



National Agency for Food & Drug Administration & Control (NAFDAC)

Pharmacovigilance Directorate

NAFDAC Good Pharmacovigilance Practice Guideline

Chapter 7 Post Authorization Safety Studies

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This chapter addresses: Good Pharmacovigilance Practice Regulations, 2021, Regulation 14 (Post-Authorization Safety Studies)

CHAPTER 7

POST AUTHORIZATION SAFETY STUDIES

7.1. Purpose

The purpose of this chapter is to:

- a. Provide general guidance for the transparency, scientific standards and quality standards of non-interventional PASS conducted by Certificate of Registration holders voluntarily or pursuant to an obligation imposed by the Agency;
- b. Describe procedures whereby the Agency may impose onto a Marketing Authorization Holder, holder an obligation to conduct an interventional or a non-interventional PASS, and the impact of this obligation on the risk management system;
- c. Describe procedures to ensure that non-interventional PASS imposed as a regulatory obligation are subject to appropriate protocol development, review, approval, and oversight; that study results are submitted to the relevant regulatory authority within stipulated timelines; and that any safety findings are duly evaluated and translated into appropriate variations to the Certificate of Registration

7.2 Scope

7.2.1 These guidelines apply to non-interventional PASS which are initiated, managed or financed by a MAH as well as those conducted by a third party on behalf of the MAH. It involves primary collection of safety data directly from patients and health care professionals and those that make secondary use of data previously collected from patients and health care professionals for another purpose.

7.2.2 The legal requirements that apply to PASS conducted as a regulatory obligation shall also apply to voluntarily conducted PASS, to ensure a consistent level of transparency, as well as high scientific and quality standards across all studies

Principles

7.2.3 A post-authorization study should be classified as PASS when the main aim for initiating the study includes any of the following objectives:

- a. To quantify potential or identified risks, e.g. to characterize the incidence rate, estimate the rate ratio or rate difference in comparison to a non-exposed population or a population exposed to another drug or class of drugs, and investigate risk factors and effect modifiers;
- b. To evaluate risks of a medicinal product used in patient populations for which safety information is limited or missing (e.g. pregnant women, specific age groups, patients with renal or hepatic impairment);
- c. To evaluate the risks of a medicinal product after long-term use;

- d. To provide evidence about the absence of risks;
- e. To assess patterns of drug utilization that add knowledge on the safety of the medicinal product (e.g. indication, dosage, co medication, medication errors);
- f. To measure the effectiveness of a risk minimization activity.

7.2.4 The PASS design should be appropriate to address the study objective(s), for example, a systematic literature review or a meta-analysis may be considered as PASS depending on their aim.

7.2.5 Good Clinical Practice guidelines (see NAFDAC GCP Guideline 2020) should be considered by the MAH and investigators for the development of study protocols, conduct of studies and writing of study reports as evaluated by the Agency.

7.2.6 For studies that are funded by a MAH, including studies developed, conducted or analyzed fully or partially by investigators who are not employees of the Certificate of Registration holder, the Certificate of Registration holder should ensure that the investigators are qualified by education, training and experience to perform their tasks. The research contract between the Certificate of Registration holder and investigators should ensure that the study meets its regulatory obligations while permitting their scientific expertise to be exercised throughout the research process.

7.2.7 In the research contract, the MAH should consider and address the following aspects:

- a. Rationale, main objectives and brief description of the intended methods of research to be carried out by the investigator(s);
- b. Rights and obligations of the investigator(s) and Certificate of Registration holder;
- c. Clear assignment of tasks and responsibilities;
- d. Procedure for achieving agreement on the study protocol;
- e. Provisions for meeting the Certificate of Registration holder's pharmacovigilance obligations, including the reporting of adverse reactions and other safety data by investigators
- f. Intellectual property rights arising from the study and access to study data; g. Storage and availability of analytical data set and statistical programmes for audit and inspection;
- h. Communication strategy for the scheduled progress and final reports;
- i. Publication strategy for interim and final results.

7.2.8 non-interventional post-authorization safety studies should not be performed where the act of conducting the study promotes the use of a medicinal product. This requirement applies to all studies and to all activities performed in the study, including for studies conducted by the personnel of the Certificate of Registration holder and by third parties on behalf of the Certificate of Registration holder.

7.2.9 Payments to healthcare professionals for participating should be restricted to compensation for time and expenses incurred.

Study registration

7.2.10 In order to support transparency on interventional and non-interventional PASS conducted voluntarily or pursuant to an obligation and to facilitate exchange of pharmacovigilance information between the Agency and Certificate of Registration holders, the Certificate of Registration holder should make available the study information, before the start of data collection, and approval by the Agency. Updates of the study protocol in case of substantial amendments, progress reports where applicable, and the final study report should be submitted to the Agency preferably within 2 weeks of completion.

7.2.11 All post- authorization safety studies must have a written study protocol before the study commences. The study should follow a scientifically sound protocol developed by individuals with appropriate scientific background and experience. The good clinical practice regulation and guidelines of the Agency should be followed for ensuring the well-being and rights of the participants. The Certificate of Registration holder (MAH) should obtain prior approval of the protocol from the Agency.

7.2.12 In order to ensure compliance of the Certificate of Registration holder with its pharmacovigilance obligations, the qualified person responsible for pharmacovigilance (QPPV) or his/her delegate should be involved in the review and sign-off of study protocols conducted in Nigeria.

7.3 Definitions

A post-authorization safety study (PASS) is any study conducted after registration to further evaluate the safety of an authorized medicinal product registration.

A post-authorization safety study (PASS) is therefore any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures. This includes studies that may have commenced prior to registration that are on-going after the product has been registered.

A PASS may be initiated, managed, or financed by a MAH voluntarily, or pursuant to an obligation imposed by the Agency.

This chapter concerns PASS which are clinical trials or non- interventional studies and does not address non-clinical safety studies.

Typical triggers for initiating a Post-Authorization Safety Study (PASS) include the emergence of new safety signals or newly identified risks, important gaps in safety knowledge (missing information), safety concerns affecting special populations such as paediatric, elderly, pregnant or renally/hepatically impaired patients, and findings from post-marketing surveillance that suggest a potential change in the benefit–risk balance. PASS may also be requested when the frequency or severity of a known risk appears to increase, when medication errors, misuse, overdose or off-label use raise safety concerns, or when additional data are required to assess

long-term safety, risk factors, or the effectiveness of risk-minimization measures. Regulatory actions such as new contraindications, warnings, restrictions, or obligations contained in the Risk Management Plan (RMP) may further trigger the need for a PASS.

Interventional PASS involves active assignment of treatment or procedures, whereas non-interventional PASS follow routine clinical practice without protocol-mandated interventions, and therefore each type carries different regulatory and reporting requirements. PASS protocols must receive prior approval from NAFDAC and an accredited Ethics Committee before study initiation, and any substantial amendments to the protocol must likewise obtain NAFDAC approval before implementation.

A PASS is non-interventional if the following requirements are cumulatively fulfilled. Non-interventional studies are defined by the methodological approach used and not by its scientific objectives. Non-interventional studies include database research or review of records where all the events of interest have already happened (this may include case control, cross-sectional, cohort or other study designs making secondary use of data). Non-interventional studies also include those involving primary data collection (e.g. prospective observational studies and registries in which the data collected derive from routine clinical care), provided that the conditions set out above are met. In these studies, interviews, questionnaires and blood samples may be used as part of normal clinical practice.

The medicinal product is prescribed in the usual manner in accordance with the terms of the Certificate of Registration

The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. PASS protocols must receive prior approval from NAFDAC and an accredited Ethics Committee before study initiation, and any substantial amendments to the protocol must likewise obtain NAFDAC approval before implementation.

No additional diagnostic or monitoring procedures are applied to the patients, and epidemiological methods are used for the analysis of collected data.

7.4 Format and content of the study protocol

7.4.1. Content of the study protocol

The study protocol should include the following information:

- a. Title: informative title including a commonly used term indicating the study design and the medicinal product, substance or drug class concerned, and a sub-title with a version identifier and the date of the last version
- b. Certificate of Registration holder: name, address and contact details
- c. Responsible parties: names, titles, qualifications, addresses, and affiliations of all main responsible parties, including the main author(s) of the protocol, the

principal investigator, a coordinating investigator for multiple center study. A list of all collaborating institutions and principal investigators should be made available to the Agency upon request.

7.4.2 Abstract

The abstract of the final study report should include a summary of the study methods and findings presented in the following format:

- a. Title, with subtitles including date of the abstract and name and affiliation of main author;
- b. Keywords (not more than five keywords indicating the main study characteristics);
- c. Rationale and background;
- d. Research question and objectives;
- e. Study design;
- f. Setting;
- g. Participants and study size, including dropouts;
- h. Variables and data sources;
- i. Results;
- j. Discussion (including, where relevant, an evaluation of the impact of study results on the risk- benefit balance of the product) and Milestones.
- k. Certificate of Registration holder;
- l. Names and affiliations of principal investigators.

7.4.3 Amendments and updates: any substantial amendment and update to the study protocol after the start of data collection, including a justification for each amendment or update, dates of each change and a reference to the section of the protocol where the change has been made should be approved by the Agency

7.4.4 Milestones: table with planned dates for the following milestones:

- a. Start of data collection
- b. End of data collection
- c. Study progress report(s)
- d. Interim report(s) of study results, where applicable, in line with phases of data analyses
- e. Final report of study results; and
- f. Any other important timelines in the conduct of the study

7.4.5. Rationale and background: short description of the safety hazard(s), the safety profile or the risk management measures that led to the initiation or imposition of the study, and short critical review of available published and unpublished data to explain gaps in knowledge that the study is intended to fill. The review may encompass relevant animal and human experiments, clinical studies, vital statistics and previous epidemiologic studies. The review should cite the findings of similar studies, and the expected contribution of the current study.

7.4.6 Research question and objectives: research question that explains how the study will address the issue which led to the study being initiated or imposed, and research objectives, including any pre-specified hypotheses and main summary measures.

7.4.7. Research methods: description of the research methods, including:

- a. Study design: overall research design and rationale for this choice.
- b. Setting: study population defined in terms of persons, place, time, and selection criteria, including the rationale for any inclusion and exclusion criteria and their impact on the number of subjects available for analysis. Where any sampling from a source population is undertaken, description of the source population and details of sampling methods should be provided. Where the study design is a systematic review or a meta-analysis, the criteria for the selection and eligibility of studies should be explained.
- c. Variables: outcomes, exposures and other variables including measured risk factors should be addressed separately, including operational definitions; potential confounding variables and effect modifiers should be specified.
- d. Data sources: strategies and data sources for determining exposures, outcomes and all other variables relevant to the study objectives, such as potential confounding variables and effect modifiers. Where the study will use an existing data source, such as electronic health records, any information on the validity of the recording and coding of the data should be reported. If data collection methods or instruments are tested in a pilot study, plans for the pilot study should be presented. If a pilot study has already been performed, a summary of the results should be reported. Involvement of any expert committees to validate diagnoses should be stated. In case of a systematic review or meta-analysis, the search strategy and processes and any methods for confirming data from investigators should be described.
- e. Study size: any projected study size, precision sought for study estimates and any calculation of the sample size that can minimally detect a pre-specified risk with a pre-specified statistical precision.
- f. Data management: data management and statistical programmes to be used in the study, including procedures for data collection, retrieval, and preparation.
- g. Data analysis: the major steps that lead from raw data to a final result, including methods used to correct inconsistencies or errors, impute values, modify raw data, categorize, analyze and present results, and procedures to control sources

of bias and their influence on results; statistical procedures to be applied to the data to obtain point estimates and confidence intervals of measures of occurrence or association, and sensitivity analyses.

- h. Quality control: description of any mechanisms and procedures to ensure data quality and integrity, including accuracy and legibility of collected data and original documents, extent of source data verification and validation of endpoints, storage of records and archiving of statistical programmes. As appropriate, certification and/or qualifications of any supporting laboratory or research groups should be included.
- i. Limitations of the research methods: any potential limitations of the study design, data sources, and analytic methods, including issues relating to confounding, bias, generalizability, and random error. The likely success of efforts taken to reduce errors should be discussed.
- j. Protection of human participant: safeguards in order to comply with the good clinical practice regulation requirements of the Agency for ensuring the well-being and rights of participants in non-interventional post- authorization safety studies.
- k. Management and reporting of adverse events/adverse reactions: procedures for the collection, management and reporting of individual cases of adverse reactions and of any new information that might influence the evaluation of the benefit- risk balance of the product while the study is being conducted.
- l. Plans for disseminating and communicating study results, including any plans for submission of progress reports and final reports.
- m. References
- n. An annex should list all separate documents and list or include any additional or complementary information on specific aspects not previously addressed (e.g. questionnaires, case report forms, informed consent), with clear document references.

7.5 Feasibility studies

7.5.1 Feasibility studies that were carried out to support the development of the protocol, for example, the testing of a questionnaire or simple counts of medicinal events or prescriptions in a database to determine the statistical precision of the study, should be reported in the appropriate section of the study protocol with a summary of their methods and results. The full report should be made available to the Agency upon request.

7.5.2. Feasibility studies that are part of the research process should be described in the protocol, for example, a pilot evaluation of the study questionnaire(s) used for the first set of participants recruited into the study.

7.6 Timelines

A clear reporting timetable should be followed, including submission of the protocol before study start, interim reports as scheduled in the approved plan, and a final study report within 12 months of completing data collection

7.7 Substantial amendments to the study protocol

The study protocol should be amended and updated as needed throughout the course of the study. Any substantial amendments to the protocol after the study start should be documented in the protocol in a traceable and auditable way including the dates of the changes. If changes to the protocol lead to the study being considered an interventional clinical trial, the Agency should be informed immediately, and the study should subsequently be conducted in accordance with The Good Clinical Practice Regulation and Guidelines

7.8 Reporting of pharmacovigilance data to the Agency

7.8.1 Data relevant to the benefit-risk balance of the product:

The MAH should monitor the data generated while the study is being conducted and consider their implications for the benefit-risk balance of the medicinal product concerned. Any new information that may affect the benefit-risk balance of the medicinal product should be communicated immediately in writing as an Emerging Safety Issue to the Agency. Information affecting the benefit-risk balance of the medicinal product may include that arising from an analysis of adverse reactions and aggregated data.

This communication should not affect information on the results of studies which should be provided by means of periodic safety update reports (PSUR/PBRERs) and in RMP updates, where applicable.

7.8.2 Reporting of adverse reactions/adverse events

Adverse reactions/adverse events should be reported to the Agency in accordance with Good Pharmacovigilance Practice Guideline Chapter 5 Procedures for the collection, management (including a review by the MAH and reporting of suspected adverse reactions/adverse events should be put in place and summarized in the study protocol. If appropriate, reference can be made to the Pharmacovigilance System Master File but details specific to the study should be described in this section of the PSMF. For study designs where expedited reporting is not required, this should be stated in the study protocol.

7.9 Study reports

7.9.1 Progress reports

Progress reports may be requested by the Agency. Requests for progress reports may be made at any time during the study conduct. They may be guided by the communication of benefit-risk information arising from the study or the need for

information about the study progress in the context of regulatory procedures or important safety communication about the product.

7.9.2 The timing of the progress reports should be agreed with the Agency and specified in the study protocol when they have been agreed before the study commences. Study progress should also be reported in any periodic safety update reports (PSUR/PBRERs) and risk management plan (RMP), where applicable.

7.9.3 The content of the progress report should follow a logical sequence and should include all the available data that are judged relevant for the progress of the study, for example, number of patients who have entered the study, number of exposed patients or number of patients presenting the outcome, problems encountered and deviations from the expected plan. The progress report may also include any interim report of study results. After reviewing the report, additional information may be requested.

Final study report

7.9.4 The final study report should be submitted as soon as possible within 12 months of the end of data collection. If a study is discontinued, a final report should be submitted and the reasons for terminating the study should be provided.

7.9.5 The final study report should include the following information:

- a. Title: title including a commonly used term indicating the study design; sub-titles with date of final report and name and affiliation of main author.
- b. Abstract: stand-alone summary in the format presented in section 7.4.2
- c. MAH: name and address of the MAH
- d. Investigators: names, titles, degrees, addresses and affiliations of all main responsible parties, including the main author(s) of the protocol, the principal investigator, a coordinating investigator for multiple center study. A list of all collaborating institutions and principal investigators should be made available to the Agency upon request.
- e. Milestones: planned and actual dates for the following milestones:
 - i. Start of data collection
 - ii. End of data collection or date of early termination, if applicable, with reasons for termination
 - iii. Study progress report(s)
 - iv. Interim report(s) of study results, where applicable
 - v. Final report of study results
 - vi. Any other important milestone applicable to the study, including date of protocol approval by an Ethics Committee, and date of study registration in the Nigerian PASS Register.

- f. Rationale and background: short description of the safety concern(s) that led to the study being initiated or imposed, and short critical review of relevant published and unpublished data evaluating pertinent information and gaps in knowledge that the study is intended to fill.
- g. Research question and objectives: research question and research objectives, including any pre-specified hypotheses, as stated in the study protocol.
- h. Amendments and updates to the protocol: list of any substantial amendment and update to the initial study protocol after the start of data collection, including a justification for each amendment or update.

7.10 Research methods:

7.10.1 Study design: key elements of the study design and the rationale for this choice.

7.10.2 Setting: setting, locations, and relevant dates for the study, including periods of recruitment, follow-up, and data collection. In case of a systematic review or meta-analysis, study characteristics used as criteria for eligibility, with rationale.

7.10.3 Participants: any source population and eligibility criteria of study participants. Sources and methods of selection of participants should be provided, including, where relevant methods for case ascertainment, as well as number of reasons for dropouts.

7.10.4 Variables: all outcomes, exposures, predictors, potential confounders, and effect modifiers, including operational definitions and diagnostic criteria, if applicable.

7.10.5 Data sources and measurement: for each variable of interest, sources of data and details of methods of assessment and measurement. If the study has used an existing data source, such as electronic health records, any information on the validity of the recording and coding of the data should be reported. In case of a systematic review or meta analysis, description of all information sources, search strategy, methods for selecting studies, methods of data extraction and any processes for obtaining or confirming data from investigators.

7.10.6 Bias: any efforts to assess and address potential sources of bias.

7.10.7 Study size: study size, rationale for any sample size calculation and any method for attaining projected study size.

7.10.8 Data transformation: transformations, calculations or operations on the data, including how quantitative data were handled in the analyses and which groupings were chosen and why.

7.10.9 Statistical methods: description of:

- a. Main summary measures
- b. Statistical methods applied to the study, including those used to control for confounding and, for meta-analyses, methods for combining results of studies

- c. Any methods used to examine subgroups and interactions
- d. How missing data were addressed
- e. Any sensitivity analyses
- f. Any amendment to the plan of data analysis included in the study protocol, with a rationale for the change.

7.10.10 Quality control: mechanisms to ensure data quality and integrity.

7.10.11 Results: presentation of tables, graphs, and illustrations to present the pertinent data and reflect the analyses performed. Both unadjusted and adjusted results should be presented. Precision of estimates should be quantified using confidence intervals. This section should include the following sections:

- a. Participants: numbers of study participants at each stage of study, e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed, and reasons for non-participation at any stage. In the case of a systematic review or meta-analysis, number of studies screened, assessed for eligibility and included in the review with reasons for exclusion at each stage.
- b. Descriptive data: characteristics of study participants, information on exposures and potential confounders and number of participants with missing data for each variable of interest. In case of a systematic review or meta-analysis, characteristics of each study from which data were extracted (e.g. study size, follow-up).
- c. Outcome data: numbers of participants across categories of main outcomes.
- d. Main results: unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). If relevant, estimates of relative risk should be translated into absolute risk for a meaningful time period.
- e. other analyses: other analyses done, e.g. analyses of subgroups and interactions, and sensitivity analyses.
- f. Adverse events and adverse reactions: summary of all adverse events/adverse reactions reported in the study. For certain study designs such as case-control or retrospective cohort studies, particularly those involving electronic health care records, systematic reviews and meta-analyses where it is not feasible to make a causality assessment at the individual case level, this should be stated.

7.11 Discussion:

7.11.1 Key results: key results with reference to the study objectives, prior research in support of and conflicting with the findings of the completed post-authorization safety study, and, where relevant, impact of the results on the benefit-risk balance of the product.

7.11.2 Limitations: limitations of the study considering circumstances that may have affected the quality or integrity of the data, limitations of the study approach and methods used to address them (e.g., response rates, missing or incomplete data, imputations applied), sources of potential bias and imprecision and validation of the events. Both direction and magnitude of potential biases should be discussed.

7.11.3 Interpretation: interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies and other relevant evidence.

7.11.4 Generalizability: the generalizability (external validity) of the study results.

7.12 **References.**

7.13 **Other information:** any additional or complementary information on specific aspects not previously addressed.

7.14 ***Publication of study results***

For studies that are fully or partially conducted by investigators who are not employees of the MAH, the MAH and the investigator should agree in advance a publication policy allowing the principal investigator to independently prepare publications based on the study results irrespective of data ownership. The MAH should be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication.

7.14.1 Regulatory submission of manuscripts accepted for publication

In order to allow the Agency to review in advance the results and interpretations to be published, the MAH should communicate to the Agency the final manuscript of the article within two weeks after first acceptance for publication.

7.15 Data protection

MAHs and investigators should follow relevant national legislation in Nigeria.

7.15.1 PASS imposed as an obligation

For PASS imposed as an obligation, the MAH should ensure that all study information is handled and stored so as to allow for accurate reporting, interpretation and verification of that information and should ensure that the confidentiality of the records of the study subjects remains protected. This provision should also be applied to PASS voluntarily initiated, managed or financed by the Certificate of Registration holder.

7.16 Quality systems, audits and inspections

The MAH should ensure the fulfillment of its pharmacovigilance obligations in relation to the study and that this can be audited, inspected and verified. For PASS imposed as an obligation, the Certificate of Registration holder should ensure that the analytical dataset and statistical programmes used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection. This provision should also be applied to PASS voluntarily initiated, managed or financed by the Certificate of Registration holder.

7.17 Impact on the risk management system

Non-interventional PASS imposed as an obligation or required to investigate a safety concern should be described in the RMP. Protocols for studies in the pharmacovigilance plan should be provided in RMP (annex 6) until submission of the final study report to the Agency. Studies looking at the effectiveness of risk minimization measures should be included in the

pharmacovigilance plan against the specific safety concern(s) as well as described in detail in the risk minimization plan.

7.17.1 Other non-interventional PASS which are not obligations or required studies in the RMP but which could provide relevant information on the safety profile of the product should be listed in the RMP “Summary table of additional pharmacovigilance activities.

7.17.2 Each PASS should be clearly linked to a specific safety concern identified in the risk-management system to ensure relevance, traceability, and alignment with ongoing pharmacovigilance activities

7.17.3 All post-authorization safety studies imposed as a condition to the Certificate of Registration will be described in the RMP and their results provided in the PSUR/PBRER following completion of the final report, where applicable.

7.17.4 All relevant sections of the RMP should be amended to document the conduct of the study, including the safety specification, the pharmacovigilance plan, the risk minimization plan and the summary of activities, as appropriate. A copy of the study protocol approved by the Agency should be provided as an annex in the RMP. When a RMP does not exist, a new RMP should be developed referring to the PASS

7.18 *Conditions for imposing PASS on MAHs*

7.18.1 *Request for a post-authorization safety study during a post-authorization regulatory procedure*

The need for a PASS could be identified by the Agency during a post-authorization regulatory procedure, for example, an extension or a variation to a Certificate of Registration or a renewal procedure

7.18.2 *Request for a post-authorization safety study due to an emerging safety concern*

After the granting of the Certificate of Registration, the Agency may impose on the MAH, an obligation to conduct a post- authorization safety study if there are concerns about the risk of the authorized medicinal product, for example following evaluation of a safety signal.

7.18.3 Joint post-authorization safety studies

7.18.4 Cases with two or more medicinal products

If safety concerns apply to more than one medicinal product, the Agency will encourage the Certificate of Registration holders concerned to conduct a joint PASS.

7.18.5 Rare diseases

A joint PASS may also be necessary where there are limited patients (rare diseases) or the adverse reaction is rare. Requests to the Certificate of Registration holders should contain the justification for the request of a joint study and the elements of the study design that support a joint protocol. Upon request from the Certificate of Registration holders, the Agency may organize a pre-submission meeting to provide suggestions for a joint study proposal and facilitate agreement in developing a joint protocol. If a joint

protocol is not voluntarily agreed and different proposals are submitted, the Agency may define, either a common core protocol or key elements (for example, the study design, the study population and the definition of exposure and outcomes) which each Certificate of Registration holder will have to implement in the study protocol to be submitted to the Agency.

7.18.6 Written observations in response to the imposition of an obligation

Within 30 days of receipt of the written notification of the obligation, the MAH may request the opportunity to present written observations in response to the imposition of the obligation. The Agency will specify a time limit for the provision of these observations. Based on the written observations submitted by the Certificate of Registration holder, the Agency may withdraw or confirm the obligation. When the obligation is confirmed, the MAH should be subject to variation to include the obligation as a condition and the risk management plan (RMP) should be updated accordingly.

7.19 ***Regulatory supervision of non-interventional post-authorization safety studies***

Non-interventional PASS conducted pursuant to obligations imposed by the agency are supervised and assessed by the Agency

7.19.1 Roles and responsibilities of the MAH

Following the imposing of the obligation to conduct a non-interventional PASS as a condition to the Certificate of Registration, the Certificate of Registration holder should develop a study protocol and submit it to the Agency for review.

7.19.2 The MAH has the responsibility to ensure that the study is not a clinical trial. If the study is a non-interventional study, the MAH should ensure that the study meets all the requirements applicable to non-interventional PASS. The MAH should ensure the fulfillment of its pharmacovigilance obligations in relation to the study and that this can be audited, inspected and verified.

7.19.3 The MAH should develop the study protocol.

7.19.4 The study may commence only when the written endorsement from the Agency has been issued.

7.19.5 Prior to submission of the protocol, the MAH may submit a request to the Agency for a pre-submission meeting with the Agency in order to clarify specific aspects of the requested study (such as study objectives, study population, definition of exposure and outcomes) and to facilitate the development of the protocol

7.19.6 After a study has commenced, the MAH should submit any substantial amendments to the protocol to the Agency, before their implementation.

7.19.7 The Certificate of Registration holder may be requested to submit study progress reports to the Agency

7.19.8 Upon completion of the study, the Certificate of Registration holder should submit a final study report, including a public abstract, to the Agency as soon as

possible and not later than 12 months after the end of data collection, unless a written waiver has been granted. The final study report should follow the format recommended earlier.

7.19.9 The Certificate of Registration holder should submit the study protocol, the abstract of the final study report and the final study report.

7.20 Changes to the Certificate of Registration following results from a non-interventional post-authorization safety study

7.20.1 The Certificate of Registration holder should evaluate whether the study results have an impact on the Certificate of Registration and should, if necessary, submit to the Agency an application to vary the Certificate of Registration. In such case, the variation should be submitted to the Agency with the final study report within 12 months of the end of the data collection.

Note that PASS results may lead to regulatory actions such as SmPC updates, additional risk-minimization measures, or variations to the Certificate of Registration.

7.20.2 Following the review of the final study report, the Agency may recommend variation or suspend or revoke the Certificate of Registration. In case a variation is agreed upon, the Certificate of Registration holder should submit to the Agency an appropriate application for a variation, including an updated summary of product characteristics (SmPC) and package leaflet within the determined timetable for implementation.

REFERENCES

1. **National Agency for Food and Drug Administration and Control (NAFDAC).**
Good Pharmacovigilance Practice Regulations, 2021 (S.I. No. 74 of 2021).
2. **National Agency for Food and Drug Administration and Control (NAFDAC).**
Good Pharmacovigilance Practice Guidelines, 2021.
3. **Federal Ministry of Health (FMoH), Nigeria.**
National Pharmacovigilance Policy & Implementation Framework (Revised Edition), 2021.
4. **International Council for Harmonisation (ICH).**
ICH E2E: Pharmacovigilance Planning.
5. **International Council for Harmonisation (ICH).**
ICH E2C(R2): Periodic Benefit–Risk Evaluation Report (PBRER).