South African Health Products
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POST MARKET SURVEILLANCE AND POST-MARKET CLINICAL FOLLOW-UP STUDIES

This guideline is intended to provide recommendations to Manufacturers, Importers, Exporters, Distributors and Holders of Certificate of Registration (HCR) of medical devices .It represents SAHPRA current thinking on the safety, quality and performance of medical devices. It is not intended as an exclusive approach. The Authority reserves the right to request any additional information to establish the safety, quality and performance of a medical device in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used but these should be scientifically and technically justified. The Authority is committed to ensure that all registered medical devices will be of the required quality, safety and performance. It is important that applicants adhere to the administrative requirements to avoid delays in the processing and evaluation of applications. Guidelines and application forms are available from the office of the website.

Document History

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Contents

Glossary

Abbreviation/ Term	Meaning
Adverse Device Effect	An adverse event related to the use of an investigational medical device
Adverse Event	means any untoward medical occurrence or undesirable incident, that may occur in association with the use of a medical device which— (a) does not necessarily have a causal relationship with its use ; or (b) may occur due to its malfunction, its deterioration of safety, quality or performance or an error of its use;
as determined by the Authority	means as determined by the South African Health Products Regulatory Authority (SAHPRA) in a guideline as published from time to time;
Authorized Representative	means a natural person, resident in the Republic of South Africa, who— (a) has the written mandate to represent a manufacturer, distributor or wholesaler in the Republic; and (b) acts on behalf of a manufacturer, distributor or wholesaler, in whose name the licence in terms of section 22C(1)(b) of the Act or certificate of registration is issued;
Classification	The medical devices regulatory framework has a classification system for medical devices and IVDs, as per the regulations of Act 101 of 1965 South African risk classification as per classification guideline 8.05.
Clinical Data	Safety and/or performance information that are generated from the clinical use of a medical 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 for an IVD Medical Device	All the information that supports the scientific validity and performance for its use as intended by the manufacturer.
Clinical Investigation	Any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety and/or performance of a medical device.
Clinical Investigation Plan	Document that states the rationale, objective, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation.
Clinical Investigation Report	The document describing the design, execution, statistical analysis, and results of a clinical investigation.
Clinical Investigator	The individual responsible for the conduct of a clinical investigation who takes the clinical responsibility for the well-being of the subjects involved
Clinical Performance	The ability of a medical device to achieve its intended purpose as claimed by the manufacturer
Clinical Performance of an IVD Medical Device	The ability of an IVD medical device to yield results that are correlated with a particular clinical condition/physiological state in accordance with the target population and intended user.
Clinical Performance Study / clinical performance assessment	A study undertaken to establish or confirm the clinical performance of an IVD medical device.

	NOTE: This term is synonymous with 'clinical trial' and 'clinical study'.
Clinical Performance Study Protocol	Document that states the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical performance study
Clinical safety	freedom from unacceptable clinical risks, when using the device according to the manufacturer's Instructions for Use. *Note: In exceptional cases where an instruction for use is not required, the collection, analysis and assessment are conducted taking into account generally recognised modalities of use.*
clinical trial	means a study in or on human or animal subjects undertaken to assess the safety or clinical performance of the medical device;
Clinical use	use of a medical device in or on living human subjects. *Note: Includes use of a medical device that does not have direct patient contact.*
Device Registry:	An organised 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(s). *Note: The term "device registry" as defined in this guidance should not be confused with the concept of device registration and listing. (See GHTF SG1N065)*
essential Essential principles	means the requirements relating to the safety and performance characteristics of medical devices as determined by the Authority;
IN VITRO Diagnostic Medical Devices (IVDs)	Means a medical device, whether used alone or in combination, intended by the manufacturer for the in vitro examination of specimens derived from the body solely or principally to provide information for diagnostic, monitoring or compatibility purposes.
Medical device	any instrument, appliance, material, machine, apparatus, implant or diagnostic reagent- (a) used or purporting to be suitable for use or manufactured or sold for use in- (i) (i) the diagnosis, treatment, mitigation, modification, monitoring or prevention of disease, abnormal physical or mental states or the symptoms thereof; or (ii) (ii) restoring, correcting or modifying any somatic or psychic or organic function; or (iii) (iii) the diagnosis or prevention of pregnancy, and which does not achieve its purpose through chemical, pharmacological, immunological or metabolic means in or on the human body but which may be assisted in its function by such means; or (b) declared by the Minister by notice in the Gazette to be a medical device, and includes any part or an accessory of a medical device
PMCF plan:	The documented, proactive, organised methods and procedures set up by the manufacturer to collect clinical data based on the use of a registered 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.
Post-market clinical follow-up (PMCF) study:	A study carried out following the registration 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.
Residual Risk:	Risk remaining after risk control measures has been taken

1. 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 to the clinical data available in the pre-market phase. Such limitations may be due to the duration of pre-market clinical investigations, the number of subjects and investigators involved in an investigation, the relative heterogeneity of subjects and investigators and/or the controlled setting of a clinical investigation versus the full range of clinical conditions encountered in general medical practice.

A precondition for placing a product on the market is that conformity to the relevant Essential Principles, including a favourable benefit/risk ratio, has been demonstrated. The extent of the data that can be gathered in the pre-market phase does not necessarily enable the manufacturer to detect rare complications or problems that only become apparent after wide-spread or long-term use of the device. As part of the manufacturer's quality system, an appropriate post-market surveillance plan is key to identifying and investigating residual risks associated with the use of medical devices placed on the market. These residual risks should be investigated and assessed in the post-market phase through systematic Post-Market Clinical Follow-up (PMCF) study(ies).

Clinical data obtained from post-market surveillance and during PMCF studies by the manufacturer are not intended to replace the pre-market data necessary to demonstrate conformity with the provisions of the legislation. However, they are critical to update the clinical evaluation throughout the life-cycle of the medical device and to ensure the long-term safety and performance of devices after their placing on the market.

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

1.1 Purpose

This document is intended to be a guide for Manufacturers, Importers, Exporters, Distributors and Holders of Certificate of Registration (HCR) on how to carry out Post-Market Clinical Follow-up (PMCF) studies in order to fulfil Post-Market Surveillance (PMS) obligations.

Adverse events occurring during the course of a PMCF study must be reported similarly to other registered devices placed on the market as per SAHPGL-MD-03- Guideline for medical device adverse events

1.2 Scope

The objective of this document is to provide guidance on the appropriate use and conduct of PMCF studies to address issues linked to residual risks.

PMCF studies are an important element to be considered in PMCF or PMS plans. The principles for PMCF studies set out in this guidance are not intended to replace PMCF or PMS plans. They are or may be applicable to PMCF studies conducted for other purposes.

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 use of study data (for example to update instructions for use and labelling);

2. LEGAL PROVISION

a. Medical device Regulations Government Gazette (No. 40480)

3. International Standards

a. ISO 14155:2011 Clinical investigation of Medical Devices for human subjects
b. Good clinical practice
c. ISO 14971:2012 Application of risk management to medical devices
d. ISO 14155:2011 Clinical investigation of Medical Devices for human subjects

4. Circumstances where a PMCF study is indicated

Following a proper premarket clinical evaluation, the decision to conduct PMCF studies must be based on the identification of possible residual risks and/or unclarity on long term clinical performance that may impact the benefit/risk ratio.

PMCF studies may review issues such as 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.

Circumstances that may justify PMCF studies include, for example:

- 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. paediatrics, elderly;
- severity of disease/treatment challenges;
- questions of ability to generalise clinical investigation results;
- unanswered questions of long-term safety and performance;
- results from any previous clinical investigation, including adverse events or from post-market surveillance activities;
- 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;
- risks identified from the literature or other data sources for similar marketed devices;
- 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;
- where device regulatory approval was based on equivalence.

PMCF studies may not be required 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.

5. Elements of a PMCF study

Post-market clinical follow-up 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 and should involve an appropriate methodology and follow appropriate guidance and standards.

PMCF studies must be outlined as a well-designed clinical investigation plan or study plan, and, as appropriate, include:

- clearly stated research question(s), objective(s) and related endpoints;
- scientifically sound design with an appropriate rationale and statistical analysis plan;
- a plan for conduct according to the appropriate standard(s);
- a plan for an analysis of the data and for drawing appropriate conclusion(s).

5.1 **Objectives of PMCF 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 clinical performance of the device. A formal hypothesis should be clearly expressed

5.2 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), study hypothesis research question and endpoints and should be scientifically sound to allow for valid conclusions to be drawn.

PMCF studies can follow several methodologies, for example:

- the extended follow-up of patients enrolled in premarket investigations;
- a new 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.

PMCF studies should have a plan describing the design and methodologies appropriate for addressing the stated objectives. The clinical investigation plan/study plan should identify and where needed justify at a minimum:

- the study population (corresponding to the scope of the registered device);
- inclusion/exclusion criteria;
- rationale and justification of the chosen study design including use of controls/control groups (where relevant; randomised or not);
- the selection of sites and investigators;
- study objectives and related study endpoints and statistical considerations;
- the number of subjects involved;
- the duration of patient follow-up;
- the data to be collected;
- the analysis plan including any interim reporting where appropriate to ensure continuous risk management based on clinical data; and

- procedures/criteria for early study termination;
- ethical considerations;
- methods of quality control of data where appropriate.

The points above may not all apply to a retrospective data review

5.3 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 clinical investigation or study 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/hypotheses.

6. The use of study data

The data and conclusions derived from the PMCF study are used to provide clinical evidence for 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.

7. REFERENCES

The following related documents are referenced:

a. Clinical Performance Assessment of Medical Devices guideline

b. Medical Devices and IVDs Essential Principles of Safety & Performance

c. SAHPGL-MD-03- Guideline for medical device adverse events

8. VALIDITY

This guideline is valid for a period of 5 years from the effective date of revision . It will be reviewed on this timeframe or as and when required.