



Centrale

Commissie

Mensgebonden

Onderzoek

Review of a clinical investigation with a medical device - guidance document for MRECs

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Colophon and disclaimer

This guidance has been written thanks to the input of a working group in which the following persons participated:

- Erik Gelderblom (medical physicist; representative of the NVKF, member CMO regio A-N),
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- Monique AI (CCMO national clinical trial office),
- Anneriet Heemskerk (CCMO national clinical trial office).
- The Health and Youth care Inspectorate (IGJ) was observer at this working group.

The guidance has been sent for consultation to the accredited MRECs. The CCMO and NVMETC have adopted the guidance.

The contents of this guidance have been written with the greatest possible care. The focus is on the quality and safety of medical devices to be used in clinical investigations and on the new procedures for the submission, assessment and conduct of clinical investigation as a result of the Medical Device Regulation (MDR, EU no 2017/745), applicable as of 26 May, 2021. The principles of medical ethical review, as laid down in the Dutch Act on Medical Research Involving Human Subjects (WMO), have not been changed and will not be addressed in this guidance. This guidance is written for the Netherlands. The procedures may be different in other member states of the European Union.

Topics relating to the scope of the MDR and the interpretation of some articles in chapter VI of the MDR were at the time of writing this guidance still under discussion in the European Commission working group on clinical investigation. The content of this guidance is not legally binding. The [official European documentation](#) is always leading.

This guidance should prove its usability in the daily practice. It will be evaluated periodically and adapted based on best practice and new developments in the field of clinical investigations. Please send questions, remarks and suggestions to improve the document to the CCMO (devices@ccmo.nl).

The Hague, September 28, 2020

List of abbreviations

ABR	General Assessment and Registration form (ABR form), the application form required for submission to the accredited review committee. In Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)
AE	Adverse Event
BCB	The decree on Central Review of Medical Research Involving Human Subjects Act. In Dutch: Besluit centrale beoordeling Medisch wetenschappelijk onderzoek met mensen
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CCMO-LB	National Clinical Trial Office of the CCMO (in Dutch: Landelijk Bureau, LB)
CEP	Clinical evaluation plan
CIP	Clinical investigation plan
CTR	Clinical trial regulation; regulation (EU) 536/2014 of the European parliament and the council of 16 April 2014.
CMR	Carcinogene, mutagene or reproduction toxic
CS	common specifications
CV	Curriculum Vitae
CIR	Clinical investigation report
DSMB	Data Safety Monitoring Board
DSMH	Sterilisation experts. In Dutch: Deskundige steriele medische hulpmiddelen
EU	European Union
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation. In Dutch: Algemene Verordening Gegevensbescherming (AVG)
IB	Investigator's brochure
IFU	Instructions for Use
IGJ	Dutch Health and Youth Care Inspectorate. In Dutch: Inspectie Gezondheidszorg en Jeugd.
ISO	International Organization for Standardization
IMDD	Investigational Medical Device Dossier

MEC-U	Medical Research Ethics Committees United (one of the accredited MREC's)
MREC	(accredited) Medical research ethics committee (MREC); in Dutch: (erkende) medisch-ethische toetsingscommissie (METC)
MDD	Medical device directive; directive 93/42/EEC
MDR	Medical devices regulation; regulation (EU) 2017/745 of the European parliament and the council of 5 April 2017
MS	Member state
NVKF	Society for Medical Physics in the Netherlands
PMCF	Post-market clinical follow-up
QMS	Quality management system
SAE	Serious Adverse Event
SIN	Single identification number
SM	Substantial modification
UDI	Unique Device Identifier
Wmh	Medical Devices Act. In Dutch: Wet op de medische hulpmiddelen
WMO	Medical Research Involving Human Subjects Act. In Dutch: Wet medisch-wetenschappelijk onderzoek met mensen
vDSMH	Dutch society for sterilization experts

Chapter 1 Introduction

As of May 26th 2021 the [European regulation \(EU\) 2017/745](#) on medical devices (MDR) applies in the European Union (EU). This regulation harmonises the rules in the EU for placing on the market and putting into service of medical devices and their accessories. It sets high standards of quality and safety for medical devices. Data generated in clinical investigations should be reliable and robust and the safety and rights of subjects participating in a clinical investigation must be protected. The new rules for clinical investigations will ensure that the procedures and conditions for conducting and assessing clinical investigation are uniform throughout the EU. This is vital to ensure that EU member states, in authorising and supervising the conduct of a clinical investigation, base themselves on the same rules.

With this harmonisation at EU level, the ultimate goal is to create an environment that is favourable for conducting clinical investigations, with the highest standards of quality and patient safety, for all EU member states. It will not only harmonise decisions, but also foster work-sharing and collaboration between member states and enhance the transparency regarding clinical investigations.

This guidance is intended for committee and staff members of accredited MRECs and the CCMO involved in the assessment of clinical investigations with medical devices subjected to the rules of chapter VI of the MDR. There are common parts that apply to all members and specific parts that will be primarily addressed by the committee members who are experts on medical devices. The common purpose is to provide information on the review procedure and to give guidance on what to review and to what extent. In general, topics applying to all types of clinical studies are not discussed in this guidance, except in cases where they need special attention in the context of the MDR.

Chapter 2 Most important changes

An overview of the most important changes applicable to clinical investigations is listed below. These points are either directly described in the MDR or a result from the Dutch Act on Medical Devices (Wet op de medische hulpmiddelen, Wmh) and the Act on Medical research involving Human Subjects (Wet Medisch-wetenschappelijk onderzoek met mensen, [WMO](#)). These and other points will be explained in more detail throughout the document.

Changes directly arising from the MDR

- The definition of a medical device in the MDR is broader compared to previous legislation bringing more products under the MDR compared to the medical device directive (MDD).
- In the MDR, there are three articles on categories of clinical investigation (Article 62, 74 or 82 clinical investigation), each having specific requirements.
- The classification rules have been altered, as a result of which some medical devices are classified in a higher risk class (Annex VIII MDR).
- The requirements for supplying clinical evidence in order to obtain the CE mark are stricter in the MDR which may result in the need for more clinical data.
- Post-Market Clinical Follow-up (PMCF) by the manufacturer is mandatory (MDR, art 10, sub 3).
- A validation procedure for Article 62 and 74.2 (MDR) clinical investigations with a validation decision including the option to appeal.
- The procedures for recording and reporting of adverse events occurring during clinical investigations have been changed and differ between Article 62/74.2, 74.1 and 82 investigations.
- The timelines of validation, assessment of initial applications and substantial modifications, notification of temporarily halt, and (premature) end of the clinical investigation may have changed.
- There will be a six-year period of voluntarily coordinated assessment of multinational clinical investigations by EU member states.

Changes specific for the Dutch procedures

- The WMO has a new article, 17a, in which the CCMO has been given new tasks with respect to the application of clinical investigation with medical devices. These are performed by the CCMO National Clinical Trial Office (in Dutch: Landelijk Bureau; CCMO-LB) and includes among others validation of specific initial applications, a coordinating and supporting role for multinational applications and collection/distribution of fee. The latter task will be postponed until the [Clinical Trial Regulation \(EU no 536/2014\)](#) (CTR) is applicable. Until then, the MREC is responsible for collection fee
- A validation decision for Article 62 and 74.2 (MDR) clinical investigations is issued by the CCMO-LB.
- Clinical investigations for conformity purposes with high risk medical devices will be assessed by selected MRECs.
- The accredited MREC needs to have an accredited 'WMO-member medical devices' if assessing clinical investigation with medical devices.
- There are some changes in the application dossier (annex XV, chapter II of the MDR). New documents to be submitted are the clinical evaluation plan (CEP) and a signed statement by

the manufacturer on the investigational medical device in case of an Article 62 or 74.2 clinical investigation (see section 5.3). For registration in forthcoming Eudamed, a submission form with details of the clinical investigation is under construction and is required as of May 26th 2021. It is not mandatory anymore to have an independent expert who can be consulted voluntarily by the subjects (WMO, Article 9).

- The Dutch model investigational medical device dossier ([IMDD](#)) has been adapted to comply with the requirements of Annex I of the MDR.
- The conditions for conducting non-therapeutic clinical investigations with minors or incapacitated persons are more restrictive than the conditions for clinical trials under the WMO and CTR.
- There are new conditions for conducting clinical investigations with pregnant and breastfeeding women (article 66 of the MDR) and/or clinical investigations in an emergency situation (article 68 of the MDR).
- The CCMO will become the competent authority for clinical investigations with medical devices. Clinical investigations do not have to be notified to the Dutch Health and Youth Care Inspectorate anymore.

Chapter 3 Definitions

This chapter describes the most important definitions in the MDR. The list follows the order and definitions as in Article 2 of the MDR. Appendix A of this guidance contains all definitions. The blue boxes are to highlight some terminology dissimilarities.

Medical device (MDR article 2.1): means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

- diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,
- investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,
- providing information by means of *in vitro* examination of specimens derived from the human body, including organ, blood and tissue donations,

and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

The following products shall also be deemed to be medical devices:

- devices for the control or support of conception;
- products specifically intended for the cleaning, disinfection or sterilisation of medical devices, accessories for medical devices, and products listed in annex XVI

In the MDR the term 'devices' refers to medical devices, accessories for medical devices and products listed in annex XVI. In this guidance, the term 'medical device' refers to all products that the MDR classifies as device.

Invasive device: means any device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body. (MDR article 2.6). 'Body orifice' means any natural opening in the body, as well as the external surface of the eyeball, or any permanent artificial opening, such as a stoma. (MDR annex VIII 2.1)

'Invasive' in the context of a medical device has a broader meaning than an 'invasive' procedure.

Conformity assessment: means the process demonstrating whether the requirements of this Regulation relating to a device have been fulfilled. (MDR article 2.40)

CE marking or CE marking of conformity: marking by which a manufacturer indicates that a device is in conformity with the applicable requirements set out in the MDR and other applicable Union harmonisation legislation providing for its affixing. (MDR article 2.41)

Clinical investigation: means any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device. (MDR article 2.45)

Sponsor: means any individual, company, institution or organisation which takes responsibility for the initiation, for the management and setting up of the financing of the clinical investigation. (MDR article 2.1) With this definition the investigator-initiated investigations are explicitly brought under the MDR.

Clinical performance: means the ability of a device, resulting from any direct or indirect medical effects which stem from its technical or functional characteristics, including diagnostic characteristics, to achieve its intended purpose as claimed by the manufacturer, thereby leading to a clinical benefit for patients, when used as intended by the manufacturer. (MDR article 2.52)

Clinical benefit: means the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health. (MDR article 2.53)

Terminology between the MDR and CTR differs. For example, MDR mentions clinical investigations (CTR: clinical trials) and clinical investigation plan (CTR: protocol).

Chapter 4 Scope of the MDR in clinical investigations

This chapter describes the scope of the MDR with respect to clinical investigations. It gives guidance on what is considered a medical device and lists specific cases of medical devices. The definition and scope of clinical investigations is described. Finally, the transitional provisions are discussed.

4.1 Relevant articles in the MDR for the scope of clinical investigations

This is a list of the most relevant articles concerning the scope of clinical investigations in the MDR:

- Article 2: definitions
- Article 5.5: in-house devices
- Chapter VI: clinical evaluation and clinical investigations (articles 62-82)
- Article 62: clinical investigation for conformity purposes
- Article 74: clinical investigation with CE-marked medical devices
 - 74.1: post-market clinical follow-up (PMCF) investigations with extra invasive or burdensome procedures.
 - 74.2: clinical investigation with CE-marked medical device used outside the scope of its intended purpose.
- Article 82: clinical investigation other than in Article 62 or 74.
- Annex I: general safety and performance requirements
- Annex II: technical documentation
- Annex VIII: classification rules
- Annex XV: clinical investigations
 - Chapter I: general requirements
 - Chapter II: documentation regarding the application for clinical investigation
 - Chapter III: other obligations of the sponsor
- Annex XVI: List of groups of products without an intended medical purpose referred to in Article 1(2)

4.2 Is the product a medical device?

The definition of a medical device is broader under the MDR as compared to the definition under the MDD, which results in more products being considered as a medical device. The following flowchart may help to decide whether a product qualifies as a medical device. The reviewing committee can reassess the qualification of a product.

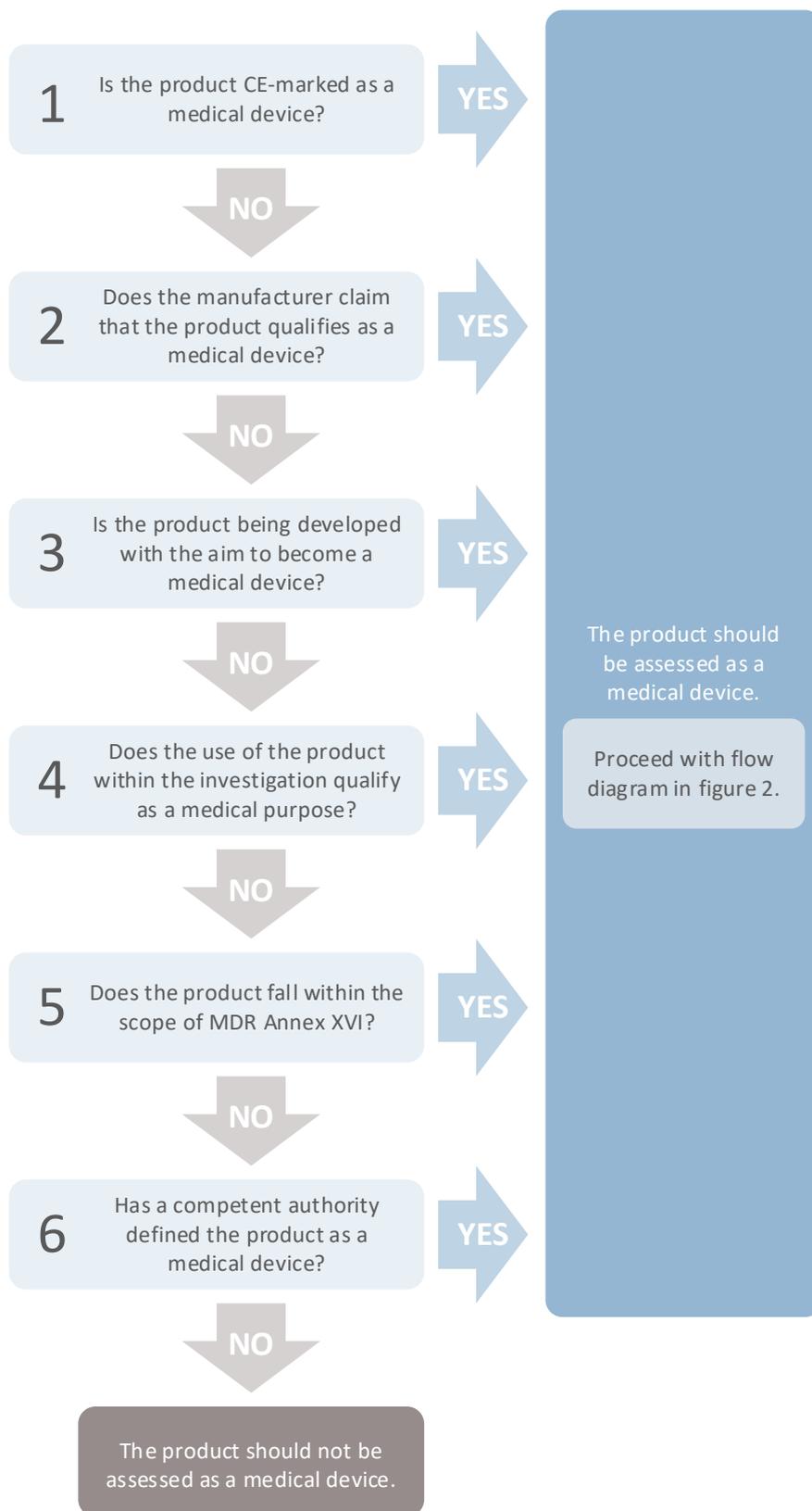


Figure 1: Flowchart to help determine if a product is a medical device.

Leading in this flowchart is the definition of a medical device (MDR article (1)), in which a medical purpose is defined. The European Commission has published several guidance documents on the qualification of medical devices. There is a [manual](#) on borderline products and qualification under the MDD which is currently under revision to conform to the MDR. Specifically for medical software a [guidance](#) on qualification and classification under the MDR has been published. Other guidance documents will follow. The steps in the flow chart are explained below.

1. When the manufacturer of a product claims that the intended purpose of the product is a medical purpose, the product should be regarded as a medical device. This claim is substantiated by the description of the intended purpose of the medical device, which can be found in the user manual, IMDD and/or the investigator's brochure.
2. A product that has a valid CE marking according to the MDD, AIMDD or MDR by definition qualifies as a medical device.
3. When a medical device is in the development phase (e.g. a prototype) a prototype may be tested on subjects in order to validate certain parts of the medical device. Although the prototype may not fulfil its intended medical purpose yet, the product nevertheless already qualifies as a medical device, since that is the potential aim of the product.
Other products are solely developed to demonstrate a working principle for academic purposes, without the aim of transforming the product itself into a medical device. In those cases, the product does not qualify as a medical device.
4. A product which is used within the investigation for a medical purpose qualifies as a medical device. Consumer products without a medical purpose, such as wearable fitness trackers, may be used for a medical purpose within the scope of a clinical investigation. This means that they should be assessed as a medical device in that specific situation.
5. Annex XVI of the MDR lists products, such as contact lenses or lasers for tattoo removal, for which analogous devices with a medical purpose exist. These devices often have an aesthetic purpose and a similar risk profile as the analogous medical device. These devices fall within the scope of the MDR and therefore qualify as a medical device.
6. Steps 1, 3 and 4 can lead to a discussion within the MREC or between the MREC and the sponsor about the qualification of the product. When no agreement is reached, the next step could be for the MREC to send a request to the CCMO for advice. Depending on the procedure and timelines, the MREC will put the assessment of the clinical investigation on hold or continue on basis of a preliminary conclusion on the status of the product. In all circumstances, the safety and quality of the product must be guaranteed before using it in or on subjects in medical research.

4.2.1 Specific cases

Extra attention should be paid to a number of products:

Modified CE-marked medical devices: these medical devices are not CE-marked anymore due to the modifications or the use of accessories other than those supplied by the manufacturer. The use of these altered medical devices is only allowed in a clinical investigation in which the safety and performance are assessed or that are modified and applied within a single institution (in-house product).

In-house product: healthcare institutions have the possibility of manufacturing, modifying and using medical devices in-house and thereby address, on a non-industrial scale, the specific needs of target patient groups which cannot be met at the appropriate level of performance by an equivalent medical device available on the market. This also includes in-house developed software. Article 5.5 lists the specific requirements for such medical devices when used for patient care. When such medical devices are being assessed in a clinical investigation, article 82 applies (see section 4.3.1).

Example software

Consider stand-alone software with the manufacturer's intended purpose to investigate the efficacy and outcomes of different programs of psycho-education. Based on information following from generic questionnaires, the patients and clients are provided with several psychotherapies, feedback, and tools for relapse prevention. Clearly, the 'software was intended by the manufacturer to be used (...) for human beings for one or more of the following specific medical purposes: (...) treatment (...) or alleviation of disease.' So, the manufacturer's intended purpose is within the scope of the MDR's definition of a medical device.

Custom-made devices: any device specifically made in accordance with a written prescription which gives specific design characteristics and is intended for the sole use of a particular patient. Clinical investigations with custom-made devices fall under article 82. More information on the procedures for custom-made devices is given in annex XIII of the MDR. There is discussion whether devices for 3D printing should be CE marked.

Annex XVI products: a group of products without an intended medical purpose but which are considered medical devices that have to be compliant with the MDR (Article 1.2). Examples are contact lenses, facial fillers and lasers for hair removal.

Software: qualifies as an active medical device when specifically intended by the manufacturer to be used for a medical purpose. Depending on its intended purpose the classification can be any of the classes. European [guidance on software](#) is available. In addition, the national expert centre on digital information exchange in healthcare ([Nictiz](#)) published an [infographic](#) and [whitepaper](#) for software (in Dutch).

Combination products: products combining a medicinal product or medical substance and a medical device are regulated either under the MDR or under the CTR. The mode of action determines which regulation applies. When the action of the medical substance is the most important, the combined product is regulated within the framework of the medicinal product. If the device, intended to administer a medical substance, supplied together is placed on the market as a single integral product intended exclusively for use in the given combination and is not reusable, the combination product is regulated within the framework of the medicinal product.

In both cases, the relevant general safety and performance requirements of the MDR apply to the device part. When the medical device is not physically combined with the medicinal product the device is regulated under the MDR.

Example combination product

Consider a drug eluting stent. The stent's primary function is to open a stenotic blood vessel by the mechanic properties of the stent, but secondary to this function a drug is added to the stent to prevent blood clotting. So, the drug eluting stent is qualified as a medical device while, of course, the drug needs to satisfy the requirements set in the law and regulations for medicinal products.

Borderline products: borderline products are considered to be those cases where it is not clear from the outset whether a given product is a medical device or not. Previously a [manual on borderline products](#) under the medical device directives was published. An updated manual is not yet available.

Combined medical devices: when multiple medical devices are combined it should be made clear whether it is one single medical device or a system composed of multiple medical devices.

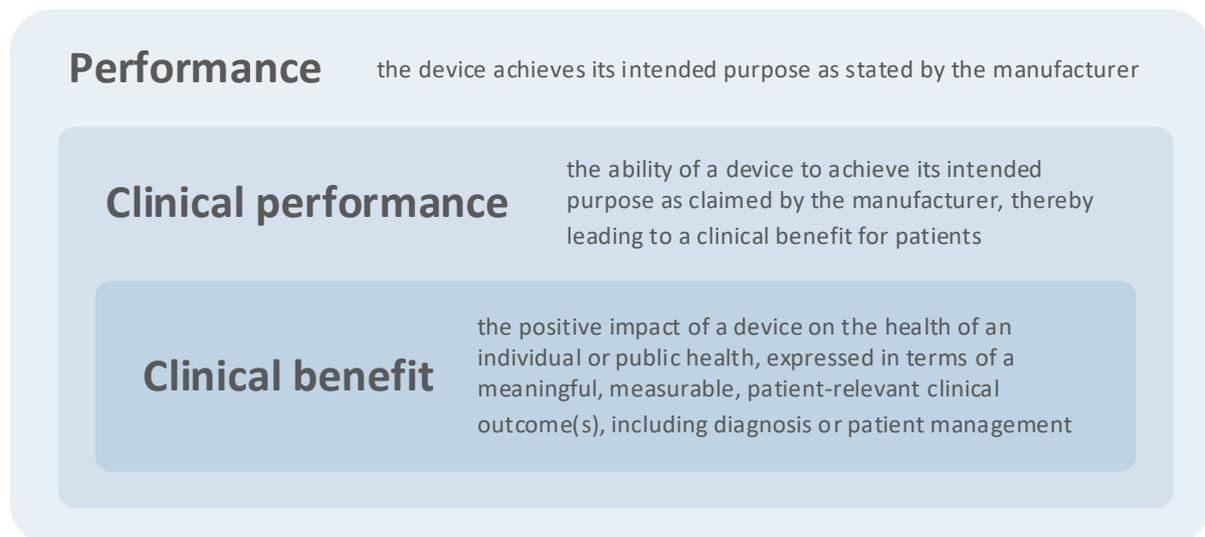
If a review committee has doubts on the claim of the manufacturer or the sponsor about the status of the product, the following escalation path can be followed:

1. Use the decision tree of Figure 1 to determine whether a product is a medical device
2. When the MREC remains in doubt, request for more information on the product from sponsor and/or manufacturer.
3. When no agreement is reached, the next step could be for the MREC to send a request for advice to the CCMO.

4.3 Clinical studies

4.3.1 Clinical investigation

A clinical investigation is defined by the MDR as any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a medical device. In terms of medical devices with a medical purpose, the performance includes the clinical benefits for patients.



The performance of a medical device is its ability to achieve its intended purpose as stated by the manufacturer. By extension, the clinical performance of a medical device would be the ability to achieve a clinical outcome(s) for the patient or public health, leading to a clinical benefit in case of positive outcome(s). This means that the medical device would lead to an improvement or have a favourable effect for the patient and/or public health. The clinical benefit should at least be comparable to the standard of care.

4.3.1.1 CLINICAL INVESTIGATIONS CATEGORIES

There are three different articles in the MDR on categories of clinical investigations with each its own specific requirements. The qualification depends on the status of the medical device, CE-marked or not, the use of the medical device, used within its intended purpose or not, and the purpose of the clinical investigation. Figure 2 shows a flowchart.

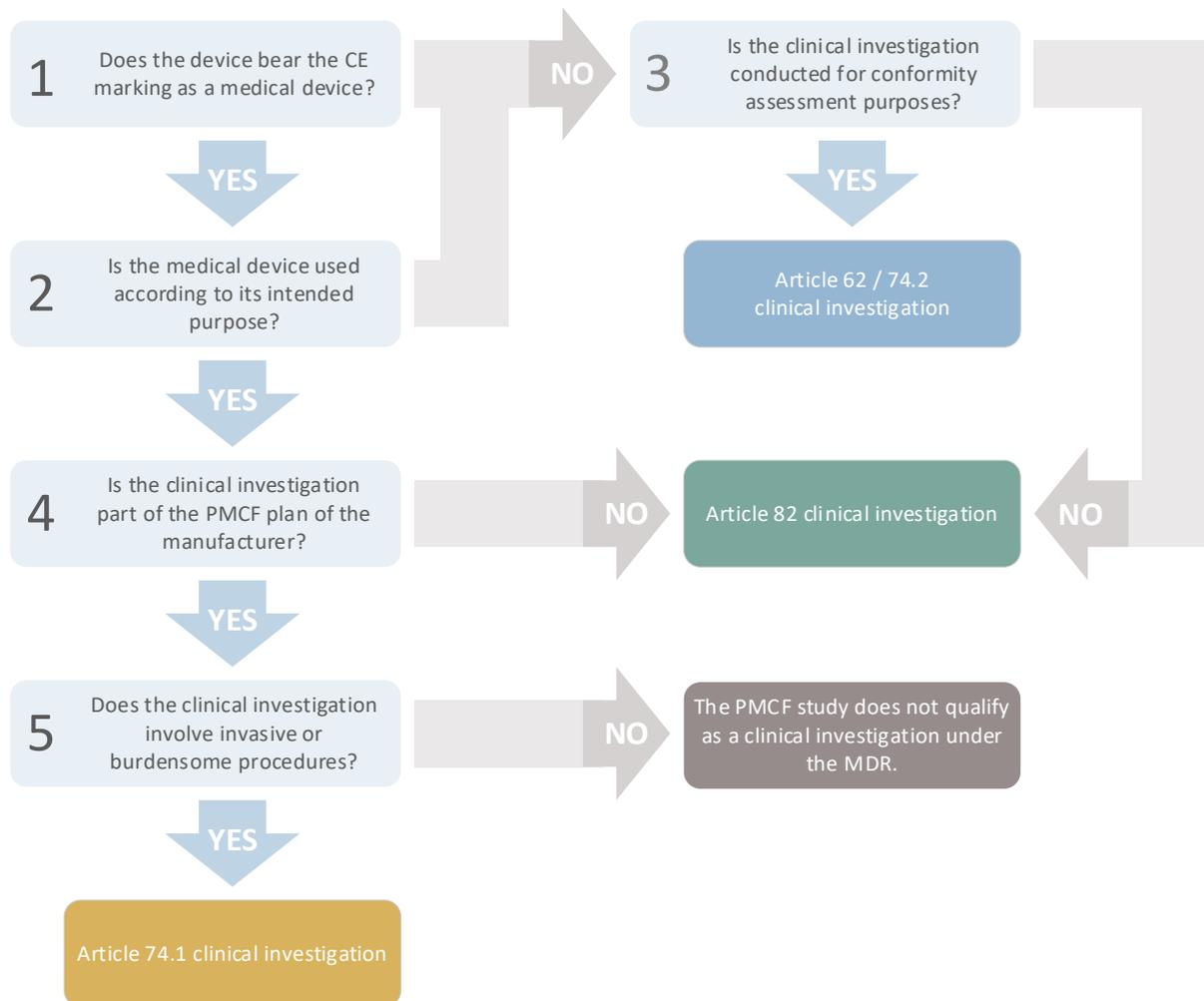


Figure 2: Flow chart to determine which MDR article is applicable for the clinical investigation.

1. Whether or not the device already bears a valid CE marking as a medical device is crucial to the classification of the investigation. The CE certificate of the medical device or the declaration of conformity for class I medical devices can be consulted to answer this question.
2. The instructions for use of a medical device must contain the device's intended purpose with a clear specification of indications, contra-indications, the patient target group or groups, and of the intended users, as appropriate.
3. When the clinical investigation is conducted for conformity assessment purposes, either for a new device (article 62) or to expand the intended purpose (article 74.2), the envisioned aim is to market the device as a medical device under the MDR. The conditions that apply to article 62 and article 74.2 clinical investigations are the same. All investigations that are/will be part of the clinical evaluation plan (article 61 and annex XIV.A of the MDR) are considered to be conducted for conformity purposes. Therefore, early feasibility investigations can fall in the category of article 62 clinical investigations.
4. Post-market clinical follow-up (PMCF) studies will be commissioned by the manufacturer of a medical device and be a part of the PMCF plan (annex XIV.B of the MDR).
5. PMCF studies are considered PMCF investigations if the subjects are submitted to additional procedures compared to the standard of care and those procedures are invasive or

*burdensome*¹. For these PMCF investigations, article 74.1 of the MDR applies. PMCF studies which are non-interventional, for instance clinical data are obtained by file research and no additional invasive or burdensome procedures compared to standard of care are applied, fall outside the scope of chapter VI of the MDR and outside the scope of the WMO and are considered nWMO studies.

* When multiple medical devices are assessed in the clinical investigation, the procedures for article 62/74.2 are applicable unless for all medical devices article 82 applies.

Article 62: the clinical investigation is carried out as part of the clinical evaluation for conformity assessment purposes, with the purpose to establish and verify:

- the intended performance as specified by the manufacturer; and/or
- the clinical benefits as specified by the manufacturer; and/or
- the clinical safety of the device and to determine any undesirable side-effects and assess whether they constitute acceptable risks when weighed against the benefits achieved by the device.

Example article 62 studies

A non-randomized feasibility study in which a prototype of a venipuncture device is tested. The primary outcome parameters are the feasibility (number of successful automated venipunctures) and the safety (number of adverse events and number of adverse device events).

A spin-off company developed an improved magnetic seed and detector for the localization of early stage (non-palpable) breast cancer. The objective of the clinical investigation is to show that the novel technology is safe and performs as intended.

A manufacturer has developed a patch for watertight dural closure after cranial surgery. The study will be conducted to clinically assess the safety and performance of the patch as a means to reduce CSF leakage after dural closure in patients undergoing cranial surgery.

An existing CE-marked cosmetic breast implant is aimed to be improved with a newly developed coating material to reduce formation of scar tissue with associated complications of pain and inflammation. To demonstrate conformity with all MDR requirements set out for new CE marking of the breast implant with the coating, a clinical investigation is conducted to investigate the clinical performance, clinical safety and clinical benefit of the coating.

¹ The scope of article 74.1 investigations is still under debate. Therefore, the interpretation of both PMCF investigations and invasive and burdensome procedures can be subject to change.

Article 74.1: a Post-Market Clinical Follow-up (PMCF) investigation is an clinical investigation of a CE-marked device used within the scope of its intended purpose, and where the investigation would involve submitting subjects to procedures additional to those performed under the normal conditions of use of the device and those additional procedures are invasive or burdensome².

An invasive procedure is considered to be a medical procedure invading (entering) the body, usually by cutting or puncturing the skin or by introducing instruments into the body.

An additional procedure is a procedure which is not foreseen by the manufacturer in the instructions for use of the medical device or not foreseen in the standard of care. An additional procedure can be interpreted as burdensome for the subject if this procedure involves a risk of causing physical or mental strain (or harm) exceeding the limits of normal daily life for the research participants. This may include non-invasive procedures, procedures related to the medical device if not standard of care, collecting biological samples, filling out questionnaires, recording diary entries, et cetera depending on the circumstances. Whether a procedure is burdensome may vary according to age, health status and vulnerability of the subject and to the duration, previous experience, repetition or accumulation of the procedure compared to the standard of care.

Example article 74.1 study

Consider a surgically invasive CE-marked medical device used within its intended purpose to fixate some thoracic vertebra in juvenile patients suffering from severe scoliosis. The manufacturer designs a clinical investigation as part of its PMCF plan to evaluate the medical device's performance in a real -life situation. An extra CT-imaging (radiation exposure of 5 mSv) will be performed from the onset of the follow-up and repeated every two years for a period of six years . Clearly, the CT-imaging is considered an additional burdensome procedures additional to the normal conditions of use of the medical device.

Article 74.2: a clinical investigation to be conducted as part of the clinical evaluation for conformity assessment purposes with a CE-marked medical device outside the scope of the intended purpose.

Example article 74.2 study

The manufacturer of a "self-expandable metal stent" CE-marked to be used for the treatment of pancreatic pseudocysts wants to conduct a feasibility study to investigate the safety and technical performance of this stent used during endo-echoscopic gall bladder drainage in patients with acute cholecystitis.

² The scope of article 74.1 investigations is still under debate. Therefore, the interpretation of both PMCF investigations and invasive and burdensome procedures can be subject to change.

Article 82: clinical investigations for other purposes than the purposes mentioned in Article 62 or 74. Article 82 investigations can for instance include clinical investigations with in-house medical devices, custom-made medical devices and investigator-initiated investigations with CE-marked medical devices.

Example article 82 studies

A clinical investigation of an in-house developed and used 3D-printed cannula for keeping the airway open in manually ventilated patients. A clinical investigation is set up to assess the safety and performance of the cannula.

A clinical investigation to assess the performance of a CE-marked blood pressure monitor to measure blood pressure in the lower leg (i.e. used outside its intended use).

A clinical investigation using a methods comparison study with an observational diagnostic design. During this clinical investigation the agreement between two methods for monitoring vital signs (respiratory rate and heart rate) will be quantified, comparing the new CE marked wearable sensors to a validated reference standard during ward admission.

4.3.2 Other studies using medical devices

Other studies using medical devices are studies in which not the safety and/or performance of the medical device is being investigated (therefore not falling under the definition of a clinical investigation and therefore chapter VI of the MDR is not applicable) but in which medical devices are used in the study for other purposes, for instance as a primary outcome measurement. The MDR states that medical devices can be put on the market or may be put into service only if they comply with the MDR when duly supplied and properly installed, maintained and used in accordance with their intended purpose (Article 5.1, MDR). An exception is made for investigational devices meaning medical devices assessed in a clinical investigation (chapter VI, MDR). The consequence of these provisions is that in studies with medical devices (other than a clinical investigation) only CE marked medical devices, in-house developed medical devices or custom-made medical devices can be used.

For these other studies with medical devices, the WMO or other legislation might apply. In all circumstances, the safety and quality of the medical device must be guaranteed before using it in or on subjects or patients. When the study is assessed by an MREC or the CCMO, the product information should be of such quality that the review committee can do their assessment. Use of the model IMDD is recommended for in-house or custom-made medical devices.

4.3.3 Other studies using devices without a medical purpose

A device without a medical purpose (other than those mentioned in MDR annex XVI) may still pose a risk to a subject. Studies with these products do not fall within the scope of the MDR but could still fall within the scope of the WMO and should then be assessed by an MREC or the CCMO. In this

assessment, the safety and quality of these products is notwithstanding of importance when using it in or on subjects or patients. The technical documentation mentioned in MDR annex II is relevant to these products. Therefore, the use of (relevant parts of) the model IMDD is recommended for these products.

4.4 Classification of medical devices

The classification of a medical device depends on several factors including the purpose, the duration of use, being an invasive/non-invasive medical device, and whether it is an active device or implant. The classification is described in annex VIII of the MDR and a total of 22 rules apply. There are four classes of medical devices: class I (including Ir, Im, and Is), IIa, IIb and III.

4.4.1 Classification of software

Software has been given its own classification rule in de MDR, rule 11. Rule 11 specifically addresses software that provides information which is used to take decisions with diagnosis or therapeutic purposes. However, other rules may also apply, possibly leading to a higher risk class. See MDR annex VIII for specific details.

4.5 Transitional provisions

4.5.1 Eudamed

The delivery of a fully functional Eudamed is delayed until 2022. Although this has consequences for the exchange of information, the MDR will nevertheless become applicable on May 26th 2021 (Article 123 sub 3d of the MDR). Until Eudamed is fully functional ToetsingOnline will be used.

The sponsor has the obligation to upload the following information in Eudamed:

Obligation	Transitional provision
Initial application	ToetsingOnline (registration via ABR form)
Substantial modifications	ToetsingOnline (only if ABR form is modified)
A single identification number (SIN)	If not already available, the CCMO-LB will request this number
Notification of Article 74.1 clinical investigation	ToetsingOnline (registration via ABR form)
Recording and reporting of reportable adverse events	ToetsingOnline
A clinical investigation report and a lay summary	ToetsingOnline

4.5.2 Authorised clinical investigations

Clinical investigations which have been authorised prior to May 26th 2021 may continue to be conducted. As of May 26th 2021, however, the reporting of serious adverse events and device deficiencies must be carried out in accordance with the MDR.

4.5.3 Clinical investigations under review

There is no transitional period for clinical investigations which are submitted to the MREC prior to May 26th 2021 and for which no decision has been reached before May 26th 2021. The following procedures apply:

- Clinical investigations must be reviewed and conducted in accordance with the MDR and the modified Act on medical devices (including the modified WMO).
- The reviewing MREC will determine under which MDR article the clinical investigation falls and requests additional information from the sponsor if needed.
- The assessment of article 74.1 or article 82 studies can be finalised by the reviewing MREC, taking into account the MDR rules.
- Article 62 or article 74.2 clinical investigations need to be resubmitted to the CCMO-LB as of May 26th 2021. The CCMO-LB validates and assigns the clinical investigation to an MREC. Clinical investigations with medical devices invasive class IIa and class IIb or class III falling under article 62 or 74.2 can only be assessed by one of the accredited academic MRECs, the MEC-U or the CCMO (see section 5.1). If another MREC had the clinical investigation under assessment the clinical investigation is transferred to one of these committees.

Chapter 5 Initial application

This chapter describes the procedures and assessment of the initial application. It gives information on the procedures and timelines for the different categories of investigations. The regulatory grounds for the assessment by the review committee are provided. Part of these procedures are laid down in the MDR others follow from national law.

5.1 Which committee?

For clinical investigations for conformity (Article 62 and 74.2), medical devices falling under class IIa invasive, class IIb invasive or class III are assessed by one of the accredited academic MRECs, the MEC-U, or in certain cases by the CCMO. All other clinical investigations may be assessed by one of the other accredited MRECs as well. The CCMO will review studies which are specifically assigned to the CCMO by the WMO or the Decree on central review of medical research with human subjects (in Dutch: Besluit Centrale Beoordeling Medisch wetenschappelijk onderzoek met mensen (BCB)).

Category investigation	Class medical device	Reviewing committee
Conformity MDR article 62 or article 74.2	Class III, class IIb invasive, class IIa invasive	Accredited academic MREC, MEC-U or CCMO
	Class IIb non-invasive, class IIa non-invasive class IIa, class I	Accredited MREC or CCMO
Post-market clinical follow-up investigation MDR article 74.1	All classes	Accredited MREC or CCMO
Other MDR article 82	All classes	Accredited MREC or CCMO

5.2 Pathways and timelines

The different clinical investigation categories and classification of the medical device results in different pathways for validation, assessment and can have different maximum timelines. Some of the timelines are determined by the MDR, when not defined the timelines of WMO studies have been adhered to.

What	Article	Class device	Timeline
Validation	62/74.2	All	Maximum 55 calendar days including response time sponsor
	74.1/82	All	No separate validation, but part of the assessment
Assessment	62/74.2	Class III and invasive class IIa and class IIb	Maximum 45 (+20 in case of consulting expert) calendar days + clock stop for response sponsor
		Class I and non-invasive class IIa and class IIb	Maximum 2x56 calendar days + clock stop for response sponsor
	74.1/82	All	Maximum 2x56 calendar days + clock stop for response sponsor
Substantial modifications	62/74.2/74.1	All	Maximum 38 calendar days (+ 7 days for consulting expert) + clock stop for response sponsor
	82	All	Maximum 2x56 calendar days + clock stop for response sponsor

5.2.1 Article 62 or Article 74.2 clinical investigation

Ultimately, the article 62/74.2 clinical investigations will be submitted through Eudamed. Until this is functional, the national web portal ToetsingOnline will be used.

5.2.1.1 PATHWAY AND TIMELINE FOR VALIDATION

Applications for clinical investigations under article 62/74.2 are validated by the CCMO-LB. The CCMO-LB checks if the clinical investigation falls within the scope of the MDR and that the application dossier is complete. After a positive validation, the CCMO-LB directly assigns the application to review committee (accredited MREC or CCMO). The CCMO-LB also notifies the IGJ. If the IGJ has any relevant safety information concerning the medical device or resembling devices, they will inform the assigned review committee and the CCMO-LB within 10 calendar days.

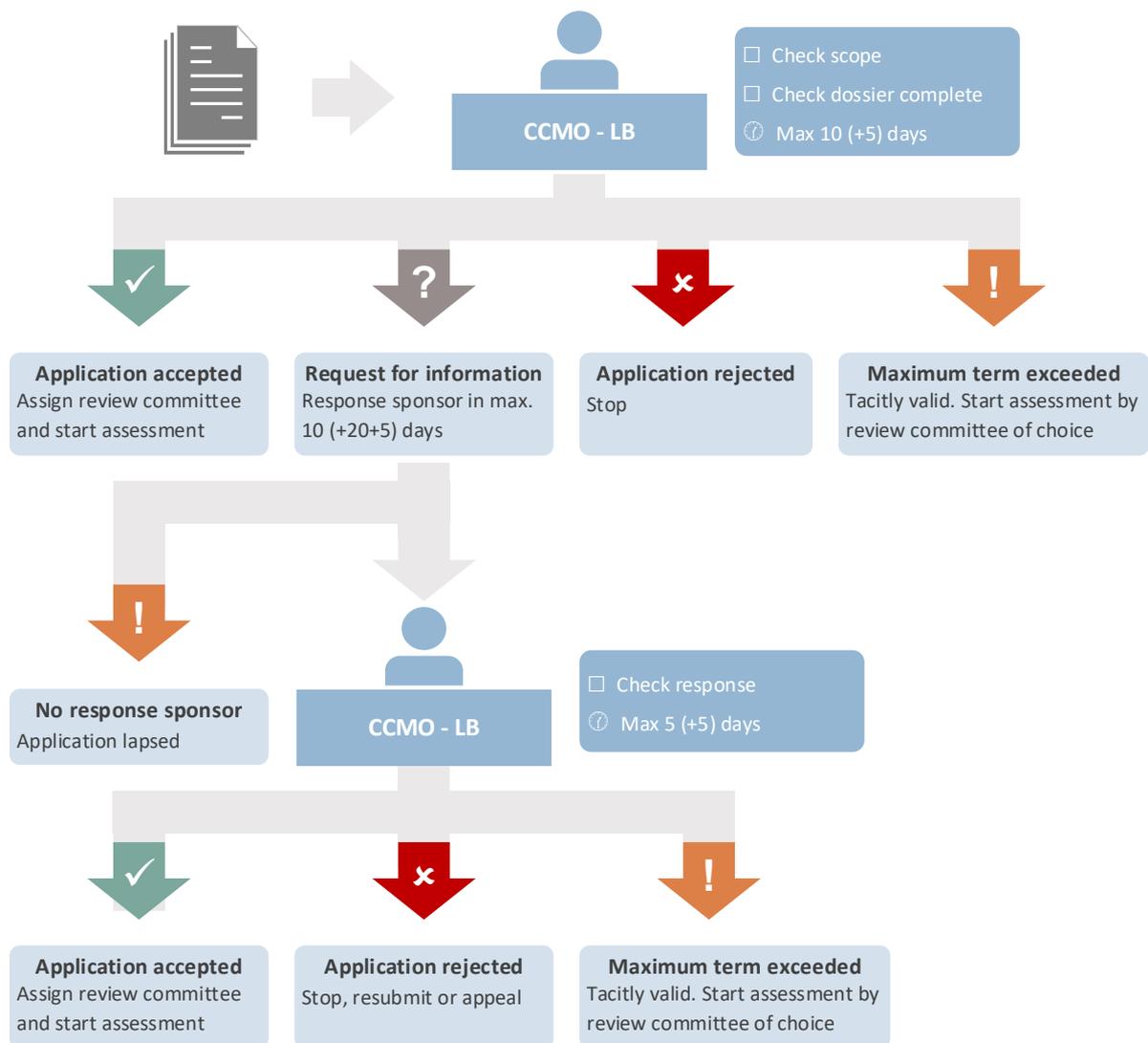


Figure 3: Overview of the validation process.

The CCMO-LB checks if the clinical investigation falls within the scope of the MDR and verifies that the application dossier is complete. The MDR specifies maximum timelines. These time periods can be extended once. When the sponsor does not respond or complete the application within the timeline set, the application shall be deemed to have lapsed. If the CCMO-LB does not notify the sponsor within the specified maximum timelines, the application is tacitly valid and considered to fall under the scope of the MDR and is complete. After a positive validation of the CCMO-LB, the CCMO-LB directly assigns the application to an MREC and the assessment starts. If the CCMO-LB issues a refusal, the sponsor has the option to resubmit the application or to start an appeal procedure. The objection to a refusal by the CCMO-LB needs to be submitted to the CCMO within 6 weeks.

The date on which the sponsor is notified of a positive validation is the 'validation date'. This date is also the start of the assessment period.

5.2.1.2 PATHWAY AND TIMELINE FOR ASSESSMENT

From the validation date the review committee has maximum 45 calendar days to reach a decision for a **class III or invasive class IIa and class IIb medical device**. This period can be extended by 20 days for consulting with experts. Additional information from the sponsor can be requested by the review committee. The review time is suspended from the date of the request until the additional information is received.

From the validation date the review committee has maximum 56 calendar days to reach a decision for a **non-invasive class IIa and class IIb or class I medical device**. This period can be extended by 56 days. Additional information from the sponsor can be requested by the review committee. The review time is suspended from the date of the request until the additional information is received.

The review committee sets a timeline for the sponsor to respond.

5.2.2 Article 74.1/82 clinical investigation

The article 74.1 and Article 82 clinical investigations are registered in the national web portal ToetsingOnline and submitted to the selected MREC immediately.

5.2.2.1 PATHWAY AND TIMELINE FOR VALIDATION

For article 74.1 and Article 82 clinical investigations, the MREC is responsible for the validation of the application. The MREC checks whether the application is complete and whether they are qualified to assess the clinical investigation. If the MREC considers the investigation is an article 62/74.2 clinical investigation, the sponsor is requested to submit the application dossier to the CCMO for validation. If the application is not complete, the MREC will request the sponsor to complete the dossier. The review time is suspended from the date of the request until the additional information is received.

5.2.2.2 PATHWAY AND TIMELINE FOR ASSESSMENT

For these studies the maximum timeline of 56 calendar days applies for the assessment (including the time used for validation). This period can be extended once with another 56 calendar days. Additional information from the sponsor can be requested by the review committee. The review time is suspended from the date of the request until the additional information is received.

The review committee sets a timeline for the sponsor to respond.

5.2.2.3 EUDAMED NOTIFICATION

For article 74.1 studies: When Eudamed is ready, the sponsor needs to notify the member states concerned through Eudamed 30 calendar days prior to the start of the clinical investigation. Until Eudamed is ready, the need to notify in the Netherlands is already fulfilled by the initial application via ToetsingOnline.

5.3 Standard research file – application dossier

There are some changes to the application dossier for clinical investigations that fall under the scope of the MDR or documents that are specific to medical devices. These are mentioned below. An overview of all the documentation is given in appendix D. This is based on the requirements for the application dossier for article 62 and 74.2 as described in annex XV of the MDR. Cross-reference between documents is allowed.

Cover letter: A template cover letter is available on the CCMO website (*in development*).

Application form: Eudamed application form and ABR-form via ToetsingOnline.

Clinical investigation plan (CIP): A template CIP is available on the CCMO website (*in development*). This CIP is the protocol in which the rationale, objectives, design, methodology, monitoring, statistical considerations, organisation and conduct of a clinical investigation are described. The template CIP contains the requirements as mentioned in annex XV chapter II.3 of the MDR.

Clinical evaluation plan (CEP): The CEP means a plan describing a systematic and planned process to generate, collect, analyse and assess clinical data pertaining to a medical device in order to verify the safety and performance, including clinical benefits, of the medical device when used as intended by the manufacturer. The exact details are described in annex XIV, part A, 1(A) of the MDR.

Investigator's brochure (IB): The IB contains the clinical and non-clinical information on the investigational device that is relevant for the investigation and available at the time of application. MDR annex XV, chapter II.2 explicitly describes which information is required.

Investigational medical device dossier (IMDD): The IMDD provides the technical documentation on the medical device. A [model IMDD](#) is available on the website of the CCMO. The use of this document is best practice in the Netherlands for clinical investigations with a medical device without a CE mark or a CE-marked medical device outside the scope of the intended purpose. If the model IMDD is not used, a justification should be given in the cover letter. A document with comparable content might also be acceptable.

Signed statement: A signed statement by the natural or legal person responsible for the manufacture of the investigational device that the medical device in question conforms to the general safety and performance requirements apart from the aspects covered by the clinical investigation and that, with regard to those aspects, every precaution has been taken to protect the health and safety of the subject. This statement is mandatory for article 62 and 74.2 clinical investigations.

Advice expert panel (if available): For all class III and some class IIb medical devices a manufacturer may consult an expert panel with the aim of reviewing the manufacturer's intended clinical development strategy and proposals for clinical investigation. The advice of the expert panel on the clinical investigations should be submitted. The sponsor can add an explanatory note if the clinical investigation differs (partly) from the advice.

For **article 74.1 clinical investigations** the applicable documents are: cover letter, ABR-form, Eudamed application form for article 74.1 (when available), CIP, CEP. In addition, the EU declaration of conformity and the instructions for use.

For **article 82 clinical investigations** the applicable documents are: cover letter, ABR-form, CIP. For non-CE marked medical devices or CE marked medical devices used outside the scope of the

intended purpose: IMDD and preferably a signed statement. For CE-marked medical devices used within the scope of the intended purpose: EU declaration of conformity and the instructions for use.

5.4 Assessment by MREC/CCMO

This section primarily focuses on the assessment of the quality and safety of the investigational device. The diversity of medical devices makes that the expertise needed for the assessment of the clinical investigation is not always available in the reviewing committee. The committee should consider whether advice from an external expert is needed. The existing procedures for external advice can be followed. Additionally, the CCMO and IGJ are working on an expert network to support committees in their assessment.

5.4.1 MREC/CCMO as part of the European regulatory system

The implementation of Chapter VI of the MDR on clinical investigations in the Netherlands is similar to that of the Clinical Trial Regulation (EU no 536/2014). This means continuation of the current review system and with the appointment of the CCMO as the competent authority for clinical investigations on medical devices. MRECs, accredited by the CCMO, and the CCMO (for specific types of clinical investigations) form the opinion on the approval of the clinical investigations on medical, scientific, ethical and methodological grounds. It is important to realise that this system with decentralised integrated assessment is unique in Europe. In other European member states, assessment of the medical and scientific grounds is carried out by centralised competent authorities. These competent authorities on medical devices perform vigilance on the entire chain of market approval and performance of medical devices on the market. Therefore, lessons learned from incidents can, in such centralised authorities, be weighed against the risks of innovative devices to be assessed in new clinical investigations.

For accredited MRECs it is therefore important to realise that they may need to include information on experience with previous versions of the innovative device or lessons learned elsewhere on comparable devices. The IGJ will be informed by the CCMO-LB about new applications of clinical investigations with medical devices and will provide requested or unrequested advice to the committees based on relevant available information which could or should be included in the assessment of the clinical investigation by the review committee. The assessing review committee shall give ample consideration to these advices (if provided) and document their response to the considerations.

Moreover, it is important that the review committee reviews clinical investigations, as part of a clinical evaluation plan, within the context of future market approval, rather than solely the question if it is acceptable for patients to participate in this one single clinical investigation. This means that the context of the clinical investigations should be considered (e.g. market approval) and that review committees consider if the medical device and clinical investigation are in line with applicable (harmonised) guidance standards and/or common specifications.

To assess clinical investigations with medical devices, the review committee has to have an accredited WMO-member with expertise on medical devices to make a valid decision.

5.4.2 Regulatory grounds for review

The clinical investigation category determines which regulatory framework applies. The European MDR takes precedence over the Dutch WMO. This can entail that clinical investigations that previously were not subject to the WMO, are now subject to the MDR. In the table a short overview is shown which regulatory grounds are applicable. In appendix F of this guidance, an overview is given of all

assessment criteria for the different categories of clinical investigations with medical devices. For article 62 and 74 clinical investigations relevant articles of the MDR are applicable. For article 82 clinical investigations some articles of the MDR are applicable plus national regulations (for the Netherlands this entails WMO articles).

In general, the rules on clinical investigations should be in line with well-established international guidances in this field, such as the international standard ISO 14155 on good clinical practice for clinical investigations of medical devices for human subjects. In addition, the rules should be in line with the most recent version of the [World Medical Association Declaration of Helsinki](#) on Ethical Principles for Medical Research Involving Human Subjects.

Category investigation	Class medical device	Regulatory grounds
Conformity MDR article 62 or article 74.2	Class III, class IIb invasive, class IIa invasive	MDR <ul style="list-style-type: none"> Articles 62-71 73-81 Annex XV
	Class IIb non-invasive, class IIa non-invasive class IIa, class I	MDR <ul style="list-style-type: none"> Articles 62-81 Annex XV Common specifications or harmonized standards (to be developed)
	Multinational assessment (voluntary until May 2027)	MDR <ul style="list-style-type: none"> Article 78 – procedure Annex XV
Post-market clinical follow-up investigation MDR article 74.1	All classes	MDR <ul style="list-style-type: none"> Article 62, sub 4b-k, m (includes articles 63-68) Article 75, 76, 77 Article 80, sub 5 documentation chapter II of Annex XV relevant provisions of Annex XV
Other MDR article 82	All classes	MDR <ul style="list-style-type: none"> Article 62, sub 2, 3, 4b-d, f, h, l (includes Articles 63-68) Article 62, sub 6 WMO <ul style="list-style-type: none"> Article 2a Article 3, sub1 b, c, e, f, g, h, l Article 3a, sub 1-3, Article 6, sub 9 Article 10 and 10a, sub 2

5.4.3 Vulnerable populations and subjects

Incapacitated subjects, minors (in the Netherlands: <16 years), pregnant women and breastfeeding women require specific protection measures. These additional measures are laid down in articles 64-68 of the MDR. These conditions are valid for all clinical investigations with medical devices (MDR article 62, 74 and 82).

MDR article 67 is about national legislation for maintaining additional measures regarding persons performing mandatory military service, persons deprived of liberty, persons who, due to a judicial decision, cannot take part in clinical investigations, or persons in residential care institutions. The Netherlands has not implemented MDR article 67.

5.4.3.1. INCAPACITATED SUBJECTS AND MINORS (ARTICLE 64 AND 65, MDR)

A full overview of the conditions to be fulfilled for clinical investigations with incapacitated subjects and/or minors is given in appendix F³.

On basis of the MDR there should always be *the prospect of direct benefit* for the incapacitated subject or minor participating in the clinical investigation. The clinical investigation is expected to deliver clinically relevant outcomes in the treatment, diagnosis, or prevention of the condition of the participant. Benefit may be obtained through either increased clinical performance or safety resulting in a better benefit-risk ratio, or through the provision of alternative treatment with at least similar expected benefit-risk ratio. Contribution to improved patient care is also a benefit. The estimation of whether there is 'prospect of direct benefit' for the participant is based on the scientific hypothesis made at the inception of the clinical investigation. This will be assessed by the review committee and weighed against the risks and burdens involved.

5.4.3.2 PREGNANT OR BREASTFEEDING WOMEN (ARTICLE 66, MDR)

The MDR mentions additional conditions for clinical investigations with pregnant and breastfeeding women (see appendix F). For these clinical investigations there must also be the prospect of direct benefit for the pregnant or breastfeeding woman concerned, or her embryo, fetus or child after birth. Clinical investigations with pregnant or breastfeeding women are assigned to the CCMO for review on basis of the BCB (effective date to be determined).

5.4.3.3 CLINICAL INVESTIGATIONS IN EMERGENCY SITUATIONS (ARTICLE 68, MDR)

New additional measures are described in article 68 for clinical investigations in an emergency situation. The conditions to be fulfilled to include subjects in the clinical investigation without prior informed consent by the subject or his/her legal representative are being addressed in the [CCMO memorandum deferred consent](#).

5.4.4 Assessment of the investigational medical device(s)

5.4.4.1 REQUIRED EXPERTISE

The review committee and in particular the WMO-member medical devices must assess whether the necessary expertise is available. If not, additional experts have to be sought externally. The WMO-member medical devices must be able to recognise the possible risks related to the medical device and its application and assess whether the proposed measures for risk-minimisation provide a sufficient level of protection. Given the broad range of medical devices, the WMO-member medical devices can and should seek assistance from external experts. Additionally, the WMO-member medical devices must determine, together with the other members of the review committee, if the overall benefit-risk ratio is sufficient to support a positive judgement of the review committee. Additional information from

³ Caution: for some conditions the MDR is stricter than the WMO.

the sponsor can always be requested when the provided technical documentation is insufficient to make a judgement by the review committee.

5.4.4.2 IMDD

The IMDD specifies all items that must be covered (if relevant) for an application to a review committee in the Netherlands. The IMDD is written for non-CE marked medical devices within the scope of the MDR, which are intended for clinical investigation. When a CE marked medical device is assessed outside the scope of its intended purpose an IMDD also applies for those parts that are relevant to the new purpose. In the Netherlands, the use of the IMDD is encouraged as it covers the technical documentation from annex II of the MDR. Within the IMDD, reference to other documentation such as the IB is allowed.

The WMO-member medical devices assesses whether the relevant parts of the IMDD have been filled out. The various subjects of the IMDD may be divided amongst the members or external experts in order to be able to assess all aspects of the IMDD. In appendix G, a number of suggestions and questions are provided to help guide the WMO-member medical devices. However, these items are by no means exhaustive. It should therefore not be used as a checklist, but rather as a guide to the thought process.

5.4.4.3 LOCAL INTRODUCTION OF THE INVESTIGATION MEDICAL DEVICE(S)

The review committee reviews the statement suitability clinical trial site. The plan for training (or the absence of a need for it) is mentioned in the IB.

It is the investigators responsibility to follow the institutes introduction procedure for new medical devices.

5.4.4.4 ASSESSMENT INVESTIGATIONAL MEDICAL DEVICE AT COMMITTEE MEETING

During the assessment, the review committee shall give full consideration to risks related to technical specifications and applications of the medical device, including questions such as:

- What are the noticeable (residual) risks as mentioned and identified from relevant items from IMDD? Are there risk that are not mentioned in the IMDD?
- What is still unknown about the technique, the medical device and/or the long-term effects?
- What clinical evidence is available, and is this appropriate to the risk of the study?
- What where the risks and most relevant adverse events with previous versions of the medical device or existing comparable devices?
- How does the new design of the medical device mitigate well-known adverse events from previous or existing comparable devices?
- To what extent do available (pre-)clinical data sufficiently prove that risks with comparable devices will not apply to the innovative devices?
- Does the medical device contain components that are also used in alternative treatments or therapies, which may be predictive for risks associated with the new device?
- Are raised expectations in the PIF in relation to the medical device correct? Are all risks sufficiently described in the PIF? Is the degree of uncertainty on the efficacy and risks sufficiently clear?
- Does the phasing of the research and the speed of patient inclusion match the risk of the (innovative) device? Has the fact that some risks may reveal themselves only after either a shorter or longer period of time sufficiently been taken into account?
- For implantable medical devices in particular, attention will need to be paid to the continued use of the investigational device after the clinical investigation has been concluded, if the

subject benefits from that particular device. Is the availability (or lack thereof) sufficiently clearly defined and safety assured? Is it clear who will be responsible for any costs that may arise?

- Is the clinical investigation set up according to the applicable common specifications or harmonized standards?
- Is the intended biological effect sufficiently achievable?
- Are the measures planned for the safe installation, putting into service and maintenance of the medical device adequate?
- Is the supplied documentation proportional with regard to:
 - the phase of the medical device development (first pilot or final step before CE marking) in relation to 'maturity' of the IMDD
 - potential added value in relation to the risk (and can this added value only be demonstrated with this particular risk on the subjects?)

The study design for medical devices is frequently different from studies with a medicinal product. Blinding or placebo controls for instance can be difficult. A careful consideration of the methodology is required to establish that the design of the clinical investigation is appropriate given the medical device and the addressed outcomes. The KNAW published a [report](#) on selecting the research method that best suits the relevant medical device.

Overall, the benefit-risk ratio should be appropriate to support a positive opinion of the review committee.

5.5 Archiving

The documentation of the clinical investigation (MDR annex XV) shall be kept by the sponsor for a period of at least 10 years after the end of the clinical investigation or, in the event that the medical device is subsequently placed on the market, at least 10 years after the last medical device has been placed on the market. In the case of implantable devices, the period shall be at least 15 years.

The review committee will archive the documentation in line with the Dutch Archive law.

5.6 Decision

The review committee will inform the CCMO-LB on their decision via the national web portal within 7 days after the decision date. In case of a negative decision for article 62 or 74.2 clinical investigations, the CCMO-LB will inform all Member States and the European Commission about this decision and the grounds for that decision (article 76.3 MDR).

If a clinical investigation has been authorized by the review committee, the decision is valid for two years. If the investigation has not started to include subjects within these two years, the decision is no longer valid. The sponsor can submit a request for prolongation of this decision to the committee that has issued the decision, together with a letter from the sponsor declaring whether or not there is any new substantial scientific information that would change the validity of the decision. If this is the case, the application shall be deemed to be a new application of another clinical investigation.

5.6.1 Administrative appeal/objection

If an investigator, sponsor or other concerned party does not agree with a negative decision made by the review committee they may, under certain conditions, start an administrative appeal procedure/submit an objection to the CCMO. This must be carried out within 6 weeks after the day on which the decision was reached.

5.7 Coordinated multinational assessment

A voluntary coordinated assessment is possible until May 2027. After that it is mandatory. The European Commission has decided that the start of the voluntary procedure is postponed until the moment that the Commission can provide administrative support to the coordinating Member State in the accomplishment of its tasks. See further Q&A CIE working group of European Commission (*in development*).

Chapter 6 Notifications and assessment during and after the clinical investigation

6.1 During the investigation

6.1.1 AE/SAE

The safety reporting requirements are different for the three types of clinical investigation identified in the MDR:

- Article 62 and 74.2 clinical investigations have to comply with article 80 of the MDR and [MDCG 2020-10/1&2](#);
- Article 74.1 clinical investigations (PMCF investigations) have to comply with the provisions of vigilance laid down in articles 87-90 of the MDR (responsibility of manufacturer), with the exception of SAEs related to an investigational procedure;
- Article 82 clinical investigations have to comply with article 10 of the WMO.

A flowchart of the (S)AE procedure is given in appendix E.

There is no transition period for the recording and reporting of adverse events that occur during a clinical investigation. This means that all clinical investigations that have been authorised before May 26th 2021 and notified to the IGJ also have to comply with article 80 of the MDR.

Since Eudamed will not be ready on May 26th, 2021, the sponsor has to upload the safety information via ToetsingOnline. The review committee will receive a message that safety information (SAE, line-listing) has been uploaded and can start the review.

6.1.2 Substantial modifications

Substantial modifications are any modifications to a clinical investigation that are likely to have a substantial impact on the safety, health or rights of the subjects or on the robustness or reliability of the clinical data generated by the investigation. This applies to all types of clinical investigations. Substantial modifications can result from for example modifications in the CIP but also to modifications of the medical device.

The MDR only describes substantial modifications rules (Article 75 MDR) for clinical investigations subject to Article 62, 74.1, 74.2 or multinational clinical investigations in a coordinated assessment procedure (Article 78, MDR)

Any application of a substantial modifications must be accompanied by a cover letter describing the modifications, an update of the application form (Eudamed and/or ABR, if applicable), the modified or new documents and the documents with track changes.

The review committee needs to validate that the category of the clinical investigation and classification of the medical device remains within the original scope. The timeline to review the substantial changes of article 62/74 clinical investigations is 38 calendar days plus a clock-stop after notification of the substantial modification. This period can be extended by 7 days for consulting experts. The timelines

for article 82 clinical investigations comprise a maximum of 56 calendar days (plus 56 calendar days in case of extension) plus a clock-stop for the sponsor.

6.1.3 Corrective measures

Where the review committee has grounds for considering that any the requirements for clinical investigations articles 62 or 74 as set out in the MDR are not met, the review committee may take a corrective measure:

- revoke authorisation;
- suspend or terminate the clinical investigation;
- require the sponsor to modify any aspect of the clinical investigation.

For article 62/74 clinical investigations: Before revoking or suspending authorisation or request for substantial modification, the review committee requests the sponsor to submit their view within 7 calendar days, except when immediate action is required. In case of a corrective measure the review committee notifies the CCMO-LB of this decision, including a justification. The CCMO-LB will inform all other Member States and the Commission. **For article 82 clinical investigations**, article 3a WMO applies. This article gives the review committee the rights to revoke or suspend authorisation of clinical investigation if the safety of the participating subjects is at risk. Before revoking or suspending authorisation, the review committee requests the sponsor to submit their view within 7 calendar days. In case a corrective measure is applied the review committee notifies the CCMO-LB of this decision, including justification.

6.1.4 Temporary halt/early termination

The review committee and the CCMO-LB are informed by the sponsor:

For article 62/74 clinical investigations article 77, MDR applies:

- within 15 calendar days, if the clinical investigation has been temporarily halted or terminated early in the Netherlands and a justification is provided.
- within 24 hours, if the clinical investigation has been temporarily halted or terminated early on safety grounds. The sponsor shall notify all member states in which that clinical investigation is being conducted.

For article 82 clinical investigations article 10, WMO applies:

- immediately for a temporary halt if the clinical investigation proved to be significantly more unfavourable to the subject than the CIP had foreseen.
- within 15 calendar days, if the clinical investigation is terminated early and a justification is provided.

A restart of a clinical investigation after a temporary halt of the clinical investigation due to safety reasons, is in the Netherlands considered a substantial modification. See paragraph 6.1.2.

6.2 End of clinical investigation

6.2.1 Notification

The end of a clinical investigation is considered to be the last visit of the last subject unless another point in time for such end is set out in the CIP.

For article 62/74 clinical investigations article 77, MDR applies: The review committee is informed by the sponsor within 15 days of the end of the clinical investigation in the Netherlands and, in case of a multinational investigation, the end of the clinical investigation in all EU member states.

For article 82 clinical investigations the national rule applies: The review committee is informed by the sponsor within 56 days of the end of the clinical investigation in the Netherlands.

6.2.2 Results of the clinical investigation

For article 62/74 clinical investigations: A clinical investigation report and lay summary is submitted to the review committee irrespective of the outcome of the clinical investigation (article 77, MDR):

- within one year of the end of the clinical investigation (or later if this is justified for scientific reasons and specified in CIP);
- within 3 months of the early termination or temporary halt⁴.

The report and lay summary becomes publicly available:

- immediately after submission in cases of early termination or temporary halt;
- when the medical device is registered (Article 29) and before it is placed on the market;
- at the latest one year after submission of the report and summary if it is not registered before that time.

For article 82 clinical investigations: Submission of a summary of results within one year after the end of the clinical investigation is mandatory as stated in the authorisation letter of review committee. This summary will become publically available (article 3, WMO) unless the sponsor has objected with arguments.

⁴ In the event that the clinical investigation is restarted within three months of the temporary halt, the sponsor does not have to submit a clinical investigation report until the clinical investigation has been completed (under discussion in CIE WG of European Commission).

Appendix

Appendix A Definitions

Accessory for a medical device: means 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).

Active device: means any device, the operation of which depends on a source of energy other than that generated by the human body for that purpose, or by gravity, and which acts by changing the density of or converting that energy. Devices intended to transmit energy, substances or other elements between an active device and the patient, without any significant change, shall not be deemed to be active devices. Software shall also be deemed to be an active device. The classification rules are specific on active devices (MDR annex VIII).

Adverse event: means any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device;

CE marking or CE marking of conformity: marking by which a manufacturer indicates that a device is in conformity with the applicable requirements set out in the MDR and other applicable Union harmonisation legislation providing for its affixing.

Clinical benefit: means the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health.

Clinical data: means information concerning safety or performance that is generated from the use of a device and is sourced from the following:

- clinical investigation(s) of the device concerned,
- clinical investigation(s) or other studies reported in scientific literature, of a device for which equivalence to the device in question can be demonstrated,
- reports published in peer reviewed scientific literature on other clinical experience of either the device in question or a device for which equivalence to the device in question can be demonstrated,
- clinically relevant information coming from post-market surveillance, in particular the post-market clinical follow-up.

Clinical evidence: means clinical data and clinical evaluation results pertaining to a device of a sufficient amount and quality to allow a qualified assessment of whether the device is safe and achieves the intended clinical benefit(s), when used as intended by the manufacturer.

Clinical evaluation: means a systematic and planned process to continuously generate, collect, analyse and assess the clinical data pertaining to a device in order to verify the safety and performance, including clinical benefits, of the device when used as intended by the manufacturer.

Clinical evaluation plan (CEP): The Clinical evaluation plan means a plan in which is described a systematic and planned process to generate, collect, analyse and assess clinical data pertaining to a medical device in order to verify the safety and performance, including clinical benefits, of the medical device when used as intended by the manufacturer. The exact details are described in Annex XIV, part A, 1(A) of the MDR. The CEP or a reference to the CEP is needed for Article 62 or 74.2 clinical investigations.

Clinical investigation: means any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device.

Clinical investigation plan (CIP): means a document that describes the rationale, objectives, design, methodology, monitoring, statistical considerations, organisation and conduct of a clinical investigation.

Clinical performance: means the ability of a device, resulting from any direct or indirect medical effects which stem from its technical or functional characteristics, including diagnostic characteristics, to achieve its intended purpose as claimed by the manufacturer, thereby leading to a clinical benefit for patients, when used as intended by the manufacturer.

Common specifications (CS): means a set of technical and/or clinical requirements, other than a standard, that provides a means of complying with the legal obligations applicable to a device, process or system.

Conformity assessment: means the process demonstrating whether the requirements of this Regulation relating to a device have been fulfilled.

Custom-made device: means any device specifically made in accordance with a written prescription of any person authorised by national law by virtue of that person's professional qualifications which gives, under that person's responsibility, specific design characteristics, and is intended for the sole use of a particular patient exclusively to meet their individual conditions and needs.

However, mass-produced devices which need to be adapted to meet the specific requirements of any professional user and devices which are mass-produced by means of industrial manufacturing processes in accordance with the written prescriptions of any authorised person shall not be considered to be custom-made devices;

Device deficiency: means any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer;

Eudamed: European database on medical devices. The development of this database is delayed and will not be available before May 2022.

Harmonised standard: means a European standard as defined in point (1c) of Article 2 of Regulation (EU) No 1025/2012;

Label: means the written, printed or graphic information appearing either on the device itself, or on the packaging of each unit or on the packaging of multiple devices;

Medical device: means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

- diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,

- diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,
- investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,
- providing information by means of *in vitro* examination of specimens derived from the human body, including organ, blood and tissue donations,

and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

The following products shall also be deemed to be medical devices:

- devices for the control or support of conception;
- products specifically intended for the cleaning, disinfection or sterilisation of medical devices, accessories for medical devices, and products listed in annex XVI

Manufacturer: means a natural or legal person who manufactures or fully refurbishes a device or has a device designed, manufactured or fully refurbished, and markets that device under its name or trademark;

Implantable device: means any device, including those that are partially or wholly absorbed, which is intended:

- to be totally introduced into the human body, or
- to replace an epithelial surface or the surface of the eye,

by clinical intervention and which is intended to remain in place after the procedure.

Any device intended to be partially introduced into the human body by clinical intervention and intended to remain in place after the procedure for at least 30 days shall also be deemed to be an implantable device. (Article 2(5) MDR)

Informed consent: means a subject's free and voluntary expression of his or her willingness to participate in a particular clinical investigation, after having been informed of all aspects of the clinical investigation that are relevant to the subject's decision to participate or, in the case of minors and of incapacitated subjects, an authorisation or agreement from their legally designated representative to include them in the clinical investigation;

Instructions for use: means the information provided by the manufacturer to inform the user of a device's intended purpose and proper use and of any precautions to be taken;

Intended purpose: means the use for which a device is intended according to the data supplied by the manufacturer on the label, in the instructions for use or in promotional or sales materials or statements and as specified by the manufacturer in the clinical evaluation;

Invasive device: means any device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body. (MDR article 2.6). 'Body orifice' means any natural opening in the body, as well as the external surface of the eyeball, or any permanent artificial opening, such as a stoma. (MDR VIII annex 2.1)

Invasive procedure: is considered to be a medical procedure invading (entering) the body, usually by cutting or puncturing the skin or by introducing instruments into the body.

Investigational device: means a device that is assessed in a clinical investigation.

Investigational medical device dossier (IMDD): The IMDD provides the technical documentation on the medical device. A [model IMDD](#) is available on the website of the CCMO. The use of this document is best practice in the Netherlands for clinical investigations with a medical device without a CE mark or a CE-marked medical device outside the scope of the intended purpose. If the model IMDD is not used a justification should be given in the cover letter. A document with comparable content might also be acceptable.

Investigator: means an individual responsible for the conduct of a clinical investigation at a clinical investigation site.

Investigator's brochure (IB): The IB contains the clinical and non-clinical information on the investigational device that is relevant for the investigation and available at the time of application. MDR Annex XV chapter II.2 explicitly describes which information is required.

Performance: means the ability of a device to achieve its intended purpose as stated by the manufacturer (article 2(22), MDR);

PMCF investigation: a clinical investigation to further assess, within the scope of its intended purpose, a device which already bears the CE marking, and where the investigation would involve submitting subjects to procedures additional to those performed under the normal conditions of use of the device and those additional procedures are invasive or burdensome.

PMCF study: a Post Market Clinical Follow-up study to collect or evaluate clinical data from the use in or on humans of a medical device which bears the CE marking and is placed on the market or put into service within its intended purpose with the aim of confirming the safety and performance throughout the expected life time of the device. These studies shall be addressed in the manufacturer's post-market surveillance plan.

Serious adverse event: means any adverse event that led to any of the following:

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

Single identification number: unique Union-wide single identification number for the clinical investigation, which shall be used for all relevant communication in relation to that clinical investigation.

Sponsor: means any individual, company, institution or organisation which takes responsibility for the initiation, for the management and setting up of the financing of the clinical investigation. With this definition the investigator initiated investigations are explicitly brought under the MDR.

Subject: means an individual who participates in a clinical investigation.

Surgically invasive device: means: (a) an invasive device which penetrates inside the body through the surface of the body, including through mucous membranes of body orifices with the aid or in the context of a surgical operation; and (b) a device which produces penetration other than through a body orifice.

Unique Device Identifier ('UDI'): means a series of numeric or alphanumeric characters that is created through internationally accepted device identification and coding standards and that allows unambiguous identification of specific devices on the market;

User: means any healthcare professional or lay person who uses a device;

Appendix B Checklist validation research dossier for clinical investigations with medical devices under MDR.

Date of receipt: Klik of tik om een datum in te voeren.

ToetsingOnline number: NL

Eudamed number (if available):

Is the clinical investigation within the scope of the MDR?

- Yes
- No, because

Type of clinical investigation: Article 62/74.1 (PMCF)/74.2/82*

Class investigational medical device(s):**

- class I
- class IIa or class IIb non-invasive
- class IIa or class IIb invasive
- class III

* strike out what's not applicable

** if there is more than one investigational device please cross box of the device with the highest class

Documents initial application

			Received			
Section		Document	Comment	Yes	No	NA
A	A1	Cover letter		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	A2	Letter of authorisation if applicant is not the sponsor		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

			Received		
Section	Document	Comment	Yes	No	NA
B	B1	ABR form	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	B1a	Eudamed form	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
C	C1	Clinical Investigation Plan (CIP)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	C2	Substantial modifications of CIP	If applicable	<input type="checkbox"/>	<input type="checkbox"/>
D	D1	Investigator's Brochure	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	D1	Other relevant safety information (not included in IB or CIP)	If applicable	<input type="checkbox"/>	<input type="checkbox"/>
	D2	Investigational Medical Device Dossier (non CE marked medical device or used outside intended purpose)	If applicable	<input type="checkbox"/>	<input type="checkbox"/>
	D2	Product information medical device: EU declaration of conformity and the instructions for use	If applicable	<input type="checkbox"/>	<input type="checkbox"/>
	D3	Example of labelling attached to CE marked device (includes packaging labels and instruction for use)	If applicable	<input type="checkbox"/>	<input type="checkbox"/>
	D4	Signed statement by manufacturer (or its authorized representative) about safety and performance investigational medical device apart from the aspects covered by the clinical investigation and that, with regard to those aspects, every precaution has been taken to protect the health and safety of the subject.		<input type="checkbox"/>	<input type="checkbox"/>
E	E1/E2	Subject information sheet(s) and informed consent form(s)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	E3	Recruitment material	If applicable	<input type="checkbox"/>	<input type="checkbox"/>
	E4	Other information materials (newsletters, general brochures about trial specific procedures, etc)	If applicable	<input type="checkbox"/>	<input type="checkbox"/>
F	F1	Questionnaires	If applicable	<input type="checkbox"/>	<input type="checkbox"/>
	F2	Patient diary	If applicable	<input type="checkbox"/>	<input type="checkbox"/>

			Received			
Section	Document	Comment	Yes	No	NA	
	F3	Patient card – for implantable devices the information required in MDR Article 18 shall be provided as far as relevant	If applicable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
G	G1	Insurance certificate WMO research		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	G2	Proof of coverage liability of sponsor or investigator		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
H	H1	CV independent expert(s)	Not mandatory	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	H2	CV coordinating investigator (multicentre research)	If applicable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I	I1	List of participating centres (or refer to section C9 ABR-form)		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	I2	Research declaration form (for each participating centre)		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	I3	CV principal investigator (for each participating centre)		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	I4	Other information per participating centre	If applicable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
K	K1	Copy of (summary of) <u>scientific/technical opinion/review</u> by other body with respect to clinical investigation or investigational device submitted (expert panel, competent authority, notified body etc)	If applicable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	K2	Copy <u>assessment</u> from other Member States (competent authority and/or ethics committee)	If applicable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	K3	Clinical trial agreement between sponsor and institution/investigator (for each participating centre)		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	K4	Relevant publications with respect to clinical investigation submitted	If applicable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	K5	Data Safety Monitoring Board (DSMB) – composition and charter		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

			Received		
Section	Document	Comment	Yes	No	NA
K6	Description of the arrangements to comply with the applicable rules on the protection and confidentiality of personal data (GDPR) if not addressed in Clinical Investigational Plan (section C1), in particular: <ul style="list-style-type: none"> organisational and technical arrangements that will be implemented to avoid unauthorised access, disclosure, dissemination, alteration or loss of information and personal data processed; a description of measures that will be implemented to ensure confidentiality of records and personal data of subjects; and a description of measures that will be implemented in case of a data security breach in order to mitigate the possible adverse effects. 		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
K7	Clinical evaluation plan	Mandatory for Article 62, 74.2 investigations	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Dossier complete?

- Yes
- No, request sponsor to complete application and start assessment postponed
- No, request sponsor to complete application and start assessment

Name validator :.....

Validation date: Klik of tik om een datum in te voeren.

Appendix C Timelines

Table currently under discussion by the CIE working group of the European Commission.

Timeline for Article 62 or 74.2 – Single Member State		
Step	Timeline for the step	Maximum timelines
Application of sponsor	0 D0	D0
MS provides the outcome of validation (extension delay possible)	Within 10 days (+5) D10	D15
If the application dossier is considered not complete, the sponsor provides additional information	Within 10 days (+20) D20...	D45
If applicable, MS reviews additional information and provides its final outcome on validation* <small>*for class I and non-invasive class IIa/IIb, unless stated in the national law of the MS, the clinical investigation would start upon the date of validation of the application if no negative opinion has been issued by an ethics committee in this same MS.</small>	Within 5 days (+5)	D55
MS provides its outcome of the assessment (request for information [RFI] or decision)	Within 45 days (+ 20)	D120
Sponsor provides the responses** in case of RFI <small>**a clock-stop, i.e. the time available for assessment by the MS, shall be suspended from the date of the request for information, until such time as the additional information has been received.</small>	Within a timeline communicated by MS (this time period is not defined in MDR)	D120+X
MS provides its decision	Within 45 days (+20)	D120+X

Appendix D Notifications sponsor to review committee

Italic notifications are national requirements (NL) as they are not defined in MDR.
SAE notifications, see flow chart in appendix E.

Notification	Definition	Timeline
Withdrawal application		Prior to decision review committee
<i>Date start clinical investigation</i>	<i>Date on which the first subject signs the informed consent form</i>	<i>< 2 years after authorisation clinical investigation</i>
Date end clinical investigation in NL	The last visit of the last subject, or at a later point in time as defined in the CIP	≤ 15 days of this date
Date end clinical investigation in all MS concerned (MSc)		≤ 15 days of this date
<i>Date end clinical trial in all MSc and in all 3rd countries</i>		<i>≤ 15 days of this date</i>
Temporary halt or early termination clinical investigation on other grounds than safety (including justification)		≤ 15 days of this date
Temporary halt or early termination clinical investigation on safety grounds (including justification)		< 24 hours of this date
<i>Resume clinical investigation after temporary halt for other reasons than safety (resume clinical investigation after temporary halt for safety reasons requires approval from review committee)</i>		<i>≤ 15 days after restart</i>
Clinical investigation report (CIR) accompanied by summary that is easily understandable to the intended user *.	CIR: see section 7 of Chapter III of Annex XV COM guideline regarding the content and structure of the summary of the clinical investigation report (to be developed).	< 3 months of date early termination or temporarily halt** < 1 year of end clinical investigation ***

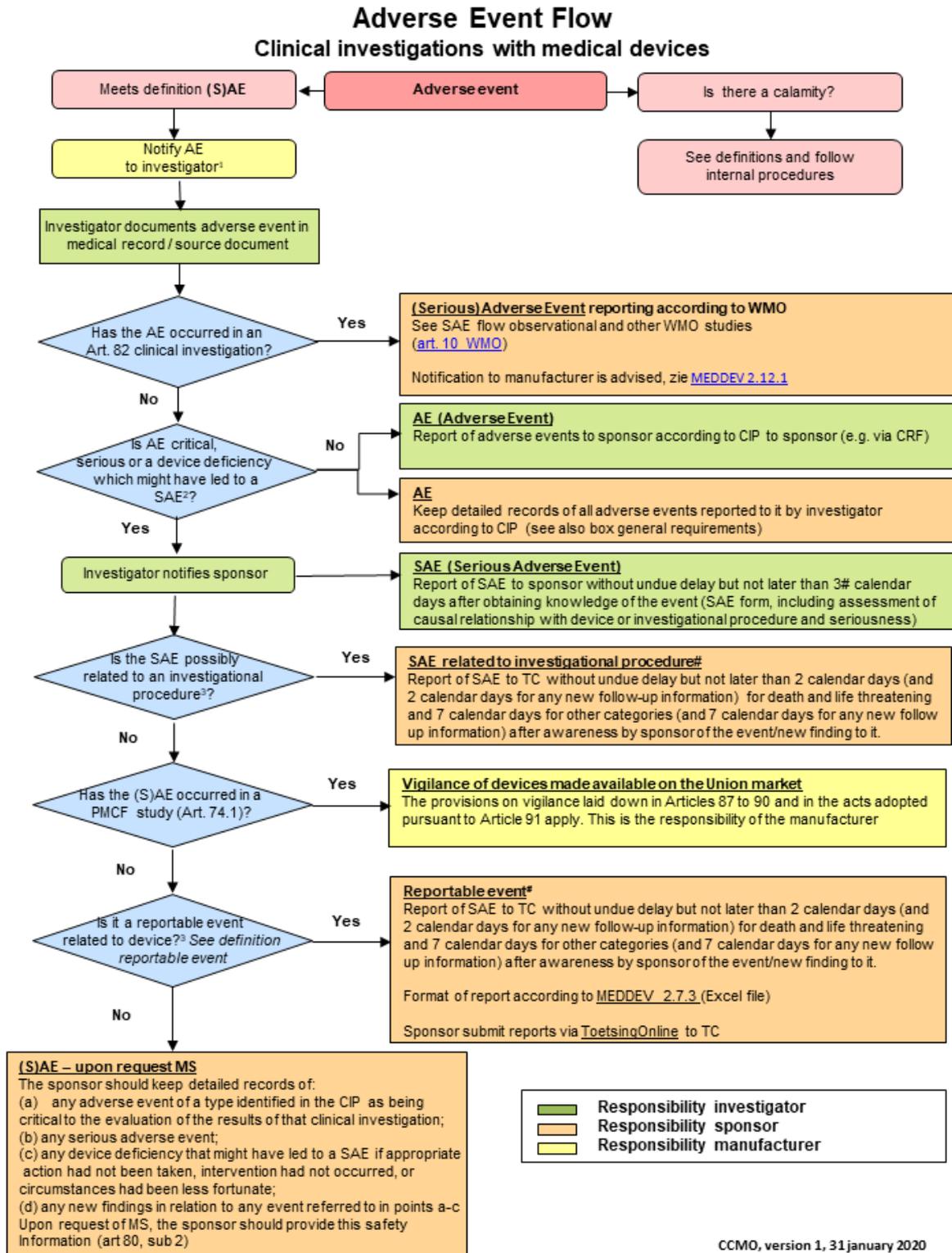
*CIR and/or summary shall become publicly accessible through Eudamed (MDR Article 77.7) or CCMO-register (WMO, in case of no objection sponsor)

** CIR after temporary halt is under discussion in CIE working group European Commission

*** Where, for scientific reasons, it is not possible to submit the clinical investigation report within one year of the end of the investigation, it shall be submitted as soon as it is available. In such case, the clinical investigation plan shall specify when the results of the clinical investigation are going to be available, together with a justification.

Appendix E Reporting SAE

The flowchart for reporting SAEs is depicted below. (TC=review committee)



Reporting timelines investigator and sponsor

General

The reporting requirements are applicable for events related to investigational device, the comparator device and investigational procedures

Timeline investigator (tentative)

- ▶ First initial report < 3 calendar days, unless a different procedure and reporting timeline has been agreed between sponsor and MREC/CCMO (for instance in oncology trials in which SAE frequency is expected to be high due to progression of disease). The SAE procedure should be laid down in the clinical investigational plan (protocol).

Timelines sponsor (tentative):

Death and life-threatening:

- ▶ First initial report < 2 calendar days after awareness sponsor
- ▶ New findings to initial report < 2 calendar days after awareness sponsor of new finding

Not fatal or life-threatening:

- ▶ First initial report < 7 calendar days after awareness sponsor
- ▶ New findings to initial report < 7 calendar days after awareness sponsor of new finding

Upload in national webportal ToetsingOnline until Eudamed is available

- Format is given in MEDDEV 2.7.3 (Excel file)

Other obligations

- A sponsor may not downgrade the causality assessment done by the investigator
- If the sponsor has temporarily halted a clinical investigation or has terminated a clinical investigation early because of safety reasons, it shall inform all MS in which that clinical investigation is being conducted within 24 hours. The notification will also provide a justification.
- The sponsor has the obligation to submit safety information other than the reportable events if the MS has requested for it (MDR, art 80, sub 2).

Sponsor is not manufacturer

- It is advised to inform manufacturer of the medical device as USER. See [MEDDEV 2.12.1](#), sectie 9 'USER's role within the Vigilance system'.

National/multinational clinical investigations

The safety reporting requirements are applicable for all clinical investigations authorised to be carried out national (Netherlands only) and multinational (Netherlands plus one or more MS(s) of the EEA plus Switzerland and Turkey and/or a third country). If an event occurred in a third country in which a clinical investigation is performed under the same clinical investigation plan as the one applying to a clinical investigation covered by this Regulation the same reporting requirements apply (art 80, sub 3).

In a multinational investigation, the sponsor of the clinical investigation must inform all MSs of the EEA plus Turkey and Switzerland in which the clinical investigation is authorized to be carried out about reportable events.

Definitions and explanatory notes

Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.

Serious Adverse Event (SAE) (MDR, art 2, 58)

Any adverse event that led to any of the following:

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

Device deficiency (MDR, art 2, 59)

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

Reportable events (MDR, art 80, sub 2)

A reportable event is:

- a. any serious adverse event that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible;
- b. any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;
- c. any new findings in relation to any event referred to in points (a) and (b).

Calamity (Wet kwaliteit, klachten en geschillen zorg (Wkkgz), art 11, lid 1 sub a)

A calamity is (in Dutch):

- een niet-beoogde of onverwachte gebeurtenis die betrekking heeft op de kwaliteit van de zorg en die tot de dood van of een ernstig schadelijk gevolg voor een cliënt heeft geleid.

A calamity must be reported to Dutch Health and Youth Inspectorate (IGJ) within 3 working days (<https://www.igj.nl/vonderwerpen/calamiteiten/melding-doen-van-een-calamiteit>)

Investigator (MDR, art 2, 54)

Investigator means an individual responsible for the conduct of a clinical investigation at a clinical investigation site

Sponsor (MDR, art 2, 49)

Sponsor means any individual, company, institution or organisation which takes responsibility for the initiation, for the management and setting up of the financing of the clinical investigation

Reviewing Committee (TC) and competent authority (CA)

For clinical investigations with medical devices the CCMO or an accredited MREC is the reviewing committee. [See committee finder tool.](#) The CCMO is also the competent authority for clinical investigations. Tasks are described in WMO, article 17a.

Footnotes and references

1. A notification to the investigator of an adverse event which took place with a subject participating in a clinical investigation to the investigator can be done by the subject, but also for example by a research nurse, partner of subject etcetera or can also be noticed by investigator himself.
2. The sponsor shall fully record all of the following (MDR, art. 80, sub 1):
 - (a) any adverse event of a type identified in the clinical investigation plan as being critical to the evaluation of the results of that clinical investigation;
 - (b) any serious adverse event;
 - (c) any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate; (
 - d) any new findings in relation to any event referred to in points (a) to (c).
3. Article 80, sub 2 of MDR describes the reportable events for the sponsor to be submitted to MS. See definition in which causal relationship with investigation procedure or device is mentioned. These reportable events are applicable for article 62 and 74.2 clinical investigations. In article 80, sub 6, it is described that for article 74.1 studies the sponsor has to report to MS any SAE for which a causal relationship has been established with the preceding investigational procedure. Therefore, in the flowchart SAE related to investigational procedure is a separate step and applicable for art 62 and 74 clinical investigations.

WMO text valid on 26 May 2020; wet van 26 februari 1998
MDR EU no 2017/745, dd 5 April 2017, applicable on 26 May 2020
MEDDEV 2.12/1 rev 8
MEDDEV 2.7/3, dd ???, applicable on 26 May 2020
ISO14155, version 2020, applicable ?

Appendix F Overview of assessment criteria described in MDR

An overview of the assessment criteria and regulatory grounds can be found in an Excel on the website of the CCMO. The items are grouped by topic. This file is unfortunately too large to be placed in this guidance.

Appendix G IMDD assessment topics

This section serves as an aid for assessing the investigational medical device based on the IMDD. A number of suggestions and questions are provided to help guide the WMO-member medical devices. However, these items are by no means exhaustive. It should therefore not be used as a checklist, but rather as a guide to the thought process.

The numbering is consistent with the sections and numbering of the IMDD (version of January 2020).

1. Device description and specification, including variants and accessories

1.1 DEVICE DESCRIPTION AND SPECIFICATION

- Is the medical device sufficiently identifiable with the supplied information?
- Is it clear who has the role of the manufacturer? Is the intended purpose consistent with the use in the study?
- Does the described intended use correspond to claims and/or other expressions, e.g. in the research proposal or patient information?
- Is the description of the users, and the patient population, consistent with the manufacturer's description?

- Is the general description of the operating principle clear?
- Is it clear which components (may) be part of the (assembled) medical device?

- Is the qualification as a medical device and the risk classification correct?
- Is it clear which rule has led to the classification of the medical device in a particular class?

1.2 REFERENCE TO PREVIOUS AND SIMILAR GENERATIONS OF THE DEVICE

If applicable and if there is a substantial build-up on the previous versions or a similar medical device

- Check whether documentation is available
- Check whether deviations are well justified and described.
- Is the knowledge from previous generations or existing comparable devices sufficiently used?
- Is the investigated device state-of-the-art compared to devices already available on the market with the same purpose?

2. Information to be supplied by the manufacturer

- Labels must be assessed by means of checks against standards. The relevant standards are indicated further on in the General safety and performance requirements.
- The instructions for use (IFU) must be verified for mandatory elements (see MDR Annex I, 23.4 for all required subjects) such as intended purpose, indications and contra-indications, required training.
- Points that have emerged from the risk analysis as residual risk should be included in the manual and if appropriate in the PIF.
- Further attention to readability (language and use of words, with respect to the intended user), completeness and where applicable, cleaning, maintenance and storage instructions, et cetera.
- Detailed information on cleaning, disinfection, sterilisation, (dis)assembly, etc. should be covered in paragraph 6.2(e) of the IMDD.

3. Design and manufacturing information

The documentation shall contain information allowing a reviewer to obtain a general understanding of the design and manufacturing processes.

During the assessment, special attention to quality control moments and/or test moments in both the design and production are needed. Also with software, a large part of the safety is often covered by design steps and (interim) test moments. This should be covered in more detail in chapter 4 "general safety and performance requirements" of the IMDD.

Checks on the presence, validity and scope of the certificates and documents/references supplied in relation to the quality management system (QMS) applied. The quality management system must be adequate for the risk and scale of the investigation. For the manufacture of devices (other than investigational devices), the quality management system must be specifically intended for medical devices. In general, this means that ISO 13485 is applied for companies. For institutions with a scientific objective, we expect, as an absolute minimum, a quality management system and sufficient building up of the technical dossier. Meaning that the design process is sufficiently described including the risk management throughout the design process. See MDR article 10.9 for a detailed description of the necessary components of a quality management system.

4 General safety and performance requirements

Have the relevant standards been applied? Finding (harmonised) standards, guidelines and common specifications can be difficult. There are tools available, but these are certainly not comprehensive for all medical devices that have already been developed or will be developed in the future. If deviations from harmonised standards, common specification or other solutions applied occur, the justification must be clear. In case of doubt, a reference to the complete technical documentation can be checked by requesting the corresponding documentation.

5 Benefit-risk analysis and risk management

This section is specific for the assessment of the benefit-risk ratio and the risk management of the medical device in the IMDD.

The method is assessed on the basis of the following (not limited) questions;

- Is the design of the risk management system appropriate for the medical device to be assessed in this study? Is ISO 14971 used, and if not, what makes the method used appropriate?
- Is the methodology correct (probability and effect, measure can reduce probability, but not limit the consequences, there are always measures if the risk matrix prescribes this, et cetera).
- Is the authorisation and version management correct?
- Has the risk benefit analysis been carried out and signed by a cross-functional team of experts with application knowledge and clinical expertise?
- Is the analysis sufficiently consistent and in line with what is described in the method (risk management plan)?
- Are the implementation and verification of the risk control measures traceable? In other words, if a measure is taken, can it be traced back?
- Do residual risks reappear in the IFU?

- Is there a risk management summary report with the results of the evaluation of the residual risks, et cetera?
- If reference is made to documents, are they present, et cetera?

In terms of content, the analysis is assessed on the following (not limited) items:

- Have the most obvious risks been identified?
- Have the probability and impact been reasonably assessed?
- Is the possible measure appropriate and traceable?
- Examine a sample (the size in accordance with the risk profile of the research proposal) of the risk analysis in detail. If necessary, add a few more distant or improbable risks in order to gain insight into the depth and accuracy of the analysis.

6. Product verification and validation

6.1 PRE-CLINICAL AND CLINICAL DATA

a. (Pre-)clinical results of tests, e.g. engineering, laboratory, simulated use and animal tests

- Is it clear why human studies are necessary at this stage of medical device development?
- Have all other ways of establishing performance and safety data been deployed and/or studied in sufficient numbers?

b. Device-specific aspects

The following aspects of the medical device may not apply to particular cases, and should only be assessed when relevant. Detailed information regarding test design, full test or study protocols, methods of data analysis should be provided in addition to data summaries and test conclusions on the following subjects;

Biocompatibility

- Have the materials that come into contact with the patient been specified?
- Is the biocompatibility of these materials known and suitable for the intended purpose? If not, how does the manufacturer demonstrate biocompatibility?
- A rationale shall be provided on the applicability of the available data and on the testing still required for the current devices. This information should be available in the biological safety evaluation report, as required by the horizontal standard on biological safety testing (ISO 10993-1).
- What material properties are relevant to the use of the device?
- How are these properties being addressed in the IMDD?
- Is there a need for supplying results of pre-clinical testing on these material properties?
- Can these properties change within the timespan of the clinical investigation?

Physical, chemical and microbiological characterisation

The applicable physical, chemical and microbiological specifications shall be provided. Is the description of the physics principles or interaction clear?

Electrical safety and electromagnetic compatibility

- Have the correct standards been applied and the necessary tests carried out?
- Are the instructions for performing a (periodic) electrical safety test clear?
- Does the application require specific demands for electromagnetic compatibility?

- Is the medical device immune for commonly used emitting sources such as WiFi, Bluetooth and cell phone?
- Is the medical device being used in an environment where electromagnetic transmission can be a risk for life-supporting equipment or monitoring of vital parameters?

Software verification and validation

- What standards have been used for the software development, verification and validation (in general IEC 62304 is applied)?
- What pre-clinical tests have been carried out and what where the results?
- Has the inter-operability between the software and intended IT-environment been addressed?
- The description of connectivity to networks is of importance. Medical devices actively seeking/making a connection outside the network e.g. for updates or maintenance are potentially more susceptible to hacking. This may increase the sensitivity to hacking on a large scale for an entire hospital network, with a major impact on the privacy of the test subjects or patients. Attention must be paid to data security (integrity, availability and exclusivity). This needs to be described in detail.

Stability, shelf life

- What is the shelf life of the medical device, how has it been demonstrated and is this sufficiently proven?
- Is the shelf life sufficient for the expected duration of the study?

Performance and safety, usability

Assess the additional information at your own discretion.

c. d. Clinical evaluation report/plan or PMCF report/plan

The clinical investigation should be reviewed as part of a clinical evaluation plan, within the context of future market approval, rather than solely the question if it is acceptable for patients to participate in this one single clinical investigation. This means that the context of the clinical investigations should be considered (e.g. market approval).

6.2 ADDITIONAL INFORMATION IN SPECIFIC CASES

The following aspects of the medical device may not apply to particular cases, and should only be assessed when applicable.

a) Medicinal substances

Involve a pharmacist in the assessment and assess the interaction between the medical device and the medicinal product together.

b) Tissues or cells of human or animal origin

- The documentation must identify all materials of human or animal origin used and provide detailed information concerning the conformity with Sections 13.1., 13.2. or 13.3, of MDR Annex I.
- Assess the specific risk management related to the tissues, cells or their derivatives and the evidence for the added value of the addition of such components with regard to the clinical benefit and/or safety of the medical device.

c) Substances intended to be absorbed by or locally dispersed in the human body

Assess the information, including the test design and, in particular, the test conclusions that demonstrate the safety of these substances. Data on absorption, distribution, metabolism and excretion, possible interactions of these substances, local tolerance and toxicity should be sufficient to justify use within the study. In the absence of such studies, justification shall be provided.

d) CMR or endocrine-disrupting substances

Involve the pharmacist and assess whether the justification concerning the presence of carcinogene, mutagene or reproduction toxic (CMR) substances and/or endocrine disrupting substances is sufficiently substantiated.

The following elements should be identified;

- The potential exposure of the patient or user(s),
- An analysis of possible alternative substances, materials or designs, arguments for the claim that possible alternative substances, materials or designs are not suitable.
- Account shall be taken of children or pregnant or breastfeeding women, or other groups of patients considered particularly vulnerable to these substances and/or materials.
- Where appropriate and available, the most recent guidance provided by the relevant Scientific Committee in accordance with sections 10.4.3 and 10.4.4 of MDR annex I. See Section 10.4.1 of MDR annex I for details.

e) Product delivered sterile, need to be reprocessed or in a defined microbiological condition

Involve the Expert Sterile Medical Devices (DSMH) in the assessment.

In case of a sterile delivered product assess the information to demonstrate that the established sterilization process, the effectiveness of the sterilisation process used and the maintenance of sterility are sufficient for this specific device. Tests related to biological loading, pyrogens and, where appropriate, disinfectant residues shall be addressed in the validation report.

In case of a medical device that is delivered unsterile and needs to be reprocessed by the hospital, substantiated information about the procedures for cleaning, disinfection and sterilization should be provided by the supplier (conform ISO 17664).

f) Measuring function

Is the description of the method of ensuring accuracy in accordance with the risk profile of the medical device?

g) Connection to other devices

Is the description of the combination sufficiently clear and is it traceable why this combination is sufficiently safe?