl • www.dicomstandard.org • www.iec.ch • www.himss.org • www.ul.com • www.snomed.org • www.who.org • www.ansi.org
Consultancy	• Consultancy offices Netherlands or	• google search: medical device regulation consultant

Resource	Topic	URL / Search term
	Belgium. • Individual consultants are not easy to find. The RAPS NL meetings are visited by a lot of consultants from the Netherlands and Belgium.	Nederland / Belgie • google search: medical device regulation consultant Belgie
Legal	• Legal advice Netherlands or Belgium • Dutch language blogs about the MDR:	• google search: medical device regulation advocaat Nederland • google search: medical device regulation advocaat Belgie
MDR blogs	• Dutch language blogs about the MDR	• medicaldeviceslegal.com/ • www.emergobyul.com/
UDI	• GS1 • HIBC • IFA • ICCBBA	• www.gs1.org • www.hibcc.org • https://www.ifaffm.de/en/home • https://www.iccbba.org/

Appendix 2: Terms, abbreviations and translations

English Term (abbreviation)	Nederlandse term (afkorting)	Remarks
Active Implantable Medical Device Directive (AIMDD)	Richtlijn Actief Implanteerbare Medische Hulpmiddelen	Definition see AIMDD
American National Standards Institute (ANSI)		
Application Programming Interface (API)		
Authorised Representative (AR)	Gemachtigde	Definition see MDR
Authorisations Dutch Government	Bevoegdheden Nederlandse Overheid	
Corrective Action and Preventive Action (CAPA)	Correctieve en Preventieve Actie	
Competent Authority (CA)	Bevoegde autoriteit	
Competent Authorities for Medical Devices (CAMD)		
Clinical Investigation	Klinisch Onderzoek	Definition see MDR
CE Mark (European Conformity)	CE Markering	CE: Conformité Européenne, Definition see MDR
Certificate of Free Sales	Export verklaring	
Code of Conduct	Gedragsregels	
Competent Authority (CA)	Bevoegde Autoriteit	Definition see MDR
Coordinating Competent Authority (CCA)	Coördinerende Bevoegde Autoriteit	
Central committee clinical investigation	Centrale Commissie Mensgebonden Onderzoek (CCMO)	
Clinical Evaluation Consultation Procedure (CECP)	Raadplegingsprocedure voor de Klinische Evaluatie	
Clinical evaluation report (CER)	Rapport klinische evaluatie	
Clinical investigation plan (CIP)	Plan voor Klinisch Onderzoek	
Coordinating Member State (CMS)	Coördinerende Lidstaat	
European Trade Association representing the medical imaging, radiotherapy, health ICT and electromedical industries (COCIR)		
Contract Research Organisation (CRO)		
Custom-Made Devices	Op maat gemaakte hulpmiddelen	Definition see MDR
Declaration of Conformity (DoC)	Conformiteitsverklaring	Definition see MDR
Designating Authority (DA)	Aanwijzende Autoriteit	
Decree Medical Devices	Besluit Medische Hulpmiddelen	
Digital Imaging and Communications in Medicine (DICOM)		
	Elektronische Gegevensuitwisseling in de Zorg (EGIZ)	Gedragscode
Electronic IFU (eIFU)		
Essential Health and Safety Requirements (EHSR)	Eisen aan Arbeidsomstandigheden (ARBO)	
European Standard (EN)	Europese Norm (EN)	
European Union Agency for Cybersecurity (ENISA)	Europees agentschap voor cyberbeveiliging	
EUDAMED Actor Module (ACT)	EUDAMED Participant Module	
EUDAMED Clinical Investigation /	EUDAMED Klinisch Onderzoek /	

English Term (abbreviation)	Nederlandse term (afkorting)	Remarks
Performance Studies Module (CIPS)	Prestatiestudies Module	
EUDAMED Certificates / Notified Body Module (CRF)	EUDAMED Certificaten/Aangemelde Instantie Module	
EUDAMED Data Exchange Module (DTX)	EUDAMED Gegevens Uitwisseling Module	
EUDAMED Market Surveillance Module (MSU)	EUDAMED Markttoezicht Module	
EUDAMED UDI / Device Module (UDID)	EUDAMED Unieke Hulpmiddel-Identificatie/Hulpmiddelen	
EUDAMED Vigilance Module (VGL)	EUDAMED Vigilantie Module	
European Commission (EC)	Europese Commissie	
U.S. Food and Drug Administration (FDA)	Autoriteit in de VS voor medische hulpmiddelen	
Fees and Fines	Vergoedingen en boetes	
Field Safety Corrective Action (FSCA)	Corrigerende acties in verband met de veiligheid in het veld	
Field Safety Notice (FSN)	Bericht inzake de veiligheid in het veld	
Groupe Européen de Curiethérapie and the European SocieTy for Radiotherapy & Oncology (GEC ESTRO)		
General Data Privacy Regulation (GDPR)	Algemene Verordening Gegevensbescherming (AVG)	
Global Harmonisation Taskforce (GHTF)		
Global Standards One (GS1)		UDI issuing agency
Graphic User Interface (GUI)	Grafische User Interface	
General Safety and Performance Requirements (GSPR)	Algemene Veiligheids- en Prestatie eisen	MDR Annex I
GS1 Global Trade Item Number (GTIN)		
Health and Care Information models (HCIM)	Zorg Informatie Bouwstenen	
Health Industry Bar Code (HIBC)		UDI issuing agency
Health and Youth Care Inspectorate	Inspectie Gezondheidszorg en Jeugd (IGJ)	
Health Level Seven (HL-7)		
Healthcare Information and Management Systems Society, Inc. (HIMSS)		
Health Products Regulatory Authority (HPRA)		CA van Ierland
Instructions for Use (IFU)	Gebruiksaanwijzing	Definition see MDR
International Atomic Energy Agency (IAEA)	Internationaal Atoom Energie Agentschap	
Informationsstelle für Arzneispezialitäten (IFA)		UDI issuing agency
Implant card	Implantaatkaart	
International Electrotechnical Commission (IEC)		
In Vitro Diagnostics Regulation (IVDR)	Europese Verordening over In-vitro Medische Hulpmiddelen	Regulation (EU) 2017/746 on In Vitro Diagnostic Medical Devices

English Term (abbreviation)	Nederlandse term (afkorting)	Remarks
Institute for Health and Environment	Rijksinstituut voor Volksgezondheid en Milieuhygiëne (RIVM)	
International Organisation for Standardisation (ISO)		
Language requirements	Taaleisen	
Dutch Implant Registry (LIR)	Landelijk Implantaten Register (LIR)	
Manufacturer and User Facility Device Experience (MAUDE)		MAUDE houses medical device reports submitted to the FDA by mandatory reporters 1 (manufacturers, importers and device user facilities) and voluntary reporters such as health care professionals, patients and consumers.
Medical Device Coordination Group (MDCG)		MDR art 103, 104, 105
Medical Device Directive (MDD)	Europese Richtlijn Medische Hulpmiddelen	
Medical Device (MEDDEV) Guidance		
Medical Device Expert Group (MDEG)		Previous name of MDCG
Medical Device Regulation (MDR)	Europese Verordening over Medische Hulpmiddelen	Regulation (EU) 2017/745 on Medical Devices
Medical Device Reports (MDR, FDA)		
Manufacturer Disclosure Statement on Medical Device Security (MDS2)		
Medical Device Single Audit Program (MDSAP)		
Medical Device Software (MDSW)	Software voor Medische Hulpmiddelen	Note: MDSW includes hardware, SaMD is Stand-Alone Software.
Manufacturer Incident Report (MIR)		
Member State (MS)	Lidstaat	
New Approach Notified and Designated Organisations (NANDO)		Notified Body Database
	Nederlandse Federatie van Universitair Medische Centra (NFU)	
Dutch competence centre for electronic exchange of health and care information (NICTIZ)	Nederlandse kennisorganisatie voor digitale informatie-uitwisseling in de zorg	
Notification	Notificatie of aanmelding	
Notified Body (NB)	Aangemelde Instantie	
Notified Body Operational Group (NBOG)	-	
Post market clinical follow up (PMCF)	Post-market Klinische follow-up	
Post Market Surveillance (PMS)	Toezicht na het in de handel brengen (post-market surveillance)	Definition see MDR
Periodic Summary Report on serious	Periodieke samenvattende verslagen	

English Term (abbreviation)	Nederlandse term (afkorting)	Remarks
incidents (PSR)	over ernstige incidenten	
Periodic Safety Update Report (PSUR)	Periodiek veiligheidsverslag	
Person Responsible for Regulatory Compliance (PRRC)	Voor de naleving van de regelgeving verantwoordelijke persoon	MDR art 15
Patient Intervention Comparison Outcome (PICO)	PICO is een methode voor het beantwoorden van een onderzoeksvraag	
Product Summary Report (PSR)		
Quality Management System (QMS)	Kwaliteitsmanagementsysteem	
Registration, Evaluation, Authorization and restriction of CHemicals (REACH)		Regulation 1907/2006
Radio Equipment Directive (RED)	Radioapparatuurrichtlijn	
Restriction of Hazardous Substances (RoHS)	Richtlijn Beperking gevaarlijke stoffen	Richtlijn 2011/65/EU
Rule Medical Devices (NL)	Regeling Medische Hulpmiddelen (RMH)	
Serious Adverse Event (SAE)	Ernstige ongewenste voorvallen	
Software as a Medical Device (SaMD)	Software als Medisch Hulpmiddel	Note: MDSW includes hardware, SaMD is Stand-Alone Software.
EUROPEAN COMMISSION HEALTH & FOOD SAFETY DIRECTORATE-GENERAL (SANCO)	EC DG Gezondheid en voedselveiligheid	Name no longer in use
EUROPEAN COMMISSION HEALTH & FOOD SAFETY DIRECTORATE-GENERAL (SANCO) EUROPEAN COMMISSION HEALTH & FOOD SAFETY DIRECTORATE-GENERAL (SANTE)	EC DG Gezondheid en voedselveiligheid	
Secure Development Life Cycle (SDLC)		
Serious Incident Report (SIR)	Verslagen over ernstige incidenten	
Single Identification Number for a CIPS (SIN)	Één identificatienummer voor een CIPS	
Steering Group (SG)	Stuurgroep	
SNOMED CT		medische standaard voor het documenteren en coderen van medische gegevens
System/Procedure Pack Producer (SPPP)	Systeem /Procedure verpakkingsproducent	
Single Registration Number for an economic operator (SRN)	Uniek registratienummer voor marktdeelnemers	
Summary of Safety and Clinical Performance (SSCP)	Samenvatting van veiligheids- en klinische prestaties	
State of the Art	Stand van de wetenschap	Definition see MEDDEV 2.7/1 rev 4
Reprocessing of single use products	Opwerking producten voor eenmalig gebruik	
Rules Medical Devices	Regeling Medische Hulpmiddelen	
Team NB (Notified Bodies)		European association for Medical Devices of Notified Bodies

English Term (abbreviation)	Nederlandse term (afkorting)	Remarks
Trend Report (TR)	Trends rapport	
Technical Report (TR)	Technisch rapport	As in CEN/TR 17223
Underwriters Laboratory (UL)		
Unique Device Identification (UDI)	Unieke hulpmiddelidentificatie	MDR art 27
Unique Device Identification - Device Identifier (UDI – DI)	Hulpmiddel identificatie	Such as Partnumber
Unique Device Identification – Production Identifier (UDI – PI)	Productie Identificatie	Such as Serial Number
Ministry of Health, Welfare and Sports	Ministerie van Volksgezondheid, Welzijn en Sport (VWS)	
Working Group (WG)	Werkgroep	
World Health Organisation (WHO)	Wereld Gezondheidsorganisatie	