LESSONS AND BEST PRACTICES FROM THE PAVIA PROJECT:

A blueprint for strengthening pharmacovigilance systems in resource-limited countries

PAVIA
PhArmaco Vigilance Africa

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List of abbreviations

3HP	A regimen of isoniazid and rifapentine taken once-weekly for three months to treat latent tuberculosis infection
ADR	Adverse Drug Reaction
aDSM	active Drug Safety Management and monitoring
AEFI	Adverse Event Following Immunisation
AHRI	Armauer Hansen Research Institute, Addis Ababa, Ethiopia
AIDS	Acquired Immune Deficiency Syndrome
AIGHD	Amsterdam Institute for Global Health and Development, Amsterdam, the Netherlands
AUDA	African Union Development Agency
BMGF	Bill and Melinda Gates Foundation
CoRH	Certificate of Registration Holder
CPD	Continuous Professional Development
DIP	Drug Information and Pharmacovigilance
DR-TB	Drug-Resistant Tuberculosis
EAC	East African Community
EDCTP	European & Developing Countries Clinical Trials Partnership
EFDA	Ethiopian Food and Drug Authority, Addis Ababa, Ethiopia
EGPAF	Elizabeth Glaser Pediatric AIDS Foundation
EPA	Ethiopian Pharmaceutical Association
GFATM	Global Fund to fight AIDS, Tuberculosis and Malaria
IHVN	Institute of Human Virology, Nigeria, Abuja, Nigeria
IRB	Institutional Research Board
KCMC	Kilimanjaro Christian Medical Centre, Moshi, Tanzania
KCRI	Kilimanjaro Clinical Research Institute
KNCV	KNCV Tuberculosis Foundation, The Hague, the Netherlands
MAH	Marketing Authorisation Holder
MDR-TB	MultiDrug-Resistant Tuberculosis
MoH	Ministry of Health
MRI	Medical Research Institute
NACP	National AIDS Control Programme
NAFDAC	National Agency for Food and Drug Administration and Control, Abuja, Nigeria
NEPAD	NEw Partnership for Africa's Development
NGO	Non-Governmental Organisation
NMRA	National Medicines Regulatory Authority
NTCP	National Tuberculosis Control Programme
NTP	National Tuberculosis Programme
PAVIA	PhArmacoVIgilance in Africa
PHP	Public Health Programme
PMS	Post Marketing Surveillance
PV	PharmacoVigilance
QPPV	Qualified Person responsible for PharmacoVigilance
SMART	Specific, Measurable, Achievable, Relevant and Timebound
SMS	Short Messaging Service
SOP	Standard Operating Procedures
SSA	Sub-Saharan Africa
TB	Tuberculosis
TIC	Treatment Initiation Centre
TMDA	Tanzania Medicines and Medical Devices Authority, Dar es Salaam, Tanzania
WHO	World Health Organisation
WP	Work Package

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Explanation of terms used

active TB Drug-Safety Monitoring and management (aDSM):	active and systematic, clinical and laboratory assessment of patients on treatment with new anti-TB drugs, novel MDR-TB regimens, or XDR-TB regimens, to detect, manage and report suspected or confirmed drug toxicities. Three packages are defined by the type of adverse events that need to be reported: the core package requires the reporting of serious adverse events only; the intermediate package requires additional reporting of adverse events of Special Interest to the national TB programme; and the advanced package requires reporting of all adverse events of Clinical Significance [1]
Adverse Drug Reaction (ADR):	response to a medicine which is noxious and unintended, and which occurs at doses normally used for treatment in humans [2-3]
Adverse Event:	any untoward medical occurrence during treatment, not necessarily causally related to the treatment. Synonym: side effect [2-3]
Adverse Event of Clinical Significance:	an adverse event that is either serious, of special interest, leads to a discontinuation or change in the treatment, or is judged as otherwise clinically significant by the clinician [1]
Adverse Event of Special Interest:	an adverse event that is documented to have occurred during clinical trials on new TB drugs and regimens and for which the monitoring programme is specifically sensitized to report regardless of its seriousness, severity or Causal Relationship to the TB treatment [1]
Causality Assessment:	comprehensive evaluation to determine the likelihood whether an observed adverse event was caused by the suspected medicine [1-3]
Causal Relationship:	a relationship between an exposure (A) and an event (B) in which A precedes and causes B [1]

Explanation of terms used

Drug Safety Profile:	description of the benefits, risks and toxicity of a medicine or regimen, specifying any known or likely safety concerns, contraindications, cautions, preventive measures and other features that the healthcare provider should be aware of to protect the health of his/her patient [1]
Pharmacovigilance (PV):	the science and activities relating to the detection, assessment, understanding and prevention of Adverse Drug Reactions or any other drug-related problems [2-3]
(safety) Signal:	the reported information on a possible Causal Relationship between an adverse event and a medicine, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a Signal,depending on the seriousness of the event and the quality of theinformation [2-3]
Serious Adverse Event:	Serious adverse event: an adverse event which either leads to death or a life-threatening experience; to hospitalization or prolongation of hospitalization; to persistent or significant disability; or to a congenital anomaly. This includes Adverse Events that require an intervention to prevent any of the outcomes listed here
Signal Detection:	Signal detection the process of actively searching for and identifying safety Signals from a wide variety of data sources, which may include the national PV database, the global PV database, literature, and concerns raised by healthcare professionals

More definitions are available via: CIOMS Cumulative Glossary, with a focus on Pharmacovigilance (Version 2.0) - CIOMS (date accessed: 17 April 2023).

Preface

Medicines safety is a pre-requisite for enhancement of quality of health care. Timely identification of adverse reactions to drugs, vaccines or other medicinal products as the entry point of pharmacovigilance is essential for evidence-based decision making on their usage. The science of detecting, assessing, understanding and preventing adverse drug reactions or other drug-related problems in order to prevent unnecessary suffering and to improve the safety of patients receiving medication is thus a critical component in any health care system. This requires engagement of all stakeholders involved in all aspects of pharmacovigilance along with well-resourced and wellequipped national pharmacovigilance units.

This Blueprint is a very elaborate and educative document, detailing lessons from a five-year engagement across four African countries of public health programmes and medical research institutions as key stakeholders for pharmacovigilance on the African continent. It presents the best practices and lessons learned from the EDCTP-funded PAVIA project whose focus was to enhance the quality of pharmacovigilance by establishing sustainable collaboration between national pharmacovigilance units, public health programmes and medical research institutions. The best practices and lessons detailed in this Blueprint cover a wide range of health system improvements related to pharmacovigilance governance and financing, innovative reporting tools, reporting flows, awareness raising and staff training, amongst others.

The findings and recommendations in this Blueprint are important as they will be useful well beyond the PAVIA project and can be cascaded to other countries in sub-Saharan Africa.

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About this blueprint

Despite reductions in morbidity and mortality in the past decades, poverty-related diseases still affect large parts of the African population, representing a massive demand for curative and preventive treatment as well as vaccines. In 2021 in sub-Saharan Africa, 20.1 million people were accessing antiretroviral treatment, yet HIV still accounted for 420,000 deaths. The burden of tuberculosis continued to be high with 2.5 million new cases and 501,000 deaths, and an estimated 234 million cases of malaria occurred with 593,000 deaths. In addition, Africa has a large burden of parasitic diseases including schistosomiasis, lymphatic filariasis and onchocerciasis with estimated needs for mass drug administration in 2021 to prevent these diseases and reduce their burden for 225 million, 342 million and 244 people, respectively.

Better drugs and new vaccines against these diseases are being developed despite limited commercial attractiveness for pharmaceutical companies. In view of the large and urgent need for such new products, they often receive regulatory approval and prequalification of the medicine by the World Health Organisation (WHO) based on relatively few and/or small-size clinical trials. While this accelerates access to these products for the people most in need it has the downside that at the time of introduction the body of safety data is limited. Therefore, post-introduction surveillance or **pharmacovigilance** (PV) of these products' safety is essential for informed clinical guidance based on the harm-benefit analysis of the product overall and in specific patient populations. National medicines regulatory authorities (NMRAs) play a key role in the process of collecting and analysing data on adverse events related to drugs and vaccines and, based on this, providing clinical guidance on their use. In many African countries however, two key circumstances hamper NMRAs in providing such harm-benefit analysis for poverty-related disease medicines. First, their capacity is often limited in several ways (legal, financial, human resource, expertise and experience, technical infrastructure for PV). Second, poverty-related disease medicines are generally not delivered by companies authorized by the NMRA to distribute, sell and commercialize these medicinal products (marketing authorization holders (MAHs) but by public health programmes (PHPs). Whereas MAHs are legally bound to systematic collection and sharing of data on the safety of their products, PHPs often are not.

The PhArmacoVIgilance Africa (PAVIA) project, implemented during the period 2018-2022 in Eswatini, Ethiopia, Nigeria and Tanzania, set out to help address these issues in the African context. Funded by the European and Developing Countries Clinical Trials Partnership (EDCTP), supported under the European Union's Framework Programme for Research and Innovation Horizon 2020, PAVIA was a collaboration of NMRAs and medical research institutes (MRIs) in these four African countries together with PV, infectious disease control and health systems expert organizations in Nigeria, Italy and The Netherlands. PAVIA aimed to bring down hurdles both in the capacity of NMRAs to conduct PV and in the collaboration and safety reporting between PHPs and these NMRAs. It did so by focusing on the treatment of multidrug-resistant tuberculosis (MDR-TB), a topical example of new drugs for a poverty-related infectious disease delivered by a PHP. The national tuberculosis control programmes in the four project countries had started introducing new and repurposed drugs for this indication based on a limited number of small trials, partially through donations. To monitor post-introduction safety, these programmes were implementing active drug-safety monitoring and management (aDSM), a system developed and recommended by the Global Tuberculosis Department of the WHO. aDSM aimed to collect (mainly serious) adverse events related to treatment with these new and repurposed drugs, and report these within and between national tuberculosis control programmes and to the WHO but not, or not systematically, to their country's NMRA. The PAVIA project thus sought to establish well-functioning collaborations between the NMRAs and national tuberculosis control programmes in reporting, sharing and analysing safety data on these tuberculosis medicines, as a model for similar collaborations with other PHPs.

During this five-year project, health system improvements were implemented in several areas: regulatory frameworks, financial sustainability, reporting tools and flows, training of health care providers to report adverse events and of NMRA staff to analyse and act on these reports, monitoring and evaluation, and stakeholder engagement. As the four project countries differed in their health systems and in the level of development and capacity of their PV centres, these improvements were tailored to the country's needs and priorities and laid down in national PV roadmaps. Baseline and endline assessments of the project allowed us to review and analyse which interventions worked well and which did less so, define best practices and draw lessons learned.

This blueprint presents these best practices and lessons learned from the PAVIA project, aiming to provide guidance and examples for improving safety surveillance for products to cure or prevent poverty-related diseases in other African countries. Both were identified from the endline assessments in a consensus process among the project partners to cover the various areas in which PAVIA introduced improvements. While PAVIA focused on new and repurposed drugs for MDR-TB, these best practices and lessons learned are intended to have wider application to safety surveillance for other poverty-related disease medicines. Although our project did not address vaccine safety, its implementation coincided with the COVID-19 pandemic and the introduction of vaccines against SARS-CoV-2. In the four project countries, improvements in safety surveillance of vaccines have therefore gone hand-in-hand with improvements in safety surveillance for poverty-related disease medicines, and the best practices and lessons learned to some extent take this into account.

We are convinced that strengthening PV will enhance the access to high-quality and safe treatment and prevention for the millions of Africans burdened by poverty-related diseases. We therefore hope that these best practices and lessons learned from the PAVIA project will be studied and, where applicable, used in other African countries, potentially modified to fit the specific circumstances of the health system and functioning of the NMRA and PHPs.

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Executive summary

The PhArmacoVIgilance in Africa (PAVIA) project, funded by the European & Developing Countries Clinical Trials Partnership (EDCTP) supported by the European Union, aimed to strengthen national pharmacovigilance (PV) systems in four sub-Saharan countries: Eswatini, Ethiopia, Nigeria and Tanzania. The PAVIA project focused on improving the collaboration between public health programmes (PHPs) and national medicines regulatory authorities (NMRAs). The project started with the National Tuberculosis Programmes (NTPs), to catalyse the processes for active drug safety management and monitoring (aDSM) of new medicines and other products.

PV is the science and activities relating to the detection, assessment, understanding, and prevention of Adverse Drug Reactions (ADRs) or other drug-related problems. The ultimate purpose of PV is to prevent unnecessary suffering and improve the safety of patients receiving medication.

A national PV system cannot function without a coherent and robust legal mandate, sustainable sources of funding for basic tasks, effective organisation and processes, and technical tools and knowledge, at all levels. To put these elements in place, strong governance is necessary (Chapter 3).

The core tasks of the national PV system are to detect signals and then to act to safeguard and improve patient safety. To perform these tasks, all stakeholders in the country need to understand the purpose and outcomes of PV and be aware of, interested in, and willing to contribute to PV. This will lead to a strong PV system, which can safeguard patients from harm.

This blueprint presents the best practices (Chapter 4) and lessons learned (Chapter 5) from the PAVIA project, to guide other countries wishing to strengthen their national PV system by improving the engagement of PHPs.

A dedicated PV policy, and a set of laws and regulations is needed (**Box 1, 2**). A national PV system should be supported by a strong national PV centre to enable enforcement of legislation. Enforcement also requires prioritized sufficient, sustainable, funding for PV operations (including personnel) (**Box 3, 4**), and active support from national governments. Larger countries will need to have subnational structures in place to bring PV to all levels of the national PHP (**Box 5**).

Electronic tools, whether domestically developed (**Box 6**) or sourced internationally (such as the MedSafety smartphone application (**Box 7**)), aid in improving ADR reporting. The availability and quality of internet access should be considered when developing and introducing tools. Efficient data flows may offer several options for reporting, including paper forms, mobile phone applications, and web-based reports, while avoiding double reporting (**Figures 3 and 4**). Ideally PV data should be fed into a single central PV database (**Box 8**).

Dedicated training of health care workers and (national) PV centre staff is critical for a functional PV system. Health care worker training should focus on improving awareness and knowledge of ADR reporting. Blended learning courses can be effective for providing such training (**Box 9, 10**). PV centre staff training should be tailored to the staff's needs and may focus on data analysis and risk assessment (**Box 11, 12**). The training should be structured to support the system, enabling healthcare workers to identify potential drug

safety issues and report these to the national PV centre (**Box 13, 14**), and national PV centre staff, at all levels, to systematically search for and investigate such drug safety issues (Box 15), and to appropriately address these issues. This blueprint also presents other examples of how awareness among potential ADR reporters (including healthcare providers and the general public) was improved (**Box 16-19**), creating demand among patients who may experience side effects (**Box 20, 21**). Providing feedback to health care workers on their ADR reports is essential (**Box 13, 17**). Such feedback may include, for example, showing how their facility is doing in comparison with similar health facilities (**Box 16, 18, 19**), and how their data can be used to improve patient management and national treatment guidelines (**Box 18**).

Engagement of partners, including the PHPs (**Box 22, 23**), universities and medical research institutes (**Box 24-26**), professional organisations and non-governmental organizations (**Box 27, 28**), is critical to strengthening national PV systems. This includes creating awareness among healthcare workers (**Box 22**) and PHP staff working on specific diseases (**Box 23**), providing support to data analysis and reporting (**Box 24**), and conducting PV research and training (**Box 25-28**).

The national PV centres in all the four project countries benefitted from a monitoring and evaluation system (**Figure 6**). This system included a comprehensive baseline assessment investigating strengths, weakness, opportunities and threats of the national PV system, a roadmap with specific, measurable, achievable, relevant and timebound (SMART) objectives to address the weaknesses identified, annual sessions to evaluate how the centres were doing with achieving the set objectives, and an endline assessment at the end of the project to assess the state of the national PV system. Maintaining a continuous monitoring and evaluation cycle will enable national PV programmes to continue to improve their effectiveness in identifying medicine safety issues. and to act upon them.

In conclusion, three of the four project countries (Eswatini being the exception) had enabling laws and regulations to conduct PV. The laws in Ethiopia and Nigeria were further strengthened during the project. In Eswatini, the lack of a strong legal framework hinders the functioning of the PV system. In all four project countries, there was insufficient funding for the PV centre to conduct all core tasks, although most national PV centres were successful in obtaining donor funding for part of their tasks. Such funding gaps make the PV programmes prone to disruption and frequent changes in focus based on donors' interests. Subnational structures were strengthened over the course of the PAVIA project in the three larger countries (Ethiopia, Nigeria and Tanzania). If subnational structures take responsibility for some tasks (e.g. training and advocacy for PV, data entry of ADR reports), this alleviates the burden of the national PV centre. Data collection was streamlined and made easier in the past few years. All countries shifted to using VigiFlow as their central PV database, and all started the introduction of mobile phone applications for the reporting of adverse events.
PAVIA contributed to knowledge building of (sub) national PV centre staff and healthcare workers. Blended training modules about PV for health care workers are now available for use and adaptation in Tanzania and Nigeria. Finally, PAVIA has strengthened the collaborations between NMRAs and PHPs, beyond the NTPs in all four countries. This has led to increases in the reporting of adverse events from healthcare workers linked to those PHPs. A strong PV system will ultimately lead to improved patient safety.

1. Introduction and aims of this blueprint

All medicines can cause Adverse Drug Reactions (ADRs). Such reactions are mostly mild in nature but may occasionally cause significant harm to patients. ADRs are a major cause of morbidity and mortality, and a significant proportion of hospital admissions are due to ADRs [4-6]. On a population level, minor, but frequent, adverse events may also cause patients to stop their treatment [4].

Pharmacovigilance (PV) seeks to detect, assess, understand, and prevent ADRs other drug-related problems to ensure the safety of medicines. An effective PV programme will:

a. efficiently identify risks of, and risk factors for, the occurrence of ADRs;
b. communicate these risks to minimize harm to patients and optimize their treatment;
c. reduce the number of adverse events; and
d. by reducing adverse events, help to support the acceptance and effectiveness of Public Health Programmes (PHPs).

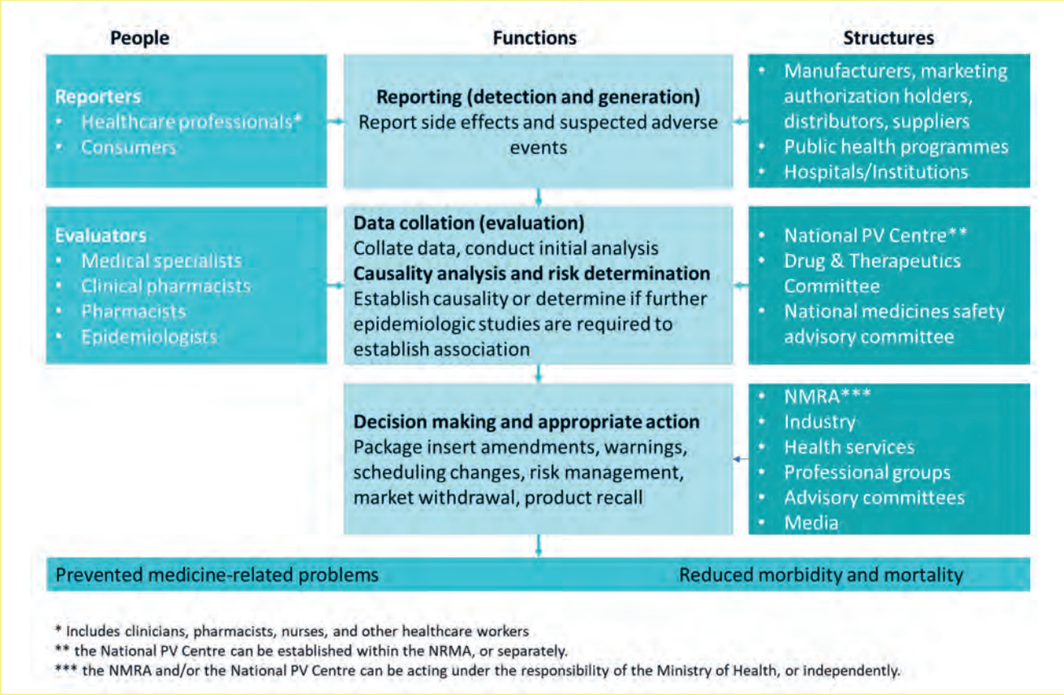
A PV system fulfils the legal tasks and responsibilities of a state in relation to PV, and is designed to monitor the safety of medicines and medical devices authorised in the state and detect and confirm any change to their risk-benefit balance. The PV system is characterised by its structures, resources, processes, tools, outputs and outcomes.

PV systems are usually overseen by national PV centres, which are, in most Sub-Saharan African (SSA) countries, part of the National Medicines Regulatory Authority (NMRAs). NMRAs, in turn, usually fall under the responsibility of the Ministry of Health (MoH). **Figure 1** provides a typical but simplified set-up of a PV system [6]. The European Medicines Agency has also provided a schematic diagram of its PV system set-up. This diagram is more complex and also includes the legislation, policies, and governance requirements of the system [8].

The PhArmacoVIgilance Africa (PAVIA) project, funded by the European & Developing Countries Clinical Trials Partnership (EDCTP), supported by the European Union, operated in four Sub-Saharan African (SSA) countries: Eswatini, Ethiopia, Nigeria, and Tanzania, between March 2018 and February 2023. The PAVIA project aimed to strengthen the national PV systems, particularly with respect to the ADR reporting mechanisms for new products introduced by the Public Health Programmes (PHPs), in order to gain a better understanding of the safety profiles of such new medicines.

The PAVIA project strengthened collaborations between NMRAs, medical research institutes (MRIs) and PHPs. The PAVIA project team initially addressed the collaboration between NMRAs and National Tuberculosis Programmes (NTPs), as these were introducing medicines and regimens for the treatment of drug-

Figure 1. Typical but simplified set up of a national PV system, presenting the people and structures involved and the functions executed. Subnational structures are not included in this figure for simplicity. Source: [7].



resistant tuberculosis (DR-TB) that had not yet been registered by the NMRAs. A closer collaboration of the NTPs with the PV centres would support improved reporting of ADRs from health facilities and healthcare providers to the national PV centre.

The PAVIA project wanted to **transfer the lessons learned to other PHPs**, such as those for HIV and malaria, as well as **to other countries**. This blueprint summarizes these lessons learned to guide other countries in strengthening their PV systems.

More about the PAVIA project can be found in **Annex 1**.

This blueprint is a guide to how the PAVIA project worked to strengthen the national PV programmes in the four SSA countries: **showing best practices and lessons learned**. We hope to inspire other PHPs and countries to strengthen aspects of their national PV system by providing guidance on key success factors and potential barriers (what to avoid) when involving PHPs in further strengthening their PV systems.

2. Methodology

2.1. National PV system assessments

The PAVIA project used a pre-structured questionnaire containing 58 primary questions (with additional sub-questions). This questionnaire (the PV Indicator Tool) was used to assess: the health system, policies, laws and financing, PV processes, capacity and infrastructure (including training needs), stakeholder environment, and communication/dissemination opportunities, in each of the four project countries. The PV Indicator Tool included indicators from several other tools, such as the World Health Organisation (WHO) list of minimum requirements for a functional PV system [10-11], the Indicator-based Pharmacovigilance Assessment Tool [12], and some of those developed and adopted by the East African Community (EAC) member states. The resulting PV Indicator Tool was used for the project baseline and endline assessments.

The baseline assessment utilised the PV Indicator Tool, interviews with key stakeholders, and onsite observations by a team of assessors. This assessment established a detailed picture of each project country's PV system and processes in general, and specifically those for multidrug-resistant tuberculosis (MDR-TB) patients, at the start of the project [13].

The PAVIA project team used this baseline assessment to identify gaps in each of the four national PV systems. The four project countries then each developed a roadmap outlining how and when they would to address the identified gaps in their respective national PV systems. At the end of the PAVIA project, the PV Indicator Tool was again applied in combination with semi-structured individual and group interviews, and onsite observations, to assess the improvements achieved over the duration of the project.
The country teams also provided updates on the implementation of their national PV strengthening roadmap each year.

2.2. Collection and analysis of information for best practices and lessons learned

Best practices and lessons learnt in each country were identified from information collected in the endline assessments. To identify and document best practices and lessons learned from the project, in-depth semi-structured interviews were conducted in each of the project countries by trained qualitative researchers. These researchers interviewed key stakeholders from each of the respective NMRAs, PHPs and MRIs involved in the project, and other relevant organizations. The interviews were conducted through video conferencing, or, whenever possible, face-to-face. The interviewers made use of topic guides prepared for policy makers at the NRMA and the MoH, health care workers and PHP management. The interview guides were structured following the PV Indicator Tool described in Subchapter 2.1.

During the interview we discussed of the progress in PV strengthening and PAVIA's role in this, specifically asking for success factors and barriers. The best practices were also documented using a "member check", in which the key stakeholders were asked to check and confirm the described practice.

For some aspects of the PV system, there was only one well-described best practice available,

and this best practice is included in this blueprint. For other aspects of the PV system, different solutions have been applied to strengthen the same PV system component. In such cases, the different solutions have been included in this blueprint.

All of the interviews were conducted one-on-one in a separate meeting room or office. Informed consent for participation and, separately, for recording the audio of the interview, was obtained prior to the start of each interview. The interviews were recorded and transcribed verbatim. Where necessary, the text of the interviews was translated into English.

The transcripts of the interviews were analysed using qualitative software (either Nvivo or Atlas.ti). A thematic approach was used based on the themes and subthemes of the interview topic guide.

The information from the interviews was enriched by on-site visits and unstructured (group) interviews undertaken by a small assessment team that visited each country, with a focus on successes achieved during the PAVIA project.

2.3. Definition of best practices

The Africa Regional Office of the WHO has published two guides for the documentation of best practices. In the *WHO's Guide for documenting and sharing "Best practices" in health programmes,* 2008 [14], "best practice" is defined as: 1) *a technique or methodology that, through experience and research, has proven reliably to lead to the desired result and 2) knowledge about what works in specific situations and contexts, without using inordinate resources to achieve the desired results, and which can be used to develop and implement solutions adapted to similar health problems in other situations and contexts*. In the WHO's, *A guide to identifying and documenting best practices in family planning programmes,* 2017 [9], the first definition, originating from business and information technology, is preferred, and a list of criteria is presented to which a practice must comply in order to deserve the qualification of a best practice (**Annex 2**).

Although this approach may lead to transparent evaluation, in this document we prefer to use the second definition, as in practice it is difficult to measure and proof effectiveness. Specifically for the purpose of this blueprint, we adapted the definition of a best practice as follows:

> **Best practice** *"A practice that worked well without using inordinate resources to achieve the desired results, and which can be used to develop and implement solutions adapted to similar programmes in other situations and contexts"*

The criteria mentioned in **Annex 2** were also assessed to check to what extent the identified best practices fulfilled the stricter definition.

2.4. Identification and documentation of lessons learned

Sharing lessons learned prevents similar organizations or projects from repeating the same mistakes and allows them to take full advantage of best practices. Lessons learned can be used to improve future projects and future stages of current projects [15].

> **Lessons learned** *"Lessons learned is the learning gained from the process of performing a project; the documented information that reflects both the positive and negative experiences of a project."*

We collected information about lessons learned from the PAVIA project during the endline assessment reports. The lessons learned that are thought to be useful to other PHPs and countries are described in the next subchapter of this blueprint document.

2.5. Building a model for pharmacovigilance strengthening

The information from the best practices and lessons learned gathered through the PAVIA project was analysed and integrated into a model for PV strengthening. The model is presented and explained in Chapter 5.

3. A model to improve a national pharmacovigilance system

3.1. The model

A national PV system can be regarded as a machine with multiple gears **(Figure 2)**. All gears need to be present to keep the machine running. If any of the gears do not function properly, the machine will work less efficiently or may even come to a halt. Strong, effective and sustainable collaborations are the lubricating oil in this machine. To make the PV system function well, elements (the 'gears') may have to be improved. Examples of how these could be improved are provided in Chapter 4. Issues that may "throw sand" in the gears are discussed in Chapter 5. Below, we provide a brief definition for each element of the national PV machine.

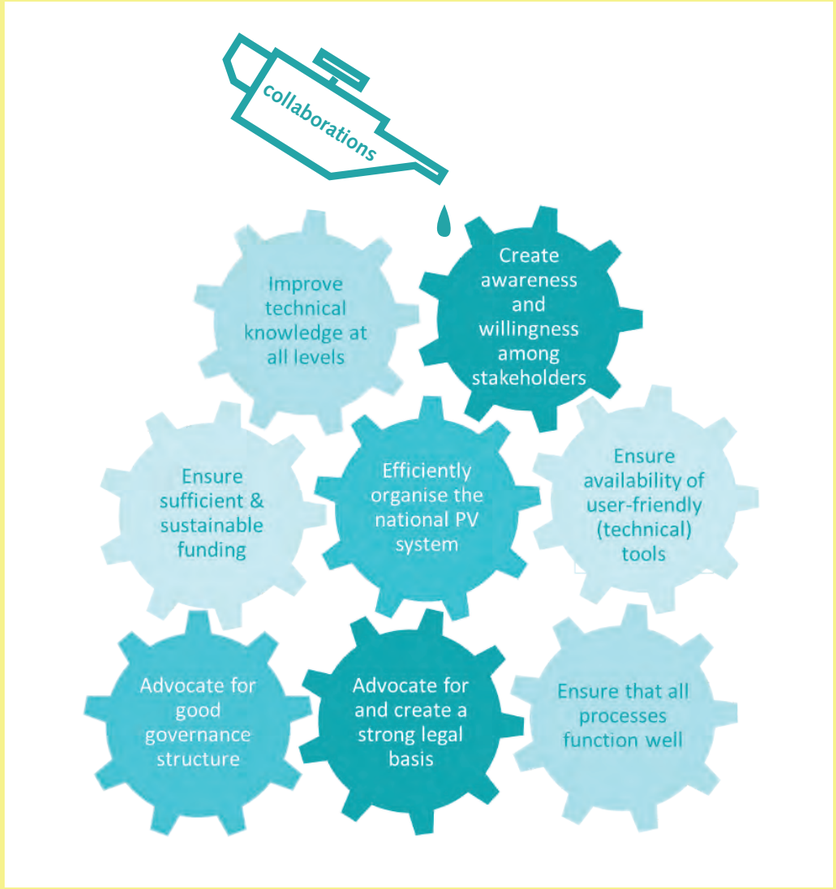


Figure 2. Elements needed for a strong national PV system.

3.2. Explanation of terms used in the model

Good governance

Governance can be defined as the system by which entities are directed and controlled. It deals with structure and processes for decision-making, accountability, control, and behaviour (ethics) of an entity. In the context of this document, leadership is an important element of governance as a national PV system can only be improved with the right **political commitment and leadership.** Political leadership is necessary to drive the country's PV priorities through the endorsement of appropriate laws, regulations and policies, the authorisation of budgets for PV, and the allocation of staff to PV activities. Examples of good governance are described in Chapter 4, and consequences of the absence of this are described in Chapter 5.

Strong legal basis

A national PV programme should be established with a strong legal basis. This requires a **framework of laws, regulations, and policies**, to establish the structure and legal basis for the PV system. A strong legal basis provides for the formation of an NMRA and a national PV system overseen by a national PV centre, established by law (by statute and/or regulation), to have a clear **mandate and authority**. The best practices for establishing a strong legal basis for a national PV programme (observed in the four PAVIA project countries) are described in Subchapter 4.1.

Sufficient and sustainable funding

The roles and responsibilities of the national PV centre can only be fulfilled if there is sufficient and sustainable funding. **Long-term government funding** provides the necessary stability to the system. Such government funding should be sufficient to cover at least the **key tasks or the most critical aspects** of the national PV programme. This will ensure continued operation of the PV centre. **Donors may fund additional and ad hoc tasks,** such as the development of new reporting tools or the conduct of drug safety studies. Examples of best practices for aiming for sustainable funding are described in Subchapter 4.2.

Efficient organisation of the national PV system

The national PV system should be able to ensure patient safety across the whole country. For this, **efficient systems and structures** are needed, as well as **coordination with all key PV stakeholders**, such as PHPs, Marketing Authorisation Holders (MAHs), distributors, vendors, healthcare providers and patients. To serve all of the country efficiently, **subnational PV structures** may be needed. The allocation of roles and responsibilities of the different actors and structures within the national PV system should be clear. Regular, open channels of communication between all people and structures involved (see **Figure 1**) need to be in place. Examples of best practices for organizing the national PV system are discussed in Subchapter 4.3.

User-friendly (technical) tools

User-friendly tools are required to report, validate and analyse ADRs. Paper forms, smart phones, and/or computer software applications are needed to report ADRs as well as **suitable infrastructure**, such as stable internet and efficient reporting chains. Electronic (web-based) platforms may facilitate data collation from different tools and projects. A **national PV database** where the reports are gathered, validated and analysed is also needed. A national PV database provides national oversight and increases the likelihood that potential signals are identified. Software algorithms may facilitate the identification of safety signals. Examples of best practices for providing tools are discussed in Subchapter 4.4.

Improved technical knowledge

Technical knowledge is defined as knowledge that is needed so that any actor within the PV system **can confidently perform all tasks assigned to him or her with regard to PV**. For example, healthcare providers and patients need to know how to use the reporting tools and what information they need to provide, PV focal persons need to know how they can advocate for PV, check filled PV forms and forward these to higher levels of the system, and national PV staff needs to have good knowledge about the whole PV system. To keep all stakeholders' knowledge up to date, and further improve their knowledge, continuous **training** is needed. Examples of best practices for providing technical knowledge are discussed in Subchapter 4.5.

Well-functioning processes

A national PV system needs a central coordination point (commonly, the national PV centre) to ensure that there is regular communication, on-going **monitoring and evaluation**, and to address any gaps that may arise in a timely manner. The PV system will not work well if this national PV centre has no clear goals and processes. Processes, such as **PV guidelines and standard operating procedures** (**SOP**s) need to be developed and updated by the national PV centre to streamline the PV system's processes. Examples of best practices for putting strong processes in place are provided in Subchapter 4.6.

Stakeholder awareness and contributions

A national PV system has multiple stakeholders, including the MoH, Ministries of Finance and Justice, MAHs, PHPs, healthcare providers and patients. Through **engagement**, these partners will become more aware of the importance of PV. The national PV centre needs to invest in communication (providing briefs, **feedback and supervision**) to engage all stakeholders and **motivate each** to perform their respective tasks and actions. The MoH and the Ministries Finance and Justice, for example, have an important role in creating the legal mandate of the PV system and ensuring that the national PV centre can enforce this mandate. MAHs, PHPs and healthcare providers need to send adverse event reports to the national PV centre. Examples of how to create awareness and demand are discussed in Subchapter 4.7.

Setting up strong collaborations

Finally, the national PV system may be further strengthened by creating **strategic partnerships** with universities, MRIs, non-governmental organisations (**NGO**s), and professional organisations. These partnerships can provide access to services and funds that may not be routinely available to the national PV system. Some best practices of how to set up strong collaborations are presented in Subchapter 4.8.

4. Best practices observed in the four PAVIA project countries

4.1. Creating a strong legal basis

A strong legal basis is needed to create mandate and obtain funding for the NMRA and PV, either through the NMRA or directly. This legal mandate needs to be enforced in enabling laws and regulations, and further specified in policies and guidelines. At baseline, three of four project countries (with Eswatini being the exception) had such enabling laws and regulations.

What is needed for a strong legal basis?

1. **A clear mandate for a national PV system through a strong statutory basis,** provided by a set of laws, regulations and policies. This system can be built around a national PV centre set up within the NMRA or as an independent organisation
2. **Political commitment** to ensure that the national PV centre is adequately staffed and that its core tasks are sufficiently funded
3. **Sufficient resources:** adequate funding and staffing to enable enforcement of laws and regulations
4. **Operational guiding tools** (guidelines, SOPs)

In most countries, explicitly authorising the PV system, by passing new or revised laws or regulations, led to a stronger position of PV (Table 1). In Eswatini, as a first step in creating a stronger mandate, a PV policy was developed and adopted (Box 1). Nigeria revised its PV policy and regulations to create a stronger mandate, especially towards PHPs (Box 2).

Table 1. Revisions in legal documents and their main effects in four SSA countries, 2018-2022*

Country	Documents implemented/ revised	Main effects
Eswatini	New PV policy (Box 1)	Increased political commitment to PV
Ethiopia	• New Proclamation 112/2019 providing for PV • New PV Directive	• New Proclamation fills gaps regarding PV in previous Proclamation (661) • PV guideline upgraded to PV Directive which gives it more status
Nigeria	• PV policy updated • PV regulations revised	• PV units instead of committees in healthcare facilities (Box 3) • Regulatory reliance (Box 3) • PHPs and MAHs together referred to as Certificate of Registration Holders (**CoRH**s) (Box 2)
Tanzania	• New Tanzania Medicines and Medical Devices Act (2019), revised in 2021 • New PV regulations	• PV focal persons and Adverse Event reporting system required in all health facilities

Box 1 Development of a national pharmacovigilance policy: Eswatini.

The Eswatini National Pharmacovigilance Policy and Implementation Framework was developed on the initiative of the national PV centre. There were several stages in the development process:

1. An advocacy and engagement meeting at the MoH to emphasize the need for a policy document to strengthen the national PV system; this led to approval from the MoH.
2. Formation of a technical writing team with seven local members, supported by the PAVIA project team, work package Policy, Law, and Regulations.
3. Desk review of existing polices and key documents in the country by the technical writing team.
4. Development of a framework based on the desk review, which captured the processes and provisions for the various elements of the policy.
5. Development and circulation of a first draft of the policy document to key stakeholders with the aim to notify them, and to request for clarifications and input.
6. Development and sharing of subsequent drafts with other structures in the system for input to avoid conflicts with extant laws and regulations.
7. A final stakeholder meeting to finalize the PV policy for endorsement.
8. Submission of the final draft PV policy to the requisite structures and the MoH for endorsement.
9. Following approval by the Senior Management Team of the MoH, the final PV policy document was formally launched by the Honourable Minister of Commerce, Industry and Trade, representing the Honourable Minister of Health, on 6 December 2021.

Official Launch of the Eswatini National PV Policy by Honourable Minister of Commerce and Trade, Mr. Manqoba Khumalo (middle), Principal Secretary, Dr Simon Zwane (right), Deputy Director Pharmaceutical Services, Ms. Fortunate Bhembe (left)

Hospital pharmacist: *"The policy tells you what to do and what is expected. So that is also very important, and really appreciated by the national PV centre."*

Box 2

Revising the PV regulations to increase the responsibilities of PHPs regarding PV: Nigeria.

Not all medicinal products used within PHPs are officially registered for medicinal use in the countries where they are deployed. For such products, PHPs can request a waiver from the drug regulatory authority for the deployment of the medicinal product in the country.

The Good PV Practice Regulations, (published in the Nigeria Official Gazette in 2021), prescribe clear roles and responsibilities to MAHs (in Nigeria called CoRHs) with respect to PV. There was, however, an issue with medicinal products deployed by PHPs that had not yet been registered in Nigeria. These unregistered medicinal products had no CoRH, and, therefore, no organisation could be held responsible for fulfilling the PV obligations stipulated in the Regulation. This was issue was resolved in the revised national PV policy (2020) by stipulating the following:

- It shall be mandatory for all MAHs, **including all PHPs**, to report ADRs.
- **PHPs shall each appoint a Qualified Person responsible for PV (QPPV)**. The QPPV shall establish an effective system for detecting ADRs associated with the medicines used in their programs, and reporting these ADRs to the national PV centre.

As such, PHPs are now responsible for the safety monitoring of the unregistered medicinal products they deploy. The goal is to promote the importance of PV within the PHPs, and increase funding for PV activities. The MoH has already seconded a QPPV staff member to the NTP.

From left to right: PV focal person for the National Tuberculosis and Leprosy Control Programme, the PAVIA project PV coordinator for Nigeria, members of the MDR-TB consilium of Abuja, Nigeria, and international assessors (3rd from left and on the far right).

4.2. Aiming for sustainable funding

A PV centre cannot function without a sustainable funding source. This primary funding source may be supplemented by short-term and/or project-related funding. Of the four PAVIA project countries, Tanzania's funding structure represented the best case: with the Tanzanian government allocating funding specifically for the PV centre (even though this constituted only a minor part of the total budget available to the PV centre). The Ethiopian government also earmarked funding for PV. In Eswatini the PV activities were largely funded by donors (see Chapter 4). The Eswatini governmental only provided funding for one part-time (50%) staff member. In Nigeria (Box 3) and Ethiopia (Box 4), the national PV centre found some creative ways to access more resources.

PV centre in Tanzania.

Box 3

Creative ways to increase the budget for PV activities: Nigeria.

At the beginning of the PAVIA project there was insufficient funding to support a strong PV system in each of the four project countries. Four years later, the funding structures for PV have not changed, and funding was still insufficient. Does this mean that nothing has changed? Not completely. Nigeria found smart solutions to ensure that PV work can be performed, without necessarily increasing the budget of the drug regulatory authority. A few snapshots:

Pharmacy students can undertake **internships** at Nigeria's National Agency for Food and Drug Administration and Control (**NAFDAC**). These interns are **paid through the general NAFDAC budget**. In previous years, Nigeria's PV/Post Marketing Surveillance (**PMS**) directorate has had a number of student interns assigned to their directorate, primarily to enter ADR data into the national PV database. This helped clearing the backlog in data entry, and enabled the PMS directorate to process all reports in real-time, even during the COVID-19 vaccination campaigns (when large amounts of reports were received over a short time period). Keeping up to date with data entry enabled real-time monitoring of vaccines safety.

Nigeria's new PV policy (2020) states that all **health care facilities should have a PV unit.** These were previously operating as PV "committees". Such "committees" are not funded by the health care facilities in Nigeria. By re-categorising these bodies as PV "units", they became entitled to have their own budget line, and to receive funding from the health care facilities.

Increasing efficiency can save funding for other PV activities. The same medicinal products are registered and used in many countries worldwide. In some countries, the nations' own drug regulatory authority reviews, and carries out any assessments necessary to register new drugs and medical devices, and the subsequent post marketing surveillance. Nigeria introduced the concept of **regulatory reliance in its' PV regulation:** Authorising the use of assessments made by the drug regulatory authorities in other countries. This action sought to reduce the (unnecessary) duplication of the registration process and the workload - and costs – for the approval such medicinal products.

Nigerian PV staff during a PAVIA project training event in Nigeria.

Box 4

Creative ways to increase the budget for PV activities: Ethiopia.

The Ethiopian Food and Drug Authority (EFDA) was able to source funding for its PV activities through a project funding programme operated by the Federal Ministry of Finance. This funding programme combines both government funds and pooled partner funding. Guided by government officials, the EFDA has developed several successful project proposals enabling it to increase its budget for PV activities. These include three years of earmarked funding for the PV and PMS desk within the Product Safety Directorate of the EFDA. 20% of this funding was provided by the government, with the balance provided by other partners through the programme. The Product Safety Directorate of the EFDA hopes to receive a 3-year extension for the projects funded through this mechanism.

Staff from the National Tuberculosis Programme, part of the MoH in Ethiopia.

4.3. Organizing the national PV system

National PV centres are, in principle, responsible for PV related activities throughout the entire country. In large and/or federalised countries, however, additional levels of responsibility may be needed to sufficiently cover subnational administrative levels.

Table 2 details the organisational structures used in Ethiopia, Nigeria and Tanzania. Eswatini is not included in this Table as the country has no official subnational structures in the form of PV offices or centres. Instead the national PV centre in Eswatini works directly with PV focal persons in the health facilities. The PV system organisational structure in Tanzania is detailed in **Box 5**.

Table 2. Creation of a nationwide coverage of the national pharmacovigilance system*.

Country	Ethiopia	Nigeria	Tanzania
National level	Directorate PV & PMS in the EFDA	PV Directorate in NAFDAC	PV and clinical trials centre in TMDA
1st sub-national level	Regional PV offices†	Zonal PV centres located in tertiary health facilities‡	PV focal persons in TMDA zonal offices¶
2nd sub-national level	Zone	State PV focal persons¶	Regional PV centres in regional hospitals
3rd sub-national level	Woreda (commune)	Local Government Area supervisors	District PV focal persons
4th sub-national level		PV focal persons in health facility	PV focal persons in health facility/ commune

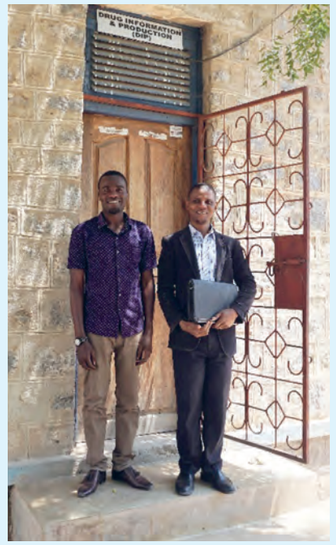
*Eswatini is not included in this Table as this small country has no formal subnational structures for PV. †accountable to regional governments, not to the EFDA, although there are direct lines of communication; ‡the head of these centres is employed by the health facility, but also accountable to Director of the National PV Centre at NAFDAC, other staff are accountable to the health facility management board; ¶these persons are accountable to the NMRA.

Box 5 How decentralization might work: an example from Tanzania.

To promote the importance of PV in general, and the reporting of ADRs in particular, the TMDA needed to reach individual health care professionals and patients at the local health facility level. For this reason, the PV system in Tanzania makes use of subnational structures. The NMRA in Tanzania, TMDA, has **zonal offices** and each of these have a **zonal PV coordinator** who coordinates all PV activities in the zone, including collection and data entry of ADR reports into the Tanzanian database VigiFlow. Each zonal office is in turn responsible for a number of **regional PV centres**. The regional PV centres, usually incorporated in regional referral hospitals, are not part of the TMDA structure. Each regional centre has a **regional PV coordinator,** often this is the regional pharmacist employed by the regional referral hospital. Furthermore, the national PV Regulation stipulates that all health facilities at the district and community level must have a PV focal person. This **PV focal person** is responsible for promoting PV and collecting reports at a local level. The national PV centre oversees and coordinates the PV related activities in the nation and shares Tanzanian ADR reports with the global database at the Uppsala Monitoring Centre.

continuation box 5.

TMDA Central Office (Dar es Salaam)	Clinical Trials Control and Pharmacovigilance Section, responsible for coordinating all PV-related activities nationwide, incl. zonal PV coordinators, collection of ADR reporting forms, data entry in VigiFlow
8 TMDA Zonal Offices	Zonal PV coordinator, responsible for coordinating all PV-related activities in the zone, incl. collection of ADR reporting forms, data entry in VigiFlow, supporting regional PV coordinators
28 regional PV Centres (3-4 per zone)	Regional PV coordinator, responsible for coordinating PV-related activities in the region (note: this coordinator is not employed by TMDA but usually by the regional referral hospital)
All health facilities in the region at district and communal level	Note: in some regions, there are hospitals with “best practice” drug information centres, which can take some of the regional functions (e.g. KCMC in Kilimanjaro region), incl. data entry in VigiFlow



Staff of the regional PV centres at Muhimibili (left) and Dodoma General hospital (middle), Tanzania.

Zonal TMDA office, Dodoma, Tanzania.

4.4 Providing technical tools

Reporting tools

All countries participating in the PAVIA project have made steps to move towards a single system to collect ADR reports. Solutions included:

- Applications on smartphones (such as the MedSafety app).
- Short messaging service (**SMS**) based reporting.
- A phone number for the general public for reporting of ADRs.
- Sending in electronic reports directly via the NMRAs website.
- Downloading an electronic form, and then sending the completed form to the PV centre via email.

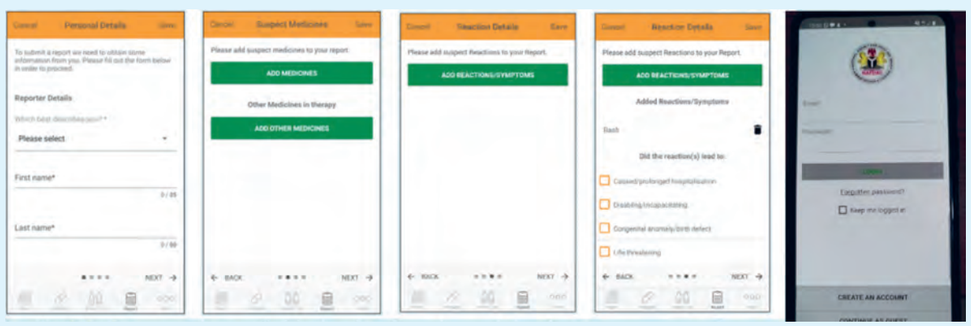
Many of the solutions included automated transfer of ADR reports into the national PV database. All four countries used VigiFlow for their PV database. Examples of digital reporting tools are provided in **Box 6**.

As long as (reliable) internet and smartphones are not universally available, physical ADRs reporting systems need to be available (see Chapter 5).

Box 6 **Examples of digital reporting tools to make reporting easier for healthcare providers and patients.**

Smartphone application: MedSafety

The MedSafety app is a free smartphone application that was developed by the Innovative Medicines Initiative. The app was made available, on a not-for-profit basis, by the United Kingdom's Medicines and Healthcare products Regulatory Agency. The app is available for Android and iPhone, and can be customized for each country's requirements at the request of the national PV centre. Reports can be filled in offline and submitted to the national PV centre (and automatically uploaded to VigiFlow) when the internet is available.



The MedSafety app is available in the Google and Apple app stores and can be customized at the request of the national PV centre (far right shows the app for Nigeria).

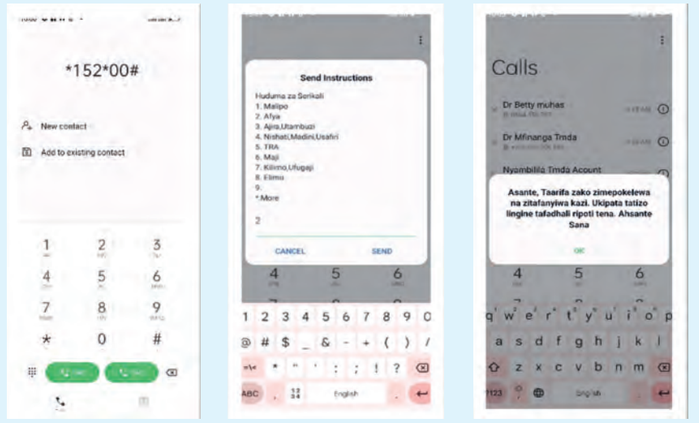
continuation box 6.

The MedSafety app is widely used in Nigeria to report ADRs and adverse events Following Immunisation (AEFIs). This has led to increases in the number of reports submitted by healthcare providers and patients. DR-TB doctors are also using the app:
"My preference is to use both the Med Safety app and also a hardcopy because there should be something to refer to as a backup. And also, as an evidence, I have copies of the ADR reports."
Ethiopia has also started using the MedSafety app.

In Eswatini, the Eswatini Standard Treatment Guidelines smartphone application, developed by the MoH and funded through Chemonics, includes an ADR reporting module. The PV reporting module has, however, not yet been widely adopted and reports are not automatically transferred to Eswatini's national PV (VigiFlow) database.

SMS-based reporting

The TMDA in Tanzania has developed its own SMS-based reporting system. This enables ADR reporting when there is no internet access. By sending a text message to *152*00# the individual is guided through the reporting tool. Both healthcare providers and the public can use this number to report drug safety issues.



SMS reporting, used in Tanzania.

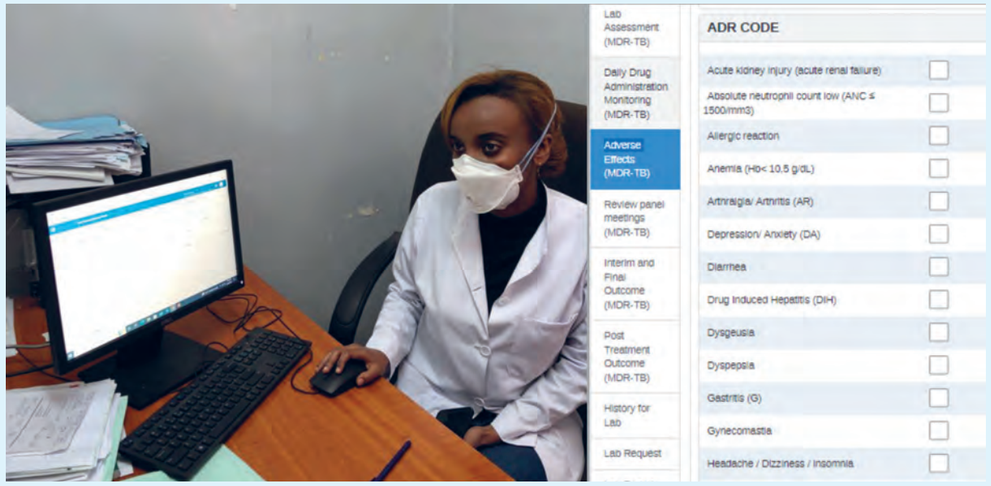
Hotline

In Tanzania, the public can also use a toll free telephone number to report ADRs. In Eswatini, health care providers and the public can report AEFIs (but only this type of ADR) via a toll-free number. The call centre staff members logs the details of the calls in an Excel file. This Excel file is reviewed by the Extended Programme on Immunisation each month. The Extended Programme on Immunisation then forwards any information regarding the AEFIs to the national PV centre. The call records cannot currently be uploaded to Eswatini's national PV database (VigiFlow).

Other tools in development

In Ethiopia, MDR-TB clinicians use the MDR-TB Tracker, a patient management system that also includes an active Drug Safety Management and monitoring (aDSM) PV module. Clinicians are enthusiastic about the Tracker. The EFDA and the NTP are currently looking into options to extract data from the Tracker and automatically upload this into Ethiopia's national PV database (VigiFlow).

continuation box 6.



Left: DR-TB clinician showing the MDR-TB Tracker, ALERT hospital, Ethiopia. Right: screenshot of the Tracker.

"After observing the problems with reporting, the national tuberculosis program has introduced a tracker for case based reporting. We customized DHIS2[1] and we have implemented it in all our centres now; that is helping us. We included a link to report adverse events and to see laboratory results." […] "We are working to install an immediate notification system which will notify us when an adverse event is entered from any facility by a health professional. […] The tracker is better, it reports in detail… The only thing left is sending the adverse events to the EFDA."

Tanzania is developing the Safety and Quality Reporting Tool, a web-based platform that will work as a hub to collect information through multiple reporting systems (such as mobile phones, laptops, computers, and the aDSM reporting system). To date, it has not be possible to automate the process to upload this information to the national PV database (VigiFlow).

To relieve the burden of the national PV centre, both Tanzania (Box 5) and Nigeria (Box 8) have established trained regional hubs to enter the data from the paper reports into the national PV database (VigiFlow). Dataflows can, however, still be further improved. Examples of efficient dataflows are included in **Figures 3 and 4. Figure 3** presents a real example (from Eswatini) of a simple dataflow, although AEFI reports are not automatically captured. **Figure 4** presents a hypothetical example including more (digital) data sources, loosely based on the Tanzanian reporting system currently being developed.

[1] **DHIS2 is an open source, web-based platform most commonly used as a health management information system. For more information, see https://dhis2.org.**

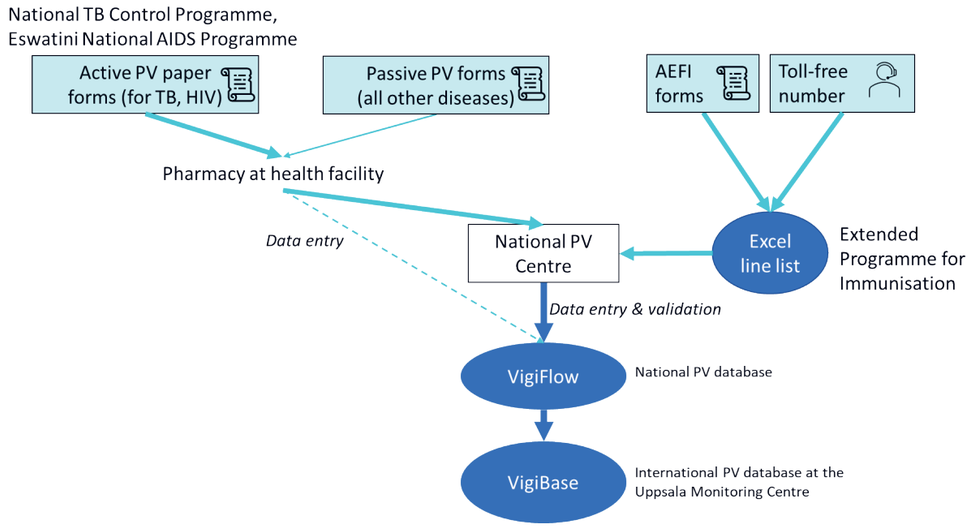


Figure 3. Eswatini's PV system has a simple flow of ADR reports from healthcare providers to the national PV centre. The AEFI reports are not currently uploaded directly to the national PV database. Eswatini uses different reporting forms: the standard Yellow Forms, used for most diseases ("passive" PV paper forms), and forms specifically developed for the conduct of aDSM for DR-TB patients ("active" PV paper forms)

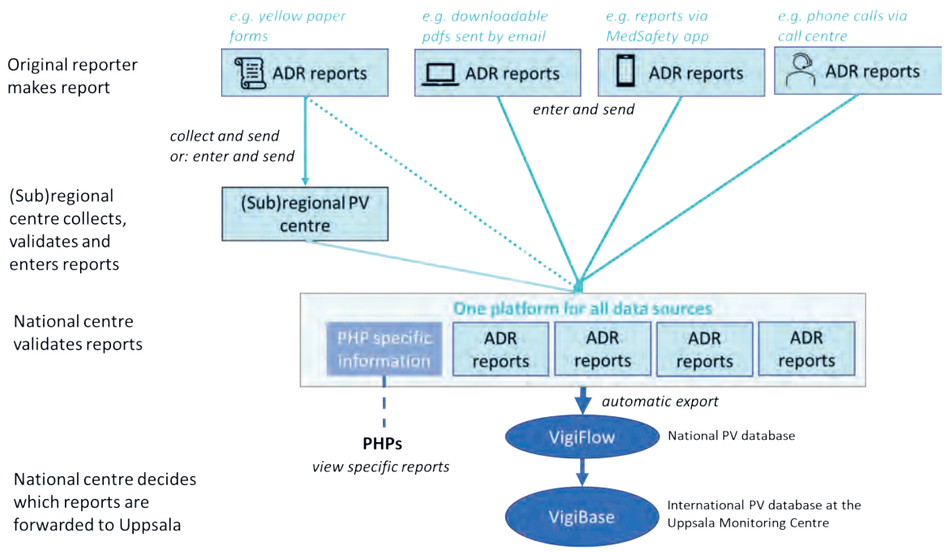
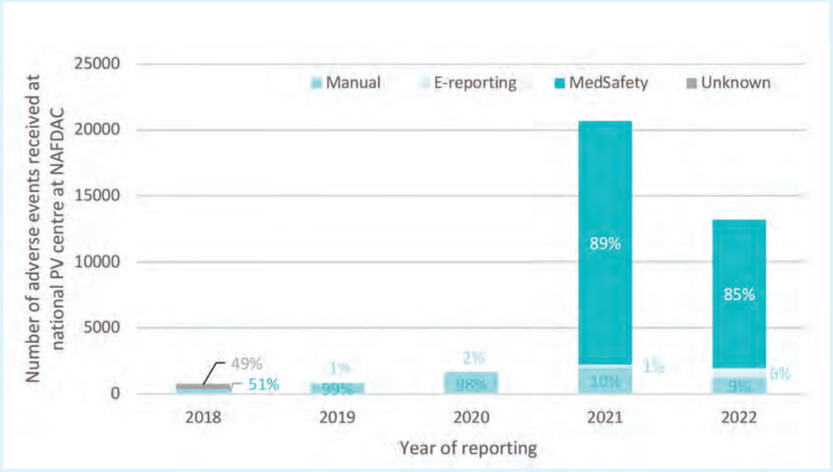


Figure 4. Hypothetical example of an efficient reporting system. Several countries involved in the PAVIA project are working towards this solution. NB: ADR reports can also be AEFI reports.

Utilising a user-friendly tool that is widely available, in combination with advocacy and actives to raise awareness of the tool and its' use, can also help to increase the number of reports received (**Box 7**).

Box 7 How introduction of a new user-friendly, low-threshold and widely available tool can improve reporting: an example from Nigeria.

In 2020, with the help of WHO, the MedSafety smartphone application was introduced in Nigeria. The MedSafety app was promoted widely among healthcare workers and patients for reporting AEFIs. The app soon became immensely popular, both among healthcare providers and patients, for reporting of AEFIs, particularly for COVID-19 vaccines (see the graph below). In 2021, an increasing number of Adverse Events from other medicines/vaccines were also getting reported via the app. While the number of AEFIs following COVID-19 vaccination dropped drastically after 2021, the MedSafety app remained the most popular reporting tool.



Absolute number of reports received per year, 2018-2022, with relative contribution per reporting tool.

Entering data from yellow forms into the national PV database (VigiFlow), Ethiopia.

A central database

It is important to have a central database for all ADR reports in order to optimize signal detection. If the data is scattered between different databases, or held only in hardcopy, a signal can easily be missed. It is also important that the data from ADR reports are entered into the database as soon as possible. Data that is not entered immediately will not become available and signal detection will be delayed. Having one central database for all ADR reports makes it easier, and faster, to track and validate the ADR reports, and to detect (unusual) patterns (**Box 8**).

Box 8 Actions taken to move to a central database for ADR reports: Nigeria.

VigiFLow is an E2B compatible database, maintained by the Uppsala Monitoring Centre. VigiFlow also supports exchange of reports with the global WHO database (VigiBase). VigiLyze is an analysis tool used to analyse the data in the VigiFlow database. During the PAVIA project, Nigeria's NAFDAC has:

- Made VigiFLow their main database, replacing the old database in Excel;
- Introduced e-reporting and the MedSafety app which directly forwards reports to VigiFlow without manual data-entry;
- Removed the backlog of reports which enables real time monitoring of the safety of drugs; and
- Increased the number of reports sent to the global database at the Uppsala Monitoring Centre (80% of all reports received by NAFDAC are currently forwarded to the Uppsala Monitoring Centre).

NAFDAC staff entering and validating reports in VigiFlow.

Figure 5. PV training can lead to improved ADR reporting.

4.5. Providing technical knowledge

Improving ADR reporting requires increased awareness among healthcare staff. This can be accomplished by training healthcare staff on PV. All staff involved in PV, from healthcare providers to national PV centre staff, require regular training to ensure their tasks and obligations with respect to PV (**Figure 5**). Separate training programmes are required for those who need to report adverse events (such as health care providers) and those who handle the reports (data analysis and interpretation) at the national PV centre. Given the frequent staff rotation in many countries and (usually) poor handover procedures, frequent staff training sessions may be required. Given these requirements, there may not be enough of staff at the national PV centres to provide all of the regular training sessions. We have collected several examples on how to involve more trainers from countries participating in the PAVIA project (**Box 9, 10, 27 and 28**).

Clear and comprehensive, step-by-step, SOPs and manuals also facilitate PV processes. Technical knowledge can also be provided through on-the-job training (**Box 9 and 26** provide examples) and supportive supervision (**Box 17**).

We also recommend investment in staff retention. Such investment would enable advanced training for high-level experts at the national PV centre capable of the undertaking the analysis of PV data and subsequent actions (**Box 13**) without external supervision. An example from Nigeria, where all staff of the national PV centre received advanced training and can now work with the VigiFlow database, is included in **Box 12**.

Box 9 Example of PV reporting skills training: the Kilimanjaro Clinical Research Institute in Tanzania.

A 5-day PV train-the-trainer course was given to 20 trainees at the Kilimanjaro Christian Medical Centre (**KCMC**) in Tanzania.
After the training, the trainees trained their colleagues in health centres and hospitals. In KCMC, a total of 62 healthcare workers received training in this way. Dr. Eva Muro gave trainings on PV and tutored trainees as they (in turn) provided PV training to their colleagues. Dr. Muro stressed the value of practicing the use of the reporting forms. Many healthcare workers do not see reporting as their responsibility, have insufficient time, experience administrative burden, or are afraid of punishment.
All employees of the Drug Information and Pharmacovigilance (DIP) department of the KCMC participated in a training on PV.
DIP staff also participate in continuous on-the-job training.

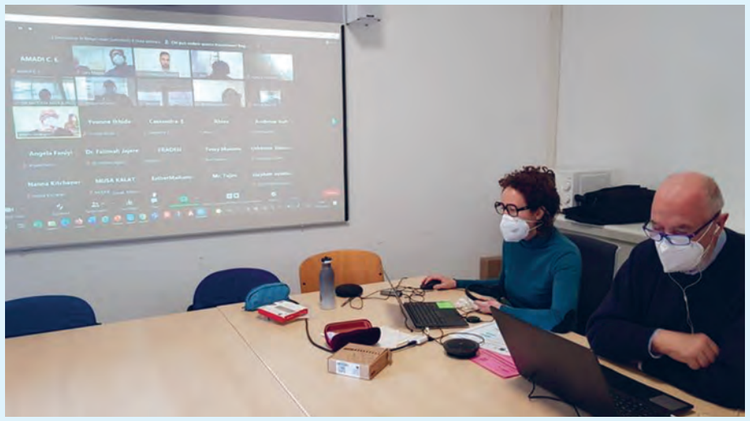
continuation box 9.

Pharmacists discuss an ADR report at the KCMC DIP.

Late Dr. Eva Muro, PV coordinator at KCMC: "*People should be made aware about the law, it is part of their duty to report ADRs. We need to do sensitization, because nurses and clinicians sometimes say: "if we report, we are getting punished."So, we told them nothing will happen, we just want to know."*

A blended training programme integrated with a train-the-trainer approach was developed for the PAVIA project by the University of Verona. This blended training involves both face-to-face class sessions and online materials and activities: essentially a "blend" of live and online learning. Staff from the University of Verona trained staff from both the national PV centre and the NTP face-to-face in Tanzania in 2019, and remotely to Eswatini, Nigeria and Ethiopia (**Box 10**). The staff from the national PV centre then trained healthcare providers working in specific healthcare facilities (step-down trainings (**Box 9**)). Two e-learning courses on the basis of PV and anti-tuberculosis drug safety were made available on a proprietary e-learning platform and later transferred to Moodle for use by several African universities.

Box 10 Example of involving more lower-cadre staff in the provision of pharmacovigilance training: the blended learning experience.

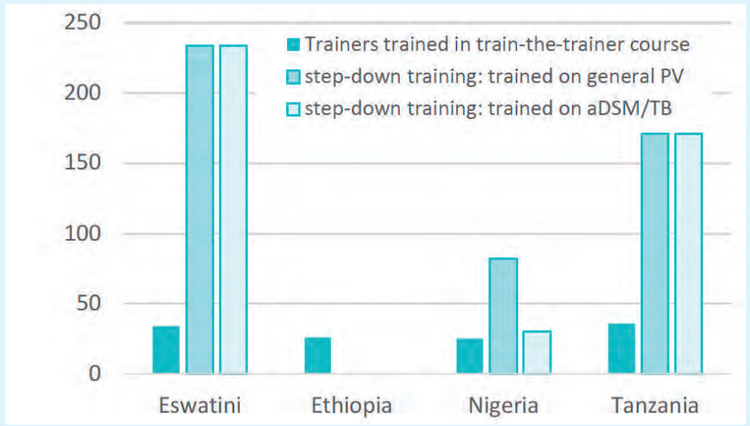


The blended learning training for trainers was intended to be provided in-person by staff of Verona University (Lara Magro (left), Mauro Venegoni (right) and Francesco Schievano (not in this picture)), but shifted to an online training due to COVID-19.

The first train-the-trainers training was attended by around 30 participants in each PAVIA country.
In this training the participants learned how to use the e-learning modules and how to cascade this training down in their own local setting. To date, 608 persons have followed the blended learning programme. The University of Verona is currently evaluating the effectiveness of this training model. This evaluation is assessing the training model on the basis of: student participation, the passing scores of participants in post-training tests, participants' satisfaction and changes in attitudes towards PV (collected through questionnaire surveys), and the total number of Individual Case Safety Reports submitted to each national PV centre before and after the training.

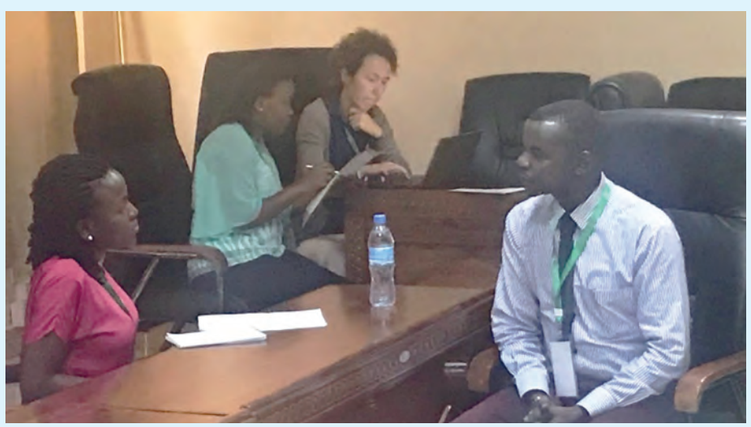
The blended learning training in Nigeria was practical and interactive.

continuation box 10.



Number of trainees reached by the PAVIA blended learning programme.

First blended train-the-trainer course, Dar Es Salaam, Tanzania, 19-25 October 2019.



Clinical PV role play during blended train-the-trainer course in Tanzania.

Blended learning for aDSM: trainee's insights

"The Blended learning training was very effective. We had an in-person introduction. You do the rest of it in your own time. So, if you have something that you do not fully understand, then you have the time to give it more consideration. That was mainly why it was helping. Also, there were offline modules, which is a facilitator. Some people do not have internet so that would be a problem. So ideally you could also download it in the office and work on it at home." -
Pharm. Hlelolwenkosi Nhlabatsi, Baylor Clinic, Eswatini

"The e-course is a very good start for someone who wants to know about PV" -
Deogratius Lyimo, volunteer, Kilimanjaro Christian Medical Centre, Tanzania

Suggested actions to support for training attendance

- Accreditation points
- Certificate from accredited institution
- Blended training (mixture of self-learning and classroom)

How to structure a training programme to deal with high staff turnover?

- Staff attending training should be required to provide step-down training to the staff in the facility
- PV focal persons within the facility should educate new staff members on PV and facility ADR reporting procedures

Box 11 An example of advanced training for staff of national PV centres, and how this helped the staff to improve their skills.

Trainees from national PV centres and trainers from the Netherlands Pharmacovigilance Centre Lareb and Uppsala Monitoring Centre during an advanced PV training session in Ethiopia.

Four training courses were held for the staff of the national PV centres of the participating countries during the period of the PAVIA project. The training courses were led by staff from the Netherlands Pharmacovigilance Centre Lareb. The aim of these courses was to build capacity in the national PV centres and to further improve the NMRA staff's skills and ability to monitor the safety of medicines. An example of this is the support that the Netherlands Pharmacovigilance Centre Lareb provided to the Eswatini PV Centre in identifying and publishing the Signal about dolutegravir and hyperglycaemia (**Box 13**).

Box 12 Increasing VigiFlow database knowledge and skills of the staff at the national PV centre by organizing step-down trainings following international trainings: example from Nigeria.

The VigiFlow database is used for the national PV database in Nigeria. VigiFlow is managed by the WHO Uppsala Monitoring Centre in Sweden. Prior to the PAVIA project, the Nigerian PV system had multiple local databases that were not regularly backed-up. During the first PAVIA training in 2018, four NAFDAC PV centre staff members were trained on use of VigiFlow and VigiBase. Upon their return to Nigeria, these staff members immediately organized a stepdown training on data entry, VigiFlow, VigiLyze, and VigiBase use for all national PV centre staff. 30 staff members have now been trained in VigiFlow and VigiBase and work with these systems on daily basis. While VigiFlow is the national database (Box 8), there are multiple data entry platforms (MedSafety, E-reporting, paper reporting) that all, partly automatically, feed ADR data into this database.

continuation box 12.

Four NAFDAC staff members attended advanced trainings on VigiFlow and VigiBase from the Netherlands Pharmacovigilance Centre Lareb (above). These four staff organized a stepdown training on the same topics for all PV staff at NAFDAC immediately after their return (below).

4.6. Putting strong processes in place

Identifying safety signals and managing risks

PV science seeks identify signals of ADRs. A Signal is a new side effect or new information about a side effect that has previously been detected. Signals can only be detected if the data collected by the PV centre is analysed regularly and outcomes are shared with those who need to know, such as PHPs so that these can revise treatment guidelines, and healthcare providers (Box 13). Signals can also be detected if concerns about certain possible medicines-related Adverse Events shared with the national PV centre by individual doctors or pharmacists are taken seriously and investigated further (Box 13 and 14). NMRAs can conduct such investigations, as is explained in Box 15, showing the example of Tanzania, where the TMDA is leading systematic investigations of potential Signals.

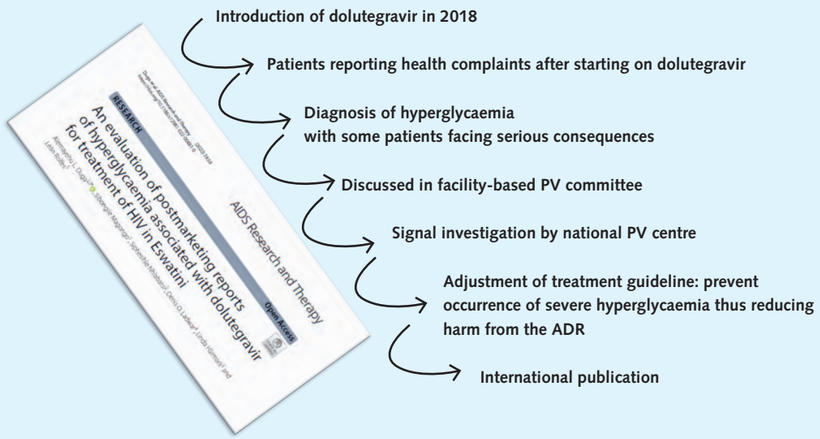
Box 13 An example of what can happen when signals from the field are taken seriously: Eswatini.

Two staff members of the national PV centre and pharmacist and PV focal person of the Raleigh Fitkin Memorial Hospital, Manzini, Eswatini hospital.

How the first ADR reports led to guideline adjustment

Immediately after the introduction of dolutegravir (an HIV medication) in Eswatini in 2018, patients of the Raleigh Fitkin Memorial Hospital in Manzini who transitioned to this new medicine raised health issues with their HIV clinicians. These health issues included weight gain and serious adverse events requiring hospitalization such as optic neuritis. Hyperglycaemia was diagnosed in a number of these patients. After withdrawing the patients from dolutegravir, the hyperglycaemia disappeared. In 2020, the number of cases was so high and the consequences so serious that the hospital's committee notified the national PV centre.

The national PV centre staff, assisted by the Netherlands PV Centre Lareb, investigated the case and generated and published the Signal [16]. This Signal led to an adjustment of the HIV treatment guideline: with potential recipients screened for risk factors of hyperglycaemia prior to commencing dolutegravir medication.



Box 14 An example of what can happen if nurses concerned with the wellbeing of their patients involve the national PV centre: Ethiopia.

DR-TB patients often suffer from severe malnutrition. To gain weight and the strength to overcome the disease and endure its challenging treatment, tuberculosis patients at the Bishoftu DR-TB Treatment Initiation Centre (TIC) in Ethiopia, receive Plumpy'Nut®. This is a ready-to-use therapeutic food formulated for nutritional rehabilitation for persons suffering from severe acute malnutrition. The TIC funds this supplemental treatment from its' own budget. Many DR-TB patients starting their treatment experience nausea and vomiting. Sr. Hiwot noticed that some patients developed persistent vomiting and abdominal cramps immediately after using Plumpy'Nut. Suspecting this therapeutic food to be the culprit, Sr. Hiwot reported the cases to the EFDA, who in turn initiated an investigation. The EFDA found that the batch of Plumpy'Nut had been contaminated with *Salmonella spp*. The batch was recalled and destroyed, preventing adverse impacts for the DR-TB patients.

Sr. Hiwot Menbere, the nurse who suspected the Plumpy'Nut as cause of gastrointestinal symptoms:
"A lot of drugs cause side effects but they are often overlooked until they become deadly. aDSM training should be given to all clinicians to prevent these iatrogenic problems."

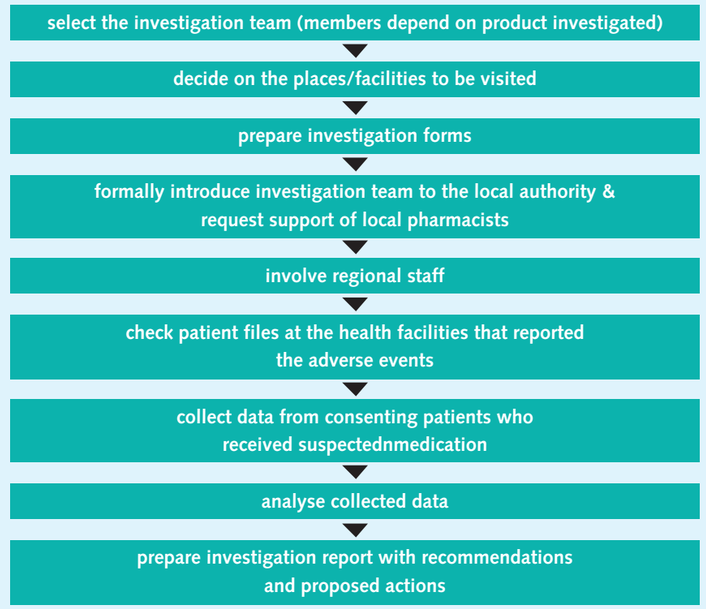
In 2020, Sr. Hiwot won the Kochon Prize for her selfless service to DR-TB patients.

Box 15 Box 15. Systematic investigations of potential signals: Tanzania.

The TMDA in Tanzania initiates investigations after receiving reports of serious ADRs/AEFIs or when a rapid and unexpected increase in the frequency of a known ADR/AEFI is observed. Investigations aim to:

- Confirm the diagnosis made by the health-care providers.
- Confirm the seriousness of the ADR/AEFI.
- Investigate how the medication or vaccine was administered and who administered it.
- Investigate whether there are other factors that contributed to the ADR/AEFI.
- Investigate whether other patients also used the same product in the visited facility, and if these developed ADRs/AEFIs that were not reported.
- Check if the same health complaints also occurred in the community: among those not exposed to the suspected product.

Investigations are usually undertaken by the zonal TMDA branch offices, with support from the national PV centre. During such investigations, the TMDA may also make use of trained staff in health facilities, also providing on-the-job training.
For each investigation, the following preparations are made by the national PV centre:



Several investigations have led to actions. The ongoing PV investigations into bupivacaine in Tanzania have also leveraged the PAVIA project's international network, reaching out to PV coordinators in other countries to gather data on similar signals. The EFDA in Ethiopia has now also started an investigation on bupivacaine.

Goal-oriented planning

One of the key lessons learned from the PAVIA project is importance of continuous improvement. The national PV systems' strengths and weaknesses should be constantly monitored and evaluated, so that gaps could be addressed through SMART action plans (**Figure 6**). All national PV centres prepared country-specific "**roadmaps towards PV strengthening**". This scope of roadmap intentionally included (achievable) goals that could not be addressed within the scope of the PAVIA project. Such, out-of-scope, goals required the assistance of other projects and/or stakeholders.

Figure 6. Monitoring and evaluation cycle.

Eswatini
"We had a meeting in which they brought the PV unit and the tuberculosis program together and we came up with a work plan, which actually helped us to facilitate activities, it was a big facilitator."
– NTP DR-TB expert

Nigeria
"An entire roadmap! The first thing that happened was that we were able to look at the gaps. The next thing that happened was that we also looked strategically at the actions we needed to take to improve PV. The roadmap served as the basis for all meetings. During the meetings, we would sometimes pick a particular activity, and look at the progress and focus on how we could address it, and who had been assigned responsibility."
– Staff of MRI

Tanzania
"This roadmap assisted in defining and clarifying roles of the key stakeholders taking part in the PV system. But it also identified the areas where we needed to evaluate resources and the areas in which skills needed to be developed."
– Staff of national PV centre

"Now after ending PAVIA, we will have to have monitoring and evaluation to assess ourselves and to see if we are staying on track"
– Pharmacist of a tertiary care hospital

Ethiopia – Accounts from staff of the Ethiopian national PV centre
"The roadmap is something which guides you to reach your goal. That is a major thing. The plans were prepared and executed based on the roadmap."

"First, a situation analysis was conducted and gaps were identified. Based on these, interventions were developed. These interventions have been implemented. This is the major reason for the changes."

"There are many enabling factors, and most are related to the preparation of the roadmap. The roadmap enabled us to accurately indicate the activities that were successfully implemented and those which were not. This in itself is encouraging"

The role of the PV roadmap in PV strengthening: First-hand accounts

"The roadmap was prepared for all types of programmes which we found encouraging"
S. Getnet

"Whenever you prepare a strategy, it should clearly indicate detailed activities and assign a responsible person for each activity with a detailed timeline"
K. Sintayehu

4.7. Creating awareness and demand

Creating awareness of a product and its' positive effects stimulates demand. By raising awareness of the benefits of strong PV system amongst healthcare providers and patients, we may harness these groups as advocates for PV.

Motivating healthcare providers by provision of feedback to health facilities

There are a number of channels to generate awareness among healthcare providers (in addition to training courses). Examples of these channels are set out in (**Box 16** and **Box 17**). Efforts of NMRAs and NTPs have led to increased reporting in all countries (**Figure 7**).

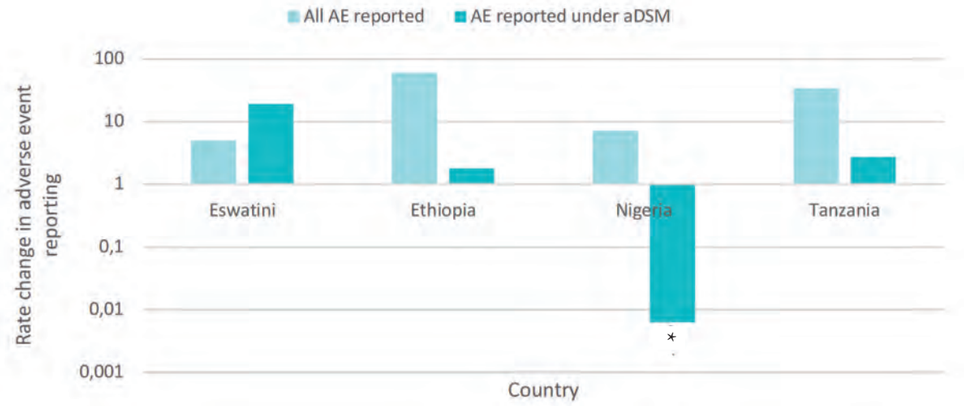
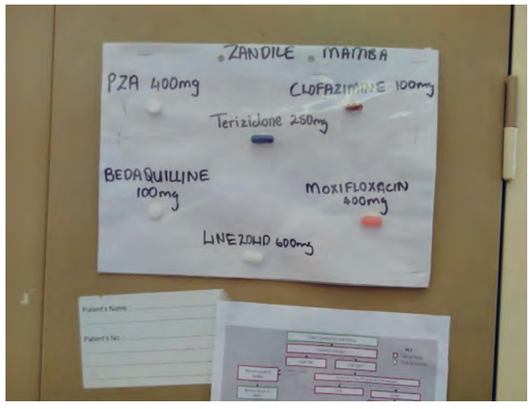


Figure 7. Changes in the number of adverse event reports received by the national PV centres in 2021 compared to 2018, overall and in the scope of aDSM.

* In Nigeria, aDSM reports are collected by the NTP and forwarded to the local NMRA (in Nigeria: NAFDAC). However, aDSM reports are also sent directly to NAFDAC. Moreover, DR-TB healthcare providers have been shifting to using the Med-Safety app (also for aDSM reports) since 2020. Reports received through these latter two mechanisms are not included in the aDSM reports presented in this graph.

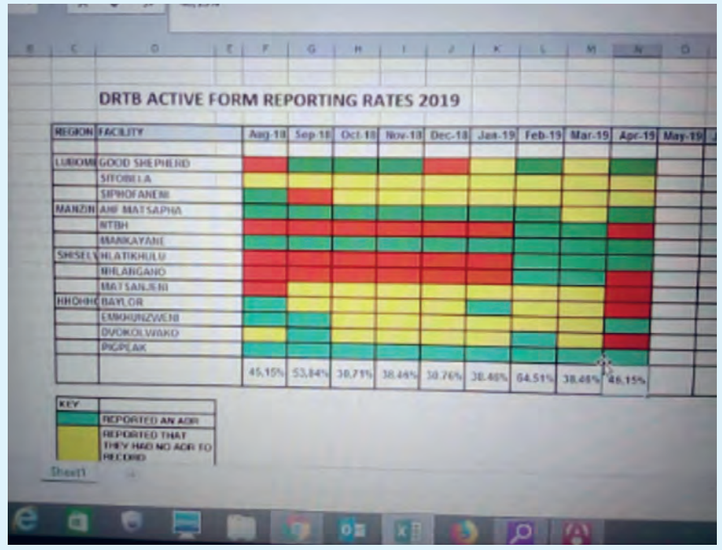


Information for health care staff about tuberculosis medicines attached to a cupboard door in a health facility, Eswatini.

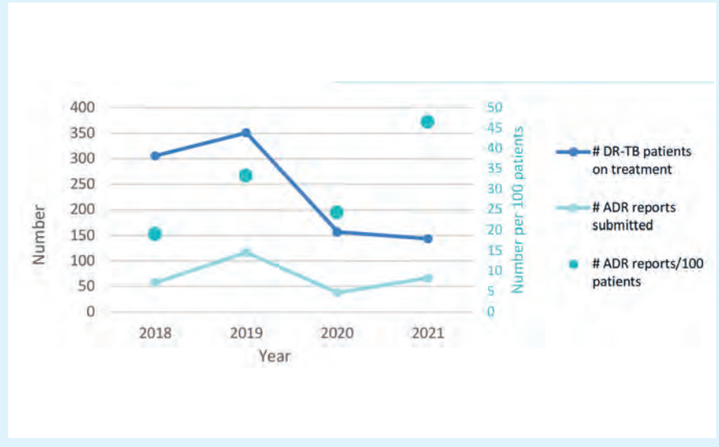
Box 16

Example of how healthcare workers in DR-TB clinics were motivated to report in the scope of aDSM: Eswatini.

In Eswatini, as an additional effort, the NTP PV focal person created a WhatsApp group that he used to communicate with the DR-TB health facilities about ADR reporting. The NTP PV focal person created a colour coded monitoring system for the 14 DR-TB clinics (Figure below) and would share this colour-coded report every month via the WhatsApp group and other existing forums. This has led to an increase in the number of ADR reports from the DR-TB sites.



Example of aDSM monitoring report sent monthly via WhatsApp to all DR-TB sites by the PV focal person within the NTP.



Number of DR-TB treatment-related ADR reports received from DR-TB treatment facilities in comparison to the total number of DR-TB patients receiving treatment. The number of reports per 100 patients was lower in 2020 as the patients receiving treatment did not attend clinic visits due to COVID-19 (Source: national PV centre of Eswatini).

Box 17 Joint supportive supervision to DR-TB clinics in the scope of aDSM: Ethiopia.

A year after introducing aDSM, not all staff at Tanzania's DR-TB TICs were fully aware of what, when and how to report adverse events. An action plan, including a health facility checklist and an SOP for supportive supervision visits, was developed by the EFDA, NTP and PAVIA's PV coordinator for Ethiopia. Supervision visits to all of the TICs were conducted jointly by experts from the NTP, the EFDA, the Armauer Hansen Research Institute (AHRI) and the PAVIA PV coordinator. In the first round of visits, in 2019, the team visited 10 TICs. These initial visits revealed that additional training was required to educate all of the clinicians and nurses on PV, aDSM, and adverse event reporting tools. In February 2020, a sensitization meeting on aDSM was organized. This meeting was attended by: DR-TB clinicians and nurses from all of the TICs; focal persons from 6 PV centres; staff members from the EFDA federal and branch offices; and focal persons from the national and regional tuberculosis programme.

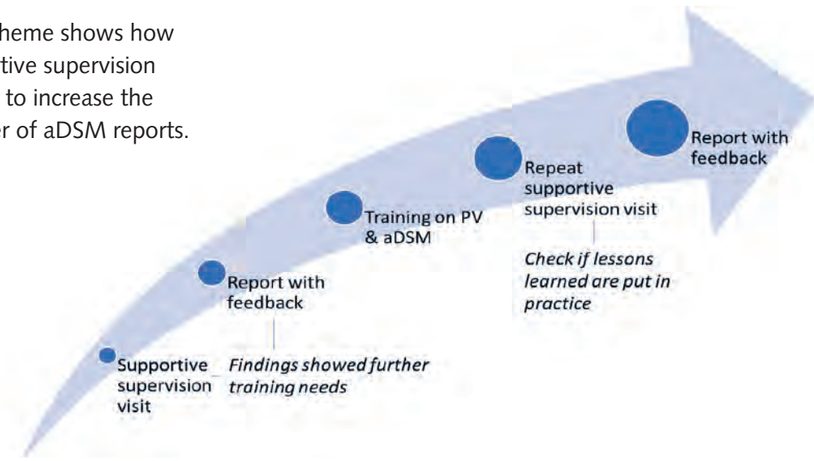
Following this meeting, the joint supportive supervision visits were resumed. Each visit followed a standard procedure, and findings were shared with the TIC's management at the end of the visit. The assessment team also shared examples from best-performing TICs during such visits to further improve reporting capacity. The findings were summarized in a short standardized report, shared with the EFDA, NTP and the TIC visited, including strengths and areas for improvement. These reports addressed general PV practices and specifically aDSM in the respective hospital, and other challenges and limitations as raised by healthcare providers.

Supportive supervision visit to a TIC site. Left: going through the patient files in the pharmacy; Right: providing feedback to TIC manager at the end of the visit.

These visits have led to improved reporting from all TICs (both those that submitted reports in the past and those TICs that had not previously made aDSM reports).

continuation box 17

This scheme shows how supportive supervision helped to increase the number of aDSM reports.



Show the data collected to healthcare providers

Healthcare providers state that one of the key success factors to stimulate adverse event reporting, is to receive feedback in the form of an overview of the data collected.

Hospital pharmacist: *"We appreciate the reports that they are sending, because you really want to know what is happening in the country and what the other facilities are experiencing and what they are doing. That is an encouragement that you know you have people to talk to and to know you can rely on their information."*

Healthcare providers like to see what kind of adverse events are reported of the types of patients that they see. In Ethiopia, aDSM reports were analysed and presented to stakeholders (Box 18). In Eswatini, subsequent publications of the Eswatini Safety Watch (**Figure 8**) contained information about the type and frequency of adverse event reports received by the national PV centre (**Box 19**).

Box 18 Joint supportive supervision to DR-TB clinics in the scope of aDSM: Ethiopia.

The Ethiopian national PV centre analysed aDSM reports received between 2017 and 2020 to identify which (serious) adverse events were reported most frequently, and what type of medication was (commonly) suspected to have caused these adverse events. The national PV centre also examined factors contributing to the occurrence of Adverse Events. The results were presented to the national tuberculosis programme and nurses and clinicians of DR-TB TICs. The meeting was well attended and the medical staff highly appreciated the feedback. The improved recognition of adverse events has led to better patient management, but, while reporting has increased, the quality of the reports still needs improvement.

continuation box 17

The joint investigation of a serious adverse event occurring in a DR-TB TIC. The EFDA, the Ethiopian NTP, and DR-TB nurses and clinicians undertook the investigation.

Box 19 The eSwatini medicine safety watch: a big motivator for ADR reporting.

The Eswatini's national PV centre publishes a PV newsletter: the "Eswatini medicine safety watch"). This newsletter provides information on the latest national and international updates on the adjustment of treatment guidelines, a summary of reports received from health facilities, and any Signal detected in and outside the country.

To healthcare providers, the newsletter is a significant motivator, encouraging them to continue reporting as they can now personally see what is being done with their reports and why their reports are relevant.

Capacity building officer: *"With this PV office, they are communicating feedback in quarterly manner, which is motivating because people feel ownership of their reporting."*

National tuberculosis programme staff member: *"The feedback was not there. Now the PV centre is giving feedback through their newsletters and that really helps to motivate facilities to report ADRs."*

continuation box 19

NPC staff working on newsletter.
"Our objective is to get to a point where the ADR reports can inform changes to the guidelines. Having the reports come in, and just being left there – really does not bring anything out in terms of public health gains. So, we use those reports for decision making and guideline changes."

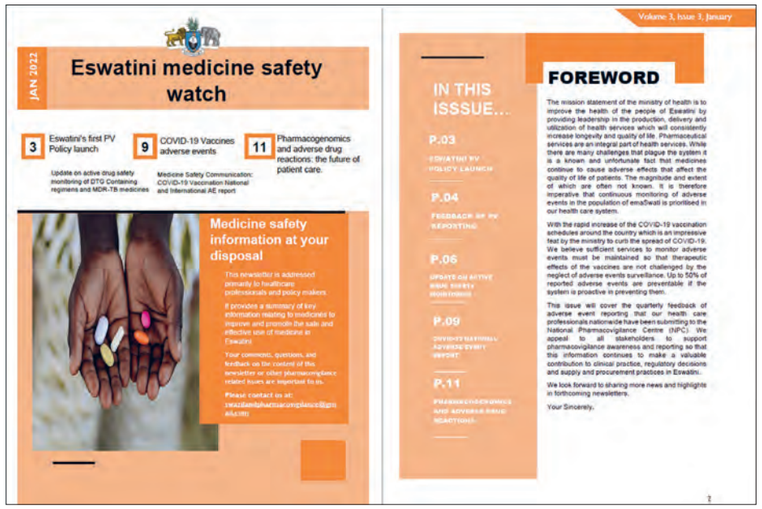


Figure 8.
The Eswatini Medicine Safety Watch, published bi-annually, contains feedback on the data received by the national PV centre.

Creating demand for patient safety

The national PV centre needs to generate media attention to reach the general public. This may include funding public broadcasts on radio and television as done elsewhere: [17-19]. The TMDA in Tanzania broadcast PV messages on television and radio and displays cartoons with PV messages for the general public on their cars (Box 20). Large public events were organised in Eswatini and Tanzania at which the respective national PV centres met with the general public and raised awareness about PV and reporting potential ADRs (**Box 21**).

Box 20 Raising awareness among the general public: Tanzania.

The TMDA has invested a lot in raising public awareness about PV. The TMDA undertook several outreach activities including: radio and television broadcasts, the development of information, education, and communication materials and the provision of training, and advertising PV messages using cartoons on drug safety on the TMDA's cars. The TMDA's cars are also used to advertise a toll free phone number that the public can use to report drug safety issues.

Public health message sharing through cartoons on TMDA cars.
The text in the cartoon reads: Patient: "I got this rash after taking the medicine you gave me". Clinician replies: "I'm very sorry for those side effects, I will provide you with treatment and I will also send a report about it to TMDA".

Box 21 Providing direct feedback to patients and stakeholders: examples from Eswatini and Tanzania.

The Eswatini national PV centre, in collaboration with Raleigh Fitkin Memorial Hospital, celebrated World Patient Safety Day in September 2021. The celebrations included several activities, such as presentations, one-on-one interactions with patients, distribution of leaflets, and a poetry contest. Key PV stakeholders, including medicine importers, private pharmacies and members of academia, took part in the event.

The staff of the Eswatini national PV centre contributing to activities during World Patient Safety Day, September 2021.

A TMDA staff member speaks with interested public about the importance of demanding safe and good quality medication during a public outreach event. Source: tmda.go.tz

TMDA staff often participates to exhibitions to inform the public about the importance of safe and quality medicinal products.

4.8. Setting up strong collaborations

Collaboration with healthcare providers is crucial to the success of national PV systems. Given that patient reporting is not yet (fully) operational in most SSA countries, the PV systems in the PAVIA project countries largely rely on healthcare providers to send ADR reports to the national PV centre. Within SSA, the healthcare system for infectious diseases is often structured through specialized hospitals for the treatment of specific infectious diseases (e.g. tuberculosis and/or HIV). These specialist hospitals operate under the umbrella of, and report to, PHPs within the MoH. As such, the PHPs are the natural partner for healthcare staff working in these specialist ('vertical') hospitals [20]. PHPs can partner with the NMRA by advocating for PV in different ways.

Examples of such actions include: ensuring that PV is well embedded in their treatment guidelines, by including PV in their standard training packages, and by monitoring how well healthcare providers are reporting suspected ADRs to the NMRA. PHPs may also assist in the development of studies and encourage specialist physicians to take part in causality assessment exercises.

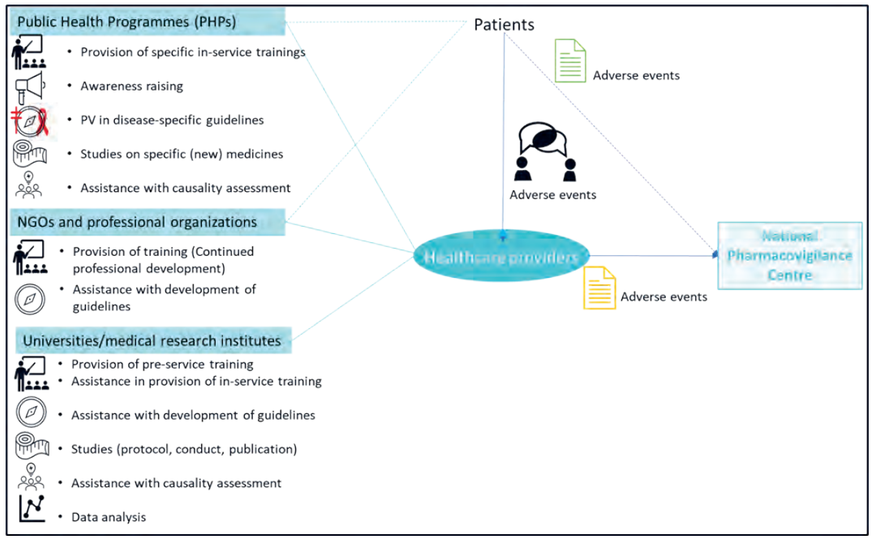


Figure 8. What partners can do to support the national pharmacovigilance system and, ultimately, increase patient safety.

Universities have thus far not been seen as an important partner for national PV programmes. They can, however, play a key role in training medical and pharmacy students on PV, assisting in the development of research proposals for drug safety (such as cohort event monitoring, targeted spontaneous reporting, and other types of studies), and data analysis and reporting.

(International) NGOs and professional organizations may also support the national PV programmes, for example, by providing training to their own professionals.

Public Health Programmes

PAVIA aimed to strengthen national PV systems by creating stronger links with national PHPs.

The project started with the MDR-TB programme which was importing new, non-registered medicines at the start of the project.

Nzolo et al., analysed best practices in PV strengthening in the Democratic Republic of Congo [19]. They noted that a strong collaboration with public health stakeholders, including PHPs, was the key contributor to success. Successful relationships between the NMRA and PHPs were set up in all of the PAVIA project countries. In Eswatini, fruitful informal collaborations were set up between the national PV centre and multiple PHPs (Box 22). In Tanzania, long-standing collaborations between the NMRA and PHPs were broadened to include more work on PV (Box 23). In a small country like Eswatini, the PV centre could build relationships directly with healthcare providers, including the pharmacists in several hospitals and the DR-TB clinicians and nurses. In larger countries, such as Tanzania, such relationships were built at the regional levels.

Box 22

Engaging PHPs: setting up personal relationships in Eswatini.

The Eswatini National Tuberculosis Control Programme (NTCP) collaborated very closely with the national PV centre in the development of the PV policy, (DR-TB) guidelines, and incorporation of PV in the tuberculosis/DR-TB training curriculum. The NTCP PV focal person actively collaborated with the national PV centre in ensuring that PV guidelines and ADR reporting were well implemented and executed at facility-level. The NTCP PV focal person was able to do this because of his continued communication and good relationships with all of the DR-TB health facilities. Over the years, ADR reporting from DR-TB sites has increased. The coordinated PV structure for new DR-TB medicines created a model for implementation of other new drugs in the country including dolutegravir and rifapentine-containing preventive treatment for tuberculosis (3HP). However, due to reduced funding, the position of the PV focal person was abolished. After the departure of the NTCP PV focal person, the number of ADR reports dropped dramatically. The current NTCP advisor and coordinator have taken over the duties of the NTCP PV focal person. However, they have indicated that PV is only a small component of their overloaded work package and they cannot match the efforts made by the previous NTCP PV focal person.

Dr Debrah Vambe, DR-TB focal person NTCP: *"Pharmacovigilance is still viewed as a component of pharmacy and less of clinical work. There is still a need for continued advocacy and sensitization of the clinical partners."*

continuation box 22

The National PV centre in Eswatini also engaged with other PHPs and hospital staff. Left: Alemayehu Duga, PAVIA PV coordinator, and Tholie Simelane, PV focal person of the Eswatini extended programme for immunisation; Right: Dr Hels Nkunku, DR-TB clinician at the AIDS Healthcare Foundation clinic in Matsapha.

Box 23 Engaging PHPs by providing support with clear roles and responsibilities: Tanzania.

In Tanzania, the PHPs have a of history of working with the TMDA. This collaboration is simplified by the fact that the TMDA and the PHPs are all located within the MoH. Representatives of National AIDS Control Programme (NACP) and the NTP mentioned collaboration with the TMDA for the approval of the import of (new) medicines, medical devices and diagnostic equipment, and to ensure that high-quality drugs are being used by the PHPs via regular inspections. New collaborations have been set up regarding PV. Regular meetings between the NTP and the TMDA helped to strengthen personal relationships, forge partnerships, and create mutual understanding of the issues. Improved collaboration led to the provision of more training and on-the-job training to tuberculosis staff in health facilities. This increased the awareness among healthcare providers and led to increased numbers of tuberculosis-related ADR reports being received by the TMDA. The TMDA helped to set up VigiFlow in several health facilities. This helped to improve the data flow from the facilities to the TMDA and beyond. There is also a clear understanding of the roles and responsibilities of both partners:

DR-TB focal person: *"NTP is just identifying the adverse events from the treatment sites, and then records the events and reports these to the TMDA, which are the ones who are supposed to do the signal detection and causality assessment." […] "The TMDA needs to provide feedback, because the policy allows them to do that, and we are supposed to follow their advice regarding the safety of the patient. If there is a need to change the treatment modality or policy, we will do that. But we cannot do that without having evidence or recommendations from the PV unit of the TMDA."*

Based on this encouraging example, the NACP is currently conducting a study with the TMDA on possible side effects of dolutegravir. The NACP and the NTP have jointly prepared a pilot study for introducing the tuberculosis preventive treatment regimen 3HP, for persons living with HIV.

Pharm. Jumanne Mkumbo, PV focal person at the NTP.

Universities and medical research institutes

Universities and MRIs can provide important contributions to strengthening the national PV system (Table 3). They can, for example, play a key role in supporting PV centres with data assessment, analysis and signal detection, particularly in selected studies. Such selected studies help understanding new developments and trends in the safety of new products and identifying potential areas for research and evidence generation. MRIs are a core element of each national PAVIA triangle (**Annex 1**). In all countries, the PAVIA collaborators from these institutes were involved in preparing scientific manuscripts for publication in international peer reviewed journals. One manuscript has already been published (**Box 13**), while other manuscripts are in preparation (**Box 24**). Examples of best practices are shown in **Box 25 and 26**.

Table 3. Activities that have been conducted by university staff to support national PV system strengthening*.

Activity	Eswatini†	Ethiopia	Nigeria	Tanzania
Develop training courses on PV in collaboration with NMRA**		X	X	X
Teach pre-service healthcare providers on PV	X	‡	‡	‡
Teach in-service healthcare providers on PV**		X	X	X
Assist in development of evidence-based guidelines, manuals**		X	X	
Provide best practices in ADR reporting**			X	X
Contribute experts to National Drug Safety Advisory Board**		X	X	X
Develop research proposals and protocols on PV**		X	X	X
Conduct research on PV system			X	
Provide IRB approval to studies**		X	X	X
Assist NMRA in conducting drug safety research**		X	X	X
Assist NMRA in data analysis**		X		X
Assist NMRA in (scientific) reporting**		X	X	X

** MRIs can also play a role in these activities; †Eswatini has no medical faculty; ‡PV is part of the standard pre-service curriculum for pharmacy students, but usually not for other types of students (medical, nursing, dentistry), and is usually part of a broader pharmacology training.

Box 24

Collaboration with medical research institutes can help in the conduct, analysis and reporting of scientific research: examples from several countries.

In Tanzania and Ethiopia, the MRIs, Kilimanjaro Clinical Research Institute (**KCRI**), respectively AHRI, organized several publication writing workshops for PAVIA partners (see the pictures below). As a result, several papers, on PV and related topics, were prepared and will be submitted for peer-reviewed publication. The staff from the MRIs in Eswatini and Nigeria were also involved in the preparation of papers, including analysis of the performance of aDSM reporting and general ADR reporting, the effect of the blended learning trainings, and the development and introduction of a PV policy.

Publication writing workshops in Tanzania.

Box 25 Examples of how universities can contribute to strengthening the national PV system: Nigeria.

Professor Ambrose O. Isah and Dr Abimbola Opadeyi both work at the University of Benin, Benin City, Nigeria. The PV unit at the University of Benin Teaching Hospital was established in 1989. Prof. Isah is the Chairman of the Nigerian National Drug Safety Advisory Committee. With support from the late Director General of NAFDAC, Prof. Dora Akunyili, he was instrumental in the **launch of the PV system in Nigeria**. Dr. Opadeyi **heads the South-South Zonal PV Centre** in the hospital.
From their current position in academia and as consultants in the teaching hospital, they have i**ntegrated PV into the training curriculum** and engaged in PV trainings at undergraduate and professional levels. The proposed acquisition of the blended learning programme (PAVIA) will consolidate this as plans aremunderway to launch postgraduate programmes.
The team, with its PV facility in the teaching hospital, provides safety information and facilitates ADR reporting using all available platforms. They have **promoted the use of the MedSafety app** especially for reporting adverse events following immunisation for COVID-19.
The team has **published articles** in national and international peer reviewed journals highlighting the importance of PV and lead work package 2 of the PAVIA project, providing opportunity to highlight issues such as the
legal framework and financial bottlenecks that hinder PV, and to offer solutions by developing standalone PV policy documents and financial sustainability models.

Professor Ambrose O. Isah (left) and Dr Abimbola Opadeyi (right) have played significant roles in the establishment, growth and continuous strengthening of PV in Nigeria – a role that was further strengthened by PAVIA.

To highlight the importance of PV, the university of Benin has awarded the Past Head of the WHO Uppsala Monitoring Centre, Sweden, Prof. Ralph Edwards, an honorary doctorate degree in Science DSc (honorary causa) in recognition of his role in the development of PV in Nigeria, Africa and globally.

Box 26 Improving reporting by healthcare providers by involving the drug information centre from a university hospital: example from Muhimbili hospital, Tanzania.

PV is intertwined in the whole organisation. People at all levels of the organization are involved. This all started with Dr Buma, head of the pharmacy department, who did his PhD on PV for HIV medication. Ever since, Dr Buma has been very motivated to help Muhimbili hospital succeed in reporting ADRs. Dr. Buma is happy with the progress Muhimbili hospital is making.
In 2021, Muhimbili hospital submitted 8675 ADR reports to VigiFlow. This is a significant contribution relative to the total numbers of ADR reports in Tanzania. Pharmacists actively counsel patients (new and continuing) on how they are feeling, and regarding their medication intake.
Staff from the Drug Information Center provided training on the collection of information from patients and what information is relevant.

Dr. Buma: "*Phase one is get them reporting, don't care about the quality. But now we go to the phase of quality reporting".*

Pharm. Mfoi: *"You don't have to wait for computers and printers, you can just start (with PV)"*

Pharm. Dominique Mfoi (far left), Pharm. Mtoke Ahmadi Uledi (centre) and Dr. Deus Buma (3rd from right) of Muhimbili Drug Information Centre with international assessors and TMDA staff.

Pharmacist Fredrick Mathube giving out medication to a patient and counseling her on potential ADRs, and the importance of ADR reporting. About reporting, he adds: *"We make a friendly environment, so they (patients) can talk freely... if they see someone that they don't feel comfortable with (colleague, neighbour, etc.), we take them here (office next to pharmacy)… this is more private".*

Professional organizations and NGOs

In most countries, healthcare professionals must participate in regular training to stay up to date in their own area of work and retain their professional licence. In Ethiopia, in collaboration with the Ethiopian Pharmaceutical Association(EPA), the NMRA has developed a course **for continuous professional development** (CPD) for pharmacists, worth 15 CPD points (**Box 27**).

Box 28 provides an example of how an NGO can provide assistance with the organisation of **step-down trainings**. In various PAVIA project countries, NGOs provided support to the national PV system. For example, the MDR-TB tracker, a patient management system for DR-TB patients in Ethiopia containing an **ADR reporting module**, was developed by an NGO (**Box 6**). In Eswatini and Ethiopia, various organizations **seconded staff** to the national PV centres to support them in their core tasks.

Box 27 Example of how a professional organisation can supports the national pharmacovigilance centre: the Ethiopian Pharmaceutical Association.

As part of CPD, healthcare professionals need to earn CPD credit points to renew their licence. CPD courses are offered by the Ministry of Health. Together with the EPA, the EFDA has developed a PV training for pharmacists, worth 15 CPD credit points:

University staff member: *"PV was thought to be among the neglected ones and the materials were prepared and the training was given by the EFDA and EPA." […] "The only course prepared on PV is that of the EFDA and the EPA. The EFDA has prepared and given the training using [this course], and the EPA provides it to the professionals in a way that fits them. This way, the EPA is contributing as much as it can, as the EFDA cannot reach to everyone in need. For the EPA, CPD is mandatory for licence renewal…"*

Policy maker at NMRA: *"Especially on pre- and post-service, among health care service providers, based on my experience, there is a gap of knowledge among them. Thus, I suggest that taking a course in pre- and in-service care, including PV, should be mandatory for all health related fields. The course on PV should not be limited to pharmacists, as it currently is, but it should be included in all health related fields."*

PV training, Ethiopia.

Box 28 Example of an NGO supporting the work of a national PV centre: The ASPIRE project in Eswatini.

The capacity building advisors from the international NGO Elizabeth Glaser Pediatric AIDS Foundation (EGPAF), attended the PV blended learning course organized by the Eswatini national PV centre and PAVIA. PV is an important aspect of EGPAF's work This work includes training and mentorship, and providing technical assistance and support (including on data quality issues) for staff working in HIV, and sexual and reproductive, health services.

Following the PV blended learning training, the advisors developed a roadmap to roll out the PAVIA blended learning at the health facility level. Following this plan, the capacity building advisors provided train-the-trainer courses to clinical teams. These clinical teams will, in turn, be training the healthcare workers on the ground (medical doctors and nurses). The PAVIA PV coordinator was present during the meetings to give technical advice and expert opinion. Through this collaboration, a total of 27 clinical mentors received PV training. One goal is to extend the PV training to pharmacists in high street pharmacies to further expand awareness and capacity in PV.

Hloniphile is capacity building technical advisor for Shiselweni region.
"Many drugs are bought over the counter, including traditional and herbal medicine, which can give an interaction with the medication that is prescribed by facilities. So, you want the pharmacists of drug stores to also look at interaction between medication and to bring awareness to people about those interactions."

International collaboration

It is critical to exploit potential synergies within the full spectrum of the networks that can add value to PV work. Engagement with **regional and global collaborators** involved in PV activities is of crucial importance. PAVIA engaged with the New Partnership for Africa's Development (NEPAD) (subsequently the African Union Development Agency-NEPAD (AUDA-NEPAD)) from the outset of the project. AUDA-NEPAD has the mandate over PV policy, laws and regulations throughout the African continent. Through AUDA-NEPAD, PAVIA was able to obtain regular advisory support on the PV developments at the continental level and was able to collect data on the different financing models in Africa. PAVIA also actively engaged with **potential international donors for PV** for poverty-related diseases, including the Bill & Melinda Gates foundation (BMGF), and the Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM). With AUDA-NEPAD and BMGF (hosted by the EDCTP team in Cape Town), the PAVIA project explored possible ways to harmonise and leverage resources to support the development of PV processes in Africa. GFATM produced technical guidance for including PV activities in country applications ("Concept Notes"). PAVIA has also held discussions with the Global Health Network regarding the possibility of hosting this blueprint. This would ensure that the PAVIA lessons remain in the public domain even after the finalization of the project.

To ensure that regional, continental and global PV trends were always considered in its activities, representatives of the EAC, the Southern African Development Community, WHO, the International Society of Pharmacovigilance, and the Uppsala Monitoring Centre, joined the PAVIA project's Advisory Board.

The TMDA is currently using the PV communication compendium developed by the EAC, which it aims to tailor further to the country's specific needs.

Other examples of international collaboration include the blended training courses provided by the University of Verona (**Box 10**), Netherlands Pharmacovigilance Centre Lareb's contributions to improving technical knowledge of staff of the national PV centres (**Box 11**) and its' on-the-job training (**Box 13**), and the technical support provided to Eswatini in developing its' national PV policy (**Box 1**).

5. The lessons learned

"We have to talk about governance. I see PV sprinkling some seeds around, but it has not rooted yet. The depth of PV has to be looked at; we have to ensure that PV gets what is needed to get entrenched, integrated into systems and settings."
– PV expert, Nigeria

Good governance is essential to operate an effective and efficient national PV system. A certain lack of good governance was observed during the initial baseline assessments, particularly in relation to transparency of funding and legal processes. The Ethiopian government set an example for more equitable and transparent funding processes (Box 4).

"As a directorate, we are supposed to have government funding, because we make budgets every year. It's just that sometimes we may not have exactly what we have budgeted for."
– NMRA senior staff member, Nigeria

We have made efforts as a unit to draft the regulations, but they have not been endorsed by Parliament. That process needs to continue. And it can only be taken through by the Minister of Health. We cannot anticipate the date it will be endorsed. All we can do is advocating and asking: "Can the process move forward? Would you please move forward the process?
– Medicines Regulatory Unit staff member, Eswatini

To protect patient safety, the principles of good governance should be followed for PV, to ensure that it is entrenched in the country's health systems and structures. This starts with political willingness to approve legislation around PV and transparent funding processes.

"Yes, the [national PV] policy is there, but some of the things need to be backed up by legislation. […] if there's anything that needs to be applied, and especially has punitive measures within that policy, then it needs to be provided for in the law, because the policy is not legislation. So you cannot hold anyone accountable to a policy."
– Staff of the Medicines Regulatory Unit, Eswatini

5. The lessons learned

The development of a PV stand-alone policy in Eswatini was a landmark achievement. The current Medicines Act does not, however, provide for PV. The national PV centre has therefore proposed amendments to the Medicines Act and has submitted these to the Eswatini Parliament for approval. The national PV centre has also developed PV Regulations, which are awaiting approval. To note is that delayed approvals hinder the enforcement of the national PV policy. Eswatini has no NMRA, which has complicated the approval of legislation and resulted in some delays due in the absence of a national PV Authority to push for parliamentary approval.

A strong legal mandate includes the anchoring of a national PV system in Acts and Regulations. If these are not in place, policies and guidelines cannot be enforced.

"The problem is that we have no budget for the PV unit. So the activities around our PV centre are largely donor driven. […] Until we have the budget for our PV centre, we're sceptical about sustainability, because all the gains that we have had will quickly fall and we'll lose them."
– Member of MoH management, Eswatini

Whilst some of the project countries have invested in PV activities, none of the governments fully funded the key operations of their national PV system (with donors needed to provide funding to support PV activities). For example, in Nigeria, funding often fell short of the requested budget even for previously approved activities. Such unsustainable and insufficient funding negatively impacts staffing, training, and the purchasing of necessary materials. This makes the PV programmes prone to disruption and frequent changes in focus based on donors' interests.

Eswatini suggested charging fees for the importation of drugs, licensing of importers, and collecting fees from pharmacies, health facilities and on drugs via a user pays fee structure.
Such structures could only, however, be implemented through an NMRA that has the necessary statutory authority. In the absence of an NMRA and sufficient government funding, the PV activities in Eswatini remain largely donor funded. Despite both Ethiopia and Tanzania governments providing dedicated PV funding, these budgets cover only a small portion of the total PV funding requirements. As such, donor funding remains necessary to carry out even basic PV tasks in all four project countries.

If government funding is insufficient, innovative funding model(s) that generate sustainable funds by execution of NMRA tasks which can be directly used for fulfilling PV-related obligations need to be explored. Additional PV activities can then be paid from donor funding.

"PAVIA has introduced us to regional pharmacovigilance. We have like 26/28 regional PV centres, which PAVIA has supplied with computers and printers for reporting. But to do better, to get more reports, we need to go further to these lower facilities."
– Staff of PV centre, Tanzania

Tanzania, Ethiopia and Nigeria had subnational PV structures, such as, zonal or regional offices or focal persons (Nigeria). These structures reflected the size of these countries and the governmental structure. When developing a PV system within a federal state (in which regional entities report to regional governments rather than to the national government), memoranda of understanding and regular coordination meetings may be needed.

High staff turnover and lack of proper handover of tasks were often mentioned as a barrier to developing a sustainable PV system. Continued sensitization and training of staff and proper handover procedures are required. Training may include courses with continuous professional development points.

"Train more people, transferring knowledge is not an easy task."
– DR-TB nurse, Tanzania

Memoranda of understanding may have to be organised with subnational PV organisations that do not fall directly under the responsibility of the national PV centre. To keep PV on the radar in all subnational structures, continuous (re)sensitization at all levels is important.

"It is better if computer and paper based [reporting] would go in parallel, because, the internet access in our country is well known to be challenging. We cannot prefer one above the other, rather they both should be improved together."
– Hospital pharmacist, Ethiopia

"The other barrier is, thinking that reporting should only be done on the hard copy [form]. There is poor use of electronic systems […]. But there is the [Med]Safety application, so why don't we use it? Currently most of the people use android phones and they spend their time on Facebook and so."
– Regional PV focal person, Ethiopia

New tools have been developed and implemented successfully in all four project countries. However, internet availability was mentioned in both Eswatini and Ethiopia, by multiple interviewees as a key barrier to e-reporting: with some staff, therefore, preferring paper-based reporting. If internet availability is a challenge, paper- or (smart)phone-based reporting should be made or remain available.

5. The lessons learned

Paperbased reporting systems also faced challenges with delays in receiving the paper reports from healthcare facilities, especially when the reports were not sent through the postal services. Printed, up to date, ADR reporting forms were not always available in all locations. Some countries, like Tanzania, offer printable forms on their internet page.

In Nigeria, some healthcare providers preferred to report both on paper and via the electronic MedSafety app to have physical proof of reporting, thereby introducing double reporting.
On the other hand, in Tanzania, a smartphone app was still functional but the reports were not uploaded into the central PV database, causing reports to be missed.

"As a preference, I'll pick the MedSafety app, and also the hardcopy because there should be something to refer to as a backup. And also, you can see I was able to show you that I have copies of the ADR reports as an evidence."
– DR-TB clinician, Nigeria

A coherent system of reporting tools should be offered that matches the country's specific situation. The system should ensure that all reports are entered in the national PV database, if possible through an automatic upload, in order to prevent duplicate reporting. An example of a strategy to avoid duplicate reporting is, for instance, offering either a 'print' or 'mail' function for reports that are sent digitally.

Improve technical knowledge at all levels

"I think it's an all-stakeholder issue. The point is, in various settings, you have the Ministry of Education, you have the Ministry of Health, depending on the operation within the countries, then you find that they have a role to play especially in establishing the environment and what sort of training they want."
– Staff of national PV centre, Nigeria

The national PV centres carried out advocacy work in all four project countries to gain support to incorporate pre-service PV training in the medicine, nursing and pharmacy student curricula. This was a challenging process in all four countries, involving multiple ministries (see quote above) and a lengthy administrative process to change these curricula.

The need for continuous (re)training of staff put pressure on the national PV centres within the project countries. The national PV centres, therefore, organised train-the-trainer sessions. Subsequent step-down trainings were organised with various success.
In Nigeria and Ethiopia, the staff expect to receive face-to-face training outside their workplace. In these countries, internet based training courses are not widely used nor accepted. In Nigeria, a venue was rented and trainees were provided a travel- and subsistence allowance. In contrast, in Eswatini, internet-based self-study was highly appreciated. We recommend that internet availability and stability and training preferences be assessed at early stages of the project planning process in order to establish an optimal training programme.

Staff from the national PV centre also need to receive specific technical training on more complex tasks, such as causality assessment and signal detection.

"Yes, we do have more people working on PV than on any other function, but we found that with time, that even this was not enough. They were being stretched thin because they were called up to build awareness, do capacity building, at times research. And also, as PV was gaining momentum in the country, you'd find that even other programs were calling on [our] people."
– Staff of Medicine Regulatory Authority, Eswatini

Continuous (re)training is needed for all persons engaged within the PV system. This includes training national PV centre staff. This can be done efficiently by training regional trainers who can cascade by training people in their own region. The training modes should match the possibilities and preferences of the trainees. National PV centres should continue to invest in causality assessment and signal detection training, as these activities were still weak in all four project countries.

Ensure that all processes function well

"For the first time, [we] had a definite roadmap on what we wanted to do around PV. So our roadmap... When the PAVIA project first started, we were told that we must have a roadmap which set out what we wanted to do during the course of the project […] Everything we wanted to achieve was set out in the roadmap. So many of the gains that have been made are due to our roadmap."
– Staff of the Medicines Regulatory Unit, Eswatini

NMRA staff in all four project countries stated that the process of making a roadmap for PV strengthening utilising SMART goals based on the baseline assessment was very useful and that the roadmap helped them to effectively improve their PV system.

5. The lessons learned

To keep on improving the national PV system, it is advised to have a continuous monitoring and evaluation system in place. Annual and strategic plans should include SMART objectives.

"The absence of reporting on safety and ADR does not necessarily mean an absence of cases but can also be an absence of responsible staff to identify and report cases."
– Regional PV staff, Ethiopia

Even if all elements of the PV system are in place, it will not function properly if health care providers are not willing or motivated to report ADRs. Patients, as well as healthcare providers, play a crucial role in ADR reporting. Raising patient's awareness of the risk of side effects from medication can encourage them to actively report potential ADRs to their healthcare provider or directly to the PV system. Commonly mentioned barriers for reporting were lack of understanding that reporting is part of any healthcare provider's duties, lack of time or interest among healthcare providers, and fear of repercussions. Some of the project countries are considering mandatory reporting requirements for healthcare providers, however, it is unclear how this can be enforced.

"Right now, it is just you who decides: should I report or not, there is no enforcement on that. […] So I think maybe come with law enforcement or any other means to motivate people to report…"
– DR-TB advisor, Tanzania

Healthcare providers' motivation to report ADRs increased when they received feedback on their reports in addition to an acknowledgement of receipt. Given that the number of signals detected remained low in all countries, it may not be clear to reporters what difference their reports make to patient safety. The medicine safety bulletins are usually not published as often as the NMRA wishes, and may contain limited information about the ADR reports. Ethiopia recently presented their aDSM data to stakeholders. The Eswatini Medicines Safety Watch provides highly appreciated updates on treatment guidelines and a summary of reports received from facilities. Also, providing prizes or honorary mentions to top reporters may act as an incentive to increase reporting rates.

"If forms would just be dropped in facilities without explanation, and be collected without any feedback, no one would be interested or know how to report. They are happy with the quarterly reports that the national PV centre sends about the number of ADRs reported, and drugs used."
– NGO staff member, Eswatini

Continuous efforts to reach healthcare providers and the public can help creating awareness among both groups and increase demand for better patient safety among patients. Providing feedback on what is done with the ADR reports, and especially, on how these helped to improve patient safety is much appreciated by healthcare providers. Other means of providing feedback may include awards for best reporters, comparisons between clinics within the country, mass media exposure, and public outreach events.

"I think it varies from place to place, but definitely, the NRMA has its mandate and the NTP has its own mandate as well. And definitely, they know that they need each other"
– Staff of PV centre, Nigeria

The collaboration between PHPs and NMRAs was not formalized in Memoranda of Understanding or Terms of Reference and mostly depended on personal relationships. (Although the EFDA in Ethiopia recently developed a stakeholder engagement guideline which has been approved by all key stakeholders). Collaborations that are not formalized are subject to individual personalities and staff changes. Mixed results were seen across the four countries depending on how good personal relationships were. Engagement of NGOs is usually donor-driven and it should therefore be carefully considered how they can best bring sustainable benefits to the PV programme.

*MRIs have been engaged with varying success. It seems most important to engage universities, as they educate healthcare students. We need to educate these students to report ADSs, as they will be the healthcare providers of tomorrow. Students can also assist in causality assessments and with various PV-related research projects.

"… a factor for significantly enhancing the collaboration with EFDA on PV is the commencement of postgraduate programs like an MSc regulatory affairs program. The students go there and conduct research, they know each other at that time, they identify the prevailing problems and when they come and defend their thesis here, this is the time when it is recommended to invite EFDA to the university. When thematizing the research for the students' thesis, the need of EFDA is taken into consideration and students do not do their thesis just only for graduation."
– University staff member, Ethiopia

Collaborations between PV programmes and partners such as PHPs, NGOs and universities are best formalized in Memoranda of Understanding or Terms of References, with a clear division of roles and responsibilities and well-defined outcomes. Engaging universities can bring the additional benefit of engaging medical students, who are the healthcare providers of tomorrow.

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Annex 1. Introduction to PAVIA

PhArmacoVigilance Africa (PAVIA) is a project funded by the European Union under the European & Developing Countries Clinical Trials Partnership (EDCTP) programme (grant number CSA2016S-1627-PAVIA). The PAVIA project's overall goal was to develop systems and approaches to improve the readiness of SSA health systems to effectively deliver new medical products and to monitor the safety of these products.

PAVIA focused on strengthening the PV systems in four SSA countries: Eswatini, Ethiopia, Nigeria, and Tanzania. In particular the PAVIA project targeted improving the effectiveness of ADR reporting mechanisms in conjunction with the introduction of new medicines by PHPs in order to gain a better understanding of the medicines' safety profiles.

The PAVIA project was initially scheduled to run for four years, from March 2018 until February 2022. However, the project was extended to February 2023 due to delays caused by the COVID-19 pandemic.

Background

PHPs play a key role in providing treatment for poverty-related infectious diseases (such as HIV/AIDS, malaria and tuberculosis) in SSA. In some cases the SSA PHPs introduce medicines and/or treatment regimens prior to full approval from, and registration with, that country's own National Medicines Regulatory Authority (NMRA). Such 'unapproved use' of drugs may rely on conditional/accelerated approval from foreign NMRAs, however, these medicines may have unknown side effects and represent a risk to patients. Medicines that receive such conditional/accelerated approval may have only been tested on a limited numbers of patients in clinical trials for a relatively short period of time. These studies often do not include children, the elderly, pregnant or lactating women, or patients with multiple comorbidities. It is, therefore, essential that countries, with the respective NMRA, undertake safety surveillance of new or repurposed medicines used by PHPs. In practice this is often not happening or only to limited extent.

To bridge this gap, EDTCP, through the PAVIA project, sought to strengthen national PV systems by setting up collaborations between the respective NMRAs and PHPs in the four project countries.

PAVIA started with the National Tuberculosis Programmes (NTPs), as these were introducing new drugs and regimens for the treatment of drug-resistant tuberculosis (DR-TB) which had not received approval from, nor were registered with, the NMRAs. To obtain insights into the safety profile of these new medicines and treatments, the World Health Organization (WHO) had required the NTPs to commit active PV, which was later defined as active drug-safety monitoring and management (aDSM).

Objectives

The objectives of the PAVIA project were to:

I) Strengthen governance of national PV systems, by strengthening regulatory and organizational structures and defining clear roles and responsibilities for all stakeholders

II) Improve efficiency and effectiveness of national surveillance systems, by strengthening active (sentinel) surveillance of ADRs and implementation of tools and technologies for their detection, reporting, analysis, and dissemination

Annex 1. Introduction to PAVIA

III) Build capacity and skills to sufficiently conduct safety-monitoring activities throughout the country
IV) Improve readiness of health systems within SSA, by undertaking performance assessments of PV systems allowing identification of enabling factors for, and barriers to, implementation.

The PAVIA project goals included transferring the lessons learned with the NTPs in the four project countries, both to other PHPs (such those for HIV and malaria) and to other SSA countries.

Description of the project

The PAVIA project was undertaken in the following countries:

- Eswatini (project country)
- Ethiopia (project country)
- Italy
- The Netherlands
- Nigeria (project country)
- Tanzania (project country)

as a partnership involving the following partners:

- Amsterdam Institute for Global Health and Development, the Netherlands (AIGHD)
- Armauer Hansen Research Institute, Ethiopia (AHRI)
- Baylor College of Medicine, Eswatini (Baylor)
- Ethiopian Food and Drug Authority, Ethiopia (EFDA)
- Institute of Human Virology, Nigeria (IHVN)
- Kilimanjaro Clinical Research Institute, Tanzania (KCRI)
- KNCV Tuberculosis Foundation, the Netherlands (KNCV)
- Netherlands Pharmacovigilance Centre Lareb, the Netherlands (Lareb)
- Ministry of Health, Eswatini (MoH-E)
- National Agency for Food and Drug Administration and Control, Nigeria (NAFDAC)
- Tanzania Medicines and Medical Devices Authority, Tanzania (TMDA)
- University of Benin, Nigeria
- University of Verona, Italy

The four SSA project countries were selected based on two criteria:

1) Each country was in the process of introducing new medicines and regimens for DR-TB and therefore (more) collaboration between the NTP and the NMRA on setting up PV for DR-TB was urgently needed; and

2) Each country represented a different level of PV system maturity [18]:

- Eswatini was a 'group 1' country, having minimal or no capacity for PV
- Ethiopia was a 'group 2' country, having established basic PV structures
- Tanzania was a 'group 3' country, having legal and organizational structures enabling the collection and evaluation of safety data
- Nigeria was a 'group 4' country with a PV system that detects, evaluates, and prevents-medicine safety issues (**Figure 10**).

The PAVIA project was structured by five Work Packages (WPs):

WP1: Coordination and Management
WP2: Policy, Law and Regulation Measures
WP3: Data collection and signal detection, including Data Management Measures
WP4: Monitoring and Evaluation
WP5: System, Structure, and Stakeholder Measures (**Figure 10**).

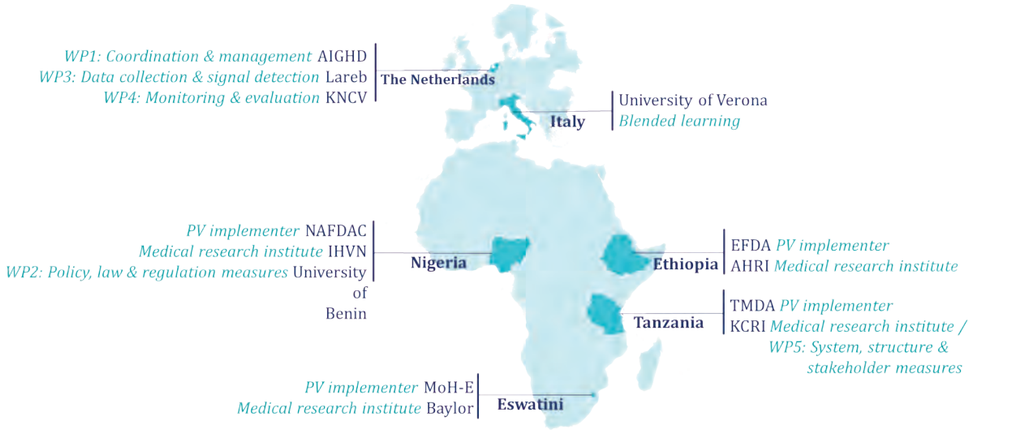


Figure 10. Overview of PAVIA partners and their key role in the project.

The PAVIA project established collaborative triangles within each project country, utilising the combined experience and expertise of the local NMRA, NTP, and an MRI (**Figure 11**).

A PV coordinator was also appointed in each country. Each PV coordinator facilitated the collaboration between the different parties, and oversaw all PAVIA-related activities, in the respective project country. The PAVIA project secured funding for each national PV coordinator for the first two years of the project. During this period, national PV coordinators were based in KNCV country offices where possible, to make it easier for them to act as an 'independent spill' within the national PAVIA triangle. After these two years, each country would incorporate the position of national PV coordinator within their NMRA. Both Nigeria and Tanzania now have PV coordinators in their national PV centres who connect with disease-specific PHPs in the country.

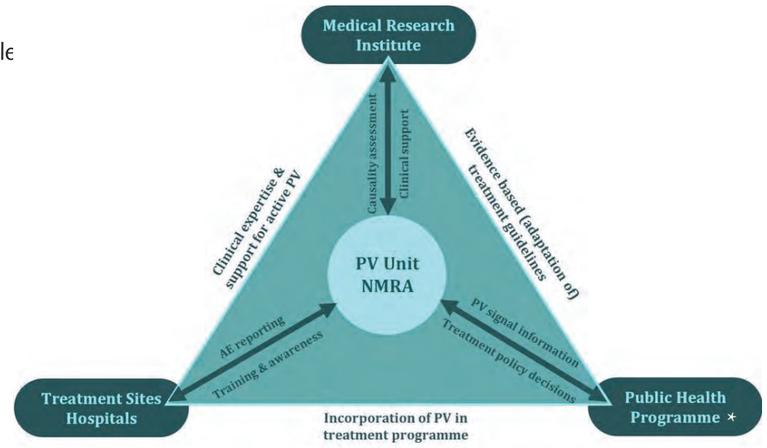
Project activities

The PAVIA project launched in May 2018, with an international kick-off meeting in Tanzania. This international kick-off meeting was soon followed by national kick-off meetings and baseline assessments in each of the project countries.

These baseline assessments evaluated the existing PV system within each country, assessing its' strengths and weaknesses, identifying gaps in the PV system, and identifying the most effective targets for interventions to be addressed through the project. The project team also identified and informed themselves on potential obstacles to the PV system improvements.

It was important that the national partners could choose how they wished to address the gaps in their PV systems. Following the findings of the baseline assessment, a roadmap workshop with broader stakeholder involvement was held in each project country. During this workshop the stakeholders discussed the findings of the baseline assessment, before defining the desired development goals for their respective national PV system. The stakeholders then developed a national PV roadmap to achieve these goals. This roadmap included specific priorities and activities that would be conducted during the project's intervention period.
The NMRAs in each country took the lead on the development of their respective national PV roadmap (in collaboration with the other national partners) and were responsible for monitoring the implementation of actions specified in the roadmap.

Figure 11.
PAVIA triangle model.



* This was the NTP for most PAVIA project countries.

The actions specified in the roadmaps ranged from the provision of diverse trainings, physically founding regional PV centres, the revision or development of digital data collection systems, policies, regulations, guidelines and SOPs, and the publication of newsletters, leaflets, job aids and other promotion materials.

The effectiveness and efficiency of a national PV system is dependent on the knowledge and active participation of all persons and institutions within the system. Each person and institution has different learning needs depending their respective role. In the PAVIA project, trainings focussed on NMRA staff and healthcare professionals. The NMRA staff participated in four training sessions during the project period. To reach healthcare professionals, PAVIA developed and deployed a blended learning programme. This programme combined face-to-face training sessions with self-study e-learning modules. To reach the greatest number of health professionals on a regional and local level the project utilised a train-the-trainer approach.

We monitored the progress of the project activities during several meetings. The PAVIA Executive Board, consisting of all work package leaders, met bi-weekly. The PAVIA PV coordinators and the leader of Monitoring and Evaluation (WP4) initially met fortnightly, and later once every three weeks. Twice per year, a Joint Steering Committee meeting was held and the PAVIA Advisory Board met annually. The work package leaders also attended these meetings.

The results of the PAVIA project were presented at several conferences (the Union World Conference on Lung Health of 2018 and 2019, the International Society of Pharmacovigilance Conferences in 2021 and 2022, the BIPAI RAISE Symposium in 2021, and the EDCTP Fora in 2018 and 2021). An international dissemination workshop was conducted shortly after project closure in the form of a webinar targeting SSA researchers through the EDCTP Networks of Excellence for Central (CANTAM), East (EACCR), Southern (TESA) and West Africa (WANETAM).

Towards the end of the project, in 2022, endline assessments were performed in all four project countries. These endline assessments used the same PV indicator tools as had been used at baseline, supplemented with stakeholder interviews and in-country observations. These assessments compared the PV system at the end of the project to the baseline situation, and to the target situation at the end of the project, as outlined in the respective national roadmap. The primary goal of the assessment was to determine what progress had been achieved within the PV system. The secondary aim of these endline assessments was to collect success stories as well as lessons learned from this project.

Annex 2. Criteria for best practices

In the Guide on the identification and documentation of best practices, published in 2017 [7], WHO defines a best practice as a *technique or methodology that, through experience and research, has proven reliably to lead to the desired result*, and further specifies that a best practice should meet all following four criteria: effectiveness, efficiency, relevance and ethical soundness [7] as well as at least one more of the criteria listed in the Table.

Table 4. Criteria for best practices. Source: [7].

Criterion	Description	Should be met
Effectiveness	This is a fundamental criterion implicit in the definition. The practice must work and achieve results that are measurable	Yes
Efficiency	The proposed practice must produce results with a reasonable level of resources and time	Yes
Relevance	The proposed practice must address the priority health problems in the region	Yes
Ethical soundness	The practice must respect the current rules of ethics for dealing with human populations	Yes
Sustainability	The proposed practice, as carried out, must be implementable over a long period with the use of existing resources	Not necessarily
Possibility of duplication	The proposed practice, as carried out, must be replicable elsewhere in the country or region	Not necessarily
Involvement of partners	The proposed practice must involve satisfactory collaboration between several stakeholders	Not necessarily
Involvement of community	The proposed practice must involve the participation of the affected communities	Not necessarily
Political commitment	The proposed practice must have support from the relevant national or local authorities	Not necessarily

In this guide, we included best practices that met the first four criteria, as well as the sixth criterion. Ideally, other criteria were also met.

Annex 3. Best practices: Overview by country and topic.

Topic	Eswatini	Ethiopia	Nigeria	Tanzania	PAVIA
Legal basis	Box 1: Approval national PV policy		Box 2: Revised PV regulations		
Funding		Box 4: Creative ways to increase budget	Box 3: Creative ways to increase budget		
Organising PV system				Box 5: Decentralisation	
Tools	Box 6: Hotline	Box 6: MDR-TB tracker	Box 7: Introduction MedSafety app Box 8: Moving to one database	Box 6: SMS reporting + hotline + SQRT	
Knowledge			Box 12: Advanced VigiFlow training for all NAFDAC staff	Box 9: Training of healthcare workers	Box 10: Blended learning Box 11: Advanced trainings for PV experts
Processes	Box 13: Introduction of dolutegravir	Box 14: Plumpy'Nut		Box 15: Investigations of potential signals	Quotes (p. 36-37)
Awareness	Box 16: Provision of feedback to healthcare providers Box 19: Eswatini Medicine Safety Watch Box 21: Public outreach	Box 17: Joint supportive supervision Box 18: analysis aDSM data		Box 20: Car cartoons Box 21: Public outreach	
Collaboration	Box 22: PHPs Box 28: NGO	Box 24: MRIs Box 27: EPA CPD course	Box 25: University of Benin	Box 23: PHPs Box 24: MRIs Box 26: Muhimbili	Annex 1: PAVIA Triangles

LESSONS AND BEST PRACTICES FROM THE PAVIA PROJECT:

A blueprint for strengthening pharmacovigilance systems in resource-limited countries

PAVIA
PhArmaco Vigilance Africa