EU

# Post-Market Clinical Follow-up Studies

## A logical start to compliance under the new Medical Devices Regulation 2017/745/EU



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# What is Post-Market Clinical Follow-up?

There are no certainties regarding the clinical performance and safety of medical devices. A device that appears safe and performs well today could be the subject of an urgent field safety corrective action tomorrow. Manufacturers must continually evaluate their devices on the market in the form of Post-Market Surveillance (PMS) and Post-Market Clinical Follow-up (PMCF). While these processes cost time and money, they also help improve the state-of-the-art in medical technology.

Post-Market Clinical Follow-up (PMCF) is part of Post-Market Surveillance (PMS). PMCF runs parallel with the processes of controlling vigilance reporting, field safety corrective actions (FSCA), complaints, and other feedback from the market. Where incident reports and complaints arrive more or less spontaneously, PMCF must be initiated by the manufacturer. In MEDDEV 2.7/1 Rev. 4, Clinical Evaluation, PMCF is defined as the process to collect:

*'clinical data based on the use of a CE-marked device corresponding to a particular design dossier or on the use of a group of medical devices belonging to the same subcategory or generic device group as defined in Directive 93/42/EEC. The objective is to confirm clinical performance and safety throughout the expected lifetime of the medical device, the acceptability of identified risks and to detect emerging risks on the basis of factual evidence.'*

This white paper focuses on Post-Market Clinical Follow-up, and, more specifically, on PMCF studies. It will discuss PMCF and PMCF studies in the context of the change from the current Medical Devices Directive 93/42/EU (MDD) to the new Medical Devices Regulation (MDR 2017/745/EU), as well as how current PMCF activities can help your transition to the MDR. It will also address compliance to the current MDD, even for products that will not be placed on the European market under the MDR.

## How does PMCF change under the MDR?

Clinical requirements will not change significantly under the new MDR compared to the current MDD. However, the procedure for demonstrating compliance will change dramatically. Demonstration of clinical compliance must be related to the device or a narrowly defined equivalent device, and it must be based on methodologically sound data.

This also means that data accepted under the current MDD may no longer be acceptable under the new MDR. Some devices that have been on the market for years--or even decades--may see their clinical investigations dismissed as inadequate because they are not compliant with the current version of the Helsinki Declaration or EN ISO 14155:2011, or do not meet higher demands for medical scientific relevance. Yet, these devices are CE-marked and used every day in compliance with the current MDD.

PMCF studies could help bridge the gap in clinical data. The PMCF plan for each device cannot be seen outside the context of the transition plan to the new MDR. It is obvious that manufacturers targeting a late transition will have more time to gather clinical data, but that does not mean PMCF activities should be postponed for devices that will be MDR certified in 2022 or later. The extra time presents an opportunity to generate clinical evidence for devices certified in 2019 or 2020.

Annex XIV, Part B of the MDR addresses the types of questions raised by PMCF:

1. Confirming the safety and clinical performance of the device throughout its expected lifetime - conditions under which the device is used may change over time, new diseases that may develop, etc. The device must remain safe and perform as intended, even with moving goal posts. Technology or devices that have been on the market for a long time are especially vulnerable.
2. Identifying previously unknown side-effects and monitoring the identified side-effects and contraindications. New devices that see a rapid acceptance on new markets require proper monitoring.
3. Identifying and analyzing emerging risks on the basis of factual evidence; where incident reports of the subject device only provide information about that specific device, incident reports of similar devices may help eliminate or mitigate risks before they manifest.
4. Ensuring the continued acceptability of the benefit-risk ratio referred to in Sections 1 and 9 of Annex I.
5. Identifying possible systematic misuse or off-label use of the device with the intent to verify that the intended purpose is correct.

The above points are not new in relation to the current MDD, but they are only implicitly mentioned. MEDDEV 2.12/2 provides guidance regarding PMCF studies and explicitly addresses the reasons justifying a PMCF study.

Note that the MEDDEV is not legally binding. Notified bodies may use the MEDDEV as a reference and compliance to the MEDDEV does not guarantee compliance to the Directive. And, non-compliance to a MEDDEV cannot be the single cause of non-compliance to the MDD. The good news is that the upcoming requirements in the MDR can be used as guidance for PMS and PMCF under the current MDD, as most of MEDDEV 2.12/2 has been incorporated into the MDR.

In conclusion, incorporating the new MDR requirements into the current PMS and PMCF procedures intended for demonstrating safety and clinical performance of a medical device contributes to compliance with the requirements for PMS in the current MDD.

## Check current clinical evidence

The second issue regarding PMCF relates to proper clinical data under the new MDR. Where the current MDD is implicit in defining the quality of clinical data, the new MDR is explicit. Claims must be supported by data related to the actual device (or a narrowly defined equivalent device) and the data quality must be specified in detail.

For example, any and all patient data derived from clinical studies must be compliant with the Helsinki Declaration. As such, current demonstration of compliance based on old studies that do not fully comply with current ethical standards may encounter issues under this requirement. This could happen with any CE marked device, as many devices reference older equivalent devices. Therefore, it is important to investigate the availability and quality of the existing clinical data when planning the transition to the MDR.

In conclusion, perform a thorough clinical data gap analysis with the MDR in mind. Then reformulate the clinical master plan (incl. the PMCF as needed) and discuss the result with your Notified Body.

# The Difference Between PMCF Studies and Clinical Investigations

Where MEDDEV 2.12/2 talks about a 'PMCF study,' the MDR refers to 'PMCF investigations.' In doing so, the legislator intended to clarify that there is little difference between a clinical investigation and the PMCF investigation. That is, the protection of subjects and high ethical standards required for a clinical investigation should also be applied in a PMCF investigation. MEDDEV 2.12/2 defines the difference between these two as follows:

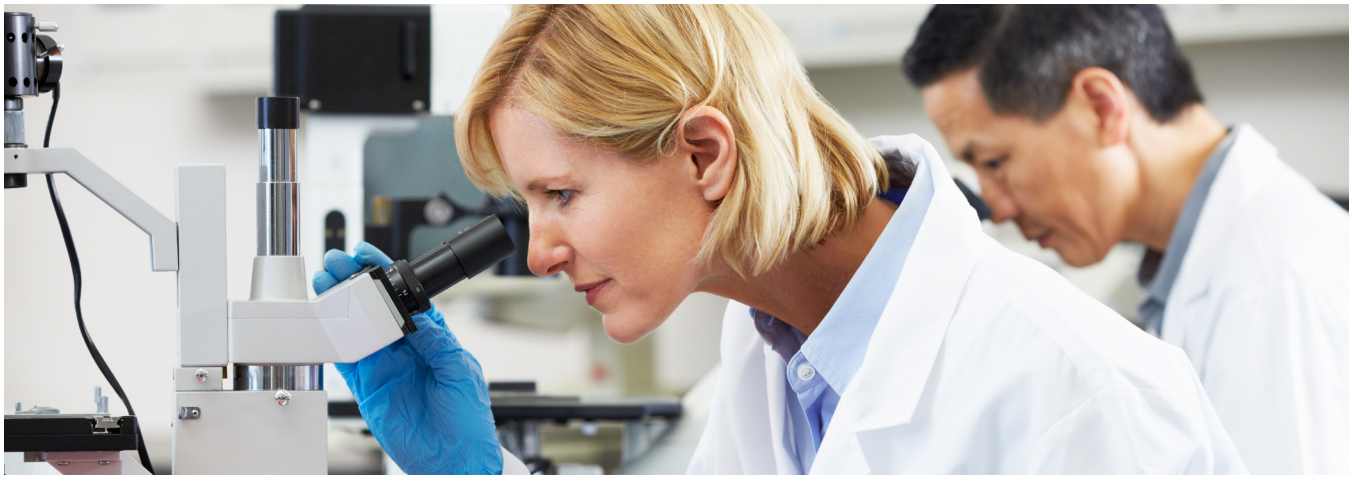
The **clinical investigation** is defined as: *any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety or performance of a medical device.*

The **PMCF study** is defined in the MEDDEV as: *a study carried out following the CE marking of a device and intended to answer specific questions relating to clinical safety or performance (i.e., residual risks) of a device when used in accordance with its approved labelling.*

In a PMCF study, the device is already CE marked and used within its intended purpose. In a clinical study, the devices are not yet CE marked for the intended purpose used in the study. Another major difference is that all patient groups within the stated intended use are included during PMCF, while clinical investigations use inclusion and exclusion criteria that are stricter than those in the intended use statement (label, IFU etc.). A PMCF study may provide an opportunity to collect additional data in a situation where a device CE marked under the current MDD has insufficient clinical data for certification under the new MDR.

However, this can only be done if the current clinical evidence is sufficiently compliant with the MDD. If that is not the case, the device may unjustly be CE Marked. In such a case a PMCF study is not appropriate, but a proper prospective clinical investigation should be performed. Several manufacturers performed PMCF studies that were rejected by their Notified Bodies because the data supporting the CE-marking was inadequate. Such a situation may even lead to termination of a PMCF investigation, or its transformation into a pre-CE-marking study with all the restrictive consequences affiliated with such a status.

Article 74 of the MDR defines the PMCF investigation as 'a clinical investigation conducted to further assess, within the scope of its intended purpose, a device that already bears the CE marking.' This definition confirms two points already mentioned: the device must already be CE marked and used within its intended purpose. Also, a PMCF study is a specific form of clinical investigation. The other consequence of this article is that PMCF studies should be treated as normal clinical investigations, with some exceptions.



As stated, clinical data intended for certification under the new MDR must comply with data quality requirements of the MDR, even if they are collected using an MDD certified device according to the current MDD requirements. It is important to inform your Notified Body about these investigations. If they agree to your study plan, they are more likely to accept the results.

You must also inform your Notified Body about the progress of the study. For all PMCF investigations, this means you must meet the following requirements (Article 62.4 MDR):

- An ethics committee, set up in accordance with national law, has not issued a negative opinion in relation to the clinical investigation, which is valid for the entire Member State under its national law. This implies that ethical committee approval must be sought;
- The sponsor ('any individual, company, institution or organization which takes responsibility for the initiation, for the management and setting up of the financing of the clinical investigation' – definition from the MDR), or its legal representative is established in the Union;
- Vulnerable populations and subjects are appropriately protected in accordance with Articles 64 to 68. These are incapacitated subjects, minors, and pregnant or breastfeeding women;
- The anticipated benefits to the subjects or to public health justify the foreseeable risks and inconveniences. Compliance with this condition is constantly monitored;
- The subject or, where the subject is not able to give informed consent, his or her legally designated representative has given informed consent in accordance with Article 63;
- The subject or, where the subject is not able to give informed consent, his or her legally designated representative, has been provided with the contact details of an entity where further information can be obtained, if needed;
- The rights of the subject to physical and mental integrity, privacy, and the protection of the data concerning him or her in accordance with Directive 95/46/EC and Regulation 2017/745/EU are safeguarded;
- The clinical investigation has been designed to involve as little pain, discomfort, fear, and any other foreseeable risk as possible for the subjects, and both the risk threshold and the degree of distress are constantly monitored and specifically defined in the clinical investigation plan;
- The medical care provided to the subjects is the responsibility of an appropriately qualified medical doctor, a qualified dental practitioner (where appropriate), or any other person entitled by national law to provide the relevant patient care under clinical investigation conditions;
- No undue influence, including that of financial nature, is exerted on the subject, or, where applicable, on his or her legally designated representatives, to participate in the clinical investigation.

Other relevant articles are:

- Article 75 MDR regarding substantial modifications to clinical investigations. It is possible to change an ongoing investigation, but take care that the authorities are involved, if the changes are likely to significantly impact safety, health, or rights of the subjects.
- Article 76 MDR regarding measures taken by Member States in relation to clinical investigation does not apply yet, but article 15.6 of the current MDD does the same: if an investigation is causing concern about public health, the authorities may interfere.
- Article 77 MDR regarding information that needs to be provided at the end of an investigation (or early termination) does not yet apply. However, if an investigation is notified to the authorities, they should be informed about these changes The Notified Body should also be kept informed.
- Finally, incidents where a patient or user was injured or could have been injured because of a malfunction of the device or its user information should be reported to the relevant authorities like any vigilance case.

We have seen instances in several countries where the Competent Authority changed the investigation from a PMCF to a regular clinical study. These clinical studies were subject to Competent Authority approval because the diagnostic, therapeutic, or patient monitoring schedule(s) deviated from the IFU or from established medical practice. It is critically important to analyze the potential for this outcome for each proposed study, as the budgetary and time consequences are significant.

## Conclusion

PMCF and PMCF studies are not new concepts in European medical device compliance. However, the MDR's definition of PMCF leaves some manufacturers wondering exactly how to comply or maintain compliance under the new regulation. Remember these key points to prepare for Notified Body expectations for PMCF under the MDR:

1. Start PMCF investigations now, with devices still CE Marked under the current MDD to prepare certification under the new MDR.
2. Perform a clinical data gap analysis with respect to the new MDR.
3. Design studies with the new MDR requirements in mind, to enable acceptability of these data for certification under the MDR.
4. Verify whether the study could trigger a status change to "pre-CE-marking" or regular, which is subject to Competent Authority approval.

Verify the updated, amended Clinical Master Plan with your Notified Body to ensure future acceptance and avoid surprises.

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## About the Author

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