Draft For Comment Purposes (Not for Implementation)

Project of Guidance on Post-Market Clinical Follow-Up Studies

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Introduction

Purpose

The purpose of this document is to provide a guidance on planning to prepare and design post-market clinical follow up studies related collecting and submitting clinical data for medical devices, in order to investigate and assess the residual risks of devices placed on the market.
It also provides a guidance on:

- SFDA expectations for cases that require PMCF studies.
- Process of fulfilling the SFDA-PMCF obligations.
- Recommended format, contents, and design of the PMCF studies.

Scope

This guidance applies for medical devices manufacturers and authorized representatives (ARs) whom requested by SFDA to perform a further post-market clinical investigation for devices placed on the KSA market, in the following criteria:

- If their devices, identified at the premarket evaluation, associate with possible residual risks.
- If their devices trigger safety signals at the post-market phase and associate with insufficient clinical data at the long-term use of the device.

Background

SFDA/MDS has issued this guidance document in reference to Articles Thirty Five and Thirty Seven of the "Medical Devices Interim Regulation" issued by Saudi Food and Drug Authority Board of Directors decree No. (1-8-1429) dated 29/12/1429 H and amended by Saudi Food and Drug Authority Board of Directors decree No. (4-16-1439) dated 27/12/2017 stipulating that:

- The SFDA shall review adverse events reported to its NCMDR and take appropriate action to safeguard public health.
- The SFDA shall monitor the use of medical devices in the KSA and take the appropriate measures to ensure their proper installation and maintenance in respect of the safety of patients, users and other persons.

The current international practice to approve placing a medical device on the market is through providing a clinical evidence to demonstrate the conformity to essential requirements, including the assessment of the benefit-risk ratio. Nevertheless, it is important to recognize that the precondition of demonstrating the conformity assessment is a premarket element, which influence the decision of placing the medical device in the market. Yet, there might be certain situations, where the manufacturer fails to detect risks that only become visible after the long-term use of the device. For that reason, manufacturers should be obliged to have an appropriate post-market surveillance plan to investigate and assess the residual risks while the device is placed on the

market. This investigation aims to collect and accumulate real-world data that address the patients' safety and the device effectiveness at the post-market phase through systematic and appropriate post-market clinical follow-up studies.

1. Situations Need To Plan for Post-Market Clinical Follow-Up Studies

There are two situations that trigger a need to plan for post-market clinical follow-up studies:

1.1 Identifying a possible residual risk by a premarket evaluation.

The decision in these circumstances is evaluated at the pre-market phase, which is undertaken based on the identification of possible residual risks and/or uncertainty on long-term clinical performance that is susceptible to affect the benefit/risk ratio. These circumstances, and as clarified by the IMDRF guidelines, include, but not limited to, the following situations:

- innovation, e.g., where the design of the device, the materials, substances, the principles of operation, the technology or the medical indications are novel;
- significant changes to the products or to its intended use for which pre-market clinical evaluation and re-certification has been completed;
- high product related risk e.g. based on design, materials, components, invasiveness, clinical procedures;
- high risk anatomical locations;
- high risk target populations e.g. pediatrics, elderly;
- severity of disease/treatment challenges;
- questions of ability to generalize clinical investigation results;
- unanswered questions of long-term safety and performance;
- identification of previously unstudied subpopulations which may show different benefit/risk-ratio e.g. hip implants in different ethnic populations;
- continued validation in cases of discrepancy between reasonable premarket follow-up time scales and the expected life of the product;
- interaction with other medical products or treatments;
- verification of safety and performance of device when exposed to a larger and more varied population of clinical users;
- emergence of new information on safety or performance;
- when the device was approved based on equivalence.

1.2 Identifying a safety signal at the post-market phase and it is associated with insufficient clinical data at the long-term use of the medical device.

The decision in these circumstances is evaluated at the post-market phase, which is undertaken based on a triggering in the adverse events reporting and/or any other means of the post-market activities. In these situations, the SFDA post-market clinical evaluation team will take the responsibilities of evaluating the medical device in question, and in case there is insufficiency in the clinical data that facilitates withdrawing a clinical evidence, the team might request a PMCF studies that address the unanswered question(s) that may impact the device benefit/risk ratio. These circumstances include, but not limited to, the following situations:

- results from any previous clinical investigation, including adverse events or from post-market surveillance activities;

- risks identified from the literature or other data sources for similar marketed devices;
- risks that relate to the variations on the local behavior, and/or environmental parameters.
- SFDA may also request PMCF studies in situation that raise post-market questions, during the post market phase, with the purpose of:
- understanding the nature, severity, or frequency of suspected problems reported in adverse event reports or in the published literature.
- obtaining more information on the device performance associated with real-world clinical practice.
- addressing long term or infrequent safety and effectiveness issues for implantable and other devices for which the premarket testing provided limited information, and
- defining the association between problems and devices when unexpected or unexplained serious adverse events occur after a device is marketed

2. Clarification of the SFDA-PMCF Studies Process

This section aims to provide clarification for the steps undertaken by SFDA to identify the issue to be complemented with PMCF studies, and the SFDA expectations afterward. Following the issue identification, manufacturers and their ARs within the KSA will be responsible of conducting the study in a manner that address the unanswered question(s). Yet, recommendations on the appropriate study format, design, and type will be suggested in this guidance.

2.1 Issue identification

First, for the circumstances where a PMCF studies are needed during the pre-market evaluation, the decision will be taken during the pre-market approval process, considering the situations elaborated in section 1.1.

Secondly, SFDA may identify issues that are appropriate for PMCF studies at any point during the life cycle of a device, considering the circumstances provided in section 1.2. Such issues may be identified through a variety of sources including analysis of adverse event reports, a recall or corrective action, post-approval data, review of premarket data, reports from other governmental authorities, or review of scientific literature.

2.2 Team review for the PMCF studies issue

Whenever SFDA identifies a potential issue for a medical device that may warrant PMCF studies (either for the circumstances described in section 1.1 or 1.2), the case will be transferred into the post-market clinical evaluation section to make a final confirmation regarding whether the issue requires a PMCF studies. Next, the post-market clinical evaluation section head will be responsible of assigning the case to a team to review the issue in greater depth, considering the internal process of the clinical evaluation of medical devices, with the ultimate goal of making a recommendation to whether or not a PMCF studies order should be issued.

2.3 Issuance of PMCF studies order

When the post-market clinical evaluation section recommends conducting a PMCF studies for a specific issue, an order will be issued by the executive director of surveillance and biometric to target the corresponding manufacturer and/or its AR in Saudi Arabia. Such order should be dated, assigned a number (i.e. MD-PMCF####), and provide a clear description of the needed clinical evidence.

A manufacturer, on the other hand, must submit a PMCF plan within 30 days of receipt of the PMCF order, and commence the study not later than 15 months after the day on which SFDA issues the PMCF order. The expected elements of the PMCF plan will be described in section 3, and SFDA guidance entitled "Guidance on Requirements for Clinical Investigations of Medical Devices (MDS-G20)".

3. Elements of a Post-Market Clinical Follow-Up Study

It is important first to highlight that the PMCF studies are to be performed on a medical device within its intended use, and should follow the appropriate guidance and standards.

The elements of a PMCF study include:

- clearly stated objective
- a scientifically sound design with an appropriate rationale and statistical analysis plan
- a study plan
- implementation of the study according to the plan, with an analysis of the data and appropriate conclusion(s)

3.1 The objective(s) of post-market clinical follow-up studies

The objective(s) of the study should be stated clearly and should address the residual risk(s) identified and be formulated to address one or more specific questions relating to the clinical safety or performance of the device. A formal hypothesis should be clearly expressed.

3.2 The design of PMCF studies

PMCF studies should be designed to address the objective(s) of the study. The design may vary based on the objective(s) and should be scientifically sound to allow for valid conclusions to be drawn. The study design can take several forms, which might be in any of the clinical studies described in Table (2).

Table (2): Examples of clinical study designs that are appropriate to fulfill the PMCF studies design.

Type	Design
Randomized Clinical Trial	Prospective study comparing the effects of one or more intervention(s) against a control group. Subjects are assigned randomly to one of the study groups.
Prospective Cohort Study	A study in which the subjects in a defined population are followed prospectively in time to assess the occurrence of outcomes of interest as they occur. Such studies can include one or more groups defined in terms of their exposure to a device.
Retrospective Cohort Study	A study in which the subjects in a defined population are followed forward in time; however, unlike a prospective cohort study, the data records documenting the device exposure and outcomes have been collected in the past relative to the time when the study is initiated. Such studies can include one or more groups defined in terms of their exposure to a device.

Cross-Sectional Study	A study in which the presence or absence of an exposure and health outcome are assessed at the same point in time.
Registry-Based study	A review of data derived from a device registry.
Meta-Analysis	Systematic review that combines the results of several studies that address a set of related research hypotheses. This is normally done by identification of a common measure of effect size, which is modeled using a form of meta-regression of the published or unpublished study data.
Prospective & Retrospective Study	A hybrid cohort study in which data are collected both retrospectively and prospectively.
Case Control Study	Study in which subjects are identified on the basis of the presence of an outcome (cases) and compared to an appropriate comparison group. The proportions with the exposure of interest are compared.
Bench/Lab Study	A study that involves bench testing (e.g., wear testing, fatigue testing).
Animal Study	A study that involves animal testing (e.g., device or material implanted in animal).

3.3 The PMCF study plan

All PMCF studies should have a plan appropriate for addressing the stated objectives. The study plan should justify, for example, the patient population; inclusion/exclusion criteria; controls/control groups (where relevant); the selection of sites and investigators; the endpoints and statistical considerations; the number of subjects involved; the duration of the study; the data to be collected; study endpoints; the analysis plan including any interim reporting; and procedures/criteria for early study termination.

3.4 Implementation of the PMCF study, analysis of data and conclusion(s)

The study should:

- be executed with adequate control measures to assure compliance with the plan;
- include data analysis with conclusions drawn according to the analysis plan by someone with appropriate expertise; and
- have a final report with conclusions relating back to original objective(s) and hypothesis, and provide a clear clinical evidence to the upraised PMCF order.

4. The Use of Study Information

The data and conclusions derived from the PMCF study are used to provide clinical evidence to support the post-market surveillance program and input into the clinical evaluation 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, or public health notifications.

Annexes

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Annex (1): Definitions & Abbreviations

KSA	Kingdom of Saudi Arabia
IMDRF	International Medical Devices Regulators Forum
Clinical Data	The Safety and /or performance information that is generated from the use of a device.
Clinical Evaluation	The assessment and Analysis of clinical data pertaining to a medical device to verify the clinical safety and performance of the device when used as intended by the manufacturer.
Clinical Evidence	The Clinical data and the clinical evaluation report pertaining to a medical device.
Clinical Investigation	Any systematic investigation or study in one or more human subjects, undertaken to assess the safety or performance of a medical device.
Device Registry	An organized system that uses observational study methods to collect defined clinical data under normal conditions of use relating to one or more devices to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure and that serves predetermined scientific, clinical or policy purpose.
Adverse Device Effect ADE	events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition also includes any event resulting from use error or from intentional misuse of the investigational medical device.
Adverse Event AE	Means any malfunction or deterioration in the characteristics and/or performances of a medical device, including any inadequacy in its labelling or the instructions for use, or use error, which may compromise the health or safety of patients, users or third parties.
Audit	Means a systematic, independent and documented process for obtaining audit evidence and evaluating it objectively to determine the extent to which audit criteria are fulfilled.
Residual risk	Means the risk remaining after risk control measures have been taken.
Risk Management	Means the systematic application of management policies, procedures and practices to the tasks of analyzing, evaluating, controlling and monitoring risk.
Post-market clinical follow-up (PMCF) study	A study carried out following the pre-market approval 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.
Post-Market Clinical Follow-Up (PMCF) plan	The documented, proactive, organized methods and procedures set up by the manufacturer to collect clinical data based on the use of a pre-market approved 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. 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.

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