Botswana Medicines Regulatory Authority

Approved By: _____ _____

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Page	Changes made	Issue No	Process owner's name	Date

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1. Purpose

The intention and purpose of these guidelines is to provide guidance for clinical evaluation to those submitting applications for registration of Medical Devices.

2. Scope

This guideline provides guidance on how to conduct and document the clinical evaluation of a medical device as part of the conformity assessment procedure

3. Definitions and Abbreviations

3.1 Definitions

The following definitions shall apply:

3.1.1 **Adverse Effect**:

Any debilitating, harmful, toxic or detrimental effect that the medical device has been found to have or to be likely to have on the body or health of humans when such a medical device is used by or administered to humans.

3.1.2 **Adverse Event:**

Any event or other occurrence, that reveals any defect in any medical device or that concerns any adverse effect arising from the use thereof.

3.1.3 **Case–Control Study:**

Patients with a defined outcome and controls without the outcome are selected and information is obtained about whether the subjects were exposed to the medical device**.**

3.1.4 **Case Series:**

The medical device has been used in a series of patients and the results reported, with no control group for comparison.

3.1.5 **Clinical Data**:

Safety and/or performance information that is generated from the clinical use of a medical device

3.1.6 **Clinical Evaluation**:

The assessment and analysis of clinical data pertaining to a medical device to verify the clinical safety and performance of the medical device when used as intended by the product owner

3.1.7 Clinical Evidence

The clinical data and the clinical evaluation report pertaining to a medical device. Figure 1 shows how the need for clinical evidence drives the processes of data generation and clinical evaluation, which produce clinical data and clinical evidence, respectively

3.1.8 **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.

3.1.9 **Clinical Investigation Plan**

Document that states the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record keeping of the clinical investigation

3.1.10 **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.

3.1.11 **Clinical Performance**

The ability of a medical device to achieve its intended purpose as claimed by the product owner**.**

3.1.12 **Clinical Safety**

The absence of unacceptable clinical risks, when using the medical device according to the product owner's Instructions for Use

3.1.13 **Cohort Study**

Data are obtained from groups who have and have not been exposed to the medical device (e.g. historical control) and outcomes compared**.**

3.1.14 **Conformity Assessment**

The systematic examination of evidence generated and procedures undertaken by the product owner, under requirements established by the Regulatory Authority, to determine that a medical device is safe and performs as intended by the product owner and, therefore, conforms to the Essential Principles.

3.1.15 **Intended use/purpose**

The objective intent of the manufacturer regarding the use of a device, process, or service as reflected in the specifications, instructions and information provided by the manufacturer of the medical device

3.1.16 **In Vitro Diagnostic**

Means a medical device, whether used alone or in combination, intended by the manufacturer for the in-vitro examination of specimen derived from the human or animal; solely or principally to provide information for diagnostic, monitoring or compatibility purposes which includes but not limited to – reagents used for IVD purposes, calibrators, control chemicals, specimen receptacles, software and related instruments or apparatus or other articles and are used for the following test purposes; diagnosis; aid to diagnosis; screening; monitoring; predisposition; prognosis; prediction; determination of physiological status.

3.1.17 **Manufacturer**

A company that carries out at least one step of the manufacture of a medical device, which includes the responsible person and/or company that designs and/or manufactures a medical device with the intention of making the medical device available for use, under his/her/its name, whether or not such medical device is designed and/or manufactured by that person or on behalf of that person by another person(s).

3.1.18 **Manufacture (manufacturing)**

All operations of generating a medical device, including purchase of materials and components, production, quality control, packing, labelling, release, storage, and shipment.

3.1.19 **Medical device**

It means any instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material or other similar or related article -

a) intended by the manufacturer to be used, alone or in combination, for humans or animals for-
   i. diagnosis, prevention, monitoring, treatment or alleviation of disease;
   ii. diagnosis, monitoring, treatment, alleviation of or compensation for an injury;
   iii. investigation, replacement, modification or support of the anatomy or of a physiological process;
   iv. supporting or sustaining life;
   v. control of conception;
   vi. disinfection of medical devices; or
   vii. providing information for medical or diagnostic purpose by means of in vitro examination of specimens derived from the human body; and
b) which do not achieve its primary intended action in or on human or animal body by pharmacological, immunological or metabolic means but which may be assisted in its intended function by such means.

3.1.20 **Product Owner**

A person who —

a) supplies the health product under his own name, or under any trade mark, design, trade name or other name or mark owned or controlled by him; and
b) is responsible for designing, manufacturing, assembling, processing, labelling, packaging, refurbishing or modifying the health product, or for assigning to it a purpose, whether those tasks are performed by him or on his behalf

3.1.21 **Recognised Standards**

Standards deemed to offer the presumption of conformity to specific Essential Principles.

3.1.22 **Technical Documentation**

The documented evidence, normally an output of the quality management system that demonstrates compliance of a medical device to the Essential Principles.

3.2 Abbreviations

The following abbreviations shall apply:

3.2.1 **IVD** - In Vitro Diagnostic.
3.2.2 **CE**- European Conformity
3.2.3 **GHTF-** The Global Harmonization Task Force
3.2.4 **IMDRF**- International Medical Device Regulators Forum
3.2.5 **SRA** - Stringent Regulatory Authority as per WHO definition prior to 23 Oct 2015.

3.2.6 **WHO** - World Health Organization.

4. General Principal of Clinical Evaluation

4.1 Scope of Clinical Evaluation- Before a clinical evaluation is undertaken the product owner should define its scope based on the Essential Principle that need to be addressed from a clinical perspective. Consideration should include

A. The clinical evaluation should cover any design features that pose special performance or safety concerns (e.g. presence of medicinal, human or animal components), the intended purpose and application of the medical device (e.g. target treatment group and disease, proposed warnings, contraindications and method of application) and the specific claims made by the product owner about the clinical performance and safety of the medical device. The scope of the clinical evaluation will need to be informed by and cross-referenced to the product owner's risk management documents. The risk management documents are expected to identify the risks associated with the medical device and how such risks have been addressed. The clinical evaluation is expected to address the significance of any risks that remain after design risk mitigation strategies have been employed by the product owner.

B. The medical devices should have the same intended purpose and will need to be compared with respect to their technical and biological characteristics. These characteristics should be similar to such an extent that there would be no clinically significant difference in the performance and safety of the medical device. The indications for use relates to the clinical condition being treated, the severity and stage of disease, the site of application to/in the body and the patient population; the technical characteristics related to the design, specifications, physiochemical properties including energy intensity, deployment methods, critical performance requirements, principles of operation and conditions of use; and biological characteristics relate to biocompatibility of materials in contact with body fluids/tissues. In such cases the product owner is expected to include the supporting non-clinical information within the technical documentation for the medical device and cite its location within the clinical evaluation report. (Note: the clinical evaluation is not intended to assess the technical and biological characteristics per se);

C. Factors that should be considered when choosing the type of data to be used in the clinical evaluation include the design, intended purpose and risks of the medical device; the developmental context of the technology on which the medical device is based (new vs established technology); and, for established technology, the proposed clinical application of that technology. Clinical evaluation of medical devices that are based on existing, well-established technologies and intended for an established use of the technology is most likely to rely on compliance with recognised standards

and/or literature review and/or clinical experience of comparable medical devices. High-risk medical devices, those based on technologies where there is little or no experience, and those that extend the intended purpose of an existing technology (i.e. a new clinical use) are most likely to require clinical investigation data. The product owner will need to give consideration to the advantages and limitations of each data type

4.2 Stages in Performing a Clinical Evaluation

4.2.1 Once the scope has been defined, there are three discrete stages in performing a clinical evaluation:

i. identification of pertinent standards and clinical data;

ii. appraisal of each individual data set, in terms of its relevance, applicability, quality and clinical significance; and

iii. analysis of the individual data sets, whereby conclusions are reached about the performance, safety, and presentational aspects (labelling, patient information and Instructions for Use) of the medical device.

4.2.2 At the end of the clinical evaluation a report is prepared and combined with the relevant clinical data to form the clinical evidence for the medical device. If the product owner concludes there is insufficient clinical evidence to be able to declare conformity with the Essential Principles, the product owner will need to generate additional data (e.g. conduct a clinical investigation, broaden the scope of literature searching) to address the deficiency. In this respect clinical evaluation can be an iterative process.

4.2 Who should perform the clinical evaluation- A suitably qualified individual or individuals should conduct the clinical evaluation. A product owner must be able to justify the choice of the evaluator(s) through reference to qualifications and documented experience. As a general principle, evaluators should possess knowledge of the following

i. the medical device technology and its application.

ii. research methodology (clinical investigation design and biostatistics); and

iii. diagnosis and management of the conditions intended to be treated or diagnosed by the medical device.

4.2 Clinical Evaluation of IVD Medical Devices-Clinical evaluation should be performed for IVD medical devices as part of conformity assessment to the Essential

Principles in a manner similar to other medical devices. The basic principles of objective review of clinical data will apply as described in this guidance document.

5. Sources of Data / Documentation Used in Clinical Evaluation

Data relevant to the clinical evaluation may be held by the product owner (e.g. product owner sponsored pre and post market investigation reports and adverse event reports for the medical device in question) or found in scientific literature (e.g. published articles of clinical investigations and adverse event reports for the medical device in question or for comparable medical devices). The product owner is responsible for identifying data relevant to the medical device and determining the types and amount of data needed for the clinical evaluation. Where data are used from a combination of sources, the principles applicable to each source apply to that data component within the clinical evaluation.

5.1 Data Generated Through Literature Searching

i. Literature searching can be used to identify published clinical data that is not in the possession of the product owner that may assist the product owner to establish acceptable performance and safety of a medical device. The data generated through literature searching may relate directly to the medical device in question (e.g. reports of clinical investigations of the medical device in question that have been performed by third parties, adverse event reports) or to comparable medical devices.

ii. For some medical devices, clinical data generated through literature searching will represent the greater part (if not all) of the clinical evidence. Thus, when conducting a literature review reasonable efforts should be made to conduct a comprehensive search.

iii. Published data will need to be assessed with respect to its possible contribution and weighting in establishing both the performance of the medical device in question and its safety. Papers considered unsuitable for demonstration of performance because of poor study design or inadequate analysis may still contain data suitable for assessing the safety of the medical device.

5.2 Key Elements of Literature Searching

5.2.1 The search strategy should be based on carefully constructed review questions. A protocol should be developed to identify, select and collate relevant publications to

address these questions. This should be developed and executed by persons with expertise in information retrieval, having due regard to the scope of the clinical evaluation set out by the product owner. The involvement of information retrieval experts will help to maximise data retrieval. The literature search protocol should include:

i. the sources of data that will be used and a justification for their choice.
ii. the extent of any searches of scientific literature databases (the database search strategy).
iii. the selection/criteria to be applied to published literature and justification for their choice.
iv. strategies for addressing the potential for duplication of data across multiple publications

5.2.2 The search strategy Once the literature search has been executed, a report should be compiled to present the results of the search. A copy of the protocol should be included and any deviations noted.

5.2.3 It is important that the literature search is documented to such a degree that the methods can be appraised critically, the results can be verified, and the search reproduced if necessary.

5.3 Required data/documentation from the literature search should be included in the clinical evaluation

A. The following documentation should be used in the clinical evaluation by the clinical evaluator:

i. the literature search protocol;
ii. the literature search report; and
iii. published articles and other references identified as being relevant to the medical device in question.

B. The literature search protocol, the literature search report and copies of relevant references become part of the clinical evidence and, in turn, the technical documentation for the medical device. With respect to the clinical evaluation, it is

important that the clinical evaluator be able to assess the degree to which the selected papers reflect the intended application/purpose of the medical device, etc.

C. Copies of the actual papers and references are necessary to allow the evaluator to review the methodology employed (potential sources of bias in the data), the reporting of results and the validity of conclusions drawn from the investigation or report. Abstracts may lack sufficient detail to allow these issues to be assessed thoroughly and independently

5.4 Data Generated Through Clinical Experience-

5.4.1 These types of clinical data are generated through clinical use that is outside the conduct of clinical investigations and may relate to either the medical device in question or comparable medical devices. Such types of data may include:

I. product owner-generated post market surveillance reports, registries or cohort studies (which may contain unpublished long term safety and performance data);
II. adverse events databases (held by either the product owner or regulatory authorities);
III. data for the medical device in question generated from individual patients under compassionate usage programs prior to marketing of the medical device; and
IV. details of clinically relevant field corrective actions (e.g. recalls, notifications, hazard alerts)

5.4.2 The value of clinical experience data is that it provides real world experience obtained in larger, heterogeneous and more complex populations, with a broader (and potentially less experienced) range of end-users than is usually the case with clinical investigations. The data is most useful for identifying less common but serious medical device-related adverse events; providing long term information about safety and performance, including durability data and information about failure modes; and elucidating the end-user "learning curve". It is also a particularly useful source of clinical data for low-risk medical devices that are based on long-standing, well-characterised technology and, therefore, unlikely to be the subject of either reporting in the scientific literature or clinical investigation.

5.5 Clinical experience data/documentation be used in the clinical evaluation

(i) If a product owner chooses to use clinical experience data it is important that any reports or collations of data contain sufficient information to be able to undertake a rational and objective assessment of the information and make a conclusion about its significance with respect to the performance and safety of the medical device in question. Reports of clinical experience that are not adequately supported by data, such as anecdotal reports or opinion, should not be used.

(ii) Post market surveillance reports are compiled by the product owner and often include details of the medical device's regulatory status (countries in which the medical device is marketed and date of commencement of supply), regulatory actions undertaken during the reporting period (e.g. recalls, notifications), a tabulation of adverse events (particularly serious events and deaths, stratified into whether the product owner considers them to be medical device-related or not) and estimates of the incidence of adverse events. Post-marketing data about adverse events are generally more meaningful when related to usage but caution is needed because the extent of reporting may vary considerably between countries. The analyses of data within these reports may, for some medical devices, provide reasonable assurance of both clinical safety and performance

(iii) It may be helpful to provide a table summarising medical device-related adverse events, paying particular attention to serious adverse events, with comments on whether observed medical device-related adverse events are predictable on the basis of the mode of action of the medical device. Comment specifically on any clinical data that identifies hazards not previously considered in the risk management documentation, outlining any additional mitigation required (e.g. design modification, amendment of product literature such as inclusion of contraindications etc).

5.6 Data from clinical Investigation

5.6.1 The guidance included within this section applies to clinical investigations carried out by or on behalf of a product owner specifically for the purposes of conformity assessment in accordance with applicable regulations. Such clinical investigations are generally expected to be designed, conducted and reported in accordance with ISO 14155, Parts 1 and 2, Clinical Investigations of Medical Devices for Human Subjects, or to a comparable standard, and in compliance with local regulations. It is recognised

that where product owners' source clinical investigation data reported in the scientific literature (i.e. investigations of either the medical device in question or comparable medical devices that are undertaken by a third party), the documentation readily available to the product owner for inclusion in the clinical evaluation is likely to be no more than the published paper itself.

5.6.2 Clinical investigation documentation / data used in the clinical evaluation

5.6.2.1 Where a clinical investigation has been carried out by or on behalf of a product owner, it is expected that documentation relating to the design, ethical and regulatory approvals, conduct, results and conclusions of the investigation needed for the clinical evaluation will be available for consideration, as appropriate. These may include

i. the clinical investigation plan;

ii. clinical investigation plan amendments and the rationale for these changes;

iii. the relevant Ethics Committee documentation, opinion(s) and comments for each investigation site, including a copy of the approved informed consent form(s) and patient information documents

iv. case report forms, monitoring and audit records;

v. Regulatory Authority approvals and associated correspondence as required by applicable regulations; and

vi. the signed and dated final report

5.6.2.2 The clinical investigation plan sets out how the study was intended to be conducted. It contains important information about the study design such as the selection and assignment of participants to treatment, masking (blinding of participants and investigators) and measurement of responses to treatment, which may be important sources of bias that can be assessed and discounted when trying to determine the actual performance of the medical device. In addition, the clinical investigation plan sets out the intended participant follow- up, approaches to statistical analyses and methods for recording outcomes, which may impact on the quality, completeness and significance of results obtained for performance and safety outcomes. Also, by having the clinical investigation plan, its amendments and the final report available, the evaluator will be able to assess the extent to which the investigation was conducted as planned and, where deviations of from the original plan have occurred, the impact those deviations had on the veracity of the

data generated and the inferences that can be drawn about the performance and safety of the medical device from the investigation.

5.6.2.3 The final report should be signed by its author and appropriate reviewers to provide assurance that the final report is an accurate reflection of the conduct and results of the clinical investigation. Another important consideration of the evaluation will be to assess whether the conduct of the investigation was in accordance with the current applicable ethical standards that have their origin in the Declaration of Helsinki and in accordance with applicable regulations. Clinical investigations not in compliance with applicable ethical standards or regulations should be rejected. The reasons for rejection of the investigation should be noted in the report.

6. Appraisal of Clinical Data-

The purpose of undertaking appraisal of the data is to understand the merits and limitations of the clinical data. Each piece of data is appraised to determine its suitability to address questions about the medical device, and its contribution to demonstrating the safety and performance of the medical device (including any specific claims about safety or performance).

6.1 Data on Appraisal cover

6.1.1 The data needs to be suitable for appraisal. It should be assessed for its quality and for its relevance to the medical device in question (i.e. the data must be either generated for the medical device in question or for a comparable medical device) and its intended purpose. In addition, any reports or collations of data should contain sufficient information for the evaluator to be able to undertake a rational and objective assessment of the information and make a conclusion about its significance with respect to the performance and/or safety of the medical device in question.

6.1.2 Further appraisal needs to be undertaken to determine the contribution of each data subset to establishing the safety and performance of the medical device. The evaluator should examine the methods used to generate/collect the data and assess the extent to which the observed effect (performance or safety outcome(s)) can be considered to be due to intervention with the medical device or due to confounding influences (e.g. natural course of the underlying medical condition, concomitant treatment(s)) or bias2.

6.1.3 There is no single, well-established method for appraising clinical data. Therefore, the evaluator should identify, in advance, the appropriate criteria to be applied for a specific circumstance. These criteria should be applied consistently.

6.1.4 For many lower risk medical devices and medical devices based on long standing technology, the available data may be qualitative rather than quantitative in nature, so the evaluation criteria should be adjusted accordingly. The criteria adopted for the appraisal should be justified by the evaluator. Although there will be some overlap of safety and performance data, the data should be categorised to allow for separate analysis. Additional categories may also be needed, depending on the nature and intended purpose of the medical device to address additional claims. The data should also be weighted according to its relative contribution.

7. Analysis of Clinical Data- The methods available for analysis of clinical data generally are either quantitative or qualitative. Given the context within which most medical devices are developed (i.e., limited need for clinical investigations because of incremental changes in medical device design and therefore high use of literature and experience data), it is most likely that qualitative (i.e. descriptive) methods will need to be used.

7.1 Any evaluation criteria developed and assigned during the appraisal stage can be used to identify those sets of data that may be considered to be "pivotal" to the demonstration of the performance and safety of the medical device, respectively. It may be useful to explore the results of the pivotal datasets, looking for consistency of results across particular medical device performance characteristics and identified risks. If the different datasets report similar outcomes, certainty about the performance increases. If different results are observed across the datasets, it will be helpful to determine the reason for such differences. Regardless, all data sets should be included

7.2 As a final step the evaluator should consider the basis on which it can be demonstrated that the combined data shows

i. the medical device performs as intended by the product owner;

ii. the medical device does not pose any undue safety concerns to either the recipient or end-user; and

iii. any risks associated with the use of the medical device are acceptable when weighed against the benefits to the patient

7.3 Such considerations mentioned in 7.2 should take into account the number of patients exposed to the medical device, the type and adequacy of patient monitoring, the number and severity of adverse events, the adequacy of the estimation of associated risk for each identified hazard, the severity and natural history of the condition being diagnosed or treated. The availability of alternative diagnostic modalities or treatments and current standard of care should also be taken into consideration. The product literature and instructions for use should be reviewed to ensure they are consistent with the data and that all the hazards and other clinically relevant information have been identified appropriately.

8. Clinical Evaluation Report-

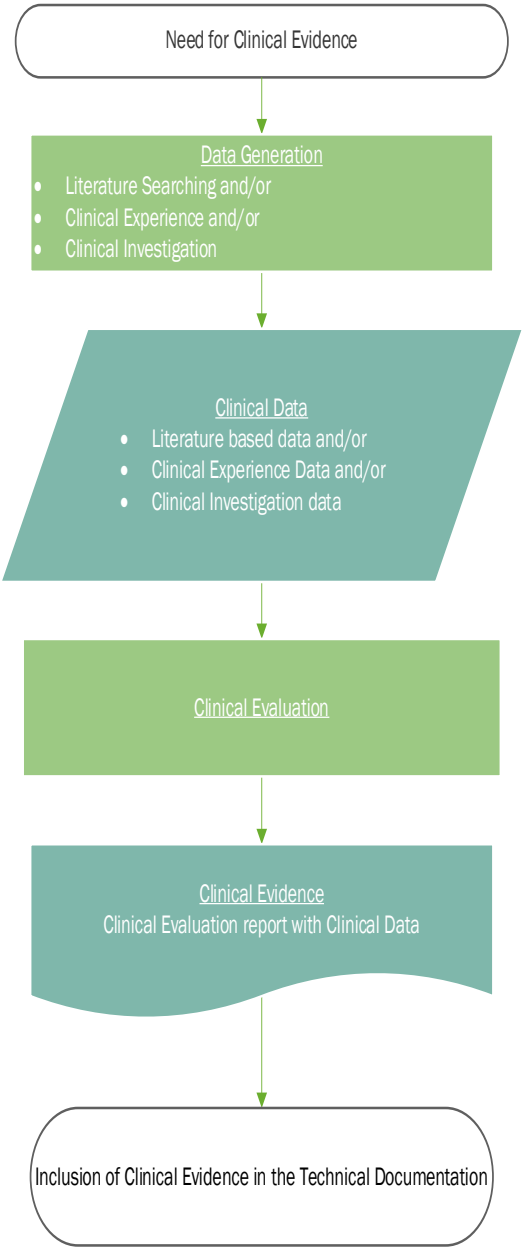
8.1 At the completion of the clinical evaluation process a report should be compiled that outlines the scope and context of the evaluation; the inputs (clinical data); the appraisal and analysis stages; and conclusions about the safety and performance of the medical device in question. The clinical evaluation report should contain sufficient information to be read as a standalone document by an independent party (e.g. regulatory authority or notified body). It is important that the report outlines

i. the technology on which the medical device is based, the intended purpose of the medical device and any claims made about the medical device's clinical performance or safety;
ii. the nature and extent of the clinical data that has been evaluated; and
iii. how the referenced information (recognised standards and/or clinical data) demonstrates the clinical performance and safety of the medical device in question.

8.2 The clinical evaluation report should be signed and dated by the evaluator(s) and accompanied by the product owner's justification of the choice of evaluator

8.3 A suggested format for the clinical evaluation report is located at Template I. Again, it should be noted that the level of detail in the report content can vary according to the scope of the clinical evaluation. For example, where a product owner relies on clinical data for a comparable medical device which has been the subject of an earlier clinical evaluation (for which the product owner holds the evaluation report), it may be possible to cross-reference the data summary and analysis sections to the earlier clinical evaluation report, which also becomes part of the clinical evidence for the medical device in question.

Fig1: Overview of Process for data generation and clinical evaluation



Template I- Suggested format for Clinical Evaluation report

1. General Details

i. State the proprietary name of medical device and any code name assigned during medical device development

ii. Identify the product Owner(s) of Medical Device

2. Description of medical device and its intended application

Provide a concise physical description of medical device, cross-referencing to relevant sections of the product owner's technical information as appropriate

3. Intended therapeutic and/or diagnostic indication and claims

State the medical conditions to be treated, including target treatment group and disease

4. Context of the evaluation and choice of clinical data types

5. Summary of clinical data and appraisal

6. Data Analysis

i. Performance

ii. Safety

iii. Product Literature and Instruction for use,

7. Conclusion