# Post-market clinical follow-up insights

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## Abstract

The EU Medical Devices Regulation (MDR) brought about new post-market clinical follow-up (PMCF) requirements for medical devices. Whereas complaint monitoring and literature searches were often sufficient under the Medical Devices Directives (MDD), a more proactive approach is now required. User surveys, data collection from registries, or PMCF studies are examples of how manufacturers can collect clinical data for CE-marked devices. All planned activities are documented in the PMCF plan, including a justification of the appropriateness of each activity. But what is appropriate for what type of device? In how much detail should the results be presented in the PMCF report without duplicating the information in the clinical evaluation report (CER)? This article shares experiences and discusses some case studies for different device types.

## Post-market clinical follow-up in a nutshell

Post-market clinical follow-up (PMCF) is part of post-market surveillance (PMS) and is the process of collecting clinical data to confirm the safety and performance of a CE-marked device during the device's lifetime after its market approval.[1] PMCF is similar to the post-approval studies for pharmaceuticals. The main difference from PMCF requirements under the EU Directive 93/42/EEC on Medical Devices (MDD) is the focus on PMCF as a continuous process. The PMCF plan describes the methods and procedures to collect clinical data, whereas the PMCF report describes and evaluates the results. These results potentially impact other documents, such as the clinical evaluation report (CER), the risk management file, and if

applicable, the Summary of Safety and Clinical Performance (SSCP).[2] The Medical Device Coordination Group (MDCG) published templates for both the PMCF plan and report in April 2020 to guide manufacturers.[4,5]

Articles on new documents under Medical Devices Regulation (MDR) 2017/745 and general principles of PMCF are shown in Box 1.

The Medical Devices Coordination Group (MDCG) is an expert committee composed of persons designated by the Member States based on their role and expertise in the field of medical devices. The MDCG "deals with key issues from the medical devices sector, from Notified Body oversight or standardisation to market surveillance, passing by international matters, new technologies, and clinical investigation".[3]

## PMCF plan and report

Guidance on how to set out the PMCF plan is given in MDCG 2020-7.[4] The PMCF plan is part of the PMS plan and of the clinical evaluation plan (CEP). The aim of the PMCF plan is to:

- Confirm the safety and performance, including the clinical benefit if applicable, of the device throughout its expected functioning lifetime.
- Identify previously unknown side-effects and monitor the identified side-effects and contraindications.
- Identify and analyse emergent risks on the basis of factual evidence.
- Ensure the continued acceptability of the benefit-risk ratio, in accordance with Annex I in the MDR.
- Identify possible systematic misuse or off-label use of the device; to verify that the intended purpose is correct.

The seven sections of the PMCF plan are shown in Box 2.

Guidance on how to set up the PMCF evaluation report are presented in MDCG 2020-8.[5] As might be expected, the PMCF report layout is very similar to that of the PMCF plan. The main difference is that the PMCF report focuses on presenting and evaluating the results of PMCF and determining the impact on the technical documentation. The sections of the PMCF report are listed in Box 3. The PMCF report is part of the CER and technical documentation. The conclusions of the PMCF report are used to update the clinical evaluation, risk management documentation, the PMS plan and, if applicable, the SSCP. Therefore, it is important to schedule the PMCF report to make the results and conclusions available for inclusion in these documents. This requires careful planning for class III devices with annual CER updates. How much detail the PMCF report should provide remains a matter of debate. It seems unnecessary to repeat the information from the PMCF report one by one in the CER. Some manufacturers only summarise the results from literature searches, surveys, and other PMCF activities in the PMCF report and analyse the results in more detail in

### *Box 1. Recommendations for further reading*

For general information about new documents under MDR and principles of PMCF, the following articles are recommended:

- Bhatia P, Collada Ali LC, Goodwin Burri K, et al. New documents required by the medical device regulation. *Medical Writing*. 2020; 29(3):24–9.
- Collada Ali LC, Friedrich KJ. First experiences writing summaries of safety and clinical performance for medical devices. *Medical Writing*. 2020; 29(4):62–5.
- Doerr B, Whimtan S, Walker S. Medical Devices Writing for medical devices compared to pharmaceuticals: An introduction Authors. 2017; 26(2):8–13
- Römermann K, Theilmann W. Post-market clinical follow-up plans and evaluation reports. *Medical Writing*. 2020;29(4):83–4

### *Box 2. PMCF plan template – sections*

A. Manufacturer contact details
B. Medical device description and specification
C. Activities related to PMCF: general and specific methods and procedures
D. Reference to the relevant parts of the technical documentation
E. Evaluation of clinical data relating to equivalent or similar devices
F. Reference to any applicable common specification(s), harmonized standard(s) or applicable guidance document(s)
G. Estimated date of the PMCF evaluation report

Source: MDCG 2020-7

### *Box 3. PMCF evaluation report template – sections*

A. Manufacturer contact details
B. Medical device description and specification
C. Activities undertaken related to PMCF: results
D. Evaluation of clinical data relating to equivalent or similar devices
E. Impact of the results on the technical documentation
F. Reference to any common specification(s), harmonised standard(s), or guidance document(s) applied
G. Conclusions

Source: MDCG 2020-8

### *Box 4. Hierarchy of clinical evidence for confirmation of conformity with GSPRs under MDR*

1. Results of high quality clinical investigations covering all device variants, indications, patient populations, duration of treatment effect, etc
2. Results of high quality clinical investigations with some gaps
3. Outcomes from high quality clinical data collection systems such as registries
4. Outcomes from studies with potential methodological flaws but where data can still be quantified and acceptability justified
5. Equivalence data (reliable/quantifiable)
6. Evaluation of state of the art, including evaluation of clinical data from similar devices
7. Complaints and vigilance data; curated data
8. Proactive PMS data, such as that derived from surveys
9. Individual case reports on the subject device
10. Compliance to non-clinical elements of common specifications considered relevant to device safety and performance
11. Simulated use/animal/cadaveric testing involving healthcare professionals or other end usersPre-clinical and bench testing/compliance to standards

GSPR = General Safety and Performance Requirements. Source: MDCG 2020-6 Appendix III

the CER. However, this can result in duplication of effort, especially when the CER is not written immediately after the PMCF report. Therefore, a complete analysis and appraisal in the PMCF report with a summary of the results in the CER might be the better choice.

## PMCF data collection – When and what to do

The first step in planning PMCF activities is to identify any gaps in the clinical evidence of a device. The clinical evaluation should analyse whether all claims are supported. If not, the PMCF plan describes how identified gaps can be closed. This might involve gathering clinical data. Examples of clinical data sources include:

- **Literature screening** which is one of the easiest methods of collecting clinical data. The PMCF plan should include a specific and objective research question and there should be a detailed literature search protocol. Reviewing case reports is a good way of identifying possible off-label use or misuse.
- **Post-market studies** can have different designs, such as extended follow-up of a pre-market investigation, a new clinical investigation, or a retrospective study. The PMCF plan should include the proposed study design, sample size, endpoints, inclusion/exclusion criteria, and a statistical rationale. Evidence from post-market studies is usually expected for implantable devices and class III devices.
- **Manufacturer or national public registries** on the device or the device group can be a good source of real-world clinical evidence. If a new registry is initiated, the PMCF plan should include a description of the registry and a preliminary specification of the expected quantity and quality of the data. A new, manufacturer-initiated registry has the advantage of being device-specific but will not contain historic data and will take time to accumulate data on a large number of patients over a long period. However, an existing national registry can be very useful if it contains historic data on similar devices from a large patient population, but has the disadvantage of not being device-specific.
- **Commercial data sets collected from electronic health records** are provided by companies that gather, process, and analyse health data from international and local markets. These data sets can include information about patient feedback, product performance, or competitors, among others.
- **Surveys,** especially when distributed online, can be good way of quickly reaching large numbers of patients or healthcare professionals. Like post-market studies, user surveys should be based on a predefined endpoint and statistical rationale.
- **Social media listening** allows for monitoring of patients' opinions on a given device as stated publicly through social media or other online means.[6]

All of these tools can be used to collect post-market data, but a certain level of clinical evidence is required depending on the device class, risk profile, and marketing history.

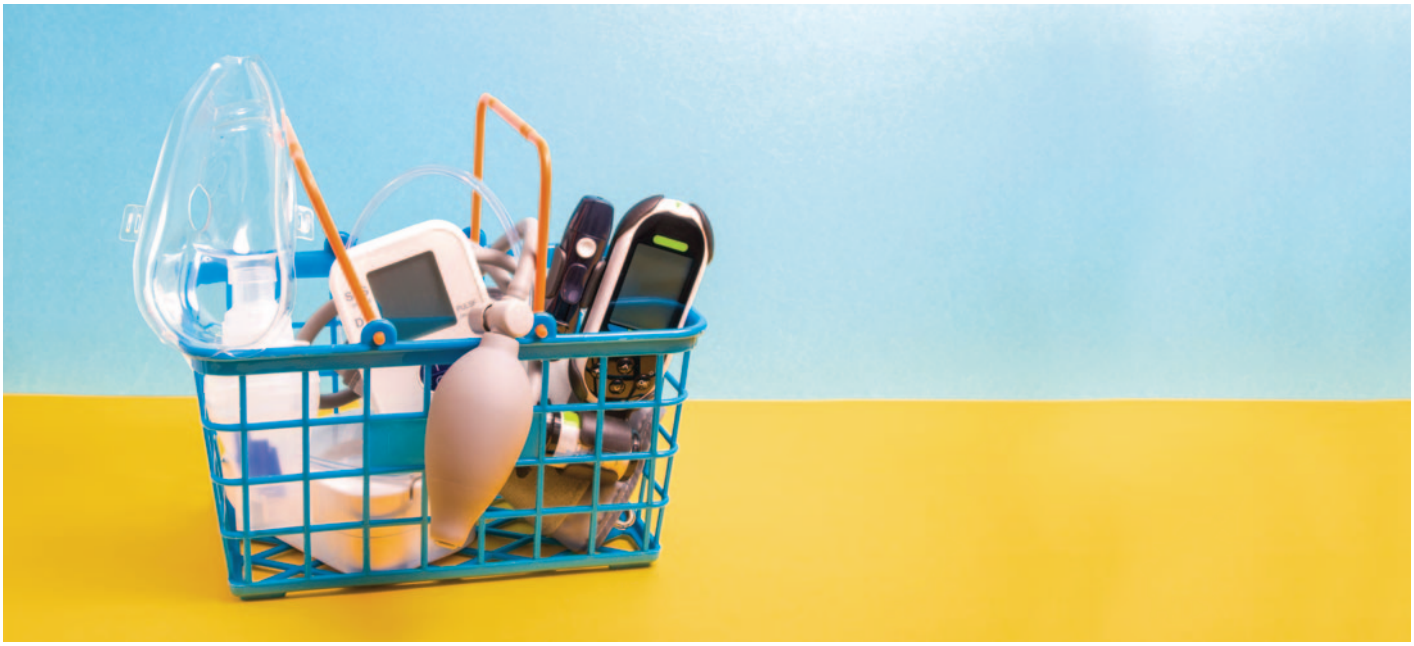
## What is "sufficient clinical data"?

Clinical data is information concerning safety or performance that is generated from the use of a device. This information can be sourced from clinical investigations of the device or equivalent devices, published peer reviewed literature about the device or equivalent devices, or clinically relevant information from PMS – especially PMCF.[7]

Clinical data is needed to:

- Confirm compliance with the applicable general safety and performance requirements (GSPRs) according to MDR Annex I.[1]
- Evaluate undesirable side effects and the acceptability of the benefit-risk ratio.

The clinical evaluation includes a thorough and objective assessment of both favourable and unfavourable clinical data that forms the clinical evidence for a device.[8] PMCF is required for all devices (new and legacy), but, current guidelines focus on legacy devices as this affects all manufacturers. However, MDR 2017/745 is often vague on when clinical data are considered "sufficient". To rectify this situation, the MDCG endorsed a guidance document in accordance with Article 105 of the MDR[9]: MDCG 2020-6 "Regulation (EU) 2017/745: Clinical evidence



needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC – A guide for manufacturers and notified bodies".[10]

This guideline sets out the clinical data requirements for a legacy device to demonstrate conformity with the MDR.

> Legacy devices are existing devices that have already been placed on the market under EU Directive 93/42/EEC on MDD or Directive 90/385/EEC on Active Implantable Medical Devices (AIMDD) before the MDR came into force.

The MDR defines clinical evidence as the "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". However, "sufficient" is not defined in the MDR. MDR Article 61 also mentions that conformity with the relevant GSPR shall be based on sufficient clinical evidence.[1] Therefore, "sufficient clinical evidence" is understood as "the present result of the qualified assessment which has reached the conclusion that the device is safe and achieves the intended benefits".[1] It is important to note that clinical evaluation is a process where this qualified assessment has to be done continuously.

The MDCG 2020-6 (Appendix III) develops the concept of a hierarchy of clinical evidence, ranked roughly in order from strongest to weakest; variations may apply depending on the device for which GSPR evidence is required and the quality of individual data sources.[10]

The strongest evidence are the results of high-quality clinical investigations covering all device variants, indications, patient populations, duration of treatment effect, etc. On the contrary, the weakest evidence are pre-clinical and bench testing / compliance to standards. (See Box 4 on p. 46.) Class III legacy and implantable legacy devices are technologies that are not well-established and should have at least Level 4 clinical data. Well-established technologies may be able to confirm conformity with GSPRs using cumulative evidence from Levels 5 to 12; they cannot rely only on complaints and vigilance data.

Well-established technologies have to meet the following criteria:

- relatively simple, common and stable designs with little evolution;
- their generic device group is known to be safe and has not been associated with safety issues in the past;
- well-known clinical performance characteristics and their generic device group are standard of care devices with little evolution in indications and the state of the art;
- a long history on the market.[10]

## Practical considerations

Medical writers are often involved in planning PMCF activities. Table 1 describes different fictional medical devices and examples of how clinical data might be collected.

In conclusion, the MDR brought about new post-market clinical follow-up (PMCF) requirements for medical devices and a more active approach is now required. There are several ways of fulfilling this requirement, such as user surveys, data collection from registries, or PMCF studies, web listening and commercial electronic health records databases. All planned activities are documented in the PMCF plan, and the results of these activities need to be presented in the PMCF report without duplicating the information that will subsequently be presented in the CER.

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## Disclaimers

The opinions expressed in this article are the authors' own and not necessarily shared by their employers or EMWA.

## Disclosures and conflicts of interest

The authors declare no conflicts of interest.

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2. Collada Ali LC, Friedrich KJ. First

*Table 1. Examples of PMCF activities per device type*

| Device description | PMCF activities suggested |
|---|---|
| **An implantable device with new technology:** This is a class III device used in cardiovascular surgery in combination with pacemakers. The device was recently CE-marked. The clinical evidence derives from a pre-market clinical investigation with a follow-up of 36 months. | **Example 1: Extended follow-up of the pre-market clinical investigation** As an implantable device used in cardiovascular surgery, notified bodies will expect a longer follow-up (e.g., up to 5 years) to provide evidence on the long-term safety. |
| | **Example 2: Manufacturer-initiated registry** PMCF is a continuous process. Once a registry has been set up, long-term data collection is possible. |
| **Well-established device (First example)** A common example of a well-established device is a prosthesis (hip, knee, etc.) which has been on the market for more than 20 years. | **Example 1: Local and international registries** There are many registries which collect data on all implanted prostheses and produce yearly reports summarizing those data. These are a real-world means of analysing performance and safety of a particular prosthesis. |
| | **Example 2: Social media listening** Patients may express their views, good and bad, on social media after having a prosthesis implanted. Web listening may help in getting patients' opinions on a given device. |
| **Well-established device (Second example)** Screws and plates are typical examples of well-established technologies mentioned in the MDR. | **Data collection from electronic health records** Manufacturers can pay for electronic health records to receive data sets about adverse events, patient feedback data, social media reporting, etc. |
| **Low-risk device** An example of a low risk device is a sterile wound dressing. | **Example 1: User survey** Inviting patients and health care professionals to give feedback by completing an online survey. |
| | **Example 2: Social media listening** Users may express their views on social media. |

experiences writing summaries of safety and clinical performance for medical devices. Med Writ. 2020;29(4):62–5
3. European Commission website. Medical Devices – Dialogue between interested parties. [cited 2022 March 27]. Available from: https://ec.europa.eu/health/md_dialogue/mdcg_working_groups_en
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6. Tecante K. Social media in the medical device industry as a tool for post-market surveillance. Med Writ. 2021;30(1):66–8.
7. Article 2 (48) Medical Devices Regulation 2017/745 [cited 2022 March 27]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745
8. Article 2 (51) Medical Devices Regulation 2017/745 [cited 2022 March 27]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745
9. Article 105 Medical Devices Regulation 2017/745 [cited 27.03.2022]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745
10. Medical Device Coordination Group (MDCG). MDCG 2020-6. Regulation (EU) 2017/745:Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC. A guide for manufacturers and notified bodies. April 2020 [cited 2022 March 27]. Available from: https://ec.europa.eu/docsroom/ documents/40904

| Pros | Cons |
|---|---|
| The previous study protocol, including endpoints and inclusion/exclusion criteria, can be used to develop a follow-up study. This requires less effort to set up than a new clinical investigation. | The longer the study the more likely it is that patients will be lost to follow-up which can affect the validity of the results. |
| Registries are one of the best ways of continuously collecting real-world clinical data. | Initiating a registry requires time and money, and appropriate endpoints. The register needs to be well maintained to generate high-quality data. |
| Registries contain an impressive amount of data and represent real-life cases on all prostheses, including competitors' devices. This is useful when comparing safety and performance data across different devices and over the long term. | Different registries may present data in different ways and formats and analysing all data together may be challenging. Annual reports are created for some registries. However, not all registries are publicly accessible. |
| These data are not influenced by the manufacturer. However, negative results are likely to be reported more frequently than positive results. | Data can be difficult and cumbersome to collect. Continuous monitoring is needed. May not be easy to analyse all data together. A per case analysis may be needed. |
| Data from scientific literature or from clinical investigations is often limited for these devices. Electronic health records are an option to collect safety and performance data for devices with a long market history. | Unambiguous identification of a device may be difficult before unique device identifiers (UDI) have been adopted. Data sets have to include information relevant to the safety and performance parameters of a device. This might not be possible depending on the device and the information available. |
| A well-structured online survey can quickly generate useful data. | Not all users will complete the survey so data may be incomplete and not representative of all users. |
| Data are supposedly unbiased as they are not directly requested by the manufacturer. However, negative results are likely to be reported more frequently than positive results. | Continuous monitoring is required. Unsolicited information can be difficult to collate and analyse. If the device is low risk, and also well-established, there may be very few comments. |


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