THERAPEUTIC ADVANCES in
Drug Safety

Original Research

Development of a checklist for the assessment of pharmacovigilance guidelines in Southern Africa: a document review

Ther Adv Drug Saf

2023, Vol. 14: 1–18

DOI: 10.1177/20420986221143272

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Abstract

Introduction: National regulatory systems in Southern Africa reflect various stages of maturity, and pharmacovigilance (PV) practices are not aligned. In the absence of guidance for formulating PV guidelines in Southern African Development Community (SADC) countries, this study aimed to create a checklist that may be used to assess the rigour of PV guidelines in this region and provide guidance for the National Medicines Regulatory Agency (NMRA) authors.

Methods: A document analysis was performed based on harmonised international guidelines ($n = 22$) that prescribed methods of PV regulation to identify themes and items to incorporate into a checklist. The contextualisation of the checklist to the African pharmaceutical environment was accomplished by referencing peer-reviewed journal articles ($n = 7$). The checklist was subjected to face and content validation by non-experts and PV experts.

Results: The document review yielded 5 themes, 18 sub-themes, and 73 items structured into the checklist. Themes encompassed PV systems, definitions, individual case safety reporting, aggregate reporting, and risk management. Under PV systems, aspects of the quality management system were outlined, that is, the legal basis for PV, a description of the marketing authorisation holder's (MAH's) PV system, archiving of data, contracting of PV tasks, and the duties of the person responsible for the MAH's PV obligations. Definitions of the key terms and major stakeholders were identified. Reporting of individual case safety reports (ICSRs) was explicated by considering the criteria for reporting, categories of reportable information, expedited reporting requirements, reporting timelines, and ICSR reporting format. Aggregate report submission during the development and post-marketing phases was addressed. Risk management encompassed signal detection, re-evaluation of the benefit-risk ratio, the safety decision-making process, risk management planning, risk minimisation and safety communication.

Conclusion: The developed checklist can contribute towards assisting SADC NMRAs to formulate national PV guidelines that reflect current international practice, with local context incorporated.

Plain Language Summary

Developing a checklist for the evaluation of medicine safety guidelines in Southern Africa

Introduction: In Southern African Development Community (SADC) countries, the guidelines for medicine safety [pharmacovigilance (PV)] that marketing authorisation holders (MAHs) and healthcare professionals need to adhere to, are not aligned. We saw the need to develop a checklist that can be used to evaluate these guidelines.

Methods: We studied international documents issued by the World Health Organization (WHO), the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), the Council for International Organizations of

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Medical Sciences (CIOMS) and the European Medicines Agency (EMA). On the organisational websites, we obtained 22 documents and identified 73 checklist items. All the items were arranged under 5 themes and 18 sub-themes to create the checklist. We adapted the checklist to the local context by using seven journal articles addressing PV concerns in Africa. Experts checked the content and usability of the checklist.

Results: The themes were PV systems, definitions, individual case safety reporting (ICSR), combined reporting and risk management. PV systems had six sub-themes: legal structure, description of the MAH's PV system, contractual agreements, information storage, the qualified person responsible for PV (QPPV) and where the QPPV is located. We included the definitions of keywords and role-players. The ICSR theme had five sub-themes, i.e. criteria for reporting, categories of reportable information, expedited reporting, reporting timelines, and reporting format. Submission of summary reports comprised an overview of the safety profile of a medicine once it is approved by regulators, as well as during clinical trials. Risk management included signal detection, re-evaluation of the benefit-risk ratio, safety decision-making process, risk management planning, risk minimisation, and safety communication. The checklist is applied by allocating yes/no scoring per item.

Conclusion: The checklist may be used by regulators within SADC to assess their PV guidelines for alignment with international standards and suitability to the local environment.

Keywords: checklist, document analysis, guidelines, pharmacovigilance, Southern African Development Community

Received: 26 April 2022; revised manuscript accepted: 15 November 2022.

Background

Despite the global regulatory shift towards harmonisation of pharmacovigilance (PV) practices,[1] the national regulatory systems in Southern Africa are at various stages of maturity, and their PV practices are not harmonised.[2] PV regulatory requirements for marketing authorisation holders (MAHs) and healthcare professionals differ among the Southern African Development Community (SADC) countries. Progress has been made in SADC by harmonising regulatory inspections, as well as approvals of biomedical products, through the participation of 13 of 16 SADC countries [Zambia, Zimbabwe, Botswana, Namibia, South Africa, The Democratic Republic of Congo, Tanzania, Malawi, Mozambique, Angola, Seychelles, Swaziland (now Eswatini), and Madagascar] in the ZaZiBoNa project.[3] The ZaZiBoNa collaboration aims to strengthen National Medicines Regulatory Agency's (NMRA's) competence in reviewing dossiers for new product applications and create regulatory convergence among the participating nations, thereby reducing product registration timelines, transferring expertise, and managing limited human and financial resources.[3]

The scope of this SADC collaborative effort, based on Article 29 (Pharmaceuticals) of SADC's protocol on health, however, does not include PV practice; hence, there is no regional guidance on the specification of PV guidelines in SADC.[4]

A conference was convened in 1990 after Western governments recognised the need to harmonise the safety monitoring of medicines to advance the harmonisation of PV practices.[5] The International Conference for Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) was established by consensus with the MAHs, the World Health Organisation (WHO), and the National Medicines Regulatory Authorities (NMRAs) of Europe, Japan and the United States. Currently, 17 members and 32 observers (including one SADC member state) cooperate in formulating harmonised guidelines for the regulation of quality, safety, and efficacy of medicines adopted by regulators worldwide.[6] The ICH work allows for adopting harmonised PV practices by national and regional regulators who embrace the ICH guidelines.

Table 1. Maturity stages of Southern African NMRAs, based on MSH country groupings.

Category	Description of PV capacity of country grouping	Southern African countries (year PIDM was joined)
1	Countries with limited or no capacity for PV	Angola (2013), Eswatini (2015), Madagascar (2009), Mauritius (2014)
2	Countries with basic organisational structures	Botswana (2009), the Democratic Republic of the Congo (2010), Mozambique (2005), Zambia (2010), Zimbabwe (1998)
3	Countries can collect and evaluate safety data based on legal and organisational structure	Tanzania (1993)
4	Countries with a basic system for active and passive surveillance	Namibia (2009), South Africa (1992)

PIDM, Programme for International Drug Monitoring; PV, pharmacovigilance.

At a regional level, the European Medicines Agency (EMA) elaborated the ICH guidelines into 16 good pharmacovigilance practices (GVP) modules from 2012 onwards.[7] Four modules (XI-XIV) were listed but not expounded, as they had been addressed in other modules. With each GVP module addressing a PV process, all modules are intended for implementation by European NMRAs and MAHs.

The templates for the transmission of safety data were formulated by the Council for International Organizations of Medical Sciences (CIOMS), particularly for the expedited reporting of ICSRs.[8] Submission of ICSRs by MAHs to NMRAs is an essential aspect of routine PV practice.[9] The CIOMS-I form is the universally accepted document for reporting single PV cases by the MAH to the NMRA.[10] In recent years, other means of electronic transmission have overtaken the CIOMS form, with the implementation of the E2B transmission mode by NMRAs in advanced PV systems in 2013.[11] Electronic transmission, now in its third revision, is known as E2B(R3). It is ideally conducted through a gateway, wherein data are transmitted directly from MAHs to NMRAs' databases.

In keeping with the principles of convergence, the WHO played a central role in establishing PV.[12] In addition to articulating some fundamental definitions, the WHO Programme for International Drug Monitoring (PIDM) was founded in 1968 and is managed by the Uppsala Monitoring Centre in Sweden.[13] Globally, NMRAs subscribe to the PIDM and routinely forward their national safety data for inclusion in VigiBase®, the WHO global database of ICSRs.[14] The purpose of the PIDM is to collect, aggregate, analyse and report on safety data (particularly signals) received from NMRAs.[15] The success of this worldwide programme depends on the voluntary participation of NMRAs. It has been 30 years since the first African country (South Africa) joined the programme in 1992, and African enrolment is ongoing.[16] Africa has attained 87% (associate and full) membership, with the participation of 45 of 55 African nations and territories in the programme, compared to 100% for Europe, while the SADC membership rate is currently 88%.[17]

While advancing PV capacity-building efforts in developing nations, Management Sciences for Health (MSH) produced a country grouping classification (four groups) based on PV systems' capacity.[18] Table 1, adapted from Ampadu *et al.*,[19] summarises the maturity stages of Southern African NMRAs, determined by their PV capacity and the year that the PIDM was joined. Only 12 of 16 SADC countries are reflected in Table 1: Nine are in categories 1 and 2, with basic organisational structures; three are in categories 3 and 4. Regarding the four countries not represented in Table 1, 3 of 16 are not PIDM members, namely Comoros, Lesotho, and Seychelles. Malawi joined the PIDM in 2019 and had not been assigned an MSH grouping at the time of this study.

At the national level, the safety information required by NMRAs is solicited from stakeholders through legislation communicated as guidelines. NMRAs produce mandatory guidelines that dictate reporting requirements to their stakeholders to obtain the desired information. Guidelines are intended to direct the delivery of a service based on a distillation of current best practices.[20]

Having taken cognisance of the fragmented regulatory framework in Africa, the heads of government of the African Union signed and adopted a treaty to establish a continental regulatory authority in 2019 called the African Medicines Agency (AMA).[21] The African Medicines Agency is projected to operate a decentralised system that relies on the harmonisation of regulatory processes within regional economic communities.[22] In the absence of guidance for formulating PV guidelines in SADC, this study aimed to develop a checklist that may be utilised to assess the rigour of PV guidelines in Southern Africa and serve as a reference for best-practice, while unlearning unneeded preferences.

Methods

Design

A document review was conducted by utilising a qualitative, descriptive research design. Purposive sampling was employed when sourcing the documents for review. The review was conducted by referencing best-practice documents.

Data collection

The objective was to conduct document reviews, select key terms from the documents and synthesise the terms into a functional checklist for national PV practice in SADC countries. The document selection was conducted in two parts. First, criterion sampling was employed to select eligible consensus documents, and second, a literature review was conducted to identify documents that could be utilised to contextualise the checklist to the SADC PV pharmaceutical environment. Documents were collected continuously by the principal researcher from March 2019 to July 2021.

The PV guidelines and guidance documents of the ICH, EMA, CIOMS, and WHO, foundational to PV, were sourced. We selected consensus, multinational documents that described PV regulation by NMRAs. The principal researcher applied her professional expertise by including those foundational documents used to define and refine the application of PV practice. All consensus documents were deemed authentic, as they were retrieved from the respective authors' organisational websites. By employing purposive sampling, we focused on those documents that would yield rich, prescriptive data on PV regulation,[23] by selecting only the PV guidelines addressed to MAHs and healthcare professionals. Where authors of reference documents had compiled a cluster of documents, such as the ICH efficacy documents, the entire series of consensus documents were identified and selected for review.[24] Only English language documents were considered for selection. The consensus documents of ICH, EMA, CIOMS, and WHO were purposively sourced.

Since most of the harmonised reference documents originated from the developed world, the literature search was expanded to source documents that can be used to contextualise the international consensus documents in the African context. The following scientific literature databases were searched: ScienceDirect®, Scopus®, PubMed®, EBSCOHost®, Google Scholar™ and Sabinet (SAePublications)®. Search terms used were 'pharmacovigilance', 'guideline', 'medicine safety', 'monitor', 'harmonisation', 'Africa' and 'pharmacovigilance systems'. The literature review yielded a plethora of data sources, including peer-reviewed journal articles, conference papers, reports, theses and legal directives. The documents retrieved from the literature search were used to contextualise the checklist for the SADC region. The keywords for eligibility of the selected documents were 'pharmacovigilance', 'guideline', 'national', 'drug safety', 'drug', 'adverse event reporting', 'vigilance', 'safety reporting', 'device' 'clinical trials', 'post-marketing', 'healthcare professionals', 'marketing authorisation holders'.

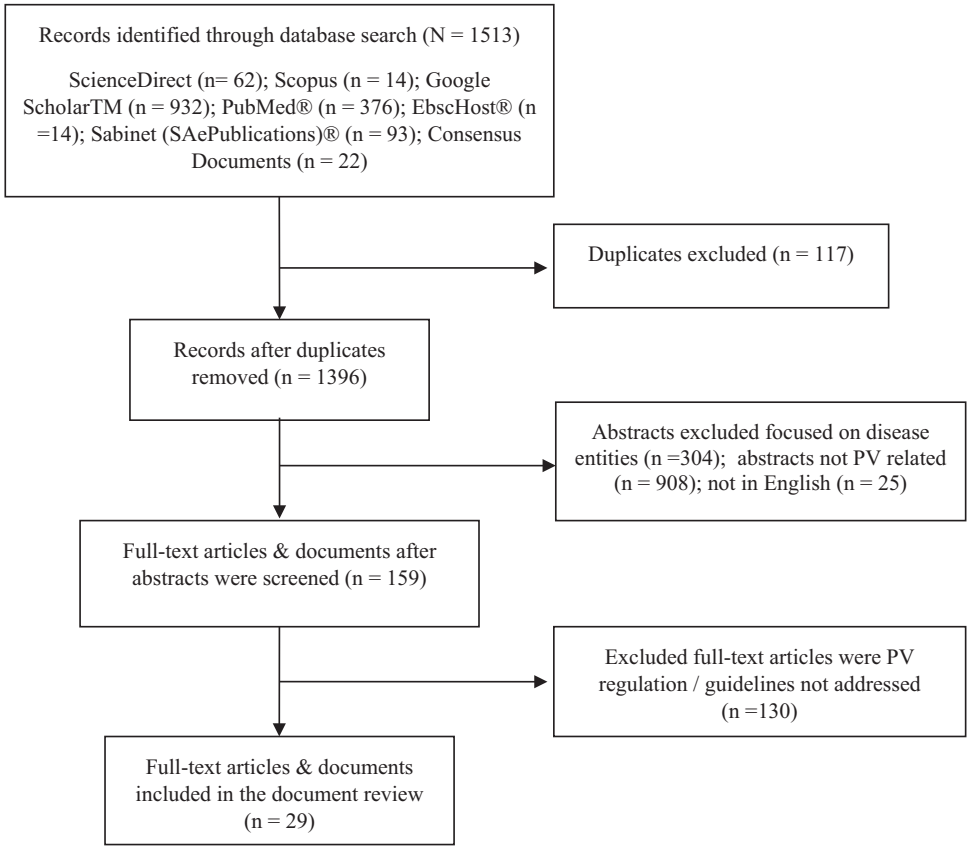

Figure 1. Flow diagram of document screening results.

The inclusion criteria were as follows:

- International (regional and global) harmonised PV guidelines.
- No restriction regarding the date.
- Peer-reviewed journal articles.
- Theses.
- Conferences.

The exclusion criteria were as follows:

- Veterinary vigilance guidelines. Some guidelines may include the safety aspects of veterinary medicines, but this study is confined to the review of the safety aspects of medicines consumed by humans only.
- Abstract-only papers.
- Articles with no available full text.
- Articles in languages other than English.

The search yielded 1513 documents. After removing 117 duplicates, 1396 documents were assessed for eligibility by reading the abstracts. From these, 1237 documents were excluded based on ineligibility; 25 documents were non-English, 908 documents were unrelated to PV, and 304 focused on disease entities. Among the remaining 159 documents, 130 were excluded for not addressing regulatory aspects of PV in Africa (Figure 1).

The document selection exercise yielded 29 final documents, including the 22 international consensus documents (Table 2). Having referenced the international documents, the additional seven peer-reviewed documents identified during the literature search were utilised to conform the checklist to the Southern African regulatory landscape. The seven documents highlight the topics which warrant attention within Southern African PV guidelines and are listed in Table 3.

Seven EMA Good Vigilance Practice (EMA GVP) modules were not included because they were not articulated or did not apply to the study. The EMA GVP documents not referenced are listed in Table 4.

Table 2. International documents referenced.

Guideline identifier/ Module number/Form	Efficacy guideline title/Module title/Document title	Effective date
International Council for Harmonisation (ICH) Efficacy guidelines referenced		
ICH E2A[25]	ICH Harmonised Tripartite Guideline, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. E2A, Current Step 4 version.	27 October 1994
	Standard definitions of terms applicable to reporting safety information during clinical trials are provided in this document. The pathway for expedited reporting during clinical trials is also addressed.	
ICH E2B[11]	ICH Harmonised Tripartite Guideline, on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports. E2B(R3), Current Step 4 version.	1 November 2012
	The format and data fields necessary for the electronic reporting of single cases are detailed in this guideline.	
ICH E2 C[26]	International Council for Harmonisation History. ICH Harmonised Tripartite Guideline, Periodic benefit-risk evaluation report (PBRER). E2 C(R2), Current Step 4 version.	17 December 2012
	The importance and frequency of aggregate safety reporting are delineated in this ICH guideline.	
ICH E2D[27]	International Council for Harmonisation History. ICH Harmonised Tripartite Guideline, Post Approval Safety Data Management: Note for Guidance on Standards and Definitions for Expedited Reporting.	12 November 2003
	Definitions and methods of reporting safety data in the post-marketing environment are provided in this guideline.	
ICH E2E	ICH Harmonised Tripartite Guideline, Pharmacovigilance Planning E2E, Current Step 4 version.	18 November 2004
	The risk management activities to be undertaken following registration of a drug are described, with particular emphasis on the immediate post-marketing period.	
ICH E2 F[28]	ICH Harmonised Tripartite Guideline, Development Safety Update (DSUR) Report E2 F, Current Step 4 version.	17 August 2010
	The structure and periodicity of submission of safety data collected and collated into a DSUR during the development phase are described.	
European Medicines Agency document(s) referenced		
EU reference dates list[29]	Periodic safety update reports (PSURs). Submission requirements and EU reference dates (EURD) list.	2019
	The document discloses the periodicity and timing of submission of the periodic safety update report in the EU	
EU Commission[30]	Volume 2A Procedures for marketing authorisation. Chapter 1 Marketing Authorisation.	July 2019
EU MDR 2017/745[31]	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices	26/May/2017

(Continued)

Table 2. (Continued)

Guideline identifier/ Module number/Form	Efficacy guideline title/Module title/Document title	Effective date
European Medicines Agency Good Vigilance Practices referenced		
Module II	Pharmacovigilance system master file	31/03/2017
Module V	Risk management systems	31/03/2017
Module VI[32]	Collection, management, and submission of reports of suspected adverse reactions to medicinal products	22/11/2017
Module VII	Periodic safety update report	13/12/2013
Module VIII	Post-authorisation safety studies	13/10/2017
Module IX[33]	Signal management	22/11/2017
Module X[34]	Additional monitoring of medicines	25/04/2013
Module XV[35]	Safety communication	13/10/2017
Module XVI	Risk minimisation measures: selection of tools and effectiveness indicators	31/03/2017
World Health Organization documents referenced		
	The importance of pharmacovigilance: Safety monitoring of medicinal products.[12]	2002
	Being a member of the WHO Programme for International Drug Monitoring.[36]	2014
Council for International Organisations of Medical Sciences documents referenced		
CIOMS I form[8]	CIOMS-I form	2002
	The document contains the essential data elements for forwarding ICSRs that most NMRAs have adopted.	
CIOMS II form (Line Listing)[37]	International reporting of periodic drug safety update summaries.	2005
	The structure for reporting individual adverse drug reactions (ADRs) as a line listing is provided.	

ADR, adverse drug reaction; CIOMS, Council for International Organisations of Medical Sciences; DSUR, development safety update report; EURD, EU reference dates; ICH, International Council for Harmonisation; PBRER, Periodic benefit-risk evaluation report; PSUR, Periodic safety update report; WHO, World Health Organization.

Table 3. Peer-reviewed documents selected as data sources for the contextualisation of the checklist.

Authors	Article title	Theme of interest
Ampadu[38]	Organisational capacities of national pharmacovigilance centres in Africa: assessment of resource elements associated with successful and unsuccessful pharmacovigilance	MAH to employ QPPV
		National law for the enactment of PV
		Need to fight against counterfeit medicines

(Continued)

Table 3. (Continued)

Authors	Article title	Theme of interest
Ayorinde and Alabi[39]	Perception and contributing factors to medication administration errors among nurses in Nigeria	Reporting medication errors is a fundamental responsibility of HCPs
Barry *et al*.[40]	Comparative Assessment of the National Pharmacovigilance Systems in East Africa: Ethiopia, Kenya, Rwanda and Tanzania	Ensure regulations undergird guidelines and policy
		Medication errors not being detected
Bencheikh and Benabdallah[41]	Medication errors: pharmacovigilance centres in detection and prevention	PV centres can detect, identify, analyse, and classify medication errors. Inform healthcare professionals about the importance of reporting them and create a culture of patient safety
Cheaib[42]	Pharmacovigilance in Clinical Trials: Current Practice and Challenges	Causality as reporting criterion – report only related ICSRs
		Submit foreign SUSARs
		Submit DSUR
Isah *et al*.[43]	Specific features of medicines safety and pharmacovigilance in Africa	Falsified and substandard medicines are not effectively regulated
Olsson *et al*.[44]	PV in resource-limited countries	Identify and detect substandard/spurious/ falsely labelled/falsified/counterfeit (SSFFC) medicines and vaccines through PV
		AEFI inclusion in PV
		Report lack of drug effect due to counterfeits
		Adapt ICH to the local context

AEFI, adverse event following immunisation; DSUR, development safety update report; ICH, International Council for Harmonisation; MAH, marketing authorisation holder; QPPV, qualified person for pharmacovigilance; SSFFC, substandard/spurious/falsely labelled/falsified/counterfeit.

Checklist compilation

Authorship was disclosed, and all documents were titled and dated, with revisions identified.[45] The purpose and intended audience were unambiguously stated. Since the consensus documents were regulatory, the tone was instructional, leaving little to no room for misinterpretation. All documents were planned and were part of a series created to establish regulatory standards in PV practice. The documents were not designed for this research question and were not always directly transferable to the SADC context. All consensus documents were deemed authentic, as they were retrieved from the respective authors' organisational websites. The literature referenced was retrieved from scientific journal databases that publish peer-reviewed articles.

The principal researcher read each document, and pertinent data were identified and extracted. Content analysis was applied as a first-pass review of the general topic of each document.[46] Thereafter, thematic analysis was utilised to identify common themes in the selected documents.[47] As themes emerged, they were explored to identify embedded patterns among the documents.

Data identified and extracted from data sources were clustered and subcategorised for further streamlining into a checklist. Descriptions of legal

Table 4. European Medicines Agency Good Vigilance Practices documents not referenced.

Module number	Module title	Reason for exclusion
Module I	Pharmacovigilance systems and their quality systems	The requirements of this module apply to the EU structure, where NMRAs are accountable to a regional regulatory agency (EMA).
Module III	Pharmacovigilance inspections	This module applies to functions performed by NMRA's inspectorate. The NMRA must fulfil it.
Module IV	Audits	This module applies to the requirement for the global function to audit their PV systems and is part of the quality system addressed within the PV system master file.
Module XI	Partners and networks (addressed elsewhere)	This module exists as a title only. No document was created by EMA.
Module XII	Post-marketing authorisation: regulatory and procedural guidance (addressed elsewhere)	This module exists as a title only. No document was created by EMA.
Module XIII	The incident management plan (addressed elsewhere)	This module exists as a title only. No document was created by EMA.
Module XIV	Partners and networks (addressed elsewhere)	This module exists as a title only. No document was created by EMA.

EMA, European Medicines Agency; EU, European Union; NMRA, National Medicines Regulatory Agency; PV, pharmacovigilance.

frameworks or laws were selected. Descriptions of PV systems, including the MAH's quality management system, were selected. Definitions of basic terms used in PV – ADE, ADR, pharmacovigilance, unexpected ADR, and serious ADR – were selected. The definitions of key PV stakeholders were also identified and extracted: healthcare professionals, consumers, and MAH. Direct instructions to stakeholders were located and terms of interest regarding ICSR reporting to NMRAs were as follows:

- Criteria for reporting – minimum reportable information, as well as detailed follow-up reports.
- Categories of reportable information – unsolicited and solicited sources of safety data.
- Expedited reporting – reports that should be forwarded to the NMRA routinely.
- Timelines for reporting – in the post-marketing phase and during the conduct of interventional trials, reports from scientific literature and ICSRs associated with the use of medical devices.
- Reporting format-specific forms or reports for transmission of safety data to the NMRA.

Aggregate reports designed for periodic submission were identified, and the methods to manage risk were detailed: signal detection, re-evaluation of the benefit-risk ratio, the safety decision-making process, risk management, risk minimisation and safety communication.

Themes, sub-themes, and items were identified for each full-text document and extracted as components of medicines' safety monitoring (Supplementary File 1). All text referring to the processing of safety information was extracted (not *verbatim*) from the reference documents and the peer-reviewed journal articles (Supplementary File 2). The themes were coded.

Data gleaned from each source were entered into tables using Microsoft® Word and Excel software. The extracted parameters (themes, sub-themes, and items) were structured logically and integrated into a thematic analysis checklist

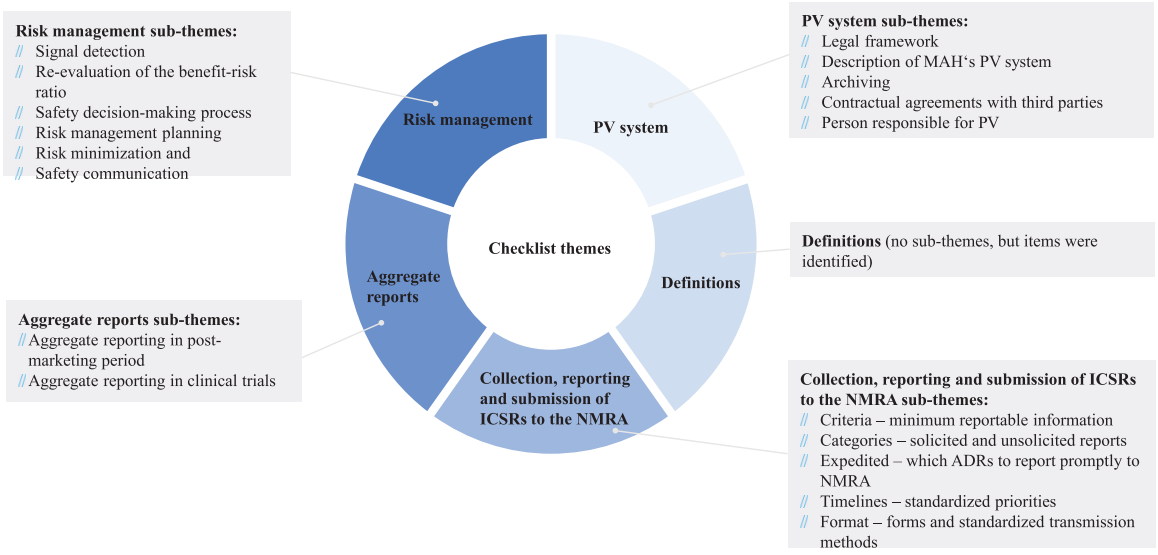

Figure 2. Themes and sub-themes of the Pharmacovigilance Guideline Checklist for Southern Africa.
Abbreviations: ICSR, Individual Case Safety Report; MAH, Marketing Authorisation Holder; NMRA, National Medicines Regulatory Authority; PV, Pharmacovigilance.

(Supplementary File 3). The findings were presented in the form of descriptive narration, as well as a structured checklist.

Validation

The checklist was subjected to face and content validity by three PV experts and two non-experts (a research methodology expert and a language and communication specialist). The PV experts performed content, as well as face validity. The three subject experts were encouraged to make recommendations, which were integrated into the checklist. The two non-PV experts performed face validity only. Aspects such as formatting, numbering, language, and flow of the document were considered. The recommendations of the experts were also incorporated into the checklist.

Authors of documents may express selection bias when compiling consensus documents.[48] In this study, the most authoritative documents reviewed were consensus documents devised by experts from developed nations and were tailored subjectively for high-income national PV systems. This selection bias is partially mitigated by the broad representation of organisations from developing countries through observer status at ICH, ensuring continuous awareness of developments in international PV policy.[49] This selection bias was accounted for by referencing PV literature applicable to the African context. It is also acknowledged that researcher bias may occur by including only data that affirm the research hypothesis. Confirmation bias was avoided through a continuous reassessment of content to ensure accurate interpretation and triangulation among the documents.[50]

Results

Integration of the extracted data yielded a checklist with 5 main themes, 18 sub-themes, and 73 items pertaining to how NMRAs require stakeholders to report safety information to national PV centres. A depiction of the 5 main themes and 18 sub-themes identified is presented in Figure 2. The 73 items are presented in the checklist.

The five themes depicted in Figure 2 are presented in summary with sub-themes and items identified as essential elements of the thematic category.

PV system

In this section, 5 sub-themes were articulated. The description of the PV system encompasses the *legal framework* and structure upon which PV activities are implemented nationally and devolved into regulations, policies, and guidelines. Second, the requirements for a *description of the MAH's PV*

system entail a PV manual that describes the processes and activities undertaken by an organisation to ensure that they meet the PV obligations mandated by the NMRA.[51] The third and fourth factors entailed aspects of *contractual agreements* when PV responsibilities are delegated to a third party and the *archiving of safety data* by the MAH. Finally, a suitably *qualified person responsible for PV* and *residency* within a prescribed territory were incorporated.

Definitions–key terms and stakeholders

While the list of definitions may be quite extensive in a guideline, only eight essential definitions were selected, and no sub-themes were identified. A definition of what *pharmacovigilance* entails was included.[52] The terms *adverse drug reaction* and *adverse drug event*, often used interchangeably, were distinguished. *Unexpected ADR* reports are sought by NMRAs, as they are fundamental for potential signal analysis.[33] *Seriousness of the ADR*, prescribed by CIOMS,[8] impacts decisions to report safety information and must, therefore, be defined. Definitions of PV stakeholders included the term *healthcare professional*, who could also be an investigator in a clinical trial; a *consumer* (or patient), and the *MAH*, who could be a manufacturer/distributor or non-profit organisation in various pharmaceutical markets.[37]

Individual case safety reports

The theme of collecting, reporting, and submitting ICSRs to the NMRA was divided into five sub-themes, i.e. *criteria for reporting, categories of reportable information, expedited reporting, reporting timelines*, and *reporting format*.

Under *criteria for reporting*, minimum data elements that constitute a reportable ADR were identified.[25] In addition, the need for detailed follow-up to complete the case record and obtain valuable safety data were deemed essential.

For *categories of reportable information*, sources of safety information are categorised into solicited and unsolicited sources. A listing of solicited sources includes organised data collection systems, such as registries, observational studies, healthcare professional or patient surveys, patient support and disease management programmes, named-patient medicine access programmes, and efficacy and compliance studies, such as post-authorisation safety studies.[27,53] Unsolicited sources include spontaneous reports, reports from local scientific literature, digital media platforms owned by the MAH, and safety information forwarded by other MAHs. Although not formalised in EMA guidelines, forwarding of reports to the product owner (courtesy reports) is expected by NMRAs and is done by MAHs. The onus to submit the ICSR lies with the product owner, thus avoiding duplication of ICSRs in the NMRA's database. This is particularly important in low-resource settings, where NMRAs do not have the use of sophisticated databases that allow for seamless duplicate checks.

Expedited reporting priorities agreed upon by CIOMS were incorporated. Local, serious, related cases (expected and unexpected) were prioritised.[32,54] Whereas the ICH did not mandate reporting of non-serious ADRs in 2003,[54] the EMA GVP module VI[32] requires reporting of non-serious ADRs within 90 days; however, in low-resource settings, it is preferable not to report routinely due to a high volume of low-value, non-serious ICSRs.[54] Reports of ADRs associated with lack of drug efficacy, overdose, pregnancy exposure and breastfeeding, misuse of medicines, abuse of medicines, off-label use, medication errors, and drug interactions were included.[32] Reporting of adverse reactions associated with product quality defects and falsified medicines were incorporated.[32] The parameters and timelines for device vigilance were premised on the recently effective medical devices regulation of the European Union (EU), which stipulates reporting within 2 days all serious public health threats, reporting within 10 days incidents of death or serious deterioration in the health of the patient or user of a device and reporting within 15 days incidents which might have caused death or serious deterioration in the health of the patient or user of a device.[31] *Reporting timelines* for expedited reports were informed by ICH standards (using calendar days).[55] During the drug development phase, local fatal or life-threatening suspected unexpected serious adverse reactions ought to be submitted in 8 days for the initial case, plus seven additional days for further information.[55] Local suspected, unexpected, serious adverse reactions that are not fatal or life-threatening must be submitted to the NMRA within 15 calendar days, as should local serious cases.[56] On the other hand, non-serious local cases need to be recorded in the annual DSUR.[28] For foreign

cases, only the suspected unexpected serious adverse reactions should be submitted. The submission period is 15 calendar days. In the post-marketing phase, serious local cases should be submitted within 15 calendar days, while non-serious local cases should not be submitted, as was formerly the case in Europe.[57] Following the amendment of the legal definition of an ADR in the EU (in 2012), the EMA included in 2017 ADRs due to the use of a medicine within and beyond their authorised use, which led to the identification of abuse, misuse, off-label use, and medication errors or occupational exposure as reportable ADRs.[58] Such non-serious cases of interest to NMRAs, including pregnancy exposure and breastfeeding, and drug interactions, may be reported within 90 days.[58] In some instances, medicines may be designated for additional monitoring.[34]

The *reporting format* was considered. A universal reporting form created by CIOMS with standardised fields was already available and enjoyed widespread international use. The preferred reporting routes were described either as the CIOMS I form or electronic E2B(R3) transmission.[59]

Aggregate reporting

An aggregate report provides collated global safety data on a specific active pharmaceutical ingredient (API) and is of value to regulators as it summarises all known safety aspects within a prescribed period.[26] Standard formatting of these reports (ICSRs in line listing format)[37] and frequency of submission are relevant to this study. Two sub-themes were identified: aggregate reporting in the post-marketing period and aggregate reporting during clinical trials. The submission of PSURs/PBRERS, according to the EURD list, was favoured as it would allow for concurrent notification of NMRAs in Europe and Southern Africa.[29,60] When conducting interventional studies, the DSUR, which summarises the safety information during the development phase, is to be submitted to the NMRA annually.[28]

Risk management

Six sub-themes were identified under the risk management theme, that is, *signal detection*, *re-evaluation of the benefit-risk ratio*, *safety decision-making process*, *risk management planning*, *risk minimisation*, and *safety communication*.[61,62] Suspected signals must be assessed, evaluated, confirmed, or refuted and managed by the MAH under the supervision of the NMRA.[63] Once confirmed communication of the safety signal and attendant risk minimisation measures to stakeholders must be assured.[36,64]

Discussion

In this document review, international PV reporting requirements and pertinent African literature were synthesised into a usable PV guideline checklist. In developing the guideline checklist, the authoritative consensus documents and the literature were referenced to find the key themes, sub-themes and items that would yield efficacious guidelines. The five themes extracted from the exercise were structured into an integrated 73-item checklist for application to existing SADC PV guidelines. The checklist assessment is conducted by completing three columns: yes/no scoring of each item, cross-referencing and comments. For yes/no scoring, a yes score would be allocated if the items are mentioned in the guideline. The alpha-numeric identifier (e.g. 7.2 iii) of the applicable guideline section is entered in the cross-reference column. Comments about deviations may be entered into the third column, e.g. 10 business days instead of 15 calendar days. The checklist is structured such that by applying the checklist and assessing its guidelines, NMRAs would be positioned to identify and fill the gaps in their PV regulatory requirements.

Ultimately, the purpose of PV is to identify and manage risks associated with medicines. NMRAs and MAHs implement measures to predict in advance the potential physiological responses of consumers when they are exposed to biomedical products.[65] Guidelines represent the aspirations of the regulators in discharging their duties to monitor and maintain the safety of biomedical products.

Although African nations have not, to date, formulated continental PV standards, their practices are guided by the consensus standards set by more experienced PV practitioners. This presents a quandary where the need for conformity is beneficial (such as PIDM membership), but the local African context has been neglected. To bridge this gap, the weaknesses of African pharmaceutical regulation identified through the literature review were accommodated in the design of the

checklist by adding items pertinent to the local context. The requirement to report ADRs due to substandard or falsified medicines was deemed necessary due to the prevalence (18.7%) of counterfeit medicines in Africa.[66] Continued submissions of CIOMS forms to NMRAs were recognised as the prevalent practice where E2B(R3) transmission was not implemented. A PV expert recommended the inclusion of device regulation in the checklist during content validity assessment, as opposed to reliance on an independent notified body (as is the case in affluent markets). Thus, presenting another opportunity to contextualise the checklist. Regulation of medical devices by NMRAs, to assure optimum safety and performance was adopted in the United States in 1976 and in 1993 in the EU.[67] The recommendation to refrain from reporting non-serious ADRs (Supplementary Table 1, Field C 4.1 b) was informed by the availability of summary data and integrated ICSR information to PIDM members through the UMC's PV data analysis tool, Vigilyse™.[68]

The constantly evolving global PV landscape, the resolute march towards regulatory harmonisation in Africa, and the disparate maturity stages of NMRA systems in Southern Africa necessitated the inclusion of multi-level standards. Some advanced PV practices, such as the DSUR and E2B(R3) submissions, were included while maintaining rudimentary ones, such as the submission of CIOMS forms.

The implementation of advanced PV practices may be constrained by the inadequate regulatory expertise of SADC NMRAs.[69] To compensate for capacity constraints, reliance models are utilised by some SADC NMRAs (South Africa[70] and Zimbabwe)[71], depending on decisions made by more experienced regulatory bodies. With the ratification of the AMA Model Law in October 2021, an opportunity has arisen to formalise the interdependence of regulatory systems through domestication of the AMA Model Law by ensuring alignment of local law with and explicitly referencing the AMA Model Law and its precepts (regional collaboration and harmonisation), in local laws, regulations and guidelines.[72] Harmonised regulatory frameworks may be facilitated by adopting the checklist since it outlines the key functions and standards that should form part of the PV regulatory system. The implementation of the checklist and AMA Model Law would allow for efficiency gains through work-sharing assessments of safety documents itemised in the checklist (RMPs, PBRERs and DSURs) within and across African RECs.[72] We anticipate that the collaborative efforts will improve regulatory systems infrastructure and create a convergence of legal and regulatory standards.

Implications

Regulators are obliged to author guidelines and set the standard of safety regulation within their jurisdictions. Often, NMRA staff lack the expertise to fulfil this obligation.[73] A checklist may provide some guidance to inexperienced NMRAs. The checklist encompassed the safety monitoring requirements of varying maturity levels. This may pose a potential threat because overly ambitious guidelines that are inappropriate for emerging national PV systems may be issued.

Strengths and limitations

Some strengths of the study were that several well-established consensus guidelines were already publicly available as reference standards. Weaknesses were the use of only English language source documents and the subjective nature of document analysis. However, the latter was mitigated by systematically extracting terms from authentic, recognisable, and verifiable sources. An additional weakness is a reliance on Western reference documents; consequently, parameters may not be readily applicable to the SADC context. Some distinctly local parameters were incorporated for context to compensate for this shortcoming.

Furthermore, only the principal researcher extracted data from the reference documents. Selection bias was avoided by incorporating African context derived from the literature. Confirmation bias was avoided through cross-referencing among the data sources. During the analysis phase, researcher bias was further avoided through the constant scrutiny of the co-authors: J.R.B., M.V., H.S. and M.S.L.

Conclusions

As with all quality management systems, continuous improvement must be ensured by assessing current systems and processes. The checklist was designed to be a tool that NMRAs and researchers

can utilise to assess how NMRAs externalise safety monitoring by stakeholders. We acknowledge that some quality indicators may be aspirational. These indicators were included to serve as pointers to advanced PV practice and accommodate the more advanced PV systems within the Southern Africa region. Applying the checklist to national guidelines will enable the identification of gaps in the regulation of PV and present an opportunity for guideline improvements to align with international best practice. The checklist was created for use in Southern Africa. Future research should examine the administration of the checklist to national PV guidelines of other African regional economic communities. Such a project would elucidate regional differences and enhance efforts towards developing a continental checklist, considering the impending establishment of the African Medicines Agency.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the North-West University Health Research Ethics Committee (Ethics approval number: NWU-00306-20-A1).

Consent for publication

Not applicable.

Author contributions

Nokuthula L. Makhene: Conceptualisation; Data curation; Formal analysis; Methodology; Visualisation; Writing – original draft; Writing – review & editing.

Hanlie Steyn: Formal analysis; Methodology; Supervision; Validation; Writing – review & editing.

Martine Vorster: Formal analysis; Methodology; Supervision; Validation; Writing – review & editing.

Martie S. Lubbe: Conceptualisation; Methodology; Supervision; Validation; Writing – review & editing.

Johanita R. Burger: Conceptualisation; Methodology; Supervision; Validation; Writing – review & editing.

Acknowledgements

The authors wish to thank Jean-Christophe Delumeau, International Society of Pharmacovigilance Executive Committee member; Sten Olsson, Member of World Health Organisation Expert Advisory Panel on Medicine Safety; Marianne Mounir, Pharmacovigilance Country Head, Middle East and Maghreb at Bayer; Fatima Mncube-Barnes, Executive Director, Health Sciences Library at Howard University, USA, and Charlotte Jean, language communication specialist, who provided invaluable guidance and expertise towards the summation of this paper.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

No datasets were generated or analysed during the current study.

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Supplemental material

Supplemental material for this article is available online.

References

1. Malikova MA. Practical applications of regulatory requirements for signal detection and communications in pharmacovigilance. *Ther Adv Drug Saf* 2020; 11: 909614.
2. Ndomondo-Sigonda M, Miot J, Naidoo S, *et al*. Medicines regulation in Africa: current state and opportunities. *Pharmaceut Med* 2017; 31: 383–397.
3. Sithole T, Mahlangu G, Salek S, *et al*. Evaluating the success of ZaZiBoNa, the Southern African Development Community collaborative medicines registration initiative. *Ther Innov Regul Sci* 2020; 54: 1319–1329.
4. Southern African Development Community. Document and publications: protocol on health 1999, https://www.sadc.int/files/7413/5292/8365/Protocol_on_Health1999.pdf (1999, accessed 20 April 2021).

5. International Council for Harmonisation. About ICH: history, https://www.ich.org/page/history (2020, accessed 1 October 2020).
6. International Council for Harmonisation. About ICH: members & observers. https://ich.org/page/members-observers (2020, accessed 1 October 2020).
7. European Medicines Agency. Good pharmacovigilance practices, https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices#final-gvp-modules-section (2020, accessed 3 April 2020).
8. Council for International Organizations of Medical Sciences. CIOMS I form, https://cioms.ch/cioms-i-form/ (2020, accessed 16 December 2020).
9. Brosch S, de Ferran AM, Newbould V, *et al.* Establishing a framework for the use of social media in pharmacovigilance in Europe. *Drug Saf* 2019; 42: 921–930.
10. Younus MM, Zweygarth M, Rägo L, *et al.* The work of the Council for International Organizations of Medical Sciences (CIOMS) in global pharmacovigilance. *Drug Saf* 2020; 43: 1067–1071.
11. European Medicines Agency. ICH guideline E2B (R3) on electronic transmission of individual case safety reports (ICSRs): data elements and message specification – implementation guide, https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-4.pdf (2013, accessed 30 November 2020).
12. World Health Organization. The importance of pharmacovigilance: safety monitoring of medicinal products, https://digicollections.net/medicinedocs/#d/s4893e (2002, accessed 22 October 2021).
13. World Health Organization. The WHO programme for international drug monitoring (Regulation and Prequalification (who.int)), https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance/health-professionals-info/pidm (2020, accessed 22 October 2021).
14. Uppsala Monitoring Centre. The story of UMC and the WHO programme, https://www.who-umc.org/global-pharmacovigilance/who-programme-for-international-drug-monitoring/ (2020, accessed 22 October 2021).
15. Kiguba R, Olsson S and Waitt C. Pharmacovigilance in low- and middle-income countries: a review with particular focus on Africa. *Brit J Clinical Pharma*. Epub ahead of print 22 December 2022. DOI: 10.1111/bcp.15193.
16. Mehta U, Kalk E, Boulle A, *et al.* Pharmacovigilance: a public health priority for South Africa. *S Afr Health Rev* 2017; 125–133, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5708547/
17. Uppsala Monitoring Centre. WHO programme members, https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance/health-professionals-info/pidm (2022, accessed 21 September 2022).
18. Thumm M, Gaparayi P, Goredema W, *et al.* Assessment of the Medicines Regulatory System in Angola: report – submitted to the US Agency for International Development by the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) program, http://siapsprogram.org/publication/assessment-of-the-medicines-regulatory-system-in-angola-report/ (2013, accessed 14 April 2020).
19. Ampadu HH, Hoekman J, Arhinful D, *et al*. Organisational capacities of national pharmacovigilance centres in Africa: assessment of resource elements associated with successful and unsuccessful pharmacovigilance experiences. *Global Health* 2018; 14: 109.
20. Gagliardi AR, Marshall C, Huckson S, *et al*. Developing a checklist for guideline implementation planning: review and synthesis of guideline development and implementation advice. *Implement Sci* 2015; 10: 19.
21. Makoni M. African Medicines Agency to be established. *Lancet* 2021; 398: 1475.
22. Arik M, Bamenyekanye E, Fimbo A, *et al.* Optimising the East African Community's Medicines Regulatory harmonization initiative in 2020–2022: a roadmap for the future. *PLoS Med* 2020; 17: e1003129.
23. Linton MJ, Coast J, Williams I, *et al*. Developing a framework of quality indicators for healthcare business cases: a qualitative document analysis consolidating insight from expert guidance and current practice. *BMC Health Serv Res* 2019; 19: 433.
24. International Council for Harmonisation. About ICH: efficay guidelines, https://www.ich.org/page/efficacy-guidelines (2020, accessed 6 December 2020).
25. International Conference for Harmonisation. ICH Harmonised Tripartite Guideline, Clinical

Safety Data Management: Definitions and Standards for Expedited Reporting. E2A, Current Step 4 version, https://www.ich.org/page/efficacy-guidelines (1994, accessed 3 May 2019).

26. International Conference for Harmonisation. ICH harmonised tripartite guideline, periodic benefit-risk evaluation report (PBRER). E2C(R2), Current step 4 version, https://www.ich.org/page/efficacy-guidelines (2012, accessed 3 May 2019). Council for International Organizations of Medical Sciences. International reporting of periodic drug safety update summaries, https://cioms.ch/publications/product/international-reporting-of-periodic-drug-safety-update-summaries/ (1993, accessed 8 December 2021).
27. International Conference for Harmonisation History. ICH harmonised tripartite guideline, post approval safety data management: note for guidance on standards and definitions for expedited reporting. E2D, Current step 5 version 2004, https://www.ich.org/page/efficacy-guidelines (2004, accessed 3 May 2019).
28. International Conference for Harmonisation History. ICH harmonised tripartite guideline, development safety update report. E2F, Current step 4 version, https://www.ich.org/page/efficacy-guidelines (2010, accessed 3 May 2019).
29. European Medicines Agency. Periodic safety update reports (PSURs). Submission requirements and EU reference dates: the EURD list, https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/periodic-safety-update-reports-psurs (2019, accessed 3 October 2020).
30. European Commission. VOLUME 2A procedures for marketing authorisation. Chapter 1 Marketing Authorisation. Revision 11, https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/vol2a_chap1_en.pdf (2019, accessed 30 November 2020). International Conference for Harmonisation. ICH harmonised tripartite guideline, clinical safety data management: definitions and standards for expedited reporting. E2A, Current Step 4 version, https://www.ich.org/page/efficacy-guidelines (1994, accessed 3 May 2019).
31. The European Parliament and the Council of the European Union. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/ EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC, https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745&from=EN https://doi.org/10.9745/GHSP-D-20-00578 (2017, accessed 29 July 2021)
32. European Medicines Agency and Heads of Medicines Agencies. Guideline on good pharmacovigilance practices: Module VI – collection, management and submission of reports of suspected adverse reactions to medicinal products, https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices (2017, accessed 3 May 2019).
33. European Medicines Agency. Guideline on good pharmacovigilance practices: Module IX—signal management, https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-goodpharmacovigilance-practices-gvp-module-ix-signalmanagement-rev-1_en.pdf (2017, accessed 30 November 2020).
34. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Module X: additional monitoring, https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-x-additional-monitoring_en.pdf (2013, accessed 29 July 2019).
35. European Medicines Agency. Guideline on good pharmacovigilance practices: Module V – risk management systems (Rev 2), https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-v-risk-management-systems-rev-2_en.pdf (2017, accessed 30 November 2020).
36. WHO Programme for International Drug Monitoring, https://who-umc.org/about-the-whoprogramme-for-international-drug-monitoring/being-a-member/ (2021, accessed 9 December 2022).
37. Council for International Organizations of Medical Sciences. International reporting of periodic drugsafety update summaries, https://cioms.ch/publications/product/international-reporting-ofperiodic-drug-safety-update-summaries/ (1993, accessed 8 December 2021).
38. Ampadu HH. *Evolving national pharmacovigilance systems in Africa*. PhD Thesis, Utrecht University, Utrecht, 2019.
39. Ayorinde MO and Alabi PI. Perception and contributing factors to medication administration errors among nurses in Nigeria. *Int J Afr Nurs Sci* 2019; 11: 100153–100160.
40. Barry A, Olsson S, Minzi O, *et al.* Comparative assessment of the national pharmacovigilance systems in East Africa: Ethiopia, Kenya, Rwanda and Tanzania. *Drug Saf* 2020; 43: 339–350.

41. Bencheikh RS and Benabdallah G. Medication errors: pharmacovigilance centres in detection and prevention. *Br J Clin Pharmacol* 2009; 67: 687–690.

42. Cheaib N. Pharmacovigilance in clinical trials: current practice and challenges. *Account Res* 2016; 23: 23–30.

43. Isah AO, Pal SN, Olsson S, *et al*. Specific features of medicines safety and pharmacovigilance in Africa. *Ther Adv Drug Saf* 2012; 3: 25–34.

44. Olsson S, Pal SN and Dodoo A. Pharmacovigilance in resource-limited countries. *Expert Rev Clin Pharmacol* 2015; 8: 449–460.

45. O'Leary Z. *The essential guide to doing your research project*. Thousand Oaks, CA: SAGE, 2017, p. 498.

46. Erlingsson C and Brysiewicz P. A hands-on guide to doing content analysis. *Afr J Emerg Med* 2017; 7: 93–99.

47. Vaismoradi M, Turunen H and Bondas T. Content analysis and thematic analysis: implications for conducting a qualitative descriptive study. *Nurs Health Sci* 2013; 15: 398–405.

48. Reiner Z. Guidelines, position papers and critical reviews: differences and similarities. *Eur J Prev Cardiolog* 2013; 20: 3–5.

49. International Council for Harmonisation. The question and answer document on membership and observership, https://www.ich.org/news/question-and-answer-document-membership-and-observership (2016, accessed 4 December 2021).

50. Dalglish SL, Khalid H and McMahon SA. Document analysis in health policy research: the READ approach. *Health Policy Plan* 2020; 35: 1424–1431.

51. European Medicines Agency. Guideline on good pharmacovigilance practices: Module II – pharmacovigilance system master file (Rev 2), https://www.ema.europa.eu/documents/scientific-guideline/draft-guideline-good-pharmacovigilance-practices-module-ii-pharmacovigilance-system-master-file_en.pdf (2017, accessed 30 November 2020).

52. World Health Organization. What is pharmacovigilance? https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance (2022, accessed 10 December 2022).

53. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Module VI: management and reporting of adverse reactions to medicinal products, https://www.psur.de/pdf/GVP-Module-VI-Management-and-reporting-of-adverse-reactions-to-medicinal-products-June-2012.pdf (2011, accessed 26 July 2021).

54. Streefland MB. Why are we still creating individual case safety reports. *Clin Ther* 2018; 40: 1973–1980.

55. Icelandic Medicines Agency. Pharmacovigilance: reporting requirements of non-serious ICSRs, applicable to marketing authorisation holders, https://www.ima.is/ima/publications/news/nr/4265 (2012, accessed 3 December 2020).

56. Bhangale R, Vaity S and Kulkarni N. A day in the life of a pharmacovigilance case processor. *Perspect Clin Res* 2017; 8: 192–195.

57. Council for International Organizations of Medical Sciences (CIOMS) Working Group VI. Management of safety information from clinical trials, https://cioms.ch/wp-content/uploads/2017/01/Mgment_Safety_Info.pdf (2005, accessed 31 May 2021).

58. Leitzen S, Dubrall D, Toni I, *et al*. Analysis of the reporting of adverse drug reactions in children and adolescents in Germany in the time period from 2000 to 2019. *PLoS ONE* 2021; 16: e0247446.

59. Vogler M, Ricci Conesa H, de Araújo Ferreira K, *et al*. Electronic reporting systems in pharmacovigilance: the implementation of VigiFlow in Brazil. *Pharm Med* 2020; 34: 327–334.

60. European Medicines Agency. Guideline on good pharmacovigilance practices: Module VII – periodic safety update report (Rev 1), https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vii-periodic-safety-update-report_en.pdf (2013, accessed 30 November 2020).

61. European Medicines Agency. Guideline on good pharmacovigilance practices: Module V – risk management systems (Rev 2), https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-v-risk-management-systems-rev-2_en.pdf (2017, accessed 30 November 2020).

62. European Medicines Agency. Guideline on good pharmacovigilance practices: Module VIII – post-authorisation safety studies (Rev 3), https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-viii-post-authorisation-safety-studies-rev-3_en.pdf (2017, accessed 30 November 2020).

63. Santoro A, Genov G, Spooner A, *et al*. Promoting and protecting public health: how the European Union pharmacovigilance system works. *Drug Saf* 2017; 40: 855–869.

64. European Medicines Agency. Guideline on good pharmacovigilance practices: Module XVI – risk minimisation measures: selection of tools and effectiveness indicators (Rev 2), https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-xvi-risk-minimisation-measures-selection-tools_en.pdf (2017, accessed 30 November 2020).

65. Weaver RJ and Valentin J. Today's challenges to de-risk and predict drug safety in human 'mind-the-gap'. *Toxicol Sci* 2019; 167: 307–321.

66. Schneider M, Ho Tu and Nam N. Africa and counterfeit pharmaceuticals in the times of COVID-19. *J Intellectual Prop Law Pract* 2020; 15: 417–418.

67. Kramer DB, Xu S and Kesselheim AS. Regulation of medical devices in the United States and European Union. *N Engl J Med* 2012; 366: 848–855.

68. World Health Organization. Being a member of the WHO Programme for International Drug Monitoring, https://www.who-umc.org/media/1434/being-a-member.pdf (2014, accessed 23 July 2020).

69. Semete-Makokotlela B, Mahlangu GN, Mukanga D, *et al*. Needs-driven talent and competency development for the next generation of regulatory scientists in Africa. *Br J Clin Pharmacol* 2022; 88: 579–586.

70. South African Health Products Regulatory Authority. Reliance guideline, https://www.sahpra.org.za/document/reliance-guideline/ (2022, accessed July 11, 2022).

71. Medicines Control Authority of Zimbabwe. Reliance policy, https://www.mcaz.co.zw/mcaz-reliance-policy/ (2021, accessed July 12, 2022).

72. African Union Development Agency. A guidance document for domestication of the African Union model law on medical products regulation, https://www.nepad.org/publication/guidance-document-domestication-of-african-union-model-law-medical-products (2021, accessed 21 September 2022).

73. Glover B, Akinbo O, Savadogo M, *et al*. Strengthening regulatory capacity for gene drives in Africa: leveraging NEPAD's experience in establishing regulatory systems for medicines and GM crops in Africa. *BMC Proc* 2018; 12: 11.