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Assessment of pharmacovigilance guidelines in the Southern African Development Community: A document review

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Abstract

Background: Lack of harmonization in pharmacovigilance (PV) practice in resource-limited states in Africa has led to differentiation and marginalization, thus creating an environment where weak or absent PV systems may benefit from regional guidelines.

Purpose: To compare the PV guidelines of Southern African Development Community (SADC) member states to international guidelines and identify areas for improvement for aligning PV practice within the SADC region.

Methods: We utilized a 73-item checklist to assess the PV guidelines of the SADC member states. Checklist parameters were rated using binary scoring.

Results: Only seven (Botswana, Mauritius, Namibia, South Africa, Tanzania, Zambia, and Zimbabwe) of the 16 SADC member states had guidelines to assess. Of these, only four had supporting legislation. All seven national medicines regulatory authorities (NMRA)'s guidelines required reporting of local serious adverse drug reactions (ADRs). Four NMRAs implemented device vigilance; none specified submission timelines for ADRs associated with substandard or falsified medicines. Only three NMRAs required electronic transmission of individual case safety reports in the E2B format. Five NMRAs mandated safety monitoring during interventional clinical trials. Five NMRAs required aggregate reporting through periodic safety update reports. Only two NMRAs required submission of the development safety update report. Regarding risk management, four NMRAs required notification of actions taken by foreign NMRAs and four NMRAs expected to review Dear Healthcare Professional Letters before distribution by the marketing authorization holder.

Conclusions: Areas for improvement of guidelines to establish common process standards and allow for synchronized submissions of comparable data to SADC NMRAs are provided.

KEYWORDS
checklist, guidelines, harmonization, pharmacovigilance, Southern African Development Community (SADC)

Key Points

- Disparity exists in PV regulation within the Southern African Development Community (SADC).
- The majority (9 of 16) of SADC NMRAs have not authored PV guidelines.
- SADC NMRAs rely on more experienced NMRAs for risk management decisions.
- Harmonization of PV guidelines is needed across SADC countries.
- Contextualization of regulations and guidelines is essential to streamline PV regulatory activities and meet local needs.

Plain Language Summary

Assessing the medicine safety guidelines from national medicines regulatory authorities of the Southern African Development Community (SADC)

The guidelines governing medicine safety are not aligned in the SADC region. We assessed the medicine safety guidelines written by SADC national medicines regulatory authorities (NMRAs) by using a checklist based on international standards. A yes/no scoring was assigned to each checklist item and data were analyzed by topic. Seven of 16 SADC countries have authored medicine safety guidelines, with four having supporting legislation. All seven expected submission of local serious side effects, safety monitoring of medical devices by four, but none stipulated submission timelines for side effects caused by fake medicines. Three required electronic (E2B) submission of cases. During clinical trials, five required reporting of side effects, and two expected submission of development safety update reports. Five required submission of periodic safety update reports. Four NMRAs expected notification about risk assessment decisions made by more experienced NMRAs. Four expected reviewing of letters containing safety warnings before marketing authorization holders sent them to healthcare professionals. Guidelines of Botswana, Mauritius, Namibia, South Africa, Tanzania, Zambia, and Zimbabwe differ. Alignment would ensure that MAHs submit data in a uniform structure, timing, and format.

1 | INTRODUCTION

Pharmacovigilance (PV) is the collection and analysis of safety data within data management systems, followed by risk assessment, decision-making, and communication.[1] Guidelines authored by national medicines regulatory authorities (NMRAs) determine the inputs into the PV data management system. It is necessary that PV practice is provided for in legislation,[2] appropriately qualified personnel are available to perform the required tasks, and that prescriptive guidelines exist for all stakeholders (NMRAs, marketing authorization holders (MAHs), healthcare professionals and consumers).[3]

Efforts to harmonize regulatory practices have been implemented successfully in Europe, resulting in skill-sharing, faster safety appraisals and the elimination of multiple submissions to NMRAs, while allowing data pooling and analysis for effective signal assessments.[4] Disharmonious PV environments foster a situation where different types of data are collected at different times in differing formats, thus precluding cohesive analysis and uniform decisions.[5] The discrepancy stresses the importance of harmonizing guidelines.

The Southern African Development Community (SADC) consists of 16 member states in the southernmost part of Africa, namely, Angola, Botswana, Comoros, Democratic Republic of Congo, Eswatini, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, Tanzania, Zambia, and Zimbabwe.[6] They constitute a regional economic community within the African Union, each with national regulatory autonomy.[6] The African Union Development Agency (AUDA) has implemented the African Medicines Regulatory Harmonization project, which is intended to establish the African Medicines Agency, a continental regulatory authority.[7] To this end, regional harmonization of medicine approval initiatives has been piloted in the East African Community, with the compendium of PV guidelines in March 2019.[8] Within SADC, successful harmonization of medicines registration processes is well established[9]; however, PV governance remains diverse and inconsistent. Maturity levels of SADC PV systems differ based on regulatory capacity and membership in the World Health Organization's Programme for International Drug Monitoring (WHO PIDM).[10] South Africa was the first SADC member state to join the WHO PIDM in 1992.[11] Almost 30 years later, SADC membership of the WHO PIDM remains incomplete at 81%.[12]

This study aimed to assess the current state of PV guidelines of SADC NMRAs to identify areas for improvement to align PV practice within the region, by comparing existing PV guidelines to international guidelines.

2 | METHODS

2.1 | Study design

A descriptive document review was conducted on the available PV guidelines of SADC member states ($N = 16$), utilizing a 73-item SADC PV guideline checklist.[13]

2.2 | Search strategy

Our search strategy was designed to identify all documents from January 2020 to July 2021 that addressed the PV legislative framework in the 16 SADC countries. The search included laws, regulations, policies, and guidelines to minimize the possibility of missing relevant documents. Our analysis focused on guidelines because the checklist was specifically developed to assess PV guidelines in SADC. The principal researcher extracted documents from national health ministries and NMRA websites, which may no longer be retrievable. Where none were available online, a written request for the guidelines was made to the NMRAs. Requests were therefore made to six NMRAs (Angola, Eswatini, Lesotho, Malawi, Mozambique, Seychelles).

2.3 | Document selection

The search strategy yielded 44 documents comprising 14 laws, seven regulations, seven policies, and 16 guidelines (Table 1). The 16 guidelines included in the analysis are listed in Table 2.

2.4 | Data analysis

The checklist[13] consists of five themes, that is, PV systems, definitions, individual case safety reports, aggregate reports, and risk management. The checklist was designed to compare current PV guidelines of SADC states to international reference guidelines.

Binary yes/no scoring was used to rate each parameter. Equivalent terminology was accepted where it was apparent that the meaning and intention were consistent with that of the checklist item. All guidelines for a specific member state were evaluated on one checklist. Test–retest reliability was assured by conducting an electronic and a manual search. During the test, for each guideline, the parameters were identified by using the electronic search function ("find"). During the retest, the researcher conducted a manual search of each guideline and identified the desired parameters. To avoid memory bias, retesting was performed a week later. The two data sets were matched.

3 | RESULTS

The results are presented under the five themes (A–E) of the checklist (Tables 3–7).

3.1 | PV systems (Theme A)

Assessments of PV systems focused on PV legislation, description of MAH's PV system, subcontracting, archiving, and the person responsible for PV. The summary of PV system requirements of SADC member states is presented in Table 3. Mauritius and Zambia have only a law pertaining to PV, with Mauritius' law only governing the conduct of clinical trials.

3.2 | Definitions (Theme B)

In the checklist, eight definitions pertaining to PV and key stakeholders were required. A summary of the definitions identified during the assessment of the SADC PV guidelines is provided in Table 4.

3.3 | Individual case safety reports (Theme C)

Five subthemes relating to the collection, reporting and submission of ICSRs to the NMRA, focusing on criteria for reporting, categories of reportable information, expedited reporting, reporting timelines, and reporting format, were examined (Table 5).

Collection, reporting, and submission of ICSRs to the NMRA—*categories of reportable information*: Categories of *solicited* and *unsolicited sources* were addressed comprehensively by South Africa and Tanzania, while Mauritius and Zambia did not include any requirements.

3.4 | Aggregate reports (Theme D)

The requirement to submit aggregate reports during the post-marketing and clinical trial phases was examined as indicated in Table 6.

3.5 | Risk management (Theme E)

A summary of the findings from the assessment of risk management is presented in Table 7, under six subthemes: signal detection, reevaluation of the risk–benefit ratio, safety decision-making process, risk management planning, risk minimization, and safety communication.

4 | DISCUSSION

The requirement for MAHs to establish PV systems that can effect continuous safety monitoring of biomedical products based on PV

TABLE 1 PV legislation of SADC member states.[a]

Member state	National Medicines Regulatory Authority	Law (Act)	Regulation	Policy	Guidelines
Angola	*Direcao Nacional de Medicamentos e Equipmentos* (DNME) (National Directorate of Medicine and Equipment)[14]	Law no. 21-B/92 of 28th of August[14]	Presidential decree no. 191/10, 1st of September[14]	Presidential decree number 180/10 Pharmaceutical National Policy[14]	None
Botswana	Botswana Medicines Regulatory Authority (BoMRA)[15]	Medicines and related substances act of 2013[15]	Medicines and related substances act regulations of 2019[16]	Botswana National Drugs Policy, 2005[17]	Pharmacovigilance guidelines for market authorization holders, 2020[18]
Comoros	None	None	None	None	None
Democratic Republic of the Congo	*Direction de la Pharmacie et du Médicament*.[19] (Directorate of Pharmacy and Medicines) now *Autorité Congolaise de Réglementation Pharmaceutique* (ACOREP) (Congolese Authority for Regulation of Pharmaceuticals)	Decree No. 1250/CAB/MIN/SP/013/CPH/OBF/2015[19]	None	None	None
Eswatini (formerly Swaziland)	National Pharmacovigilance Unit[20]	Medicines and Related Substances Control Act 9 of 2016[20]	None	None	None
Lesotho	None	None	None	None	None
Madagascar	Agence du Médicament de Madagascar[21] (Medicines Agency of Madagascar)	Décret 98-086/SAN du 27 Janvier 1998[22] Décret no 2010–0960 MSANP du 30 Novembre 2010[22]	None	National Pharmacovigilance Policy for Madagascar 2011[22]	None
Malawi	Pharmacy and Medicines Regulatory Authority (PMRA)[23]	Pharmacy and Medicines Regulatory Authority (PMRA) Act 9 of 2019[23]	None	None	None
Mauritius	Pharmacy Board, Ministry of Health and Wellness[24]	The Clinical Trials Act 8 of 2011[24]	None	None	Reporting Guidelines for Mauritius, 2018[25]
Mozambique	*Departamento Farmacêutico* (Directorate of Pharmacy)[26]	Law no. 12/2017 of 2017[26]	Ministerial order no. 53/2010[26]	None	None
Namibia	Therapeutics Information and Pharmacovigilance Centre (TIPC)[27]	Medicines and Related Substances Control Act 13 of 2003[27]	Regulation 17[28]	National Drug Policy of 1998[29]	National Guidelines for Medicines Safety Surveillance, 2011[30]
Seychelles	None	None	None	None	None
South Africa	South African Health Products Regulatory Authority (SAHPRA)[31]	Medicines and Related Substances Control Act 101 of 1965[32]	Regulation 40[32] Regulation 17[32]	The National Vigilance Policy for Health Technologies in South Africa, May 2020 (draft)[33]	Post-Marketing Reporting of Adverse Drug Reactions to Human Medicines in South Africa, 2021[34] Safety Reporting During Clinical Trials in South Africa, 2019[35]

TABLE 1 (Continued)

Member state	National Medicines Regulatory Authority	Law (Act)	Regulation	Policy	Guidelines
					Guideline for Handling Dear Healthcare Professional Letters Relating to Medicine Safety, 2020[36] Guideline for adverse drug reaction reporting for healthcare professionals, 2021[37] Recall, adverse event and post-marketing vigilance reporting of medical devices and in vitro diagnostics, 2019[38]
Tanzania	Tanzania Medicines and Medical Devices Authority (TMDA)[39]	The Tanzania Food Drugs and Cosmetics Act (Act 1 of 2003)[39]	The Tanzania Food Drugs and Cosmetics Regulations (Pharmacovigilance) 2018[39]	National Drug Policy of 1991[39]	National guidelines for monitoring medicines safety, 2018[40] Guidelines for Reporting Safety Data in Clinical Trials, 2011[41] Guidelines for Surveillance of medical devices vigilance system, 2020[42]
Zambia	Zambia Medicines Regulatory Authority (ZAMRA)[43]	Medicines and Allied Substances Act No. 3 of 2013[43]	None	None	A Guide to Detecting and Reporting Adverse Drug or Vaccine Reaction/ Events in Zambia, 2006[44]
Zimbabwe	Medicines Control Authority of Zimbabwe (MCAZ)[45]	Medicines and Allied Substances Control Act [15:03] of 1969[46]	None	Zimbabwe National Pharmacovigilance Policy Handbook, 2016[b47]	Guidelines for the Notification of a Medicinal Problem/ Defect and Recall Procedure, 2016[48] Zimbabwe National Pharmacovigilance Policy Handbook, 2016[b47] Guidelines for Good Clinical Trial Practice in Zimbabwe, 2020[49] Pharmacovigilance Guidelines for Pharmaceutical Industry, 2021[50]

[a]Guidelines published and retrieved before July 2021.
[b]Called a policy, but includes a guideline.

legislation is a vital element of a robust national PV system.[51] It thus seems that Mauritius, Zambia, and Zimbabwe need to complete their set of PV-enabling national laws, regulations, and policies. The MAH's *PV system elements* were not comprehensively itemized. The availability of a *PV system master file or manual*, the *designation of an appropriately trained regional QPPV* and information on *subcontracted tasks* are

TABLE 2 Reviewed guidelines of SADC member states.[a]

SADC member state	Name of pharmacovigilance guideline
Botswana	Pharmacovigilance Guidelines for Market Authorization Holders, 2020[18]
Mauritius	Reporting Guidelines for Mauritius, 2018[25]
Namibia	National Guidelines for Medicines Safety Surveillance, 2011[30]
South Africa	• Post-Marketing Reporting of Adverse Drug Reactions to Human Medicines in South Africa, 2021[34] • Safety Reporting During Clinical Trials in South Africa, 2019[35] • Guideline for Handling Dear Healthcare Professional Letters Relating to Medicine Safety, 2020[37] • Guideline for adverse drug reaction reporting for healthcare professionals, 2021[37] • Recall, adverse event and post-marketing vigilance reporting of medical devices and in vitro diagnostics, 2019[38]
Tanzania	• Guidelines for Reporting Safety Data in Clinical Trials, 2011[41] • Guidelines for Surveillance of medical devices vigilance system, 2020[42] • National Guidelines for Monitoring Medicines Safety, 2018[40]
Zambia	A Guide to Detecting and Reporting Adverse Drug or Vaccine Reaction/Events in Zambia, 2006[44]
Zimbabwe	• Guidelines for the Notification of a Medicinal Problem / Defect and Recall Procedure, 2016[48] • Zimbabwe National Pharmacovigilance Policy Handbook, 2016[47] • Guidelines for Good Clinical Trial Practice in Zimbabwe, 2020[49] • Pharmacovigilance Guidelines for Pharmaceutical Industry, 2021[50]

[a]Guidelines published and retrieved before July 2021.

part of the PV system[52] that needs to be mandated by more SADC NMRAs. Specifications on *archiving* of safety data (not addressed by any member states) are needed to ensure uniform availability of data for future reference.

Essential definitions were not explicated by all NMRAs. Definitions of the terms *healthcare professional*, *consumer*, and *marketing authorization holder* were variable or absent and should be completed. Defining all key PV terms is recommended for all NMRAs, to avoid misunderstanding and establish a common premise.[53]

ICSR reporting received more attention (*definitions*, *reportable items*, *timelines for reporting*) from NMRAs, but still required more thorough consideration.[54] Inclusion of the criterion an *identifiable reporter* facilitates the next criterion *follow-up*, consequently, inclusion of both is recommended for Botswana and Zimbabwe. All ICSR reporting criteria need to be included by Mauritius and Zambia. All seven NMRAs required that *serious local ADRs* be reported. *Reporting timelines* varied from 48 h to the international standard of 15 days[55] for serious local ADRs. In evaluating the categories of ADRs prioritized for submission, the following were under-represented: *serious local ADRs* arising from *medication errors*, *off-label use* and *overdose*, despite being prioritized by the ICH and EMA since 2017.[56] The MAHs should ensure *screening of the local scientific literature* for local ADRs.[57] Responsibility for *ADRs arising from MAHs' social media*[58] should be ensured, as should reporting of ADRs during *pregnancy exposure and breastfeeding*.

Safety monitoring by SADC NMRAs, during *clinical trials*, was incomplete. This aspect of PV regulation is still developing in SADC, where only four of the seven member states assessed have made limited safety monitoring provisions during clinical trials. This incongruence between clinical trial activity and PV regulation, as emphasized by Grenham and Villafana[59] warrants SADC regulators' attention, as it exposes the study population and users to medicines whose safety profiles local regulators are unfamiliar with.

Medical devices are typically regulated by an authorized center separate from NMRAs, called the notified body.[60] This separation may not be feasible in resource-constrained nations, but the NMRA can ensure adequate device regulation within existing structures. While device vigilance in SADC is at a fledgling stage (Table 5, C 4.4), developed countries progressed (in 2017) from routine device vigilance to the inclusion of *aggregate reporting requiring periodic submission of a post-marketing surveillance report*.[60] This aggregate report is compiled by the manufacturer, detailing all safety topics of a device over a defined period.[60]

In risk management, continuous safety monitoring of the MAH's products is vital to detect new adverse trends.[61] An emerging safety issue is a topic that may impact public health and is deemed to require immediate attention by the MAH.[57] This topic is communicated to the NMRA for their assessment and direction on appropriate risk minimization measures for implementation. *Reliance on other NMRAs was evident*, as five of seven NMRAs required *notification of steps taken by foreign NMRAs*. Lastly, *review and approval by NMRAs of safety communication* disseminated by MAHs should be mandatory.[62]

Based on the assessment of the guidelines, the following areas for improvement have been identified for individual countries to align PV practice within the SADC region:

4.1 | Botswana

Botswana has appropriate PV legislation in place. Adding HCP and consumer definitions is recommended, and ADR categories of solicited and unsolicited reports should be explicated. For expedited reporting, the inclusion of pregnancy exposure and breastfeeding, adverse events following immunization, ADRs associated with substandard and falsified medicines and ADRs arising from social media and the scientific literature should be described. The submission of DSURs should be mandated to avail safety information to BoMRA as

TABLE 3 Evaluation of requirements for PV systems.

Subtheme	Item	Botswana	Mauritius	Namibia	South Africa	Tanzania	Zambia	Zimbabwe	Total
A 1 PV Legislation—Law/Regulation/Policy	A 1.1 Law	✓	✓	✓	✓	✓	✓	✓	7
	A 1.2 Regulation	✓	×	✓	✓	✓	×	×	4
	A 1.3 Policy	✓	×	✓	✓	✓	×	✓	5
A 2 Description of marketing authorisation holder's (MAH's) pharmacovigilance system	A 2.1 Scope of activities described in a pharmacovigilance manual or pharmacovigilance system master file	✓	×	×	✓	✓	×	✓	4
A 3 Subcontracting	A 3.1 Permitted, but MAH retains responsibility	✓	×	×	✓	✓	×	×	3
	A 3.2 A legally binding contract must be in place	×	×	×	✓	✓	×	×	2
A 4 Archiving	A 4.1 Archive PV records for 10 years after withdrawal, recall or deregistration	×	×	×	×	×	×	×	0
A 5 Person responsible for pharmacovigilance	A 5.1 Regional PV Officer/Qualified Person for PV (QPPV)	✓	×	×	✓	✓	×	✓	4
	A 5.2 Suitably qualified—desired qualifications described	✓	×	×	✓	✓	×	✓	4

Abbreviations: MAH, marketing authorization holder; PV, pharmacovigilance; QPPV, qualified person for pharmacovigilance.

TABLE 4 Assessment of definitions required for PV guidelines.

Item	Botswana	Mauritius	Namibia	South Africa	Tanzania	Zambia	Zimbabwe	Total
B 1 Pharmacovigilance (PV)	✓	×	✓	✓	✓	✓	✓	6
B 2 Adverse drug event (ADE)	✓	×	✓	✓	✓	✓	✓	6
B 3 Adverse drug reaction (ADR)	✓	×	✓	✓	✓	✓	✓	6
B 4 Serious adverse drug reaction or event	✓	×	✓	✓	✓	✓	✓	6
B 5 Unexpected adverse reaction	✓	×	✓	✓	✓	✓	✓	6
B 6 Healthcare professional (HCP)	×	×	×	✓	✓	×	✓	3
B 7 Consumer	×	×	×	✓	×	×	×	1
B 8 Marketing authorization holder (MAH)	✓	×	✓	✓	✓	×	✓	5

Abbreviations: ADE, adverse drug event; ADR, adverse drug reaction; HCP, healthcare professional; MAH, marketing authorization holder; PV, pharmacovigilance.

it develops.[63] Completion of risk management parameters is recommended by including the following items: submit supporting documents upon request by NMRA, implement as agreed with NMRA and DHCPL posted on NMRA's website.

4.2 | Mauritius

More laws, regulations, and policies pertaining to PV are needed as PV is currently only described in clinical trial law and reporting guidelines. A description of MAH's PV system, subcontracting terms, archiving and the qualified person responsible for PV should be specified.[64] Inclusion of definitions in the guideline is recommended to provide context and common understanding for stakeholders.[65] For ICSR reporting, listing of solicited and unsolicited sources of ADRs; for PSUR submission, consideration of the EURD list[66] and DSUR submission are recommended. Steps taken by other NMRAs are required, however, other risk management measures must be elaborated to facilitate timely awareness and management of emerging risks by the MAH and NMRA.[67]

TABLE 5 Individual case safety reports requirement evaluation.

Subtheme	Item	Botswana	Mauritius	Namibia	South Africa	Tanzania	Zambia	Zimbabwe	Total
C 1 Collection, reporting and submission of ICSRs to the NMRA|Criteria	C 1.1 Identifiable patient: age/gender/unique identifier	✓	×	✓	✓	✓	×	✓	5
	C 1.2 Identifiable reporter	×	×	✓	✓	✓	×	×	3
	C 1.3 Suspected company drug	✓	×	✓	✓	✓	×	✓	5
	C 1.4 Adverse reaction	✓	×	✓	✓	✓	×	✓	5
	C 1.5 Follow up: concomitant medication; medical history; course of disease; severity, treatment and outcome of current disease	×	×	✓	✓	✓	×	✓	4
C 2 Collection, reporting and submission of ICSRs to the NMRA|categories of reportable information	C 2.1 Unsolicited sources	×	×	×	✓	✓	×	×	2
	C 2.1 a Spontaneous reports	✓	×	×	✓	✓	×	✓	4
	C 2.1 b Local scientific literature—screen for ICSRs & submit the article to NMRA	×	×	✓	✓	✓	×	×	3
	C 2.1 c Social media sponsored/owned by MAH—screen for ICSRs	×	×	×	✓	×	×	×	1
	C 2.1 d ICSRs from other MAHs' products—forward to relevant MAH	✓	×	✓	✓	✓	×	×	4
	C 2.2 Solicited (Organized post-approval data collection)	×	×	×	✓	✓	×	✓	3
	C 2.2 a Observational studies	×	×	✓	✓	✓	×	✓	4
	C 2.2 b Post-authorisation safety studies	✓	×	✓	✓	✓	×	✓	5
	C 2.2 c Named patient medicine access programmes	×	×	×	✓	✓	×	×	2
	C 2.2 d Registries	×	×	×	✓	✓	×	×	2
	C 2.2 e Patient support and disease management programmes	×	×	×	✓	✓	×	×	2
	C 2.2 f Surveys of consumers for healthcare professionals	×	×	×	✓	✓	×	×	2
C.3 Collection, reporting and submission of ICSRs to the NMRA|Expedited reporting	C 3.1 Adverse drug reactions	✓	×	✓	✓	✓	✓	✓	6
	C 3.2 Lack of drug efficacy	×	×	✓	✓	✓	✓	×	4
	C 3.3 Overdose	×	×	×	✓	✓	✓	×	3

TABLE 5 (Continued)

Subtheme	Item	Botswana	Mauritius	Namibia	South Africa	Tanzania	Zambia	Zimbabwe	Total
	C 3.4 Pregnancy exposure and breastfeeding	×	×	✓	✓	✓	✓	×	4
	C 3.5 Misuse of medicines	×	×	✓	✓	✓	×	×	3
	C 3.6 Abuse of medicines	×	×	✓	✓	✓	✓	×	4
	C 3.7 Off-label use	×	×	✓	✓	✓	×	×	3
	C 3.8 Medication errors	×	×	✓	✓	✓	✓	✓	5
	C 3.9 Drug Interactions	×	×	✓	✓	✓	✓	✓	5
	C 3.10 Product quality complaints	×	×	✓	✓	✓	✓	✓	5
	C 3.11 Substandard and Falsified medicines	×	×	✓	✓	✓	×	✓	4
	C 3.12 Devices	×	×	✓	✓	✓	×	✓	4
C 4 Collection, reporting and submission of ICSRs to the NMRA|Reporting timelines	C 4.1 Post-marketing								
	C 4.1 a Serious local ADRs: 15 days	✓	✓	✓	✓	✓	✓	✓	7
	C 4.1 b Non-serious local ADRs: do not submit	×	×	✓	×	×	✓	×	2
	C 4.1 c Adverse events following immunization: 15 days	×	✓	✓	✓	✓	✓	✓	6
	C 4.1 d ADRs and lack of drug efficacy due to substandard and falsified medicines: 15 days	×	×	×	×	×	×	×	0
	C 4.2 Interventional trials								
	C 4.2 a SUSARs from local study sites. Fatal or Life-threatening: Initial information—7 days, Follow-Up information—8 days	✓	✓	×	✓	✓	×	✓	5
	C 4.2 b Local serious ADRs: 15 days	✓	✓	×	✓	✓	×	✓	5
	C 4.2 c Local non-serious in annual DSUR, as line listing	×	×	×	×	×	×	×	0
	C 4.2 d SUSARs from foreign study sites. Serious: 15 days	×	×	×	✓	✓	×	×	2
	C 4.2 e SUSARs from foreign study sites	×	×	×	✓	✓	×	×	2
	Fatal or Life threatening:								
	Initial information—7 days								
	Follow-Up information—8 days								
	C 4.3 Scientific literature								
	C 4.3 a Serious local ADRs: 15 days	×	×	✓	✓	×	×	×	2

(Continues)

TABLE 5 (Continued)

Subtheme	Item	Botswana	Mauritius	Namibia	South Africa	Tanzania	Zambia	Zimbabwe	Total
	C 4.3 b Screen local scientific literature for ADRs	×	×	✓	✓	✓	×	×	3
	C 4.3 c Submit the full article which contains the ADR to NMRA	×	×	✓	✓	×	×	×	2
	C 4.4 Devices								
	C 4.4 a Serious threat to public health—48 h	×	×	×	✓	✓	×	✓	3
	C 4.4 b Death or serious deterioration in the health of patient or user of the device—10 days	×	×	×	✓	✓	×	×	2
	C 4.4 c Might have caused death or serious deterioration in the health of patient or user of the device—15 days	×	×	×	✓	✓	×	×	2
C 5 Collection, reporting and submission of ICSRs to the NMRA|Reporting format	C 5.1 E2B(R3) gateway or XML	✓	×	×	✓	×	×	✓	3
	C 5.2 CIOMS-I form, if E2B submission not available	✓	×	×	×	×	×	×	1

Abbreviations: ADR, adverse drug reaction; DSUR, development safety update report; EURD, European Union reference dates; ICSR, individual case safety report; MAH, marketing authorization holder; NMRA, National Medicines Regulatory Agency; SUSAR, suspected unlisted serious adverse reaction.

TABLE 6 Assessment of submission of aggregate reports.

Subtheme	Item	Botswana	Mauritius	Namibia	South Africa	Tanzania	Zambia	Zimbabwe	Total
D 1 Aggregate reporting in the post-marketing period	D 1.1 PSUR/PBRER—submit in line with the International birth date or EURD List	✓	×	✓	✓	✓	×	✓	5
D 2 Aggregate reporting in clinical trials	D 2.1 DSUR submit annually	×	×	×	✓	✓	×	×	2

Abbreviations: DSUR, development safety update report; EURD, European Union reference dates; PBRER, periodic benefit risk evaluation report; PSUR, periodic safety update report.

4.3 | Namibia

The Namibian PV system is supported by appropriate legislation, however, a description of the MAH's PV system, terms for subcontracting, archiving conditions and the qualified person responsible for PV should be included in their guidelines. To avoid misinterpretation, adding the definitions for healthcare professionals and consumers is recommended. For ICSR processing, it is recommended to provide a complete listing of unsolicited (spontaneous reports and social media sponsored/owned by MAH) and solicited (post-authorization safety studies, named patient medicine access programs, registries, patient support and disease management programs and surveys of consumers or healthcare professionals) ADR sources. Inclusion of expedited reporting of serious or unexpected ADRs associated with overdose is needed. Submission of ADRs and lack of drug efficacy due to substandard and falsified medicines within 15 days is recommended. It is recommended to conform to the current requirement to report serious ADRs of new chemical entities within five business days to the

TABLE 7 Assessment of risk management.

Subtheme	Item	Botswana	Mauritius	Namibia	South Africa	Tanzania	Zambia	Zimbabwe	Total
E 1 Signal detection	E 1.1 Continuous monitoring of the safety of MAH's products	✓	×	✓	✓	✓	×	✓	5
	E 1.2 Emerging Safety Issue: submit to NMRA within 5 calendar days	✓	×	✓	✓	✓	×	✓	5
E 2 reevaluation of the risk–benefit ratio	E 2.1 Steps taken by foreign NMRAs—submit to local NMRA within 5 calendar days	✓	✓	✓	✓	✓	×	×	5
E 3 Safety decision-making process	E 3.1 Submit supporting documents upon request by NMRA	×	×	✓	✓	✓	×	×	3
E 4 Risk management planning	E 4.1 Submit Risk Management Plans: Upon request by NMRA	✓	×	✓	✓	✓	×	✓	5
E 5 Risk minimization	E 5.1 Propose and discuss suitable measures with NMRA	✓	×	✓	✓	✓	×	×	4
	E 5.2 Implement as agreed with NMRA	×	×	✓	✓	✓	×	✓	4
E6 Safety Communication	E 6.1 DHCPL—review by NMRA	✓	×	✓	✓	×	×	✓	4
	E 6.2 Distribution by email or post	✓	×	✓	✓	×	×	✓	4
	E 6.3 DHCPL posted on NMRA's website	×	×	×	×	×	×	✓	1

Abbreviations: DHCPL, dear healthcare professional letter; MAH, marketing authorization holder; NMRA, National Medicines Regulatory Agency.

norm of 15 days.[68] Device safety reporting is recommended. Aligning the reporting timelines for PSUR submission with the EURD list, addressing clinical trials (including annual submission of the DSUR) safety reporting is recommended. Safety communication to PV stakeholders by publishing the DHCPL on the NMRA website is recommended. These parameters all contribute towards a complete and effective PV system.[69]

4.4 | South Africa

The PV system in South Africa is premised upon suitable legislation and met the requirements, apart from stipulating conditions for archiving safety data by MAHs, possibly due to the relative longstanding WHO PIDM full membership.[70] Definitions of key PV terms were provided in full. For ICSR reporting, submission of ICSRs due to serious or unexpected substandard and falsified medicines should be addressed, to facilitate the contribution of PV towards the quantification of this public health threat.[71] Aggregate reporting was appropriately addressed. In risk management, updating the guideline to specify the publication of DHCPLs on the NMRA's website rather than the MAH's website is recommended, in line with the EMA good vigilance practices.[72]

4.5 | Tanzania

The PV system of Tanzania is supported by a legal framework consisting of laws, regulations, policies, and clear guidelines.[73] It is recommended that the guidelines for MAHs address the terms for archiving documents and the definition for a consumer. In ICSR reporting, it is recommended to mandate the screening of social media owned by MAHs, reporting of ADRs and lack of drug efficacy due to substandard and falsified medicines within 15 days, the inclusion of non-serious ADRs in the DSUR and reporting timelines and submission of the relevant article, for ADRs from the worldwide scientific literature, with copyright provisions observed. Aggregate reporting was adequately addressed. Risk management can address safety communication through DHCPLs, as this presents an opportunity to relay new safety information and any required risk mitigation steps.[74] Review of the letter by the NMRA prior to distribution, specifying distribution by email or post and posting of the letter on the NMRA website are recommended.[75]

4.6 | Zambia

The PV legislation of Zambia consists of a law and one PV guideline. It is recommended to include the requirement for the MAH to describe

the scope of the PV system in a manual, subcontracting of PV activities, archiving of PV documents and the qualified person responsible for PV, as these items ensure the implementation of effective PV systems by MAHs.[76] Definitions included PV, adverse drug event, adverse drug reaction, unexpected ADR and serious ADR; it is therefore recommended to add healthcare professional, consumer and MAH in keeping with international standards.[77] The following ICSR reporting parameters warrant inclusion in the Zambian guideline: ADRs from scientific literature, interventional trials and devices. Where ICSR submission is required, timelines are needed to ensure prompt risk awareness by NMRAs. The inclusion of aggregate report submission and risk management requirements is recommended, for mutual review of safety concerns by MAHs and NMRAs.[78] The lag in PV regulation can be attributed to the Zambian guideline being 15 years old at the time of this study; reviewing this guideline will assist in facilitating good PV governance in Zambia.

4.7 | Zimbabwe

The PV legislation of Zimbabwe was supported by law, no regulation, a combined policy and guideline, as well as three separate guidelines. It is recommended to separate the policy and guideline, as policies generally proclaim official positions and instructive guidelines support the efficient implementation of policies and avoid variance.[79] Inclusion of conditions for subcontracting of any PV services (e.g., literature screening) by the MAH and prescribing archiving terms is recommended. Adding the definition of consumer is recommended. For ICSR reporting, the reporting of serious or unexpected ADRs due to lack of drug effect, overdose, exposure during pregnancy and breastfeeding, misuse and abuse of medicines and off-label use are recommended. Reporting of ADRs and lack of drug efficacy due to substandard and falsified medicines within 15 days as well as screening of the worldwide scientific literature for local ADRs are recommended.[80] Reporting of device incidents other than public health threats is recommended. Within interventional trials, submission of foreign SUSARs is recommended, as is the annual submission of the DSUR (local non-serious ADRs included).[81] For risk minimization, submission of supporting documents upon request by the NMRA and discussing and proposing suitable measures are recommended. It is suggested to specify the reporting timeline for emerging safety issues.

4.7.1 | Strengths and limitations

The study was limited by only assessing PV guidelines from seven countries and comparing them to advanced PV systems. The possibility exists that guidelines could have been missed because they were not available at the time of the study, although we tried to reduce the likelihood of this by repeating the search and sending requests to the relevant NMRAs. The guidelines assessed during this study may have been updated or new PV laws, regulations, policies or guidelines may have been implemented or disseminated by SADC NMRAs since finalization of this study. Researcher bias was avoided through test–retest application and manuscript review by the co-authors. Future studies could investigate the impact of harmonized guidelines in Africa and assess PV guidelines in SADC[82,83] published or disseminated after July 2021.

5 | CONCLUSION

The safety monitoring of biomedical products and devices in SADC member states is incomplete due to varying national PV guidelines. SADC member states would benefit from regional guidelines that appropriately address the governance of medicines, vaccines, and devices in clinical trials and post-marketing settings to ensure uniformity and convergence. This study illustrates the need for PV guidelines harmonization in SADC and may be used as a baseline to reduce the dissimilarities identified. Areas for improvement of existing guidelines to establish common process standards and allow for synchronized submissions of comparable data to SADC NMRAs have been identified.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ETHICS STATEMENT

The study was approved by the North-West University Health Research Ethics Committee (NWU-00306-20-A1) in South Africa.

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