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WHITEPAPER

Medical Device Clinical Investigations

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New Medical Device Regulation (EU) 2017/745 was adopted by the European Parliament. The new Regulation (EU) 2017/745 was published on May 5, 2017 and came into force on May 25, 2021. It emphasizes the need for clinical evidence to enhance performance, safety, and transparency. Even with current guides and lengthy transition periods, it still takes work to bring devices into conformity with EU-MDR. To prove compliance with EU-MDR, it is crucial to produce clinical evidence that takes into account that are clinical, analytical, and scientific aspects of Safety and efficacy for every individual indication in normal use. Manufacturers must demonstrate that their product is effective and safe through more comprehensive validation, scientific support and studies of the clinical performance of their products. Therefore, it is necessary for medical device manufacturers and end users in health care institutions to get guidance on how to provide this clinical evidence.

A complete clinical evidence portfolio that proves the following will be necessary for MDR Compliance:

- Conformity to the Annex I General Safety and Performance Requirements
- Acceptability of benefit-risk ratio
- Acceptable levels of side-effects and adverse events
- Safe and effective real-world use
- Adequate responses to serious incidents

Fulfilling these prerequisites will require:

- Performing literature searches, evaluating sources, conducting a scientific analysis, and compiling findings into a report
- Developing Clinical Investigations in Compliance with Annex XV MDR, GDPR, and Good Medical Practice
- Using various forms of clinical investigation for various objectives
- Knowing how to collaborate with clinical sites to improve compliance with data gathering
- Ensuring that the conditions for ethical clearance and patient consent are fulfilled
- Implementing well-structured Vigilance systems and applying a medical interpretation to the results

Clinical investigations for medical devices

A clinical investigation is defined by the MDR/ ISO 14155 standard as any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device. Clinical investigations are defined as clinical trials utilizing medical devices, with the aim of addressing significant scientific inquiries. It needs to adhere to stringent scientific guidelines (such ISO 14155), which can safeguard patients and yield trustworthy scientific findings. While not all clinical trials utilizing medical devices are clinical investigations, they do not have the purpose of conducting a systematic study with one or more human participants in order to evaluate the effectiveness or safety of the device(s) being utilized. One of the last stages of a protracted and frequently tedious research and development process is the clinical investigation, which is done to determine what treatments for humans are effective and ineffective.

Before getting started, it's crucial to understand that the words "clinical investigation," "clinical trial," and "clinical study" are interchangeable and correspond to the ISO 14155 standard.

Purposes of a clinical investigation

A clinical investigation may have the goal of establishing and verifying clinical safety, which is the knowledge of how to avoid and minimize risks, mistakes, and harm to patients and staff, including physicians and nurses. Providing a constant improvement of treatment procedures based on the

knowledge and learning from errors and adverse events observed is the cornerstone of all clinical research.

Moreover, establishing and validating a device's performance might also be the goal of a clinical trial. This entails determining if a device can operate as intended. This is accomplished by examining the device's functional, technical, or even diagnostic features. It must be confirmed that the device will assist patients clinically and that its manufacturer can fulfill the goal for which it was designed. Another goal is to demonstrate and validate clinical benefits, which is essentially examining the beneficial effects of a technology that can have on a person's health. It is articulated in terms of a significant and quantifiable patient-centered result.

And lastly, side effects are especially important when doing a clinical study. Finding previously unidentified adverse effects and obtaining more information about existing side effects can be two of a clinical investigation's objectives.

The overall purpose of a clinical investigation can be summed up to say that it is meant to translate scientifically tested innovations into clinical practice to provide patients with new (or improved) treatments.

Clinical investigation vs. clinical evaluation

It is crucial to realize that clinical investigation and clinical evaluation are two different things and should not be used interchangeably. It is rather simple to mistake or even to use the terms synonymously, but understanding the distinction is necessary to be able to discuss one topic or another.

Clinical investigation	Clinical evaluation
Use on real human subjects **Safety and performance**	**Theoretical assessment**

The distinction is in the definitions:

A *clinical evaluation* is a theoretical and scientific assessment and appraisal of existing data from numerous sources of clinical data, implying that human subjects are not directly involved.

A *clinical investigation*, on the other hand, is a new study employing a medical device in patients to demonstrate the safety and performance of that medical device in human subjects.

Clinical evaluation is defined as a systematic and planned process to continuously generate, collect, analyze, and assess the clinical data pertaining to a device in order to verify the device's performance and safety, including its potential clinical benefits when used in accordance with the manufacturer's instructions. This definition can be found in the European Medical Device Regulation, or MDR.

It is important to keep in mind that there are differences in the definitions of clinical evaluation between the MDR, the ISO 13485 standard, and the MEDDEV clinical evaluation guidance document.

Clinical evaluation

Clinical evaluation is the theoretical assessment that should begin throughout, or even before, the development of a new product since a scientist or a clinician would review pertinent literature linked to the product and indication before ever considering doing a clinical research. This is a continuous procedure that evaluates and examines all of the device's clinical data; it is not a one-time job.

Finding the pertinent literature typically requires a significant amount of time and may involve reading through hundreds of publications, all of which must be evaluated, assessed, and summarized for a report known as a clinical evaluation report. Depending on the kind of product, this report may end up being extremely detailed and a hundred pages long. It is recommended that the clinical evaluation report be updated during the course of the product's lifecycle.

Thus, the main goal of clinical assessments is to ascertain whether a medical device:

- Achieves its intended purpose
- Is safe
- Its benefits outweigh the risks
- It is state-of-the-art
- Has any equivalent devices for comparison

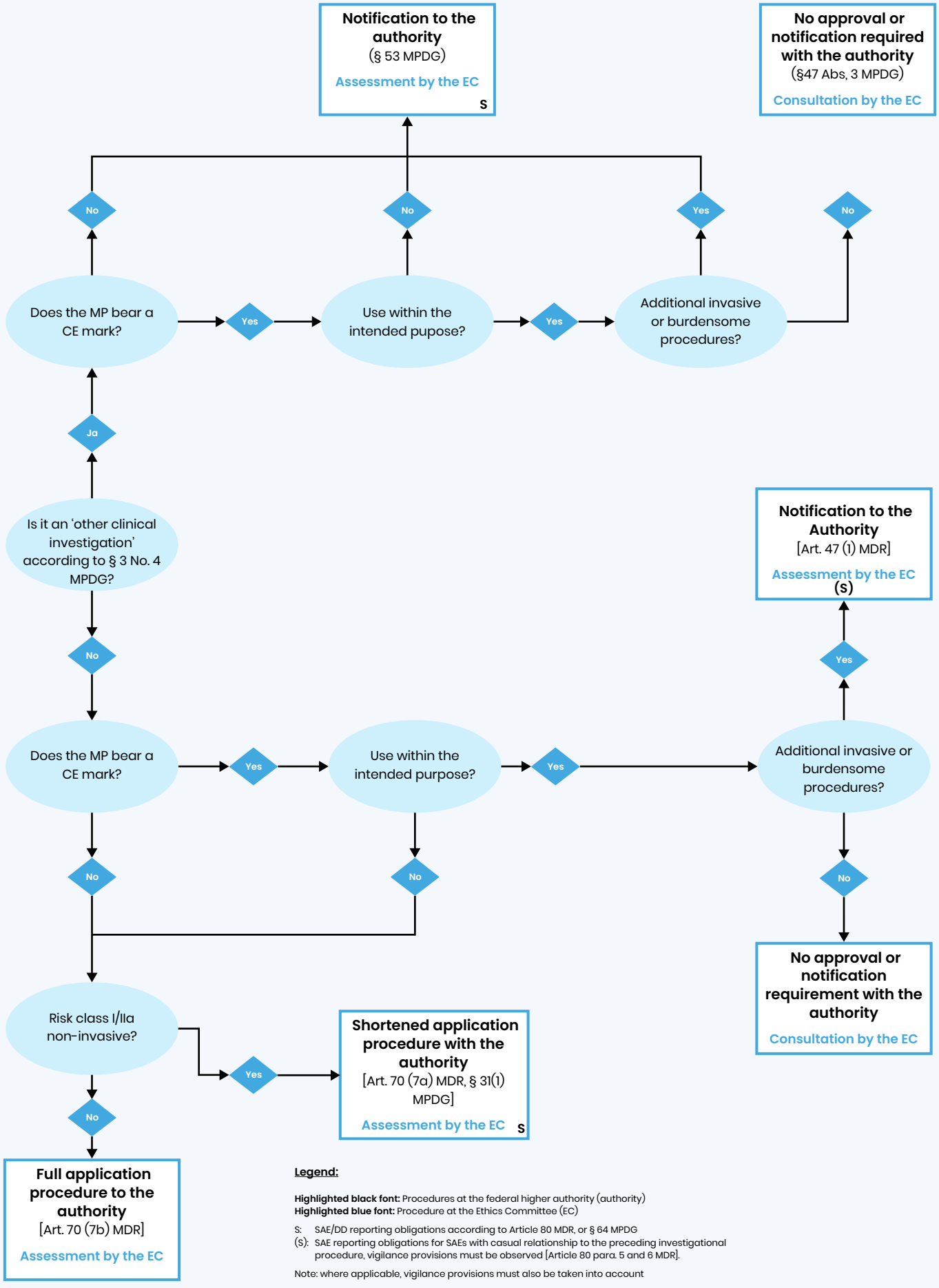
To sum up, both clinical investigation and clinical evaluation are important in the medical device world. They are, however, very different even though they sound similar, and it is of utmost importance to know the difference well. Finally, the clinical evaluation process has a much broader purpose than a clinical investigation.

Which Medical Device production needs Clinical investigations?

Before being put on the market, medical devices may need to go through a clinical trial in the US and the EU. A clinical study is necessary for some risk classes and involves a methodical evaluation of the device's safety and/or effectiveness using human participants.

- According to EU MDR, clinical studies are required for all implanted devices classified as Class III and Class IIb in the EU.

Premarket approval (PMA) for all Class III devices in the United States is contingent upon clinical research conducted by the FDA.



Legend:

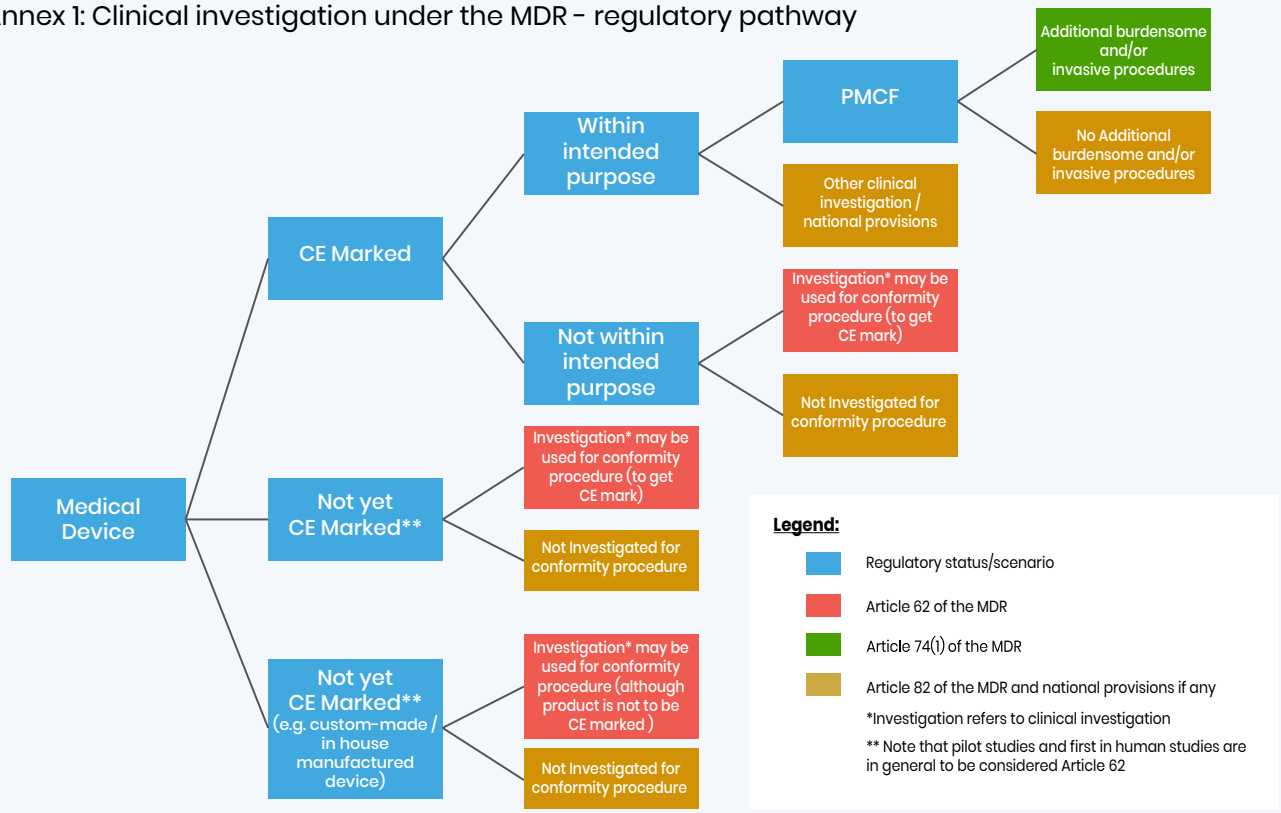
Highlighted black font: Procedures at the federal higher authority (authority)
Highlighted blue font: Procedure at the Ethics Committee (EC)

S: SAE/DD reporting obligations according to Article 80 MDR, or § 64 MPDG
(S): SAE reporting obligations for SAEs with casual relationship to the preceding investigational procedure, vigilance provisions must be observed [Article 80 para. 5 and 6 MDR].

Note: where applicable, vigilance provisions must also be taken into account

MDR compliance - The medical device regulation environment

Annex 1: Clinical investigation under the MDR - regulatory pathway



Regulatory Pathways - Clinical Investigations under EU-MDR

EU MDR has 20 articles outlining the requirements for clinical investigations of medical devices, spanning articles 62 through 82. Within these articles, the regulation lays out three regulatory pathways manufacturers can take:

- Article 62 covers investigations that are performed in order to demonstrate conformity and obtain a CE marking. This is the pathway medical device companies will use if their device classification (for Class III or Class IIb implantables) requires a clinical investigation.
- Article 74(1) covers the regulatory pathway for devices that already have a CE marking if the parameters of the investigation are within the device's intended purpose. In other words, if conducting a clinical investigation as part of Post-Market Clinical Follow-Up (PMCF), then Article 74(1) will guide.
- Article 82 covers clinical investigations that are not being performed in order to demonstrate conformity. Additionally, the Member State in which the study initiated may have relevant national provisions to follow.

Conclusion

The European Medical Device Regulation (2017/745) (MDR) sets important new requirements for pre- and post-marketing clinical investigations. Conducting a clinical investigation is one of the most time-consuming and resource-intensive activities a medical device manufacturer faces. For these reasons, manufacturers must ensure that the purpose of the clinical investigation is clear. All applicable regulations, common specifications (e.g. on device-specific requirements for clinical trials), international standards, European guidance documents and national guidance documents are identified; all persons participating in the study understand their roles and responsibilities; and the study is well organized and conducted according to appropriate quality management practices.

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