Clinical investigations with medical devices

Guidance

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NEDERLANDSE FEDERATIE VAN UNIVERSITAIR MEDISCHE CENTRA

Contents

Medical device definition:

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.

1. Voorwoord bij dit handvat en disclaimer (in Dutch)

De inwerkingtreding van de Medical Device Regulation (Verordening (EU) 2017/745) en de In Vitro Diagnostic Regulation (Verordening (EU) 2017/746) heeft grote gevolgen voor fabrikanten, marktpartijen en zorginstellingen.

In september 2019 is door de NFU het programma “Veilige Zorg door Veilige Technologie” gestart. Doel van het programma is een efficiënte en effectieve implementatie van beide verordeningen binnen de universitaire medische centra, umc’s, in Nederland.

Als onderdeel van dit programma zijn een aantal handvatten opgesteld. Doel van de handvatten is het duiden van een aantal belangrijke veranderingen ten gevolge van de inwerkingtreding van beide verordeningen (en de hiervan afgeleide Nederlandse wetgeving) voor zorginstellingen en umc’s in het bijzonder en het aangeven van mogelijkheden voor umc’s om hiermee om te gaan. Bij het opstellen van de handvatten is uitgegaan van de medio 2020 beschikbare relevante publicaties, bijvoorbeeld de guidances vanuit de EU. De handvatten geven geen kant en klaar implementatie recept voor zorginstellingen, de implementatie van beide verordeningen in een specifieke zorginstelling vereist altijd maatwerk. De handvatten kunnen bij het opstellen van het noodzakelijke implementatieplan en de uitvoering hiervan gebruikt worden.
Ieder handvat is opgesteld door een team van experts uit de umc’s, aangevuld met vertegenwoordigers uit de Federatie Medisch Specialisten en een aantal algemene ziekenhuizen. De concept handvatten zijn voorgelegd aan VWS, IGJ en de CCMO, het ontvangen commentaar is verwerkt in de definitieve versies. IGJ geeft hierbij aan: “IGJ heeft geen rol in het toetsen of beoordelen van documenten die zijn opgesteld voor en door het veld. De IGJ geeft aan situationeel te handelen op mogelijke activiteiten die door veldpartijen worden ondernomen naar aanleiding van de handreiking en daarbij vanuit haar autonome rol als toezichthouder te beoordelen in hoeverre deze als wetsconform kunnen worden beschouwd.”

Naast de handvatten is een “*startdocument*” opgesteld waarin aan de hand van de levenscyclus van medische hulpmiddelen de samenhang tussen de verschillende handvatten wordt aangegeven.

Disclaimer

Dit handvat heeft ten doel een aantal veranderingen voor zorginstellingen en met name umc’s ten gevolge van de inwerkingtreding van de Medical Device Regulation (Verordening (EU) 2017/745) en de In Vitro Diagnostic Regulation (Verordening (EU) 2017/746) te duiden.

De implementatie van deze verordeningen in een specifieke zorginstelling vereist maatwerk, dit handvat kan daarbij slechts behulpzaam zijn. Dit handvat dient daarom niet beschouwd te worden als de enige en juiste wijze waarop de implementatie plaats dient te vinden.

Dit handvat is gebaseerd op de medio 2020 beschikbare relevantie publicaties.

Aan de totstandkoming van de inhoud van dit handvat is uiterste zorg besteed. Voor informatie die desondanks onvolledig of onjuist is opgenomen aanvaardt de NFU geen aansprakelijkheid.

Dit handvat is bedoeld voor eigen gebruik binnen de zorginstelling en mag niet verder verspreid worden zonder de toestemming van de NFU.

Mocht u eventuele onjuistheden tegenkomen, dan stellen wij het op prijs als u deze door wilt geven aan de NFU: hulpmiddelen@nfu.nl

2. Colophon and scope

This guidance contains recommendations for the investigations of medical devices within hospitals under the Medical Devices Regulation (MDR) and for investigations in which (medical) devices are used. This includes all categories of devices covered by the MDR, such as equipment, software, disposables, reusables and implants.

This guidance describes the requirements when conducting clinical investigations with people (subjects or patients). This guidance does not address the requirements of other types of studies such as technical, lab or animal studies.

Parts of this document are reproduced (with permission) from the concept guidance document "Review of a clinical investigation with a medical device - guidance document for MRECs (February 6th 2020)" written by the CCMO. This guidance document will be made publicly available on the website of the CCMO (https://www.ccmo.nl/).

This document tries to summarize the current procedures on clinical investigations of medical devices. On some topics, there is still debate in the Netherlands and Europe how the exact MDR procedures should be interpreted or implemented. Topics are: Post Market Clinical Follow-up investigations, scope of WMO with relation to MDR, etc. It is therefore advised to check websites regularly like that of the EU and CCMO.

As a general remark on how to deal with choices (and the uncertainty often surrounding it) is the suggestion to always describe the uncertainty in the documentation and the rationale why a certain choice has been made. This makes it is easier for reviewers to judge whether a choice has been considered and why it can be accepted or not.

4. Target audience

This guidance is intended for two audiences within the Dutch University Medical Centres (UMC's) and possibly other research institutes that are involved in clinical investigations with medical devices. On one hand, the researcher who wants to investigate a medical device or wants to do an investigation in which a (medical) device is used. On the other hand, other professionals who are involved in all kinds of clinical investigations with medical devices. In addition to investigations initiated by hospitals themselves (investigator-initiated research), there are also investigations initiated by manufacturers or other hospitals. Please note that this document is not intended for manufacturers or universities that want to conduct an investigation in a healthcare institution.

A prerequisite for the proper use of this guidance is knowledge of the relevant MDR passages and other sources of information. The authors of this document do not claim that every possible situation or exception has been described.

5. Relevant passages from the MDR and other sources

The MDR contains various articles and supplements that are relevant for clinical research with medical devices. More specifically, chapter VI of the MDR (Articles 62-82) and Annex XV cover the requirements of clinical investigations. The most important ones are listed and briefly described below.

Part	Title	Description
Article 62	Clinical investigation for conformity	Requirements for clinical investigations conducted as part of a conformity assessment procedure.
Articles 63-69	Other requirements regarding clinical investigations	Requirements regarding informed consent, incapacitated subjects, minors, pregnant or breastfeeding women, national measures, emergency situations
Article 71	Scientific and ethical review of clinical investigations	Requirements for validating and assessing the application, and deciding on it.
Article 74.1	Clinical investigation with CE-marked medical device: post-market clinical follow-up (PMCF) with extra invasive or burdensome procedures.	Requirements for clinical investigations with a CE-marked medical device as part of the post-market clinical follow-up (PMCF) in which participants undergo additional invasive or burdensome procedures
Article 74.2	Clinical investigation with CE-marked medical device used outside the scope of its intended purpose	Requirements for clinical investigations with CE-marked medical device used outside the scope of its intended purpose.
Article 80	Recording and reporting of adverse events	Requirements for the recording and reporting of adverse events.
Article 82	Requirements regarding other clinical investigations	Requirements for clinical investigations not conducted as part of a conformity assessment procedure or PMCF.
Annex I	General safety and performance requirements	Requirements for the development of medical devices.
Annex II	Technical documentation	Information that is required for the technical documentation.
Annex VIII	Classification rules	Contains the rules to be followed to determine the classification of the device.
Annex XV	Clinical investigations	Requirements for clinical investigations with medical devices, including the relevant information about the medical device.

Other sources of useful information

Source	Description	Link
MDR and IVDR	European Regulations, Regulation (EU) 2017/745 for medical devices and Regulation (EU) 2017/746 for in-vitro diagnostics	Link
Guidances MDCG	Guidances for the application of the MDR and IVDR	Link
IMDD template	Template for an investigational medical device dossier.	Link
Healthcare Quality, Complaints and Disputes Act (WKKGZ)	General law for health care institutions on the provision of responsible care.	Link
Decree on the Wkkgz	Artxcle 4 decribes the het legal framework for the application of medical technology	Link
Act on Medical Devices (Wmh)	Act containing rules on the safety and quality of medical devices. Provides guidance on topics that a Member State may fill in independently.	Link

Source	Description	Link
Decree on Medical Devices (Bmh)	Implementation decree of the Wmh with rules on the implant card, wrinkle fillers and reprocessing of medical devices.	Link
Covenant on the safe application of medical technology in specialist medical care (covenant)	Field standard for the application of medical technology in hospitals and other healthcare institutions where specialist medical care is provided.	Link
MDCG guidances	More detailed guidances on how to interpret the Medical Device Regulations	Link
IMDD template	Format voor een investigational medical device dossier.	Link
ISO 13485	International standard for the development and manufacturing of medical devices.	Link
ISO 14155	International standard for clinical investigation of medical devices for human subjects — Good clinical practice.	Link

6. Most significant changes introduced by the MDR[1]

The MDR has many similarities with the Medical Research Involving Human Subjects Act (WMO). This means that, in general, the changes will not have a major impact. An overview of the most important changes that apply 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 and the Act on Medical research involving Human Subjects (WMO). These and other points will be explained in more detail throughout the document.

- The definition of a medical device is broader compared to previous legislation bringing more products under the MDR compared to the MDD.
- There are three Articles on categories of clinical investigation (Article 62, 74 or 82 studies), each having specific requirements.
- The classification rules have been altered, as a result some medical devices are classified in a higher risk class (Annex VIII MDR).
- The requirements for obtaining a CE mark are higher which may result that more clinical data is needed.
- Post-market clinical follow up (PMCF) by the manufacturer is mandatory (MDR, art 10, sub 3).
- 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) and includes among others validation of specific initial applications, a coordinating and supporting role for multinational applications and collection/distribution of fee. The latter one will be postponed until the Clinical Trial Regulation (EU no 536/2014) is applicable.
- A validation procedure for Article 62 and 74.2 clinical investigations with a validation decision including the option to appeal. The validation decision is issued by the CCMO.
- Clinical investigations for conformity with high risk medical devices will be assessed by selected MRECs.
- The accredited MREC needs to have an accredited “member medical devices” if assessing clinical investigation with medical devices.
- There are some changes in the application dossier. 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. 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. An independent expert for the subjects to be consulted voluntary (WMO, Article 9) is not mandatory anymore.
- The Dutch model investigational medical device dossier (IMDD) has been adapted to comply with the requirements of Annex I of the MDR.

[1] Reproduced from “Review of a clinical investigation with a medical device - guidance document for MRECs” by the CCMO (with permission). These chapter will be removed when the CCMO document becomes publicly available.

- On basis of the MDR there should always be *the prospect of direct benefit* for the incapacitated subject, minor participating or pregnant and breastfeeding woman in the clinical investigation.
- As from May 26 2021, clinical investigations with medical devices for conformity purposes (art 62, 74.2, MDR) do not have to be notified to IGJ anymore. The CCMO will notify IGJ as part of their validation procedure.
- The procedures for recording and reporting of adverse events that occur 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 and substantial modifications applications, notification of temporarily halt, and (prematurely) end of the clinical investigation might change.
- There will be a seven year period of voluntary coordinated assessment of multinational clinical investigations by Member States.
- Certain conditions apply to emergency clinical investigations involving deferred consent. The conditions can be found in the step-by-step plan published by the CCMO: "Stappenplannen inzake uitgestelde toestemming ('deferred consent') bij onderzoek in noodsituaties".

7. Copy from CCMO Chapter 3 Definitions[2]

The most important definitions in the MDR are described in this chapter. The list follows the order as in Article 2 MDR. Other definitions or abbreviations are described in Annex A of this guidance.

MDR: Medical device regulation; regulation (EU) 2017/645 of the European parliament and the council of 5 April 2017.

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.

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.

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

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 (Annex VIII MDR).

Notice that "invasive" in the context of a medical device has a different meaning than an "invasive" procedure.

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

[2] These chapter will be removed when the CCMO document becomes publicly available.

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.

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. '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.

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.

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

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

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 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 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.

Notice that terminology between the MDR and CTR differs. For example MDR mentions clinical investigations (CTR: clinical trials) and clinical investigation plan (CTR: protocol).

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.

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.

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 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 subjects, when used as intended by the manufacturer.

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.

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

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

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.

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.

8. Introduction flowchart

The MDR has an impact on all the phases that are typically involved in a clinical investigation: the preparation phase, the execution phase and the finalization phase. During each phase there are multiple steps to take. In the next chapter, for each phase, the impact of the MDR on each step will be discussed.

9. Determine whether the product is a medical device

Under the MDR, more products are considered to be a medical device as compared under the definition under the MDD. The following flow chart in Figure 1 can be helpful in choosing whether a product should be assessed as a medical device. When it is unclear whether the product should be considered a medical device, consultations can be held with the MREC/CCMO and more information on the product from sponsor and/or manufacturer can be requested.

Special cases that require extra attention:

Modified CE-marked medical devices: The use of these altered medical devices (non-CE) is only allowed in a clinical investigation where the safety and performance is assessed.

In-house product: 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, also Article 82 applies.

Custom-made devices: Clinical investigations with custom-made devices fall under Article 82. More information on the procedures for custom-made devices is described in Annex XIII of the MDR.

Annex XVI products: a group of products without an intended medical purpose but which are considered medical devices which have to be compliant with the MDR (Article 1.2).

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.

Combination products: Products which combine a medicinal product or substance and a medical device are regulated either under the MDR or under directive (EU) 2001/83/EC. 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.

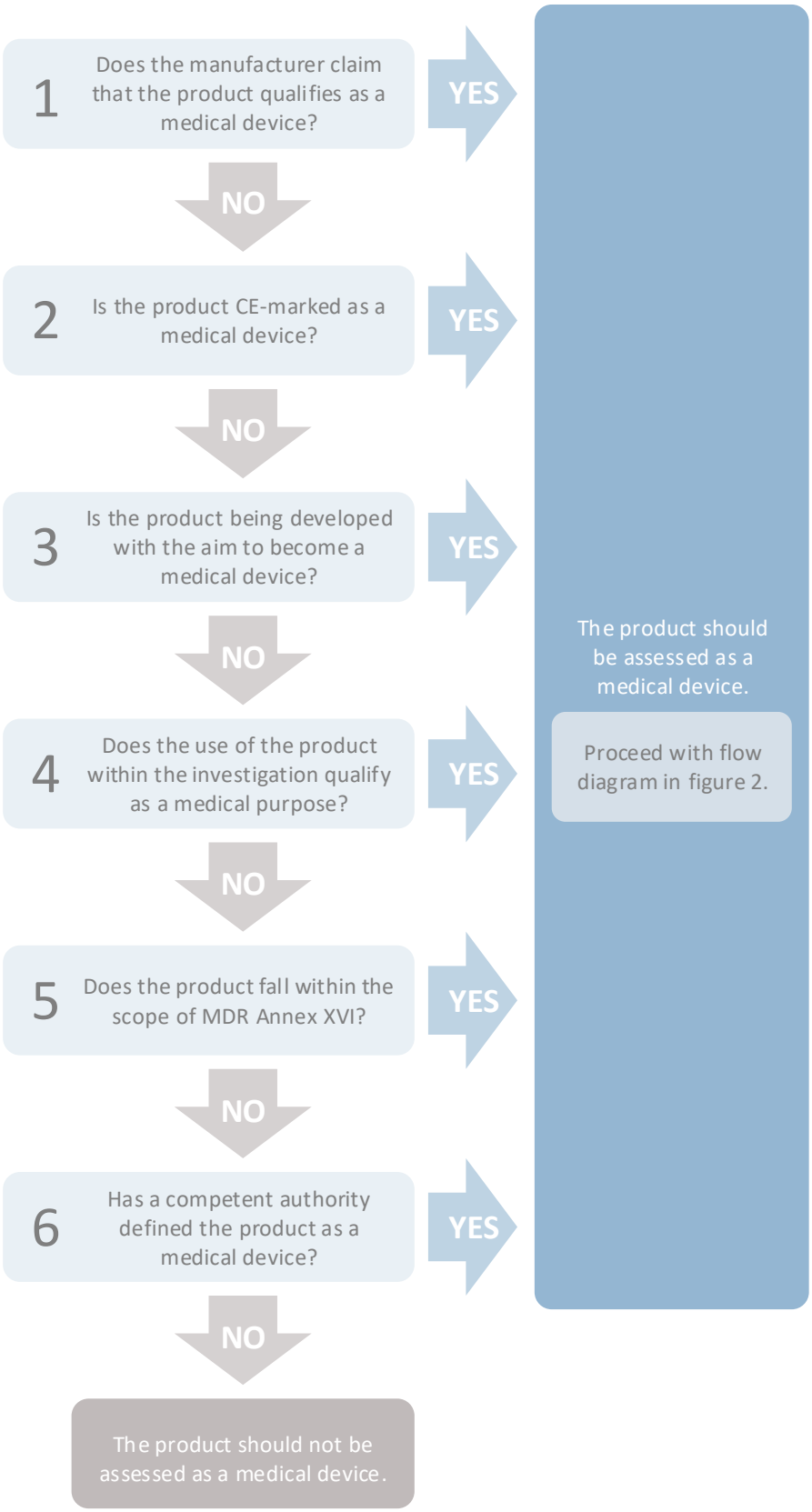


Figure 1 from CCMO guidance, determination whether a product should be assessed as a medical device.

10. Determine the risk classification of the medical device

Medical devices are classified in a risk class based on their characteristics and risks. The MDR contains more classification rules which means that some medical devices that under the MDD have a low risk classification may fall into a higher risk class (annex VIII MDR). Classification of a medical device in a higher risk class generally requires more extensive clinical research and evaluation. Note that the MDR introduces for software a new classification rule 11.

Determine whether the investigation falls within the scope of the MDR.

Whether an investigation falls within the scope of the MDR depends on the purpose of the investigation. A clinical investigation is defined in the MDR as follows: systematic study of one or more human subjects conducted to assess the safety or performance of a device. For investigations falling under this definition there are different categories defined in the MDR with each its own article. These are described below. Each article determines what the requirements are and have implications for the medical ethical assessment of the investigation.

Article 62: Clinical investigations carried out in the framework of a conformity assessment (i.e. in the framework of product development and obtaining CE marking).

Article 74.1: Clinical investigation with a CE-marked medical device as part of a post-market clinical follow-up (PMCF) in which subjects undergo additional invasive or burdensome procedures.

Article 74.2: Clinical investigation with a CE-marked medical device carried out as part of a conformity assessment for another application.

Article 82: Clinical investigation studying a medical device not covered by Article 62 or Article 74. This includes, for example, clinical investigation of in-house or custom-made medical devices or clinical investigation comparing two medical devices (CE marked and applied in accordance with the CE marking).

The process flow below can assist in deciding which article applies to a clinical investigation (Figure 2). The CCMO/MREC to which the study has been submitted will ultimately determine at the time of validation under which article the study falls and will request further information when necessary.

Non MDR investigation: When a clinical investigation uses a medical device but has a different purpose than assessing the safety and/or performance of the medical device, the investigation does not fall under the MDR, but may fall under the WMO. The safety and quality of the medical device(s) in these studies must be guaranteed before using it in or on subjects. When the study is assessed by an MREC/CCMO, the product information should be of such a quality that a MREC can do their assessment. Studies with medical devices (other than a clinical investigation) can only use CE marked medical devices, in-house developed medical devices or custom-made medical devices.

11. Process flow clinical investigation

In the MDR regime the flow from Figure 2 can be followed:

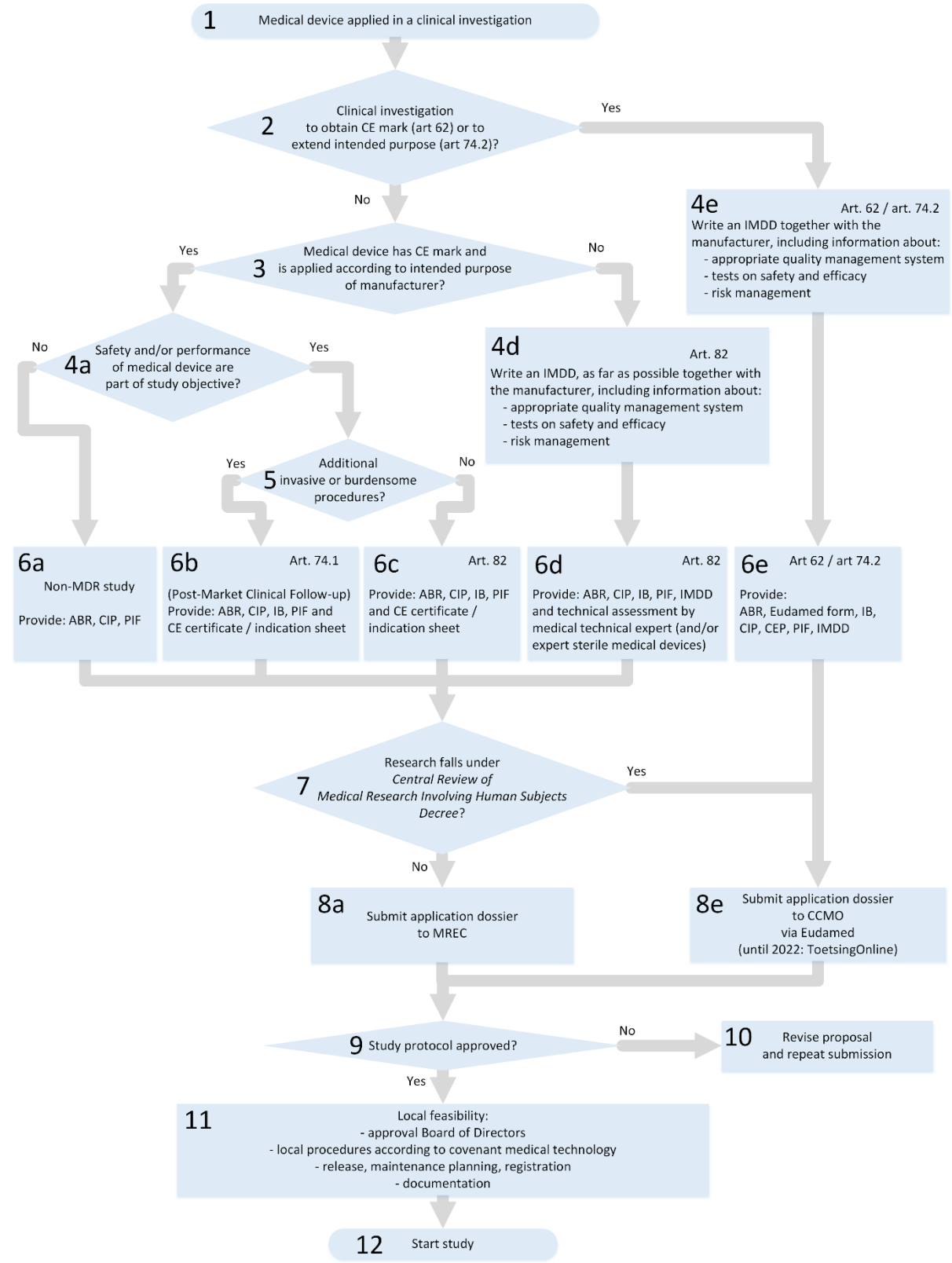


Figure 2 Process flow

12. Explanation for each step of the flowchart

Step 1 Medical device applied in clinical investigations

Based on the criteria described earlier, it has been determined that the product should be considered a medical device and that it will be used in a clinical investigation.

Step 2 Type of clinical investigation

Is the study a conformity assessment to obtain a CE mark (article 62) or to extend the intended purpose belonging to the CE mark (article 74.2)?
Conformity assessments are to be submitted for by CCMO which, after validation, relays the submission to a selected MREC (see step 8e).

Step 3 within intended purpose of CE mark?

Does the medical device have a CE mark and is it applied during the study according to the intended purpose as described by the manufacturer?
The intended purpose can e.g. be found in the instructions for use, on the CE certificate or on an indication sheet.

Step 4a Safety/performance part of objective?

The medical device bears a CE mark and it is applied within the scope of its intended purpose.
Is the safety and/or performance part of the study objective?
This criterion determines whether one of the clinical investigation articles of the MDR are applicable. E.g., using a standard blood pressure monitor used in daily clinical practice for blood pressure measurement does not put the study under the scope of clinical investigations under the MDR.

Step 4d Write IMDD

The medical device has no CE mark or is used outside the scope of its intended purpose as described by the manufacturer.
Determine who is ultimately responsible for the IMDD. That person should maintain the QMS.
An Investigational Medical Device Dossier (IMDD) is to be written, preferably and as far as possible in cooperation with the manufacturer of the device. The IMDD should include at least information about the appropriate quality management system applied, the tests performed regarding safety and efficacy, and the risk management overview. If desired, the information may be provided using alternative formats than an IMDD, such as an Investigator's Brochure (IB), or a technical file if that is available from previous usage of an in-house developed medical device in the context of patient care under MDR article 5.5.

Step 4e Write IMDD

Also for a conformity assessment, an IMDD is to be written together with the manufacturer, including at least information about the appropriate quality management system applied, the tests performed regarding safety and efficacy, and the risk management overview. If desired, the information may be provided using alternative formats than an IMDD, such as an Investigator's Brochure (IB).

Step 5 Additional invasive or burdensome procedures?

The medical device has CE mark and is used according to its intended purpose as described by the manufacturer.
Can the study be classified as a Post-Market Clinical Follow-up (PMCF) investigation according to article 74.1 of the MDR (see step 6b) or as other clinical investigation (MDR article 82, see step 6c)? For example subjects of the study are exposed to additional invasive or burdensome procedures during the study on top of regular patient care.

Determine who is ultimately responsible for the IMDD. That person should maintain the QMS.

Step 6a-e Prepare and submit the application dossier (standard research file)

Depending on the type of study, provide the required documentation as part of the application dossier.
There are no major changes in the application dossier (standard research file) compared to the situation under the MDD, with some exceptions: 1) An independent expert for the subjects to be consulted voluntary (WMO, Article 9) is not mandatory anymore (H1. CV independent expert), 2) for Article 62 and 74.2 studies a clinical evaluation plan (CEP) and a signed statement (from the manufacturer) must be submitted. The CCMO website (https://english.ccmo.nl/investigators/standard-research-file) provides the standard research file templates. The table below provides an overview of the documents that are required for medical device investigations:

1) Application form (AF): Eudamed form (PDF) and ABR form via Toetsingonline: Eudamed form is new under the MDR
2) Clinical investigational plan (CIP). In the MDR, the Clinical investigational plan refers to the standard research protocol (C1. Research protocol).
3) (Reference to) Clinical evaluation plan (CEP): new under the MDR.
4) Investigator's brochure (IB): probably unchanged under the MDR. Updates are required after major changes.
5) Investigational medical device dossier (IMDD): expanded under the MDR. See chapter IMDD for more details/tips.
6) Signed statement: new under the MDR.
7) Advice expert panel (if available): new under the MDR.
8) *Proefpersonen Informatie Formulier (PIF)* (Information leaflet and consent form): unchanged under the MDR.
9) For 6b and 6c, provide documentation that contains the intended purpose as described by the manufacturer, such as the instructions for use, the EU declaration of conformity (CE certificate) or an indication sheet.

Artikel 62 Class I and non-invasive class IIa and class IIb	**Artikel 62** Class III and invasive class IIa and class IIb	**Artikel 74.2** Class I and non-invasive class IIa and class IIb	**Artikel 74.2** Class III and invasive class IIa and class IIb	**Artikel 74.1**	**Artikel 82**
Eudamed- and ABR-form	Eudamed- and ABR-form	Eudamed- and ABR-form	Eudamed- and ABR-form	Only ABR-form	Only ABR-form
CIP	CIP	CIP	CIP	CIP	CIP
CEP	CEP	CEP	CEP		
IB	IB	IB	IB	IB	
IMDD	IMDD	IMDD for those parts that are relevant to the new purpose	IMDD for those parts that are relevant to the new purpose	EU declaration of conformity and instructions of use / technical file	Non-CE: IMDD. CE: EU declaration of conformity and instructions of use / technical file
Signed statement manufacturer	Signed statement manufacturer	Signed statement manufacturer	Signed statement manufacturer		
	Advice expert panel (if applicable)		Advice expert panel (if applicable)		
PIF	PIF	PIF	PIF	PIF	PIF

Step 7 Special clinical investigation

There are a few other conditions that may require the clinical investigation to be reviewed by the CCMO. Clinical investigations with pregnant or breastfeeding women are reviewed by the CCMO on basis of *the decree on Central Review of Medical Research Involving Human Subjects Act* (in Dutch: *besluit centrale beoordeling, BCB*). Additionally, if the study involves human or animal cells or tissues that are still alive and/or if the study involves genetically modified organisms or human embryos, the research is to be submitted for review by the CCMO. Other specific fields of research that is reviewed by the CCMO can be found on the CCMO website (https://english.ccmo.nl/investigators/primary-submission-to-the-review-committee/review-committee-accredited-mrec-or-ccmo/review-by-the-ccmo).

Committee finder tool:
https://pauljanssenfuturelab.eu/tools/clinical_research_in_the_netherlands/committee_finder/?user%5Fid=0&token=

Step 8 Submit the application dossier (standard research file) to the MREC/CCMO

All submissions will go through ToetsingOnline as long as the Eudamed portal has not yet been implemented (expected 2022). Applications for clinical investigations under Article 62/74.2 are validated by the CCMO and will be carried out by the national clinical trial office (in Dutch: Landelijk Bureau, LB). During the validation, 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 assigns the application to an accredited MREC (8a) or the CCMO (8e). The CCMO_LB also notifies the IGJ. For article 74.1 and Article 82 clinical investigations, the MREC is responsible for the validation of the application.

Article 62 Class I and non-invasive class IIa and class IIb	**Article 62** Class III and invasive class IIa and class IIb	**Article 74.2** Class I and non-invasive class IIa and class IIb	**Article 74.2** Class III and invasive class IIa and class IIb	**Artikel 74.1**	**Artikel 82**
Submission via ToetsingOnline	Submission via ToetsingOnline	Submission via ToetsingOnline	Submission via ToetsingOnline	Submission via ToetsingOnline	Submission via ToetsingOnline
Validation via national clinical trial office (CCMO_LB, Landelijk Bureau)	Validationvia national clinical trial office (CCMO_LB, Landelijk Bureau)	Validation via national clinical trial office (CCMO_LB, Landelijk Bureau)	Validation via national clinical trial office (CCMO_LB, Landelijk Bureau)	Validation and assessment by local MREC	Validation and assessment by local MREC
Assessment by reviewing committee (accredited MREC/CCMO)	Assessment by reviewing committee (accredited MREC/CCMO)	Assessment by reviewing committee (accredited MREC/CCMO)	Assessment by reviewing committee (accredited MREC/CCMO)		

Timelines (CCMO 5.2)

Article 62 Class I and non-invasive class IIa and class IIb	**Article 62** Class III and invasive class IIa and class IIb	**Article 74.2** Class I and non-invasive class IIa and class IIb	**Article 74.2** Class III and invasive class IIa and class IIb	**Artikel 74.1**	**Artikel 82**
Submission: max 55 days including response time sponsor	Submission: max 55 days including response time sponsor	Submission: max 55 days including response time sponsor	Submission: max 55 days including response time sponsor	Part of assessment.	Part of assessment.
Assessment: max 2x56 calendar days + clock stop for response sponsor	Assessment: max 45 (+20 in case of consulting expert) calendar days + clock stop for response sponsor	Assessment: max 2x56 calendar days + clock stop for response sponsor	Assessment: max 45 (+20 in case of consulting expert) calendar days + clock stop for response sponsor	Assessment: max 2x56 calendar days + clock stop	Assessment: max 2x56 calendar days + clock stop
Substantial amendment: max 38 days + 7 days for consulting with experts + clock stop for response sponsor	Substantial amendment: max 38 days + 7 days for consulting with experts + clock stop for response sponsor	Substantial amendment: max 38 days + 7 days for consulting with experts + clock stop for response sponsor	Substantial amendment: max 38 days + 7 days for consulting with experts + clock stop for response sponsor	Substantial amendment: 38 days + 7 days for consulting with experts + clock stop for response sponsor	Substantial amendment: max 2x56 calendar days + clock stop for response sponsor

Step 9, 10 Revise protocol when protocol has been disapproved

Step 11 Obtain Local Feasibility (local approval Board of Directors)

As part of the Local Feasibility, the covenant 'Safe Application of Medical Technology' must be followed. This means that an introduction dossier should be created to mitigate the risks still open from the IMDD. This will often involve installation and user training issues. This introduction dossier will often be written in consultation with the medical technology department. This department is often also responsible for final (electrical) safety checks of the devices. After the reviewing MREC/CCMO has approved the application dossier and Local Feasibility has been obtained, the study can start.

Step 12 Start investigation (execution phase)

1. Conduct investigation according to ISO14155 standard (Good Clinical Practice)

Conducting clinical investigations according to Good Clinical Practice (GCP) is important not only to collect good quality data under ethical conditions but also for compliance with the MDR. For clinical research, there are two guidances on GCP available: the ICH GCP E6 and the ISO 14155:2020. The ICH GCP is obligatory to clinical studies involving pharmaceuticals where the ISO 14155:2020 is applicable for clinical studies involving medical devices. The changes implemented in the third edition are mostly related to the MDR and the development of more stringent MDCG guidances. All clinical investigations that fall under the MDR must be carried out in accordance with the ISO14155 standard. Previously, this was only mandatory in the context of conformity assessments.

2. Submitting substantial amendment(s)

For the MDR this process of submitting substantial amendments has not substantially changed from the process under the MDD.

3. Recording and reporting of (serious) adverse events.

The safety reporting requirements depend on the legal frameworks that have been identified: only SAEs with a causal relationship with the medical device need to be reported. Also, the timelines are changed under the MDR and it is no longer necessary to report SAEs to the IGJ. See the Adverse Event Flow by the CCMO for more detailed information (also Annex E of the CCMO Guide). Note that these changed requirements also apply to investigations initiated under the MDD before 26 May 2021.

4. Corrective measures imposed by the MREC/CCMO

Where the MREC/CCMO has grounds for considering that the requirements for clinical investigations Articles 62 or 74 as set out in the MDR are not met, the MREC/CCMO may take a corrective measure: revoke authorisation (NL: besluit intrekken), suspend or terminate the clinical investigation, require the sponsor to modify any aspect of the clinical investigation. See the table below for a detailed description.

Artikel 62 / 74	Artikel 82
Before revoking or suspending authorisation or request for substantial modification, the MREC/CCMO request the sponsor to submit their view within 7 days, except when immediate action is required. In case a corrective measure is applied the MREC notifies the CCMO about this decision, including a justification. The CCMO_LB will inform all other Member States and the Commission.	Article 3a WMO applies. This Article gives MREC/CCMO 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 MREC/CCMO request sponsor to submit their view within 7 days. In case a corrective measure is applied the MREC notifies the CCMO about this decision, including justification.

13. Finalisation phase

5. Report premature termination of investigation (if applicable)

In case of premature termination, the MREC and the CCMO (if applicable) must be informed by the sponsor. Reporting to the Inspectorate (IGJ) is no longer necessary under the MDR. See the table below for a detailed description.

Artikel 62 / 74	Artikel 82
Within 15 days, if the clinical investigation has been temporarily halted or terminated early in the Netherlands and a justification is provided.	Immediately for a temporary halt if the clinical investigation proved to be significantly more unfavourable to the subject than the CIP had foreseen.
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.	Within 15 days, if the clinical investigation is terminated early and a justification is provided.

6. Notifying the end of the study and reporting results

The sponsor is required to submit a summary of the clinical trial results to the review committee (MREC or CCMO). See the table below for a detailed description.

Artikel 62 / 74	Artikel 82
Notifying the end of the study: The MREC/CCMO 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.	Notifying the end of the study: The MREC/CCMO is informed by the sponsor within 56 days of the end of the clinical investigation in the Netherlands.
Reporting results: A clinical investigation report and lay summary is submitted to the MREC 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 halt unless (in case of temp halt) the investigation has been restarted within this three months period.	Reporting results: 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 MREC/CCMO

14. Archiving

The documentation of the clinical investigation (annex XV MDR) 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 (CCMO 5.5). Note that this is different from the usual minimum retention periods for archiving research advised by the CCMO, namely 30 years for advanced therapeutic medicinal products, 25 years for research into medicines and 15 years for other studies required by the WMO.

15. Putting medical device out-of-service

If applicable, the covenant 'Safe Application of Medical Technology' must be complied with when decommissioning and physical removal of medical devices. Involve the local medical technology department of the institution in this process.

16. Investigator-initiated studies with CE marked medical devices (Article 82)

The new term 'Sponsor' brings 'Investigator Initiated' research explicitly under the MDR (MDD only knows 'manufacturer'). The sponsor is defined as any individual, company, institution or organization which assumes responsibility for the initiation, including management and arrangement of financing the clinical investigation. Investigator initiated studies, in which the manufacturer is not the sponsor of the study or is insufficiently involved in preparing the study protocol, are permitted under the MDR. However, aspects such as product liability do require extra attention in such studies. Clinical investigations of a medical device without CE marking or a medical device with CE marking that is applied outside its intended use is preferably conducted on behalf of the manufacturer of the device.

17. Studies under MDR, not under WMO

For some studies, the MDR may be applicable, and yet the WMO is not applicable. The MDR is applicable if the safety and/or performance of a medical device is part of the objective of the study, e.g. for conformity assessment. The WMO is applicable if the subjects are exposed to risks or to invasive or burdensome procedures. An example of a non-WMO study for which the MDR is applicable, is a conformity assessment of a diagnostic medical software where the diagnostic performance of the software is assessed retrospectively on anonymized patient data by verifying whether the software enables diagnosing at least as reliably as an existing validated and known method. For the diagnosis of the subjects in this study, the existing validated and known method is used. Hence, no additional risks or procedures are imposed upon the subjects in the study.

For such studies, an ethical review by MREC or CCMO is not required, considering the absence of risks or invasive or burdensome procedures. The study can be submitted to Eudamed (or ToetsingOnline until 2022) for review by CCMO concerning MDR aspects.

Once the conformity assessment is completed, and the medical device is being introduced on the market, risks for subjects such as misdiagnosis are managed in the context of other review processes than the MREC review. These other review processes is e.g. the review process of a Notified Body for medical devices of class IIa and higher. For class I medical devices that are made available on the market, the manufacturer is allowed to perform the review of safety and performance characteristics

of the medical device without a review by a Notified Body. For in-house developed medical devices that are only applied within the same institution and not made available on the market, a risk management system (Annex I, 3a) is part of the compliance criteria listed in MDR article 5.5.

18. Clinical examination in which the hospital is the manufacturer

Researchers who intend to develop, manufacture and market a medical device themselves are referred to the guidance document 'Het ziekenhuis als fabrikant'. The MDR sets high requirements for manufacturers of medical devices. Only devices for which there is sufficient clinical evidence to demonstrate their safety and effectiveness may be placed on the market. For this purpose, a clinical evaluation plan must be drawn up describing how the clinical data that will provide sufficient clinical evidence will be collected. Clinical studies in subjects will most likely be part of this.

18.1. Post-market surveillance en Post Market Clinical Follow-Up (PMCF)-studies (article 74.1)

The MDR requires manufacturers to consider in advance how to evaluate the use of a medical device in order to keep the device state-of-art and safe. For this purpose, a post-market surveillance plan (PMS plan) will be required. If necessary, this plan also includes additional clinical studies, so-called post-market clinical follow-up studies (PMCF studies). PMCF studies in which subjects undergo additional invasive or invasive procedures fall under article 74.1 of the MDR. PMCF studies in which subjects do not undergo additional invasive or invasive procedures (such as retrospective dossier studies or data obtained from standard care) do not fall under the MDR or WMO.

19. Investigational Medical Device Dossier (IMDD)

In the MDR, Annex I 'GENERAL SAFETY AND PRESTATION REQUIREMENTS' for a manufacturer and Annex II 'TECHNICAL DOCUMENTATION' are relevant for this purpose. Especially when you place a device on the market you have to meet all requirements and the documentation has to be in order. For clinical trials with medical devices in which the investigator starts an investigation from a hospital, the requirements are less strict. The CCMO/MREC requires an IMDD, an Investigational Medical Device Dossier, which can be seen as a summary of the technical documentation. When a manufacturer develops a medical device with a quality management system, the technical documentation often contains many different documents, often maintained in a document management system. It is then convenient to have one umbrella document, the IMDD, to facilitate the reviewer to overview the technical documentation. When technical documentation already has been written, it is certainly wise to send it along as an appendix. Re-typing is not efficient and not useful with different versions.

The following hint may be useful for studies in which multiple (medical) devices are used:

- Make a list of all the devices you want to use during the investigation. From devices to cables, accessories to software.
- Determine the extent to which each device is or will be used as a medical device.
- For each device that has a medical CE and is to be used for its intended purpose, add a CE certificate or part of the manual that shows that it has a CE certificate and for which purpose it is certified. If a device is used as a standard in the healthcare setting and has already been introduced in accordance with the covenant, a statement to confirm this will suffice.
- For any device that does not have CE or is applied outside its intended purpose and is used as a medical device in the examination:

    - Develop the tool according to an appropriate quality management system.
    - Use MDR Annex/Annex I for the requirements.
    - Document relevant parts in a technical file, Annex/Annex II or via an IMDD (website CCMO https://www.ccmo.nl/, also has a guidance).
- Create one IMDD for the entire system in which the tools are used together. There may be multiple configurations in which the tools are applied in different phases of the investigation. Perform a risk analysis for the entire system and the different configurations in which it is used.

19.1. Suggestion on general safety and performance requirements

These requirements include which ISO/NEN/IEC standards have been used in the development of the medical device. The use of standards is not mandatory, but is strongly recommended because otherwise it is difficult to prove that you meet a requirement.

There are several standards that frequently apply: ISO 13485 (QMS), ISO 62304 (software), ISO 60601-X (hardware/electrical safety), ISO 14971 (risk analysis), ISO 14155 (examination with medical devices). The overview of all standards is itself a standard: ISO 16142-1. All standards are available via https://connect.nen.nl/.

19.2. Suggestion on acquiring expertise on MDR and relevant standards

The MDR is not a simple law and is often underestimated. When you really want to do it well and especially when you want to become a manufacturer of medical devices, it is recommended to follow MDR training or to employ experts on the MDR and Quality Management Systems. In a hospital, this expertise may be found in the medical technology department or by medical technical experts such as clinical physicists.

19.3. Appropriate quality management system for in house developed medical devices (MDR Article 5.5b)

It is obvious to look at existing standards for quality management systems, where ISO 13485 is most relevant for the development of medical devices. It is advisable to set up a quality system along the lines of ISO 13485 to cover all aspects from development to use and evaluation. For certain categories of devices, other standards may also be applicable and serve as a source of information. Software development in turn has specific points of attention, for example when it comes to information security, which are better described in the IEC standard 62304 - medical device software.

Certification of the quality system is not a requirement, but gives more certainty through external supervision of the development and manufacturing process. The scope of the quality system can also be chosen differently. This can be invested in the central medical technology department, which then supervises the entire process. If in-house development mainly takes place within a specific healthcare department, the system can also be tailored to this.

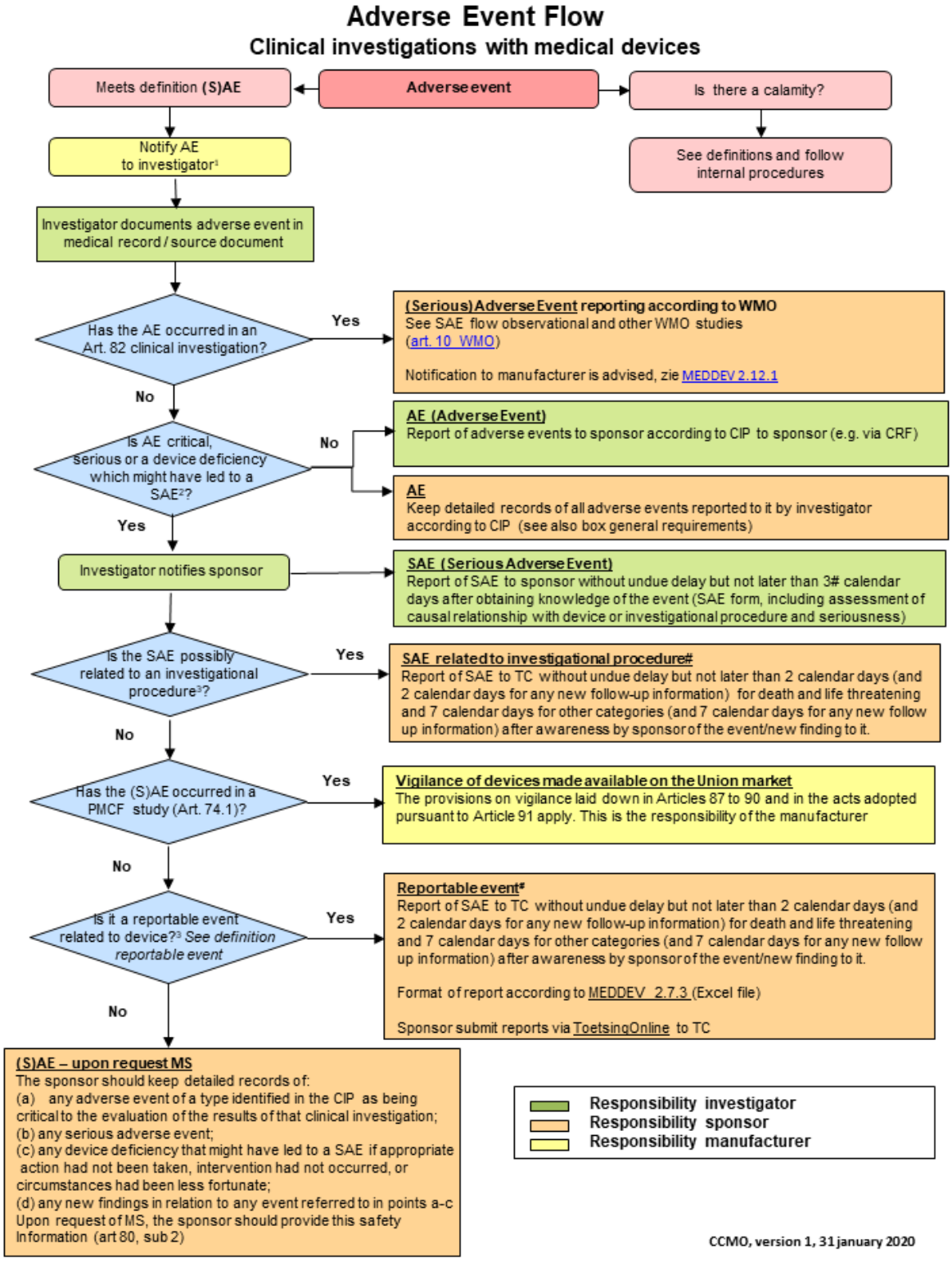
19.4. Proportionality

Ethical committees use the motto proportionality. The detail of the documents provided must be tailored to the risk that an medical device may pose in the study. In particular, the aim is to identify the risks and describe what measures have been taken to keep these risks minimal.

20. Continued use after investigation

In some cases medical devices like implants may stay in a subject as removal is not considered ethical. When the medical devices stays within the subject, the guidance In-huis development should be considered, especially on topics like Post Market Surveillance and vigilance procedures.

CCMO Annex E Reporting SAE The flowchart for reporting SAEs is depicted below. (TC=MREC/CCMO). New MDR version.



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-threatining:
► 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 untill 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 MEDDVEV 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.

21. Annex I Questions to and answers from CCMO

When we wrote this report we had several questions regarding the CCMO guidelines. Here is an overview of the questions and the answers we received. Keep in mind that these were quick answers and should not be considered as an official standpoint of the CCMO.

1. Is een (evt. multicenter) studie met (a) een off-label toegepast of (b) een door een *ander* instituut zelf-ontwikkeld medisch hulpmiddel toegestaan onder art 82?
   Als het onderzoek zich richt op de veiligheid en prestaties van het medisch hulpmiddel en niet gedaan wordt in het kader van het verkrijgen van data voor een conformiteitsbeoordeling (de studie resultaten maken geen deel uit /zullen geen deel uitmaken van de aanvraag voor een CE-markering) dan vallen deze studies onder artikel 82.
   Moet zo'n studie ergens worden gemeld?
   De indiening en beoordeling van artikel 82 studies verloopt hetzelfde als nu: indiening via ToetsingOnline en beoordeling door een erkende MREC.

2. Wat maakt van een studie een hulpmiddelenstudie?
   In de MDR gaat hoofdstuk over klinisch onderzoek (clinical investigations). De definitie is hiervoor "systematisch onderzoek bij een of meer menselijke proefpersonen dat wordt uitgevoerd om de veiligheid of de prestaties van een hulpmiddel te beoordelen". In de MDR moet daar waar hulpmiddel staat "medisch hulpmiddel" worden gelezen. Dus het betreft onderzoek naar de veiligheid en prestaties van het medisch hulpmiddel. M.a.w. het medisch hulpmiddel is onderwerp van studie.
   Concreet: hoe voorkomen we dat elke gebruikte infuusspuit of bloeddrukmeter in een studie ertoe leidt dat het een art 82 studie wordt waarvoor CE certificaten moeten worden aangeleverd?
   Zie hierboven, als de bloeddrukmeter geen onderwerp van studie is maar alleen gebruikt wordt om bloeddruk te meten omdat dit bijvoorbeeld een primair eindpunt is van de studie dan is artikel 82 niet van toepassing.

3. Moeten ook niet-WMO conformiteitsbeoordelingen worden ingediend bij CCMO via ToetsingOnline?
   De definitie van de MDR is bepalend. De WMO geldt niet meer. Kan je een voorbeeld geven van een niet WMO studie in het kader van conformiteit? Het betreft toch altijd een niet CE-gemarkeerd medisch hulpmiddel. Deze mogen alleen toegepast worden in een klinisch onderzoek. (in house medische hulpmiddelen of op maat gemaakt niet meegerekend; deze producten krijgen nooit een CE-markering nl))

4. CCMO leidraad par. 5.2.2: moeten art 74.1 en art 82 studies via CCMO worden getoetst?
   Nee, tenzij het niet-therapeutisch interventie onderzoek is bij minderjarige of wilsonbekwame volwassen proefpersonen (en op grond van toekomstige wijziging BCB: bij zwangere en borstvoeding gevende vrouwen). Deze art 74.1 en art 82 studies worden via ToetsingOnline ingediend en kunnen direct door een erkende MREC worden beoordeeld.

5. Is een IMDD verplicht voor zelf-ontwikkelde medische hulpmiddelen?
   De IMDD is een hulpmiddel om op een gestructureerde wijze de informatie over de veiligheid en kwaliteit van het product vast te leggen. Onderdelen die niet van toepassing zijn kunnen worden overgeslagen. Het is niet verplicht maar wel zeer wenselijk. Een andere vorm van product informatie zal niet worden afgewezen zolang de informatie toereikend is voor een adequate beoordeling door de MREC.

6. Geldt CCMO leidraad par. 5.4.4 ook voor art 74.1 en art 82 studies of alleen voor art 62 en art 74.2 studies?
   Ja, ook voor deze studies dient in een MREC een deskundige medische hulpmiddelen betrokken te zijn bij de beoordeling en moet beoordeeld worden of het product veilig genoeg is om toe te passen bij de mens. Uiteraard hangt de mate van beoordeling af van de status van het product, de risicoclassificatie en de risico's van het gebruik en toepassing ervan. Voor een PMCF studie (artikel 74.1) wordt het medische hulpmiddel gebruikt binnen de verleende CE-markering (en mogelijk is het gebruik ook al de normale klinische praktijk). Een IMDD zal dan veelal niet nodig zijn en voldoet een samenvatting van de productinformatie.

7. In de CCMO leidraad staat dat voor het Clinical investigational plan (CIP) het standaardonderzoeksdossier gebruikt kan worden. Wordt het template op de CCMO website tzt aangepast?
   Er komt een template CIP (template onderzoeksprotocol specifiek voor medische hulpmiddelen) , wordt aan gewerkt.

8. Application form: Eudamed form (PDF); is dit een document dat pas met de lancering van Eudamed verplicht wordt?
   Als Eudamed gereed is moet je een x-aantal vragen beantwoorden in het systeem ter registratie van het onderzoek. Dit vragenformulier is al beschikbaar. Echter, we overwegen een afgeslankte versie te gebruiken. De CCMO moet deze studies nog wel in het huidige Eudamed registreren. Bij de indiening komt dus nog een apart "Eudamed formulier"

9. Is een Quality Management System (QMS) alleen verplicht als je ontwikkelaar/fabrikant bent van een medisch hulpmiddel? Of ook als je een klinisch onderzoek uitvoert?
   QMS weet ik niet. Ik ga ervan uit dat dit afhangt wie de verantwoording draagt voor het product.

10. In de oude situatie (MDD) wordt bij de IGJ notificatie gekeken of er een bewijs van de verzekering ligt van aansprakelijkheid van de fabrikant. Ik zie deze in de CCMO leidraad niet direct terug, ik had deze verwacht in de "Checklist validation research dossier for clinical investigations with medical devices under MDR". Of zit de product aansprakelijkheidsverzekering in de 'Signed statement'.
    Bewijs verzekering fabrikant onder huidige MDD komt te vervallen. Dit is nu de WMO-proefpersonenverzekering samen met de bewijs dekking aansprakelijkheid van opdrachtgever of onderzoeker (conform de huidige WMO).

11. Moet een bevestiging van de goedkeuring van de Raad van Bestuur van elk deelnemende centrum nog ingediend worden bij de MREC? Om daarmee aan te tonen dat er voldaan is aan de convenant 'Veilige Toepassing van Medische Technologie'?
    Dit is iets lokaals. Voor de indiening bij de CCMO/MREC volstaat vooralsnog de Onderzoeksverklaring per deelnemend centrum.

12. Uit eerdere vragen en antwoorden maken wij op dat de verplichting voor een bewijs van de verzekering van de fabrikant komt te vervallen, en dat dit nu de WMO-proefpersonenverzekering wordt. Dekt deze WMO-proefpersonenverzekering ook problemen met het medisch hulpmiddel, bijv. als de proefpersoon een elektrische schok krijgt van het medisch hulpmiddel
    De verplichting voor een verzekering vanuit MDR is in artikel 7 van de WMO vastgelegd. Dit betekent dat er een bewijs dekking aansprakelijkheid moet zijn van de opdrachtgever of de

uitvoerder EN de opdrachtgever moet zorgen voor een WMO-proefpersonenverzekering. Dat is nu ook zo voor WMO-plichtig onderzoek en blijft hetzelfde. De verplichting van verzekering voor klinisch onderzoek van de fabrikant volgt uit Besluit medische hulpmiddelen en dat komt te vervallen als MDR van toepassing is.

13. De wijze van aanmelden van SAE's is gewijzigd. Deze wijze van aanmelden staat beschreven in de veiligheidsparagraaf van het protocol. Moet er nu voor alle onder de MDD al goedgekeurde studies een amendement komen waarbij deze veiligheidsparagraaf wordt aangepast?
Een separaat amendement is niet nodig, wel een notificatie aan de METC waarin staat dat de SAE's conform MDR gemeld zullen worden. Bij het eerst volgende substantiële amendement dient de veiligheidsparagraaf tevens aangepast te zijn.

14. Geldt voor conformiteitsbeoordelingen die vóór 26 mei 2021 zijn goedgekeurd onder de MDD, dat amendementen ná 26 mei 2021 nog mogelijk zijn? Of moet de studie dan in zijn geheel onder de MDR opnieuw worden getoetst?
Amendementen van studies die voor 26 mei 2021 zijn goedgekeurd kunnen op de huidige manier worden beoordeeld. De gehele studie hoeft niet opnieuw te worden getoetst.

15. Moet multicenter art 82 onderzoek met een medisch hulpmiddel zonder CE of toegepast buiten beoogd gebruik (dus geen conformiteitsbeoordeling) worden gemeld bij IGJ?
Als de MDR van toepassing is hoeft geen enkel klinisch onderzoek meer bij IGJ gemeld te worden. Dit is overigens voor genoemd type onderzoek onder de huidige wetgeving ook niet nodig.