Medical device launch is surmounted by many pitfalls, which a medical device has to undergo at the time of trial lifecycle. The success of this launch greatly depends on satisfactory data obtained during clinical trials. Though clinical evidence/data is an essential component for determining premarket conformity assessment process for demonstrating conformity to essential requirements, it is yet again surrounded by many limitations in the premarket phase. These restraints could be due to length of time of pre-market clinical investigations, number and relative mix of subjects and investigators involved in investigation, controlled setting versus full range of clinical conditions that has come across in general medical practice.

After undergoing several hurdles a medical device is on shelf, thereby conforming to essential safety standards and requirements that include an acceptable benefit/risk ratio. Even after medical device launch, one can’t be sure of its perfect adherence to expected standards which has its base in data gathered from pre market phase. The level to which data is gathered does not necessarily enable the manufacturer to detect rare complications or problems, which becomes only apparent after wide-spread or long term use of the medical device. So here post-market surveillance plan becomes the only key for identification and investigation of residual risks associated with the use of medical device placed on the market by use. Therefore, systematic Post-Market Clinical Follow-up (PMCF) studies are an essential tool in assessment of residual risks associated with any medical device.

By the use of post-market surveillance and PMCF studies manufacturer does obtain some kind of clinical data, but this is not intended to replace any kind of premarket data necessary to demonstrate conformity with the provisions of the legislation. The PMS & PMCF data is however critical for updating clinical evaluation during the life-cycle of medical device and ensuring long term safety and performance of devices after they are placed on the market. PMCF studies have become an accessible option in post-market surveillance and effectively add on to risk management process.

1.0 Circumstances where a PMCF study is indicated

After a proper premarket clinical evaluation, decision to conduct PMCF studies can be taken for identification of any possible residual risks and/or if there is any ambiguity on long term clinical performance that can impact the benefit/risk ratio. PMCF studies can review issues like long-term performance and/or safety, the occurrence of clinical events (e.g. delayed hypersensitivity reactions, thrombosis), events specific to defined patient populations, or the performance and/or safety of the device in a more representative population of users and patients. There are certain circumstances which can justify where PMCF studies can be included as stated below: 

- Innovation: eg: - if the design of the device, materials/substances used, operating principles, technology or the intended medical use are new.

- Significant changes have been made to medical device or to its intended use for which premarket clinical evaluation and recertification has already been done.
• Medical device confers significant related risk. E.g.: - based on its design, materials, components used, invasive property and clinical procedures used.

• Use of medical device in:
  - anatomical locations having high risk
  - high risk target populations (E.g. pediatrics, elderly)
  - severity of disease/treatment challenges
  - previously unstudied subpopulations which may show different benefit/risk-ratio (E.g. hip implants in different ethnic populations)

• If the medical device have questions
  - of ability to generalize clinical investigation results.
  - unanswered on its long-term safety and performance.
  - results from any previous clinical investigation, including adverse events or from post-market surveillance activities.

• Continued validation is required in cases of discrepancy between reasonable premarket follow-up time scales and the expected life of the medical device.

• There are risks identified from the literature or other data sources for similar marketed devices.

• Medical device has interactive properties with other medical products or treatments.

• Verification of safety and performance of device is essential when exposed to a larger and more varied population of clinical users.

• If there is an emergence of any new information on safety or performance of the medical device.

• Where CE marking was based on equivalence.

PMCF studies may not be required or essential when the medium/long term safety and clinical performance are already known from previous use of the device or where other appropriate post-market surveillance activities would provide sufficient data to address the risks. [1]

2.0 Elements of a PMCF study

PMCF studies are done on device with its intended purpose/use as per instructions for use. It is imperative that studies involving PMCF should be in accordance to applicable laws and regulations and must involve
appropriate methodology and follow guidance and standards. Also, PMCF studies should be outlined as a well designed investigation plan or study plan, and, as appropriate, include noticeably stated research questions, objectives and related endpoints; design which is scientifically sound with suitable basis and statistical analysis plan; conduct plan as per proper standards; data analysis plan for drawing correct conclusions. \[1\]

The PMCF plan needs to be included in the Post-Market Quality Assurance plan, as presented for the review of the Notified Bodies prior to the CE-Marking. In case the plan for a PMCF is not included, a strong argument needs to be present, to justify why a PMCF is not needed for the Medical Device.

For conducting studies, using CE-marked medical devices, for the indications / purpose it has been approved for, no notification is needed to the competent authorities. \[1\] For cases like a comparative study wherein two medical devices are used, one CE-marked and another non-CE-marked, if the study is to use the CE-marked device within its approved indication, no notification would be needed, but for the non-CE-marked device the competent authority’s approval would be required.

There are multiple models for gathering PMCF data, and for example if the chosen model is a new clinical investigation, wherein the medical device is used within its approved purpose, these clinical investigation still needs to follow the established guidelines for good clinical practices and the guidelines of Annex X of the Medical Device Directive 93/42/EEC.

Additionally the important factor is the approval from Ethics Committees. For PMCF studies, approval from Ethics Committees is mandatory, from all the countries where the study is to be conducted, before initiating the study. It is advised to approach the Regional Ethics Committees (RECs) first, if not, other nationally recognized Ethics committees or local ECs who are expert in the particular area of medical device’s application.

The PMCF plan, data collected and its analysis comprise an essential element for review by the notified bodies and competent authorities, in their future audits. The adverse event reporting requirements, however, will be based on the post-market surveillance guidelines, in place of those listed in the section 2.3.5 of Annex X of Medical Device Directive 93/42/EEC. \[1\]

### 3.0 Objectives of PMCF studies

PMCF study should have clear objective and address the identified residual risks and be devised to answer one or more specific questions that relates to clinical safety or clinical performance of the device. A formal hypothesis should be clearly expressed. \[1\]
4.0 **Design of PMCF studies**

Design of PMCF studies should be in such a way that addresses the objective of the study clearly. Designs may change depending on the objective, study hypothesis research question and endpoints and be scientifically sound for allowing valid conclusions to be drawn. The PMCF study can follow several methodologies like: a new clinical investigation; review of data derived from device registry and review of relevant retrospective data from patients previously exposed to the device. There has to be an accurate plan for describing design and methodologies of stated objectives. The clinical investigational plan/study plan should identify basic elements and where needed minimum justify the study population (corresponding to the CE-mark scope), inclusion/exclusion criteria, rational behind and justification of chosen study including use of control groups (randomized or not), selection of sites & investigators, objectives of study and related study endpoints & statistical considerations, subject number, follow up period of patient, data to be collected, analysis plan that includes any interim reporting where appropriate to ensure continuous risk management based on clinical data and criteria for termination of the study, ethical considerations if any, quality control methods. However, these points may not be applicable in a retrospective data review.\(^\text{[1]}\)

5.0 **Implementation of the PMCF study, analysis of data and conclusions**

The PMCF study should be executed with sufficient control measures in assuring compliance with the clinical investigation or study plan; include data analysis with drawn conclusions as per analysis plan having expertise in the same and final report must be presented with conclusions that relates to original objective and hypothesis.\(^\text{[1]}\)

6.0 **Use of PMCF study data**

Data and conclusions obtained from PMCF study are used to provide clinical evidence for clinical evaluation process. This can result if there is a need to reassess if the device continues to abide by essential requirements. This kind of evaluation may result in corrective actions, like for example if there is any change in labeling or instructions for use, change in manufacturing process, device design changes if any or public health notifications.\(^\text{[1]}\)

7.0 **The role of the notified body in PMCF**\(^\text{[1]}\)

Notified Body (NB):-

- Audits quality system of manufacturer and aptness of manufacturer’s general post-market surveillance procedures and plans, including plans for PMCF, as pertinent.
• Verifies that PMCF as part of the overall clinical evaluation is conducted by or on behalf of the manufacturer by appropriately competent assessors.

• Verifies that clinical investigations conducted as part of PMCF plans are conducted in accordance with the relevant provisions of Annex X (as per Article 15.8 of 93/42/EEC), related guidance and relevant standards.

• Verifies that manufacturer has suitably considered for need of PMCF as part of PMS based on residual risks including those identified from the results of the clinical evaluation and from the characteristics of the medical device in accordance with section 5 of the guidance.

• Verifies that PMCF is conducted when clinical evaluation was based exclusively on clinical data from equivalent devices for initial conformity assessment and that PMCF addresses the residual risks identified for the equivalent devices.

• Assesses the suitability of justification presented by the manufacturer for having not conducted specific PMCF plan as part of PMS and seeking appropriate remedy where there is no valid justification.

• Assesses the appropriateness of PMCF plan that is proposed that is showing manufacturer’s stated objectives and addresses the residual risks and issues of long term clinical performance and safety identified for that specific device.

• Verifies that PMCF data collected by the manufacturer is favorable or unfavorable and is actively being used in updating clinical evaluation (as well as the risk management system).

• Considers whether data obtained from PMCF should be sent to NB between scheduled assessments activities (e.g. surveillance audit, recertification assessment) for specific device under question.

• Considers a suitable time point for medical device to give certification after assessment by NB or specific conditions related to certification and subsequent follow up. (This decision is based on residual risks and clinical evaluation report which is presented at the time of initial assessment. Also, the need for manufacturer to submit interim reports between certification reviews, of the clinical data generated from the PMCF and post-market surveillance system).
8.0 Process by Notified Bodies

- **NB Clinical Strategy Review**
  - Manufacturer evaluates all relevant available Literature
  - Manufacturer determines if sufficient clinical evidence already exists to support CE Marking or is a Clinical Investigation is required
  - Manufacturer submits Clinical Evaluation Plan to NB
  - NB conducts Clinical Review based on Plan

  - **Literature Review**
    - NB provides feedback on the manufacturers’ conclusion on their clinical data

  - **Clinical Investigation**
    - NB provides feedback on proposed Clinical Investigation Plan

  - Manufacturer attains a High Level of Confidence

  - Manufacturer completes the final Clinical Evaluation Report based on analysis of all relevant data including from Literature, Investigation and Experience

  - Manufacturer submits full Clinical Evaluation Report to NB as part of their normal Technical/Dossier Review

  - NB conducts a full Technical/Dossier Review to determine compliance to the Directive. If consistent with above expectations, process would be streamlined. If certified by NB, the manufacturer can then affix CE Marking.
9.0 Challenges of PMCF study

- Device marketed is new and not much data is available from PMS Studies.

- Medical device registries collect data from patients who have been exposed to particular devices. Device PMS possess unique set of challenges related to diversity and complexity of these medical devices in terms of nature of product development, technology behind it, and relatively short product life cycle.

- Device registries often include data for users of the device and not for non-users. This may be enough for within device comparisons and not sufficient for device vs. non-device comparisons.

- Disease registries may include users of specific device in question but number of those devices may be too small and not representative.

- As compared to drugs, devices lack unique device identifiers (UDI), which is a major impediment for safety monitoring, thus compromising patient safety.

- Ethics committee approval is essential to evaluate the safety and efficacy of medical device on which PMCF study is needed, not having enough information it may be difficult for EC as well.

- Patients participating in study might not meet eligibility criteria and not in a position sometimes to give informed consent.

- Manufacturer’s vigilance system may not be well equipped or functioning for giving systematic access to notified bodies, healthcare professionals and patients in reporting of any adverse events and take necessary corrective actions.

- For device, to be marketed in other countries, Manufacturer has to satisfy and pass applicable regulatory requirements in those countries and this becomes complicated if device manufacturer has limited or no access in those countries. For this selecting right partner becomes very important who has presence in respective locations.

- Manufacturer should have sound design plan for PMCF study as per appropriate standards. Lack of clear objectives, endpoints and research questions including indentifying residual risks hampers PMCF studies.
• Risk management plays a crucial role in pre and post market phases of medical device. In adequacy at this level poses a serious risk. This shortage can be in terms of no proper personnel for carrying out the risk management plan, lack of proper documentation and file in documenting data gathered thereby hindering out to carry effective PMCF study through which any kind of residual risk can be measured.

10.0 Conclusion

Though clinical evidence is an essential element of premarket conformity assessment process, there are limitations intrinsic to premarket clinical investigations. Having said that, the length of data that can be collected in premarket phase does not facilitate finding of infrequent complications or problems associated which can only become obvious after extensive usage. Also, they don’t allow finding of long term performance issues. Hence suitable post market surveillance programmes from manufacturer’s quality point of view are needed for identification and investigation of risks associated with use of medical device placed on the market. Moreover, not only effective post market surveillance systems are needed from manufacturer’s side but also well defined strategy associated with post market surveillance has to be in place for each medical device range. PMCF plays an exact role in defining undefined objectives and strategies by means of clinical studies and registries. It is left on manufacturer’s to decide use of PMCF with a specific criteria and purpose. Need for PMCF arises when medical devices are assessed through their equivalent nature and in cases of devices where identification of possible emerging risks and long term safety evaluation and performance remains critical.

References


3. Donawa M; US and European Postmarket Clinical Data Requirements; 2005; 36-38

This information does not constitute a written advisory opinion of the Author, but rather is official information available through up to date literature survey. This information does not necessarily represent the formal position of MakroCare MedTech, and does not bind or otherwise obligate or commit the MakroCare MedTech to the information presented.