

## **MDCG 2021-6**

### **Regulation (EU) 2017/745 – Questions & Answers regarding clinical investigation**

**April 2021**

This document has been endorsed by the Medical Device Coordination Group (MDCG) established by Article 103 of Regulation (EU) 2017/745. The MDCG is composed of representatives of all Member States and it is chaired by a representative of the European Commission.

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## Abbreviations

CE	Marking on a product to signify that it meets the legal requirements to be sold on the extended Single Market in the European Economic Area (EEA).
CIP	Clinical investigation plan
MDCG	Medical Device Coordination Group
MDR	Medical Device Regulation, referring to Regulation (EU) 2017/745 on medical devices
MS	Member State
PMCF	Post-market clinical follow-up

## Introduction

This document is intended for sponsors of clinical investigations of medical devices conducted within the scope of the Regulation (EU) 2017/745 (MDR). This document may be supplemented in due course with further questions and answers.

## General questions

### **1. What are the general differences and improvements related to clinical investigations under the new Regulation (EU) 2017/745 (MDR) as compared to the Directives 93/42/EEC and 90/385/EEC?**

Regulation (EU) 2017/745 (MDR) will progressively replace both Directives (93/42/EEC and 90/385/EEC) and their transpositions in national law.

The first difference is regarding the type of the law. A Directive is a legislative act that sets out a goal that all EU countries must achieve. However, it is up to the individual countries how to reach these goals by the implementation of national laws. A Regulation, as opposed to a Directive, is a binding legislative act that must be applied in its entirety across the EU on the date of application. It means that the rules are applied in an identical manner throughout the EU. Member States, in authorising and supervising the conduct of a clinical investigation, will be required to base their assessments and decisions on the same rules.

The MDR contains greater detail than the Directive, which is a result of implementing aspects related to good clinical practice, many of which have previously been present in the form of guidance and standard documents.

Further harmonisation at European level will provide greater certainty, which will support an environment that provides greater predictability and is more favourable for conducting clinical investigations, with the highest standards of 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 these studies.

For certain clinical investigations,<sup>1</sup> the sponsor still needs to check and follow any specific national provisions which may apply.

### **2. What is a 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 device<sup>2</sup>.

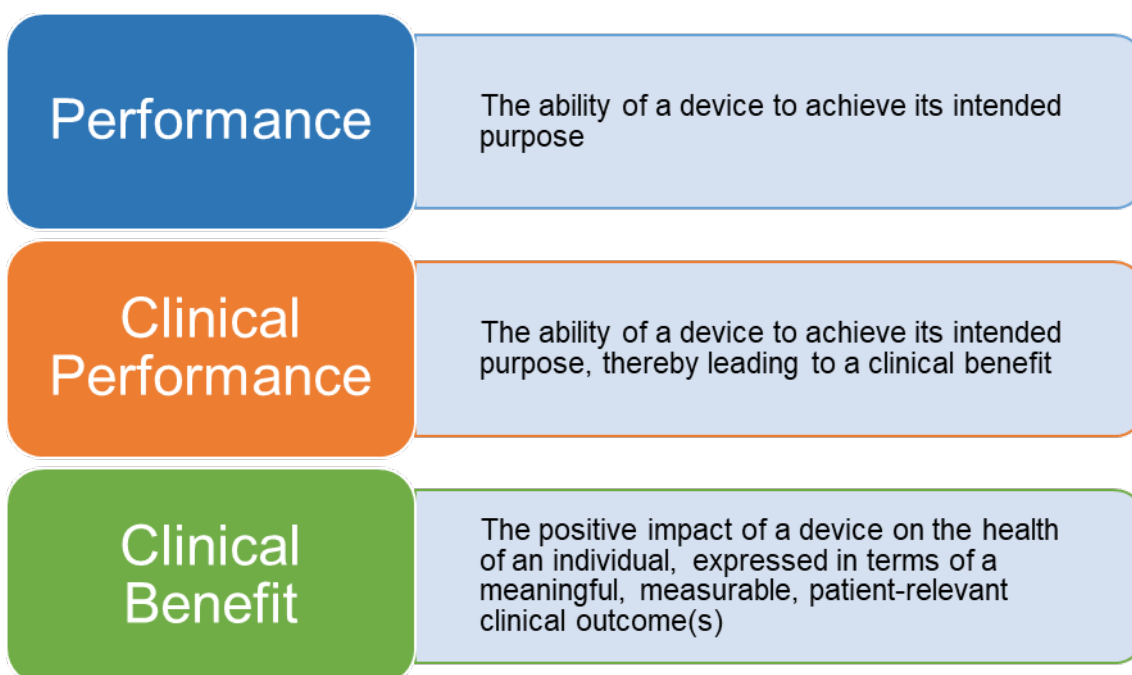
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<sup>1</sup> Article 82(2) of the MDR, Article 70(7)(a) of the MDR.

<sup>2</sup> Article 2(45) of the MDR

### 3. What is the difference between the performance, clinical performance and clinical benefit?

In accordance with the MDR, the performance<sup>3</sup> of a device is its ability to achieve its intended purpose as stated by the manufacturer<sup>4</sup>. By extension, the clinical performance<sup>5</sup> of a medical device is the ability of the device to achieve its intended purpose, thereby leading to a clinical benefit<sup>6</sup> when used as intended. 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.



### 4. Which regulatory pathway shall a sponsor follow in order to conduct a clinical investigation to collect clinical data that will be used to support the conformity assessment procedure of the investigated medical device?

Article 62(1) of the MDR foresees that the clinical investigations carried out, as part of the clinical evaluation for conformity assessment purposes, shall be designed, authorised, conducted, recorded and reported in accordance with the provisions of Articles 62 to 80 of the MDR. There are one or more purposes of clinical investigations; e.g. to establish and verify performance, clinical benefits, clinical safety and any undesirable side-effects.

For clinical investigations of class I, or non-invasive class IIa or class IIb devices, it is necessary to check national provisions. A global overview of the different pathways outlined in the MDR, including national possibilities of Article 82 of the MDR, is described in Annex I of this document.

<sup>3</sup> Defined in Article 2(22) of the MDR

<sup>4</sup> For some medical devices, performance may relate to the user of the device.

<sup>5</sup> Defined in Article 2(52) of the MDR

<sup>6</sup> Defined in Article 2(53) of the MDR

## 5. What is a pilot clinical investigation?

A pilot clinical investigation is typically an early-stage clinical investigation, which includes the following types:

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

These clinical investigation designs are further described in the standard ISO 14155:2020<sup>7</sup>.

In general, pilot stage clinical investigations are designed to enrol a limited number of subjects to assess a device early in its development phase with respect to the initial clinical safety and performance (e.g. device functionality). The results of this kind of clinical investigation may guide further device design modifications or provide further information for the design of a subsequent clinical investigation. The outcomes of an early-stage clinical investigation can often support further development and iterative changes to the device. The data generated in pilot stage clinical investigations are in general insufficient to CE mark the device.

More information on the different development stages and related types of clinical investigation design for investigational medical devices may be found in the standard ISO14155:2020 and its Annex I.

## 6. Which regulatory pathway should a sponsor follow to conduct a clinical investigation in the pilot stage (i.e. first in human, early feasibility) in accordance with the Regulation (EU) 2017/745 (MDR)?

The MDR provides for a number of clinical investigation types. The regulatory pathway chosen depends on the clinical development plan<sup>8</sup>, and the proposed use of the clinical data. If the clinical data will be used to support conformity assessment, the clinical investigation will fall under Article 62 of the MDR, otherwise another regulatory route may be chosen (e.g. a national regulatory pathway (Article 82 of the MDR) in the Member State where the clinical investigation would be conducted).

In general, as pilot stage clinical investigations are conducted to gather preliminary safety and/or performance data, the use of Article 62 of the MDR should be foreseen. In cases of doubt, it is recommended to apply under Article 62 of the MDR. Annex I of this document may guide you in the different possible pathways to apply for a clinical investigation.

## 7. A CE marked medical device is planned to be further investigated in a clinical investigation – how does a sponsor determine the regulatory pathway for this clinical investigation?

To determine the regulatory pathway for studies with CE marked devices it is necessary to understand what the intended purpose of the device is and to check whether the planned use in the clinical investigation is within its intended purpose.

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<sup>7</sup> Clinical investigation of medical devices for human subjects – Good clinical practice (ISO 14155:2020)

<sup>8</sup> According to Annex XIV to the MDR

The regulatory pathway for studies with CE marked devices is detailed in Annex I of this document. Question 8 provides further guidance on how to assess the planned use in the clinical investigation with respect to its intended purpose.

Once it has been determined if the investigational medical device will be used within its intended purpose, please refer to the following to determine the appropriate regulatory pathway:

- a) When the CE marked device is further assessed, for safety or performance within the intended purpose it is a post-market clinical follow-up (PMCF) investigation. 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, the sponsor shall notify the Member State(s) concerned at least 30 days prior to its commencement, in accordance with Article 74(1) of the MDR. If the sponsor is uncertain whether such additional procedures are considered invasive or burdensome, they are encouraged to request the opinion of the relevant authority in the Member State(s) prior to commencement of the investigation. See question 9 for further information.
- b) If safety and performance of a CE marked device is being further investigated and Article 74(1) of the MDR is not applicable, Article 82 of the MDR may apply. It is also necessary to check and follow national provisions in the Member State where the clinical investigation will be conducted. Registration in a publicly available database of clinical investigations falling under Article 82 of the MDR is encouraged.
- c) When the CE marked device is assessed outside the intended purpose, Article 74(2) of the MDR foresees that the requirements for pre-market clinical investigation apply (Articles 62 to 81 of the MDR). If the clinical investigation is not performed for conformity purposes, Article 82 of the MDR applies.
- d) When the CE marked device is used in a clinical study but the device itself is not assessed for safety or performance, this is outside the scope of the MDR definition of clinical investigation, and it is necessary to check national provisions in the Member State where the clinical study will be conducted.

It should be noted that when a CE marked device is modified<sup>9</sup>, Article 74(1) of the MDR is not applicable.

## **8. How can a sponsor assess if the planned use of a medical device in the clinical investigation is covered by the intended purpose?**

In order to assess if the use of a medical device in a clinical investigation is within its intended purpose, first determine the device's intended purpose, which could be identified by reviewing the instructions for use, and if available, the following documents:

- The EU declaration of conformity;
- The labelling<sup>10</sup> supplied by the manufacturer;

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<sup>9</sup> Modifications of medical devices may be made by a health institution provided that conditions in Article 5(5) of the MDR are met and any national provisions are adhered to.

<sup>10</sup> Article 2(12) of the MDR defines "intended purpose" as "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".



- Where applicable, the CE conformity certificate<sup>11</sup> for the device;
- The clinical evaluation report.

The next step is to determine how the device will be used in the clinical investigation:

- Review the clinical investigation plan to determine the details of the planned use of the medical device. Details to review include the target population, the indications/contraindications, anatomical location where the device will be used, the duration of use, the planned procedures, and the planned users.
- Check if the intended user in the clinical investigation will use the device as stated in the instructions for use.

From these documents, compare the intended purpose with how the device will be used in the clinical investigation and assess if these are aligned. An investigational medical device can only be considered to be used within its intended purpose if the planned use of the device during a clinical investigation is aligned with the device's intended purpose.

## 9. What is considered burdensome or invasive?

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, the sponsor shall notify the Member States concerned at least 30 days prior to its commencement, in accordance with Article 74(1) of the MDR.

Additional procedures which are burdensome can include a wide variety of different interventions, this may include procedures which may cause pain, discomfort, fear, potential risks or complications/side-effects, disturbances of lives and personal activities, or otherwise unpleasant experiences. It is mostly determined from the perspective of the person bearing the burden.

Additional procedures which are invasive include (but are not limited to) penetration inside the body through the surface of the body, including through mucous membranes of body orifices, or penetration of a body cavity via a body orifice.

The understanding of what is considered to be invasive or burdensome is expected to develop over time. Sponsors are encouraged to document their assessment whether the additional procedures imposed by the clinical investigation plan are considered as burdensome and/or invasive, and where appropriate, contact the relevant authority in the Member State(s) to discuss cases where the sponsor is uncertain.

## 10. Who is responsible for determining the correct regulatory pathway for a clinical investigation?

It is the sponsor's responsibility to determine the correct regulatory pathway for their clinical investigation. Guidance is provided in this document, but the MDR and national legislation contain the legally binding requirements.

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<sup>11</sup> EU technical documentation assessment certificates, EU type-examination certificates or EU product verification certificates as appropriate.

Note that the MDR introduces a requirement for manufacturers to have access to a Person Responsible for Regulatory Compliance (Article 15 of the MDR).

Sponsors are encouraged to document their assessments and choices of regulatory pathways.

If the sponsor is uncertain about which route to apply for a particular clinical investigation, the National Competent Authority may be consulted.

## **11. What are the safety reporting requirements for clinical investigations?**

The requirements for safety reporting will depend on whether you are using the investigated medical device within its intended purpose:

- If the investigated medical device is CE marked and will be used within its intended purpose, the provisions on vigilance laid down in Article 80(5) and Articles 87 to 90 of the MDR and the acts adopted pursuant to Article 91 of the MDR shall apply for PMCF clinical investigations.
- If the investigated medical device is not CE marked, or is CE marked but will be used outside its intended purpose, the provisions on safety reporting laid down in Article 80 of the MDR shall apply.

Please refer to MDCG 2020-10/1 'Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745' for further guidance<sup>12</sup>.

## **12. Does a manufacturer of devices without a medical purpose included in Annex XVI of Regulation (EU) 2017/745 (MDR) have to conduct clinical investigations?**

To ensure the same level of protection of consumers for some products which could be similar to medical devices but without a medical purpose, devices described in Annex XVI to the MDR have to comply with the applicable general safety and performance requirements. Clinical evaluations of those products shall be based on relevant data concerning safety, including data from post-market surveillance, PMCF, and, where applicable, specific clinical investigations. Clinical investigations shall be performed for those products unless reliance on existing clinical data from an analogous medical device is duly justified<sup>13</sup>. Please refer to MDCG 2020-5 Clinical Evaluation – Equivalence, section 4 (f) for further guidance<sup>14</sup>.

## **13. What procedure applies for clinical investigations of custom-made devices or in-house manufactured devices?**

Custom-made devices are defined in Article 2(3) of the MDR.

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<sup>12</sup>[https://ec.europa.eu/health/md\\_sector/new\\_regulations/guidance\\_en](https://ec.europa.eu/health/md_sector/new_regulations/guidance_en)

<sup>13</sup> Article 61(9) of the MDR

<sup>14</sup> [https://ec.europa.eu/health/md\\_sector/new\\_regulations/guidance\\_en](https://ec.europa.eu/health/md_sector/new_regulations/guidance_en)

In-house manufacturing, modifying and use of devices within health institutions is provided for in Article 5(5) of the MDR.

The relevant general safety and performance requirements set out in Annex I of the MDR apply to both of these device types. As such, clinical investigations may be undertaken with respect to these device types, and they may fall under Article 62 or 82. See Annex I of this document for further information.

## **14. Are coordinated assessment procedures in accordance with Article 78 of Regulation (EU) 2017/745 (MDR) available?**

For the time being, no coordinated procedure is available.

## Modifications to clinical investigations

### **15. How is a substantial modification defined?**

A substantial modification of a clinical investigation is a change to the clinical investigation which is likely to have a substantial impact on the safety or health or rights of the subject, or on the robustness or reliability of clinical data generated by the investigation. Modifications of the clinical investigation plan (CIP), investigators brochure, the subject information sheet and other clinical investigation documentation may or may not be considered as substantial modifications.

Sponsors should also take into consideration the fact that some modifications may seriously impact the design or scientific outcome of the clinical investigation, and may require the initiation of a new clinical investigation. The procedure is further described in Article 75 of the MDR. A non-exhaustive list of modifications that may be interpreted as substantial can be found in Annex II of this document.

### **16. When can a sponsor submit a substantial modification notification?**

A notification of substantial modification may be submitted in accordance with Article 75 of the MDR<sup>15</sup> as soon as a clinical investigation is allowed to commence in accordance with the MDR.

In general, it is not recommended to submit another substantial modification while assessment of the previous is still ongoing. It is also important to consider if there are national procedures which may apply regarding modifications to clinical investigations.<sup>16</sup>

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<sup>15</sup> Please refer to Q.25 of this document for further details.

<sup>16</sup> For example, national procedures relating to Ethics Committee opinions.

**17. Is a change to the investigational medical device to be considered as a substantial modification to the clinical investigation or does it lead to the submission of a new clinical investigation?**

In general, a change to the investigational medical device is a substantial modification.

Some modifications to the investigational medical device may require a new application for clinical investigation. This will be assessed by Member States on a case-by-case basis with reference to public health, subject and user safety or health, and public policy.

Modifications to the device which alter the suitability of the clinical investigation design to provide evidence for the safety, performance or clinical benefit of the device, may result in refusal of the modification and the submission of a new clinical investigation application may be required.

**18. According to Article 75 of the MDR, if a sponsor intends to introduce modifications to a clinical investigation which are substantial, the sponsor has to notify the Member State within 'one week'. From which point in time does this 'one week' start?**

The 'one week' period starts from the date when the relevant documents (such as clinical investigation plan, investigator brochure, subject information sheet and informed consent form) are issued in an updated version.

It is acknowledged that changes to e.g. a CIP may require subsequent changes to other documents such as patient information, and that these changes may be done on a different date. Such changes can be collected and submitted together when the last affected document is issued, but note that the implementation of the changes to the clinical investigation can not be done until the deadline in Article 75 of the MDR has expired or an authorisation letter is issued by the Competent Authority and/or Ethics Committee if this is required according to national provisions.

**19. Can the sponsor start to implement the substantial modification after 38 days of the notification date to the Member State?**

Yes, if the sponsor has not heard from the Member State after 38 days the substantial modification may be implemented, provided that an Ethics Committee in that Member State has not issued a negative opinion in relation to the substantial modification. This 38-day period may be extended by a further 7 days in order to consult with experts. Member States will notify the sponsor if such a consultation is taking place. The substantial modification can be implemented sooner if the Member State has authorised the substantial modification.

If the Member State has sent a request for information, there may be, depending on national provisions, a clock-stop, as long as the Member State has not received the additional information.

## **20. What notification requirements apply to non-substantial modifications?**

Article 75 of the MDR does not describe how sponsors or authorities shall deal with non-substantial modifications. Once EUDAMED is available, sponsors are expected to keep the information in the database up to date in accordance with Article 70(2) of the MDR. However, in the absence of EUDAMED Member States have not yet harmonised their approach, and it is thus necessary to check the national requirements.

## Timeline considerations for clinical investigations

### **21. Which date is considered as the start of the clinical investigation?**

Reporting of the study start date is not explicitly required by the MDR, but in some Member States it is required by national legislation to report this to the relevant Authority.

Further, the start date of a clinical investigation should be indicated in EUDAMED (once available) to disseminate relevant information to the public and for Competent Authority inspection planning purposes. The start date of a clinical investigation should be described in the clinical investigation plan. In general it is considered to be, the first act of recruitment in the clinical investigation in a Member State. The first act of recruitment should be specified by the sponsor and could be, for example, the date of initiation of the clinical investigation in the first site or the date when the first investigation-specific advertisement is published. In any case the clinical investigation cannot start earlier than the authorisation date (or commencement date notified for PMCF investigations) or not later than the date recruitment starts.

### **22. Which date is considered as the end date of a clinical investigation?**

As stated in Article 77(2) of the MDR, the end of a clinical investigation shall be deemed to coincide with the last visit of the last subject unless another point in time for such end is set out in the clinical investigation plan (for example site closure occurring after the last visit of the last subject).

### **23. Does the sponsor have to notify the end of the clinical investigation when it is concluded in one or more Member States, or when the overall clinical investigation is completed globally?**

According to Article 77(3) of the MDR the sponsor shall notify each Member State in which a clinical investigation was being conducted of the end of that clinical investigation in that Member State. That notification shall be made within 15 days of the end of the clinical investigation in relation to that Member State.

If a clinical investigation is conducted in more than one Member State the sponsor shall also notify all Member States in which that clinical investigation was conducted when the clinical investigation is completed in all Member States. That notification shall be made within 15 days of the end of the clinical investigation in the last Member State.

If the clinical investigation is still ongoing in one or more third countries when the end of the clinical investigation in the EU is reported, this will impact the sponsor's ability to provide a clinical investigation report of the overall study (i.e. fulfil the reporting requirements of Article 77(5) of the MDR). Therefore the sponsor should inform the concerned Member States of the expected end of study globally if this does not coincide with the end of study in the EU. Sponsors are encouraged to notify the Member States concerned to confirm the actual end of study globally, once reached.

## **24. When does the sponsor have to submit a summary of results?**

Irrespective of the outcome of the clinical investigation, within one year of the global end of the clinical investigation the sponsor shall submit to all the Member States in which a clinical investigation was conducted a clinical investigation report as referred to in Section 2.8 of Chapter I and Section 7 of Chapter III of Annex XV to the MDR.

Following a decision of an early termination or temporary halt, a clinical investigation report is required to be submitted within 3 months to all Member States in which the clinical investigation was conducted. Sponsors are expected to submit a risk analysis concerning any safety grounds related to the temporary halt.

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. The final clinical investigation report should include detail with respect to the temporary halt.

## Clinical investigation reports

### **25. What shall be the content of the clinical investigation report?**

The minimum requirements for content of the clinical investigation report (which will be made public according to Article 77 of the MDR) are defined in Chapter III point 7 of Annex XV to the MDR. The standard ISO 14155:2020, Annex D also has information which is relevant regarding the content of a clinical investigation report.

It is important to note that the summary of serious adverse events, adverse device effects and device deficiencies should only present aggregated information related to these events.

Descriptions of single events or line listings with direct or indirect personal data may jeopardise subject privacy and should be avoided in a report which will be made public.

To put the information that is required (minimum content) in a relevant context and enhance the understanding of the clinical investigation report, sponsors are encouraged to also include the following information in the report:

#### ***Clinical investigation background***

Presentation of the context and reasons for conducting the clinical investigation.

## ***Outcome measures***

Description of the selected outcome measures and their relevance for the assessment of safety and performance of the investigational device.

## ***Clinical investigation conduct***

- Include information on the dates defining the periods of recruitment and follow-up of subjects in order to describe the time period during which the clinical investigation was conducted.
- Interventions: Precise details of the interventions intended for each group and how and when they were actually administered should be included in the report. State the precise dose (if relevant), treatment duration, control interventions and additional treatment for each of the groups.

## ***Clinical investigation subjects***

Baseline data (baseline demographic and clinical characteristics of each group) should be included.

Also describe the flow of subjects through each stage (diagram, if appropriate).

For each group the numbers of subjects randomly assigned, receiving intended treatment, completing the clinical investigation, and analysed for the primary outcome should be stated.

Indicate the number of subjects in each group which have been included in each analysis and whether the analysis was by "intention-to-treat" or "per protocol".

## ***Deviations and amendments***

Deviations from the initial clinical investigation plan and a description of any CIP amendments should be described and justified.

## Arrangements for the transitional period

### **26. The clinical investigation module in Eudamed will not be ready by May 2021, how can the sponsor follow the regulation without this functionality in Eudamed?**

Clinical investigation sponsors will not have the opportunity to be recorded in Eudamed as of the date of application of the MDR.

#### **To submit an application:**

All requested information to apply for or notify a clinical investigation should be submitted to the national competent authorities unless otherwise specified in the MS concerned. Check with the relevant National Competent Authority which system will be used for submission.

The Commission has a listing of the contact details for National Competent Authorities, which is available at:

[https://ec.europa.eu/health/sites/health/files/md\\_sector/docs/md\\_clinical\\_investigation\\_contact\\_points.pdf](https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_clinical_investigation_contact_points.pdf)

#### **To fulfil the safety reporting requirements of MDR Article 80:**

Please see MDCG 2020-10/1 'Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745' for guidance.

**27. What will happen to those clinical investigations that started prior to the date of application of Regulation (EU) 2017/745?**

Clinical investigations that are currently being conducted with respect to Directive 93/42/EC and Directive 90/385/EC by the date of application of the MDR, can continue to be conducted. Nevertheless, serious adverse events (SAEs) and device deficiencies occurring after the date of application of the MDR, shall be notified to the MS according to the rules defined in Article 80 of the MDR.

To facilitate the transition and give time for sponsors to update Clinical Investigation Plans and procedures in clinical investigations a sponsor may continue to report all SAEs to National Competent Authorities until Eudamed reporting is mandatory. This applies only to studies which have started to be conducted in accordance with Article 10 of Directive 90/385/EEC or Article 15 of Directive 93/42/EEC prior to 26 May 2021. Please refer to MDCG 2020-10/1 'Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745' for further guidance.

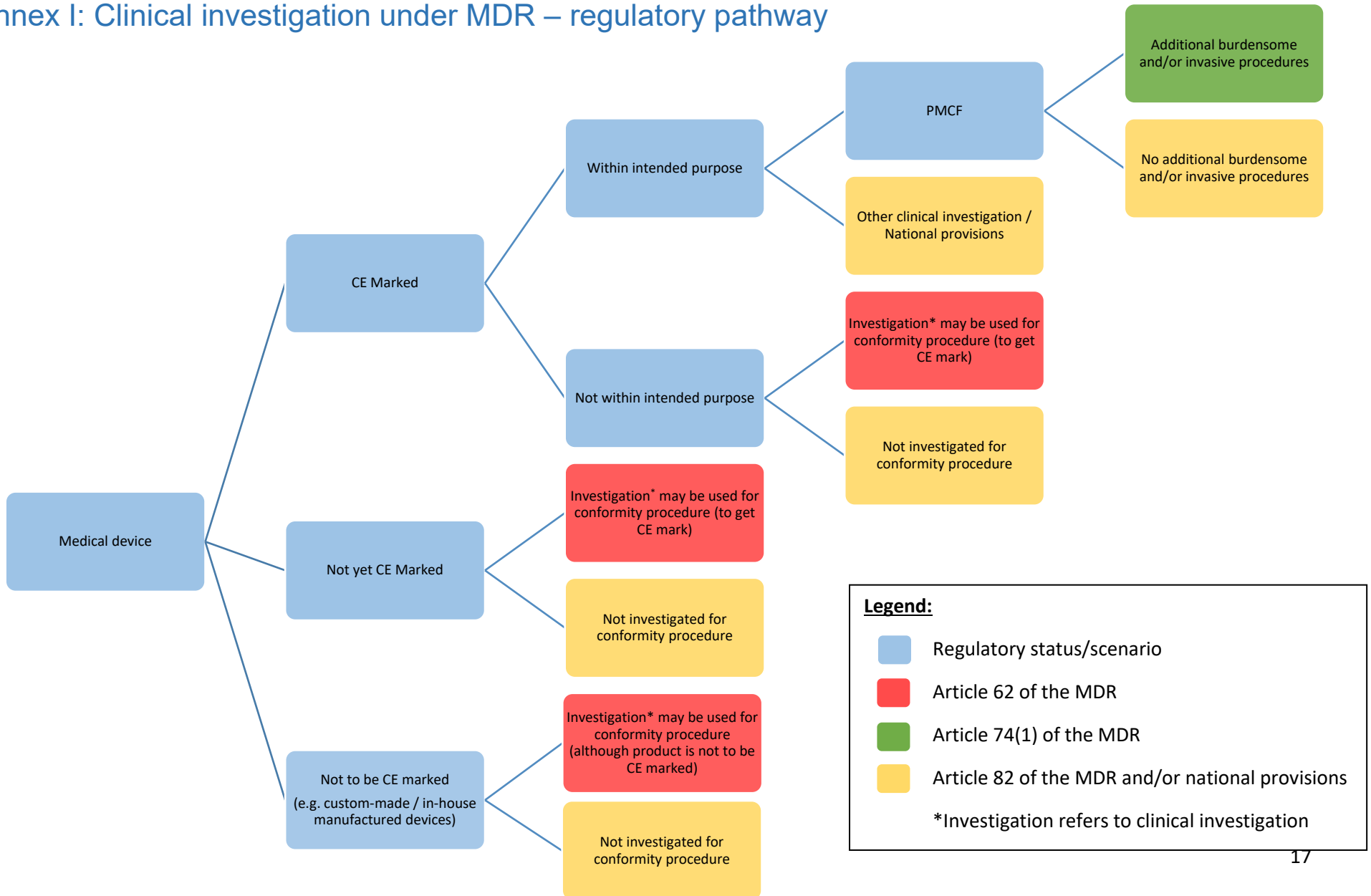
**28. How should Article 120(11) of the MDR be interpreted – when is a clinical investigation to be considered started to be conducted in accordance with Article 10 of Directive 90/385/EEC or Article 15 of Directive 93/42/EEC?**

As national interpretations and implementation of the directives in national legislation may differ between Member States, please check with the national competent authority in the Member State where the clinical investigation is to be conducted as to what they consider as started/starting date.



# Medical Devices

## Annex I: Clinical investigation under MDR – regulatory pathway



## Annex II: Non-exhaustive list of modifications that may be interpreted as substantial

### **Amendments related to the protocol or subject information**

1. Change to a primary or secondary endpoint;
2. Use of a new mode of measurement for the primary endpoint;
3. A change of clinical investigation design which is likely to have a significant impact on the statistical analysis or the benefit/risk assessment;
4. A change in the definition of the end of the clinical investigation;
5. A modification of the duration of treatment and/or the follow up of patients;
6. Changes in the number of scheduled subject visits;
7. Change of a diagnostic or other assessment procedure which is likely to have a significant impact on the safety of the subject or the scientific value of the clinical data collected in the clinical investigation;
8. Changes to the data monitoring committee which may affect, for example, the safety evaluation, or the independence and impartiality of the committee;
9. Amending the number of subjects to be included in the clinical investigation, either due to an adaptation of the sample size calculation or to maintain a previously defined sample size calculation due to an increased unanticipated dropout rate;
10. Addition of an interim analysis not planned in the initial CIP;
11. Deletion of an interim analysis;
12. Change of safety criteria to modify or interrupt treatment;
13. Content change in the subject information sheet and informed consent forms, or other information provided to the subject;
14. Change of inclusion or exclusion criteria if these changes are likely to have a significant impact on the safety of the subject or scientific value of the clinical data collected in the clinical investigation.

### **Amendments related to the benefit/risk of the clinical investigation**

15. New preclinical or clinical data which is likely to impact on the benefit/risk assessment;
16. The revocation or suspension of the conformity assessment certificates related to the medical device under investigation.

### **Amendments related to the use of the investigational device**

17. Change of treatment modalities (modification of procedure, techniques, instructions for use) of the investigated medical device;
18. The type and/or duration of the investigator's training.

### **Amendments related to other information**

19. A change of sponsor or the sponsor's legal representative;
20. Change/addition of a clinical investigation site;
21. Change of manufacturer;
22. New insurance policy;
23. Change in compensation paid to subjects and/or investigators/site;
24. Change of /addition of new investigator(s).

### **Amendments related to the manufacturing process**

25. Modification of the process of manufacturing, sterilization or packaging.