IMDRF International Medical Device Regulators Forum

PROPOSED DOCUMENT

Title: Post-Market Clinical Follow-Up Studies

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Preface

The document herein was produced by the International Medical Device Regulators Forum (IMDRF), a voluntary group of medical device regulators from around the world. The document has been subject to consultation throughout its development.

1.0 Introduction

While clinical evidence is an essential element of the premarket conformity assessment process to demonstrate conformity to Essential Principles, it is important to recognise that there may be limitations in the clinical data available in the premarket phase. Such limitations may be due to, for example, the duration of premarket clinical investigations, the number of subjects and the study sites involved in an investigation, the relative homogeneity of subjects and investigators and the control of variables in the setting of a clinical investigation versus use in the full range of conditions encountered in routine use. Also, for some devices based on scientifically well-established technologies, it may be important to recognise that there may be limitations in the applicability of clinical data from comparable devices to the device in question.

It is appropriate to place a product on the market once conformity to the relevant Essential Principles, including a favorable risk/benefit ratio, has been demonstrated. Complete characterization of all risks and potential benefits may not always be possible or practicable in the premarket phase. Therefore, there may be uncertainties (such as rare adverse events, potential benefits, long-term safety, clinical performance and/or effectiveness,) that should be addressed in the post-market phase using one or more systematic post-market clinical follow-up (PMCF) studies. PMCF studies are not intended to replace the premarket data necessary for market authorization.

PMCF studies are one of several options available in a post-market surveillance program and contribute to the risk management process.

2.0 Scope

This document is intended to provide guidance on the design, implementation and appropriate use of PMCF studies.

This document provides guidance in relation to:

i) the circumstances where a PMCF study is indicated;

ii) the general principles of PMCF studies involving medical devices;

iii) the design and implementation of PMCF studies; and

iv) the use of information from PMCF studies

For clinical evaluation for the purposes of regulatory decision, refer to IMDRF MDCE WG/ N55FINAL:2019 *Clinical Evidence – Key definitions and Concepts,* IMDRF MDCE WG/N56FINAL:2019 *Clinical Evaluation,* IMDRF MDCE WG/N57FINAL:2019 *Clinical Investigation*.

This document does not apply to *in vitro* diagnostic devices.

3.0 References

IMDRF Documents:

IMDRF GRRP WG/N47 FINAL: 2018—Essential Principles of Safety & Performance of Medical Devices *and IVD Medical Devices*

IMDRF MDCE WG/ N55FINAL:2019 *Clinical Evidence – Key definitions and Concepts*

IMDRF MDCE WG/N56FINAL:2019 *Clinical Evaluation*

IMDRF MDCE WG/N57FINAL:2019 *Clinical Investigation*

IMDRF Registry WG/N33FINAL:2016 *Principles of International System of Registries Linked to Other Data Sources and Tools*

IMDRF Registry WG/N42FINAL:2017 *Methodological Principles in the Use of International Medical Device Registry Data*

IMDRF Registry WG/N46 FINAL: 2018 *Tools for Assessing the Usability of Registries in Support of Regulatory Decision-Making*

GHTF Documents:

SG1/N065:2010 *Registration of Manufacturers and Other Parties and Listing of Medical Devices*

SG1/N44:2008 *The Role of Standards in the Assessment of Medical Devices*

International Standards:

ISO 14155: 2020 *Clinical investigation of medical devices for human subjects*, *Good clinical practice*

ISO 14971: 2019 *Medical devices -Application of risk management to medical devices*

Others:

Agency for Healthcare Research and Quality *Registries for Evaluating Patient Outcomes: A User's Guide*

4.0 Definitions

Clinical data: Safety, clinical performance and/or effectiveness information that ~~are~~is generated from the clinical use of a medical device.

Clinical evaluation: A set of ongoing activities that use scientifically sound methods for the assessment and analysis of clinical data to verify the safety, clinical performance and/or effectiveness of the medical device when used as intended by the manufacturer.

Clinical evidence: The clinical data and its evaluation pertaining to a medical device.

Clinical investigation: Any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety, clinical performance and/or effectiveness of a medical device.

Post-market clinical follow-up study: A study carried out following marketing authorization intended to answer specific questions (uncertainties) relating to safety, clinical performance and/or effectiveness of a device when used in accordance with its approved labelling.

5.0 Circumstances Where a PMCF Study May Be Indicated

When considering the overall benefit-risk profile of a device for market authorization, uncertainties may remain regarding the extent of potential benefits and residual risks of the device. PMCF studies can be used to collect additional clinical data to address the remaining uncertainties about a device.

In some jurisdictions, PMCF studies may also be appropriate to address new concerns arising from post-market adverse event trends, information from the literature, signals from adverse event reports, active surveillance program or other sources.

Uncertainties in the benefit-risk profile of a device are more likely to exist when dealing with the following:

- ***Unanswered questions of long-term safety, ~~and~~ clinical performance and/or effectiveness***. Long-term safety, clinical performance and/or effectiveness of a specific aspect of a device may be difficult to assess in a premarket study as it may be necessary to collect data over several years in order to fully establish the long-term safety, clinical performance and/or effectiveness of the device. Additionally, unanswered questions about long-term safety, clinical performance and/or effectiveness of the device may arise from other information, such as:
    - ***results of existing clinical investigations;***
    - ***adverse events identified from post-market surveillance activities;***
    - ***interaction with other medical products or treatments;***

- ***Novel technologies or new intended use.*** New technological characteristics, e.g., the design, the materials, the principles of operation are novel; or extending/expanding intended use of existing technologies, e.g., new indication or new patient population;

- ***Higher-risk device and use scenarios.*** Higher risk anatomical locations; or higher severity of disease/treatment challenges;

- ***Uncertainties in generalizing clinical investigation results;*** Generalizing results from study populations to other populations, e.g. from adults to children, from an ethnicity to others. Generalizing results from other jurisdictions to intended jurisdictions.

- ***Devices approved with clinical data from comparable devices.*** For devices based on scientifically well-established technologies that have been approved with clinical data from comparable devices and/or preclinical data, it may be appropriate for some of the clinical data collection to occur post-market.

- ***Emergence of new information relating to safety, clinical performance and/or effectiveness.*** When unexpected or unexplained serious adverse events occur after a device is marketed, or if there is a change in the nature (e.g., severity) or an increase in

the frequency of expected serious adverse events, PMCF studies may be conducted to evaluate the potential association of the safety signal and the device.

- ***Urgent market access in public health emergencies.*** In event of public health emergencies (e.g., a pandemic), considerations of benefit-risk profiles of some devices may be different. Expedited market access may be granted with some data generation to occur post-market.

- ***Rare anticipated adverse events.*** Rare anticipated adverse events (e.g. stent thrombosis of the coronary stent) may be difficult to assess in a premarket study but could potentially be identified using large datasets; therefore, it may be necessary to assess the rare adverse events as part of a PMCF plan;

- ***Effectiveness for a known risk***. Mitigations may be necessary for known safety risks associated with the use of the device. Confirmation of the adequacy of the mitigation may be evaluated post-market.

PMCF studies may not be necessary in cases where the medium/long-term safety, clinical performance and/or effectiveness are already known from previous use of the device or where other appropriate post-market surveillance activities would provide sufficient data to address the uncertainties.

6.0 Elements of a PMCF Study

PMCF studies are performed on a device within its intended use/purpose(s) according to the instructions for use. It is important to note that PMCF studies must be conducted according to applicable laws and regulations, ethical requirements and should follow appropriate guidance and standards.

The elements of a PMCF study should include:

- Clearly stated objective(s);
- Scientifically sound study design with an appropriate rationale and statistical analysis methods summarized in a study plan;
- Implementation of the study according to the plan, an interpretation of the results and appropriate conclusion(s).

6.1 The Objective(s) of PMCF Studies

The objective(s) of the study should be stated clearly and should address one or more remaining or newly developed uncertainties related to the safety, and clinical performance and/or effectiveness of the device. A formal hypothesis should be clearly expressed, with the acknowledgement that formal statistical hypothesis testing may not be necessary in some circumstances, e.g. descriptive studies.

6.2 The Design of PMCF Studies

The study should be designed to address the objective(s) of the study. The PMCF study can take several forms, for example:

- the extended follow-up of patients enrolled in premarket investigations;
- a new post-market clinical investigation;
- a review of data derived from a device registry; or
- a review of relevant retrospective data from patients previously exposed to the device.

For additional information on the design of clinical investigations, refer to *IMDRF MDCE WG/N57FINAL:2019:Clinical Investigation.* After a device has obtained market authorization, there may be more opportunities to address device safety, clinical performance and/or effectiveness questions using clinical experience data[1] collected or generated from routine use under ordinary care, with appropriate study designs. Examples of clinical experience data sources for PMCF studies are described in **Appendix A** (informative).

An appropriate study design should be scientifically sound to allow for valid conclusions to be drawn. Several factors should be considered during the design of the study, for example:

- Study setting should be clearly described, including the locations and selection of sites and investigators;
- Study population should be clearly targeted by providing inclusion and exclusion criteria, and the sources and methods for the selection of subjects;

1 In some jurisdictions, clinical experience data relating to patient health status and/or the delivery of health care under routine use is described in the term of "real-world data" (RWD),which can be collected from a variety of sources.

- The control/comparison groups (if any) should be clearly defined and justified;
- Sample size should be clearly stated and justified, if applicable;
- All variables/indicators/measures should be clearly defined, including outcomes/endpoints, adverse events, risk factors, confounding factors, and effect modifiers. For some PMCF studies, data are obtained from routine use in clinical practice. The sources of data and methods of assessment should be provided. Considerations for using clinical experience data for a PMCF study are described in **Appendix B** (informative);
- The duration of patient follow-up
- Potential sources of bias should be identified and evaluated; and related control methods should be discussed (potential biases in PMCF studies and controlling methods are described in **Appendix C** (informative)).
- Statistical analysis methods should be clearly described. Appropriate statistical methods should be considered to examine impact of potential factors, such as confounding factors, effect modification, or missing data, on the analysis results.

For PMCF studies that involve a treatment assignment, including randomization, the approach and procedures used for assigning treatment should be clearly described. If a case-control or cohort design is used, the exposure classification, choice of cases and controls including matching ratio, as applicable, should be described.

6.3 The Implementation of PMCF Studies

The study should be executed according to the study plan, and the collected data should be analysed and interpreted to draw the conclusion.

Some factors should be considered during the implementation of the study, for example:

- Data collection: validated measurement methods/instruments should be utilized, and heterogeneity of data should be considered and controlled;
- Quality control: investigator selection, training, inspection and supervision of the study should be performed to ensure quality;

- Results reporting and interpretation: a study report should be developed to demonstrate if conclusions relate back to original objective(s) and hypothesis/hypotheses.

7.0 The Use of Information from PMCF Studies

The data and conclusions derived from the PMCF studies are part of the post-market surveillance program and used as input to the clinical evaluation and risk management process. This may result in the need to reassess whether the device continues to comply with the Essential Principles. Such assessment may result in corrective or preventive actions, for example：

- changes to the labelling/instructions for use,
- changes to manufacturing processes,
- changes to the device design,
- public health notifications, or
- product removal.

In addition, clinical data/evidence generated from PMCF studies can be used to:

- become the part of premarket clinical evidence when applying for marketing authorization in other jurisdictions.
- derive objective performance criteria and performance goals;
- form control/comparison groups;
- serve as supplementary data supporting marketing authorization of next-generation or similar technologies.

APPENDICES

Appendix A: Examples of Clinical Experience Data Sources for PMCF Studies

Appendix A.

(Informative)

Examples of Clinical Experience Data Sources for PMCF Studies

PMCF studies can be designed to collect data from routine use in clinical practice. Such study designs range from practical/pragmatic investigations to various types of observational studies, including cross-sectional study, cohort study, case-control study. Some basic concepts and principles of the above study types are provided in the guidance document *IMDRF MDCE WG/N56FINAL:2019*.

Data generated from real-world clinical experience is an important data source that should be considered for PMCF studies. Clinical experience data provide valuable real world experience obtained in larger, heterogeneous and more complex populations, with a broader (and potentially less experienced) range of end-users (IMDRF MDCE WG/N56FINAL:2019). Examples of such data sources are listed below.

- **Patient-generated health data**: Data created, recorded or gathered by or from patients, family members or caregivers to help address a medical concern, i.e. health data collected via mobile and/or wearable devices.
- **Device Registry**: An organized system with a primary aim to increase the knowledge on medical devices contributing to improve the quality of patient care that continuously collects relevant data, evaluates meaningful outcomes and comprehensively covers the population defined by exposure to particular device(s) at a reasonably generalizable scale (e.g. international, national, regional, and health system).
- **Health Record / Medical Record**: Clinical data that are generated from routine clinical and medical practice and are maintained by professionals over-time.
- **Administrative data**: Administrative data can include claims, health insurance data, and other sources.
- **Survey Data**: Data collected by means of surveying healthcare professionals, customers and patients (e.g. preference testing).

Appendix B

(Informative)

Considerations for Using Clinical Experience Data for PMCF Studies

The PMCF study should be based on scientifically robust methods and approaches resulting in clinical evidence that is of sufficient quality to support its objective(s). Quality requirements for clinical experience data depend upon the application of the PMCF, such as the safety assessment and possible benefits mentioned in section 7.

Legal and ethical considerations

First and foremost, it is important that clinical experience data used for PMCF studies comply with national / regional legal requirements for data collection and handling (data protection). Personal information about patients should be treated as confidential and appropriate measures to protect personal information are taken during the collection and analysis of clinical experience data. Approval by an ethics committee and appropriate informed consent, if applicable, should be obtained before data collection. Essential information such as clinical data should also be available for regulatory bodies to verify and audit the data.

Considerations during the study design phase

When PMCF studies are designed to use clinical experience data from routine use under ordinary care, it is important to determine if the data can adequately address the study objectives. Considerations include:

- subject population needed for the study;
- key variables/data elements;
- appropriate length of follow-up;
- identification and usage information of devices; and
- information on potential confounding factors.

Considerations for clinical experience data quality

To support its use in a PMCF study and to ensure the quality of the data source, the following principles should be considered:

- Representation – whether the population within the data source adequately represents the target population;
- Completeness - the extent to which data elements used within analyses are consistently collected and captured.
- Accuracy – the extent to which data collected is an accurate reflection of the healthcare event – e.g., correct patient age, correct device, and correct procedure type.
- Consistency – the uniformity to which data sources follow the same processes and procedures for data capture, including harmonized data definitions and relative stability of the Case Report Form, or other data collection form with version control.
- Integrity – the extent to which medical devices are uniquely identified within the data source, and that the unique identifiers are consistently recorded – such that all procedures using a device can be identified and analysed.
- Reliability – the extent to which data elements are reproducible.

PMCF studies that collect data from existing data sources such as a device registry or medical records can be prone to bias and confounding. Therefore, appropriate study designs and statistical methods should be considered when analysing the data to help control the impact of bias and confounding (see Appendix C for more details).

Appendix C

(Informative)

Potential Biases in PMCF Studies and Controlling Methods

Bias is defined as the result of a systematic error in the design or conduct of a study. This systematic error results from flaws in either the method of selecting study participants or in the procedures for gathering relevant exposure and/or disease information. Consequently, the results of the study tend to be different from the true results.

Common types of bias and confounding in PMCF studies

In general, PMCF studies can be prone to bias and confounding. Examples of potential biases in PMCF studies include selection bias, information bias, attrition bias, non-response bias, volunteer bias, recall bias, and interviewer bias. Confounding is a distortion of the true association between the exposure and outcome of interest, and it occurs when the study groups differ with respect to other factors.

Methods of controlling bias in PMCF studies

Examples of methods to control bias and confounding in a PMCF study are listed below:

- Example methods to control bias:
  - Appropriate selection of study populations and definitive inclusion and exclusion criteria;
  - Randomization on group assignment and blinding during data collection and analysis, if applicable;
  - Use of validated and consistent survey instruments and measurements;
  - Standardized training of study staff;
  - Appropriate methods to avoid loss of follow-up, and to improve response rate and validity;
  - Selection of appropriate statistical methods, e.g. stratification analysis and sensitivity analysis.

- Example methods to control confounding:
  - Appropriate restriction, randomization, and matching on study populations;
  - Multivariate models with adjustment of confounding factors;
  - Mantel-Haenszel adjustment on outcomes.

For more information on ensuring the quality of the data collected in a PMCF study, consider use of the PICO method [2] for evidence-based outcome research, CONSORT[3] guideline for clinical investigations, STROBE[4] guideline for cohort study, case-control study, cross-sectional study and PRISMA[5] guideline for meta-analysis, or other scientific best practice as appropriate.

[2] PICO (Populations/People/Patient/Problem, Intervention(s), Comparison and Outcome) is a framework to format a well-focused clinical question and facilitate creating an effective search strategy for evidence. https://handbook-5-1.cochrane.org/
The PICO framework can be expanded to PICOTT, adding information about the type of question being asked and the best type of study design for that particular question.
[3] CONSORT (Consolidated Standards of Reporting Trials) is an evidence-based, minimum set of recommendations for reporting randomized trials. It offers a standard way to prepare reports of trial findings, facilitating their complete and transparent reporting, and aiding their critical appraisal and interpretation. http://www.consort-statement.org
[4] STROBE (Strengthening the Reporting of Observational studies in Epidemiology) is a checklist of items that should be addressed reports of observational study designs including cohort study, case-control study, cross-sectional study. https://strobe-statement.org
[5] PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) is an evidence-based, minimum set of items for reporting in systematic reviews and meta-analyses. http://prisma-statement.org