Pharmacovigilance in the Kingdom of Eswatini: a situational analysis at the start of the PAVIA project

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List of abbreviations

ADR	adverse drug reaction	ND	new (TB) drugs
aDSM	active TB drug-safety monitoring and management	NEMC	National Essential Medicines Committee
AE	adverse event	NGO	Non-governmental organization
AEFI	adverse event following injection	NMRA	National Medicines Regulatory Authority
ART	antiretroviral treatment	NPSMC	National Patient Safety Monitoring Committee
CEM	Cohort Event Monitoring	NTCP	National Tuberculosis Control Program
CIOMS	Council for International Organizations of Medical Sciences	PAVIA	PhArmacoVIgilance Africa
CMIS	Client Management Information System	PEPFAR	United States President's Emergency Plan For AIDS Relief
CMS	Central Medical Stores	PHP	Public Health Program
DCAT	data catalogue vocabulary	PRD	Poverty-related disease
DR	drug-resistant	PV	Pharmacovigilance
DTG	Dolutegravir	SC-PASS	Supply Chain and Pharmaceutical Assistance for Sustainable Systems
ECG	Electrocardiogram	SIAPS	Systems for Improved Access to Pharmaceuticals and Services
EGPAF	Elizabeth Glaser Pediatric AIDS Foundation	SOP	Standard operating procedure
ENAP	Eswatini National AIDS Program	SPS	Strengthening Pharmaceutical Systems
EPI	Expanded Programme on Immunisation	SSA	Sub-Saharan Africa
fte	full-time employee	SSASSA	Sentinel Site-based Active Surveillance System for Antiretroviral and anti-TB medicines
HCW	Health care worker(s)	STR	Shorter (9-month) treatment regimen (for DR-TB)
MAH	Marketing Authorization Holder	TB	Tuberculosis
MDR	multi-drug resistant	UMC	Uppsala Monitoring Centre
MoH(-S)	Ministry of Health (of Eswatini)	UNISWA	UNIversity of SWAziland
MRA	Medicines Regulatory Authority	URC	University Research Co.
MRU	Medicines Regulatory Unit	WHO	World Health Organization
MSH	Management Sciences for Health	XDR	extensively drug-resistant
MSF	Médecins Sans Frontières		

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1. Introduction

In Africa communicable diseases are a major cause of morbidity and mortality. In recent years access to essential medicines for malaria, HIV/AIDS and tuberculosis (TB) has improved dramatically due to efforts of global health initiatives. Recently, two new TB drugs (bedaquiline and delamanid) have become available in many African countries. They were registered based on data from phase IIb trial, which means that the drug has only been tested in a small number of patients, thus little is known about its safety in diverse patient groups. Increased monitoring is required to gather more information about the drug's safety profile. In addition, many new drugs for poverty related diseases are in the pipeline of which some will be conditionally approved based on limited clinical trial data, and these drugs will be launched mainly in settings with little or no capacity for post marketing surveillance.
The introduction in sub-Saharan Africa (SSA) of new drugs and vaccines for poverty-related diseases (PRDs) is hampered by the absence of functional comprehensive pharmacovigilance (PV) systems. Such systems are essential, not only for the safe use of medicines, but also to create trust with governments, clinicians and patients. Ultimately effective PV systems will facilitate an improved delivery of - and access to - new medical interventions for PRDs.

1.1. PAVIA

PhArmacoVIgilance Africa (PAVIA) is a consortium funded by the European Developing countries Clinical Trials Partnership. The PAVIA project aims to strengthen PV in four African countries: Ethiopia, Nigeria, Eswatini and Tanzania. To achieve this aim, collaborative support will be harnessed across several institutions in Europe and Africa.
In each of the participating countries, a triangle will lead the project, consisting of the National Medicine Regulatory Authority (NMRA, including the national pharmacovigilance unit), a National Public Health Programme (PHP) introducing a new product and a local Medical Research Institute. PAVIA will have its initial activities premised on the introduction of new drugs (NDs) and treatment regimens for multidrug-resistant tuberculosis (MDR-TB) by the National Tuberculosis Programs (NTPs). PAVIA's focus will include strengthening the processes of routine adverse event reporting in accordance with country policies that already exist (or which will be put in place or strengthened during the course of the PAVIA project). In addition, expert guidance will be provided on causality assessment, signal detection and raining at the national and lower levels to support the linkage process between disease control programmes (notably the NTPs) and the NMRAs/PV Agencies.

PAVIA's objectives are:
I) To strengthen governance of PV systems, by strengthening regulatory and organizational structures and defining clear roles and responsibilities for all stakeholders;
II) To improve efficiency and effectiveness of national surveillance systems, by strengthening active (sentinel) surveillance of adverse drug reactions and implementation of tools and technologies for their detection, reporting, analysis and dissemination;
III) To build capacity and skills to sufficiently conduct safety-monitoring activities throughout the country;
IV) To improve readiness of health systems within SSA, by improving performance assessment of PV systems allowing identification of enablers and barriers for implementation.

PAVIA's strategy is to strengthen national PV systems in a collaborative effort with PHPs, building up medicines safety surveillance activities in the context of the introduction of new drugs for MDR-TB. Capacity at the national PV Centre/NMRA will be built gradually taking the PV activities for TB as the "building and training ground" for a generic PV system including data collection, database entry, data analysis, causality assessment and signal

identification. The results and lessons learned will be transferred by PAVIA to other PHPs, for example HIV or malaria. Combined with identified enablers and barriers in addressing regional differences and needs, a blueprint will be developed that can guide other countries in strengthening their PV systems.

1.2. Pharmacovigilance

The World Health Organization (WHO) has defined PV as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems."[1] The aim of the PV system is to protect the public from medicines-related harm. Currently few low- and middle-income countries have a well-functioning PV system to support the timely identification, collection, and assessment of medicine-related adverse events and the benefit-harm assessment which follows the identification of a signal. A signal being defined as "Information that arises from one or multiple sources (incl. observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action"[2].
Active surveillance for monitoring the safety and effectiveness of medical products is increasingly recognized as a complement to spontaneous reporting commonly used by PV systems.

1.3. Active TB-drug safety monitoring and Management

Since 2013, after introduction of two new TB drugs (bedaquiline and delamanid), WHO recommends active TB-drug safety monitoring and management (aDSM) when using one of these drugs. aDSM is defined as the active and systematic clinical and laboratory assessment of patients on treatment with new TB drugs, novel MDR- or extensively drug-resistant (XDR) TB regimens to detect, manage and report suspected or confirmed adverse drug reactions. The overall objectives of aDSM are to reduce risks from drug-related harms in patients on treatment for drug-resistant TB and to generate data to inform future policy updates on the use of such medicines[3].

In the lightest version, aDSM applies targeted reporting of serious adverse events, in the intermediate form adverse events of special interest are added. In its most rigorous form, the advanced aDSM package targets all AEs of clinical interest and thus approaches cohort event monitoring (CEM) where all adverse events of a patient in a TB cohort are collected during the treatment. CEM is not considered feasible for routine monitoring. However, depending on the information and setting, CEM might be considered for a limited period of time.

1.4. The Kingdom of Eswatini country profile

The Kingdom of Eswatini is a land-locked country of 17.363 km² in the South of Africa, neighbouring South Africa on the north, west and south, and Mozambique on the east (Figure 1). In 2017, it had 1,467,152 inhabitants. With a GDP (purchasing power parity) of $11.34 billion, the Eswatini ranks 158th in the world. The GDP per capita is $9,900. The country heavily depends on South Africa for its exports (60%) and imports (>90%). The

[1] WHO, 2009. The importance of pharmacovigilance. Safety monitoring of medicinal products. Geneva.
[2] CIOMS Working Group VIII, 2010. Practical Aspects of Signal Detection in Pharmacovigilance. Geneva.
[3] WHO, 2015. Active TB drug-safety monitoring and management (aDSM). Framework for implementation.

unemployment rate was as high as 28% in 2014. The country's workforce is largely employed in agriculture.[4]

Figure 1. Map of Eswatini showing the four regions where partners are implementing TB/HIV activities through PEPFAR funding

The country's health care system consists of the formal and the informal sector. The informal sector consists of traditional health practitioners and other unregulated service providers. In the formal health sector there are both public and private health service providers, including public health facilities (45%), private practitioners (23%), faith-based organizations (15%), industry-owned facilities (12%), and NGOs (5%). There are five levels at which health services are delivered: national referral hospitals, regional hospitals, primary health care facilities including health centers, public health units, rural clinics and outreach sites, and lastly community based care provided by volunteers.[5] Some major health indicators are provided in Table 1[6].

[4] Source: CIA World Fact Book, 2018. http://www.aho.afro.who.int/profiles_information/index.php/Swaziland:Index

[5] African Health Observatory. http://www.aho.afro.who.int/profiles_information/index.php/Swaziland:Index. Date accessed: 10 December 2018.

[6] Global Health Observatory. From: WHO country profiles. https://www.who.int/countries/swz/en/. Date accessed: 10 December 2018.

Communicable diseases continue to be a major challenge for the country. According to Health Statistics Reports, respiratory conditions account for about a quarter of all outpatient visits. In 2010, mortality was mostly caused by pulmonary tuberculosis, gastroenteritis, colitis, and pneumonia.[5] Malaria is endemic in Eswatini. In 2017, 27.4% (uncertainty interval, 25.2-28.8) of the adult population was infected by HIV/AIDS, which corresponded to the world's highest HIV prevalence rate.[7] After an increase in the burden of tuberculosis disease between 2008 and 2010, the country is successfully combatting the disease, and estimated incidence rates have gone down from over 1,000 per 100,000 inhabitants in 2010 to 308 (uncertainty interval, (236–389) in 2017[8].

Table 1. Overview of important general health indicators[8].

Indicator	Value
Life expectancy at birth m/f (years, 2016)	55/60
Probability of dying under five (per 1 000 live births, 0)	not available
Probability of dying between 15 and 60 years m/f (per 1 000 population, 2016)	464/338
Total expenditure on health per capita (Intl $, 2014)	587
Total expenditure on health as % of GDP (2014)	9.2

1.5. Pharmacovigilance in Eswatini

Eswatini has been engaged in PV activities to assess the impact of adverse drug reactions on public safety and health since 2009. Activities have evolved from spontaneous reporting to encompass active surveillance systems in 2015 for patients receiving TB and/or HIV medicines in sentinel sites.

2. Baseline situational analysis: justification and aim

This report presents the situational analysis of the various aspects and needs of the PV systems in Eswatini at the start of the PAVIA project, including its strengths and gaps. The baseline situational analysis will be followed by a workshop with broader stakeholder involvement to discuss the findings, define the desired 'end state' for the country and develop a PV plan or roadmap to achieve this 'end state', including activities and priorities. A final assessment will be conducted at the end of the PAVIA project period, using the same methodologies as in the baseline situational analysis. The situation will be compared against the anticipated 'end state'. Lessons learned on how the true 'end state' was achieved will be defined, including how challenges were addressed and best practices identified. Also, challenges encountered that could not be overcome will be analysed for potential alternative approaches to address those in the future and in other settings. Lessons learned within PAVIA will be packaged in a practical blueprint for use in other Sub-Saharan African countries.

The aim of the baseline situational analysis is to get a good understanding about the strengths and weaknesses of the current PV system in Eswatini, as well as to get a good understanding on training needs that can be addressed by the PAVIA project.

[7] UNAIDS, 2018. http://www.unaids.org/en/regionscountries/countries/swaziland. Date accessed: 10 December 2018.
[8] WHO Global Tuberculosis Report, 2018. https://www.who.int/tb/country/data/profiles/en/. Date accessed: 10 December 2018.

3. Methodology and team

3.1. Assessment strategy

The following strategy was used to assess the baseline situation:

1. PV indicators were assessed using a standardized assessment tool (see paragraph 3.2). For filling the list of indicators, documentation was reviewed if available. Additional information was provided through interviews with stakeholders.
2. Additional information regarding the current situation of the PV system was obtained through key informant interviews. This was to gain more insight in the PV system in the country, ascertain training needs, and get recommendations for the future from these key stakeholders.
3. Site visits to DR-TB treatment facilities were also conducted, to assess the current reporting of adverse events at health facility level and its barriers and facilitators.

3.2. PV indicator assessment tool

PV indicators were assessed using a slightly modified questionnaire developed and already used by the East African Community which is based on the Indicator-based PV Assessment Tool[9] and the WHO PV indicators[10]. The indicator tool has been developed together with PROFORMA (another EDCTP funded project working on PV strengthening in four SSA) and will be used for assessment of the PV system in 6 SSA countries. The tool for assessment of the national medicine regulatory authority (NMRA) contains 58 indicators that address five PV components: i) policy, law, and regulation; ii) systems, structures, and stakeholder coordination; iii) signal generation and data management; iv) risk assessment and evaluation; and v) risk management and communication (Annex 1). PHPs consists of 20 indicators addressing components two to five (Annex 2).

3.3. Assessment team

The assessment was conducted by a team consisting of national staff and international consultants.

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[9] Strengthening Pharmaceutical Systems (SPS) Program, 2009. Indicator-based pharmacovigilance assessment tool: manual for conducting assessments in developing countries. Submitted to the U.S. Agency for International Development by the SPS Program. Arlington, VA: Management Sciences for Health.

[10] WHO, 2009. pharmacovigilance indicators: a practical manual for the assessment of pharmacovigilance systems. Geneva.

3.4. Documents reviewed

Documents reviewed included legal documents, other official/published documents and internal unpublished documents. Also other sources of information were consulted (e.g. databases).

Legal documents reviewed included:

- Medicines & Related Substances Control Act 9 of 2016;

Policies and guidelines:

- National pharmaceutical policy (2011);
- National health policy (2006);
- Standard Treatment Guidelines and Essential Medicines List of Common Medical Conditions in the Kingdom of Swaziland (2012);
- Integrated HIV management guidelines (2018);
- Bedaquiline and delamanid for the treatment of drug resistant TB. Guidelines for clinicians (2015);
- Short-course treatment regimen for multidrug resistant tuberculosis. Interim guidelines for Swaziland (2017);
- Standard treatment policies and guidelines of the TB and HIV PHPs.

Other official/published documents reviewed:

- National patient safety monitoring committee, terms of reference (2015);
- National TB strategic plan 2015-2019;
- SIAPS Swaziland Final Report (September 2011–March 2018) (2018);
- Different items of the Swaziland Medicines Safety Watch;
- DR TB/HIV management training curriculum;
- adverse drug reaction (ADR) forms for active and passive surveillance;
- product complaint form.

Other documents included in the review were:

- vigiGrade™ - Completeness score Swaziland, UMC (2018);
- Monitoring of ototoxicity for 2015/2016/2017, NTCP (2018);
- Pharmacovigilance in Swaziland, National PV Unit (2017);
- Passive Surveillance Data Analysis, National PV Unit (2017).

3.5. Sites assessed and stakeholders interviewed

- MoH: Deputy director pharmaceutical services, Deputy director clinical services
- National tuberculosis control program (NTCP)
- Swaziland national AIDS program (SNAP)
- National laboratory services
- Client Management Information System (CMIS)
- Médecins Sans Frontières (MSF)
- Baylor College of Medicine
- Supply Chain and Pharmaceutical Assistance for Sustainable Systems (SC-PASS)
- The United States President's Emergency Plan for AIDS Relief (PEPFAR)
- University Research Co. (URC)
- ICAP
- Elizabeth Glaser Pediatric AIDS Foundation (EGPAF)
- National TB hospital
- Matsapha health centre
- Good Shephard hospital
- Pigg's Peak government hospital

- Nhlangano hospital

3.6. Analysis of the indicator tool and interviews

The indicator tool (see Annex 1 and 2) was used as a guide for structured interviews. Answers to the questions of the indicator tool as well as additional information provided by interviewees is described in the results section. At the end of the project the same indicator list will be used, and results will be compared to those obtained during the baseline assessment.

3.7. Limitations

There are some limitations to this assessment. First of all, only DR-TB treatment facilities were visited, with less attention to adverse event reporting by all health care workers. The results may not represent other health facilities. Furthermore, not all responses were verified by documentation. Also, answers to questions may have been subjected to data collector's judgement. Despite these limitations, we feel that the assessment gives a reliable overview of the current situation of the PV system in Eswatini.

4. Results

4.1. Policy, law and regulations

Twelve indicators were collected for this area (see Annex 1).

4.1.1. Medicines and Related Substances Control Act

The Medicines and Related Substances Control Act of 2016[11] (Act No.9 of 2016) dated 20th October 2016 and approved by the King provides for "the establishment of a Medicines Regulatory Authority, the registration of medicines and medical devices, the control of medicines and scheduled substances, and incidental matters". The Act has been published in the State's gazette, however the regulations that will facilitate the enforcement of the Act are yet to be passed in parliament. Different provisions of the Act may come into force at different dates, to be decided upon by the Minister of Health.

There are no legal provisions for PV or medicine safety in the Act. Since the Act does not prioritise PV it can only be expected that the subsequent Regulations will address issues concerning the Monitoring of medicines post licensure. Part X of the Act provides for the Authority to participate and cooperate with any regional or Continental Medicines Regulatory Agencies as well as Regulatory Harmonization activities. This allows for domestication and alignment with the AU Model Law which provides for pharmacovigilance. However, further elaboration of the provisions therein is required to underscore its importance and relevance.

In Part II, article 16, the funding of the Medicines Regulatory Authority will initially be drawn following appropriation from the Consolidated Fund. Subsection 3 states that the Authority shall not accept any donation or bequest without the approval of the Minister. The funding of PV and related activities is yet unclear and will depend on downstream discourse as the regulations are articulated.

The Act prescribes that within one year after being enforced, a Medicines Regulatory Authority shall be established consisting of minimum 5 and maximum 9 Board members with pre-defined education and background. The Authority however has not been established due to constraints in funding. Instead, in 2016 the Ministry established a Medicines Regulatory Unit (MRU) to start to implement some of the functions of the NMRA. There are currently two pharmacists deployed to this Unit.

[11] Eswatini Parliament, 2016. Medicines and Related Substances Control Act, 2015

Funding is needed to appoint staff for the Authority and for the implementation of the mandate of the Authority. The Act has a provision stating that initial funding for establishing the Authority will be obtained from the Consolidated Fund (government funding). The Act further prescribes that subsequent funding for the Authority shall come from the Consolidated Fund, as well as from fees and other sources.
PV does not have a prominent place in the Act but is mentioned as a topic to become (part of) regulations to give effect to, amongst others, "mandatory PV reporting by the manufacturers, wholesalers and health care professionals". The Act does not have explicit legal provisions for PV.
The Act lays down the procedures for Registration of Medicines (Part III) and issuance of Licences (Part VI).
Probably related to the fact that there are currently no formal law-enforced PV regulations and there is no national PV guideline, PV has no clear place in national policy documents, including national strategic plans and those of PHPs.

4.1.2. Market authorization holders, importers, and private health care providers

There are no marketing authorization holders in the country; all medicines are imported from international manufacturers. However, Suppliers and Importers of Medicines are responsible to an interim unit in the MoH. There are therefore no operational extant provisions requesting MAHs to submit Pharmacovigilance Plans, Risk Management Plans, Risk Minimization/Mitigation Plans, Periodic Safety Update Reports, report adverse drug reactions/medicine safety related issues, etc. These remain in view and will be hopefully addressed with subsequent regulations. Medicines, medical and laboratory equipment enter the country through the Central Medical Stores (CMS),Swaziland Health Laboratory Service and biomedical department of the Ministry..
Since the MoH does not register medicines itself, medicines which are registered elsewhere are imported into the country for use. The product must be registered in the country where it is manufactured; if not registered in that country, then there must be a valid reason for this *e.g.* the condition for which the medicine is indicated is not prevalent in the country where the medicine is manufactured. Importers of medicines are required to register with MoH and get an import certificate, the products they import are also listed by the Ministry, but they are not considered as being registered.
Private health providers are licensed by several councils: The Nursing Council for private nurses and the Medical and Dental Council for accreditation of private health facilities. Private pharmacies need a trading license from the Ministry of Commerce, Industry & Trade. To obtain such license, the pharmacy will need to present a letter of approval from the MoH (Deputy Director Pharmaceutical Services). This letter of approval will only be provided if the pharmacist does meet prespecified conditions (regarding premises, drug storage, pharmacist's registration as a practitioner, etc.). There is also a database of these community pharmacies within the Ministry. This database was initiated in 2016.

4.1.3. Essential medicines

An essential medicines list was published in 2012 as a section to the first National Standard Treatment Guidelines[12], which was published by the MoH with support of the Strengthening Pharmaceutical Systems (SPS) Program and funded by USAID and PEPFAR. The first edition of the published list has not been updated since then, however the list is used to post government tenders and thus facilitate procurement of medicines for the public sector is updated each time a new tender is to be floated.

[12] Ministry of Health of Swaziland, 2012. Standard Treatment Guidelines and Essential Medicines List of Common Medical Conditions in the Kingdom of Swaziland. 1st edition.

The National Essential Medicines Committee (NEMC) consults medicine safety information for decision making processes. It is chaired by the senior medical officer of the National TB hospital; the secretary is the Deputy Director Pharmaceutical Services of the MoH. The last meeting was in August 2017. Through the NEMC, prescribers and PHPs can advocate for a medicine to be added or deleted from the list. The process has several requirements including a motivation that provides the latest scientific evidence on the medicine.

4.1.4. Political willingness

Interviews with the senior management of the MoH (Deputy Director Clinical Services and Deputy Director Pharmaceutical Services), stressed the importance of setting up an NMRA with PV functionality. The funding for the erection of the NMRA should come from the Consolidated Funds. Obtaining funding requires a lobby within the MoH with competing programs. Currently, there are two pharmacists within the MRU and the Ministry is in the process of deploying more staff. The focal person for PV will now be integrated into the MRU and will be expected to focus on PV and the quality control of laboratory activities. All staff of the MRU including those for PV are presently funded by government.

4.2. Systems, structure and stakeholder coordination

In this area, fifteen indicators were assessed at the level of the NMRA (Annex 1), and six indicators at the level of the PHPs (Annex 2).

4.2.1. National pharmacovigilance unit

The Kingdom of Eswatini initiated systematic PV in 2009 by establishing a National PV Unit and designating one focal person for these activities at Central Medical Stores (CMS). Though the focal person was based at CMS, all PV activities were under the office of the Deputy Director Pharmaceutical Services. The PV focal person is responsible for the day to day implementation of PV activities but also has other duties not related to PV. The coordination of PV activities has been the responsibility of the National Patient Safety Monitoring Committee (NPSMC) since 2015. The committee aims to provide technical assistance to the National PV Unit on data analysis and validation including causality assessment, risk assessment, risk management, case investigation and, where necessary, crisis management including crisis communication. The NPSMC is chaired by the Deputy Director Pharmaceutical Services and the National PV Unit acts as secretariat. The NTCP, ENAP, national malaria control program, and the expanded program on immunisation are also represented on this committee. There is also representation from implementing partners, the national TB referral hospital and the WHO.[13]

Since the NMRA with a PV unit formally does not yet exist, there is no clear mandate for the PV unit, nor a structure. A short document[14] briefly summarizes the tasks of the National PV Unit to involve training, as well as collecting, collating, analysing and disseminating information on ADRs in the country both from spontaneous reporting and active surveillance, to inform clinical practice and improve patient outcomes.
Specific tasks outlined are:

- To characterize patients (age, weight and sex) most affected in the reports;
- To determine the medicines or medicine combinations most frequently involved in ADR reports in the database including the indications for use, route of administration and number of medicines per report;

[13] Ministry of Health, Kingdom of Swaziland, November 2015. National Patient Safety Monitoring Committee (NPSMC) Terms of Reference.
[14] National Pharmacovigilance Unit, 2017. Pharmacovigilance in Swaziland. Internal document summarizing the country's PV activities since inception of the PV Unit.

- To identify the most frequently reported ADRs including the severity, time to onset of reaction, category of ADR and outcome of the reactions;
- To determine the distribution of reporters by professional cadre;
- Produce a newsletter titled 'Medicine Safety Watch'.

There are no Standard Operating Procedures available to the PV unit.
The Eswatini national PV Centre has been a member of the WHO Programme for International Drug Monitoring since 2015.
Once formally established, the NMRA will be separated from the MoH and function as an independent medicine regulatory authority, giving it autonomy and independence from the Government. The board of the NMRA will report to the Minister of Health (see Figure 2). Once the NMRA is fully established and functioning, the PV unit will be founded within the NMRA.
For as long as there is no formal NMRA, the MRU is reporting to the Deputy Director Pharmaceutical Services.

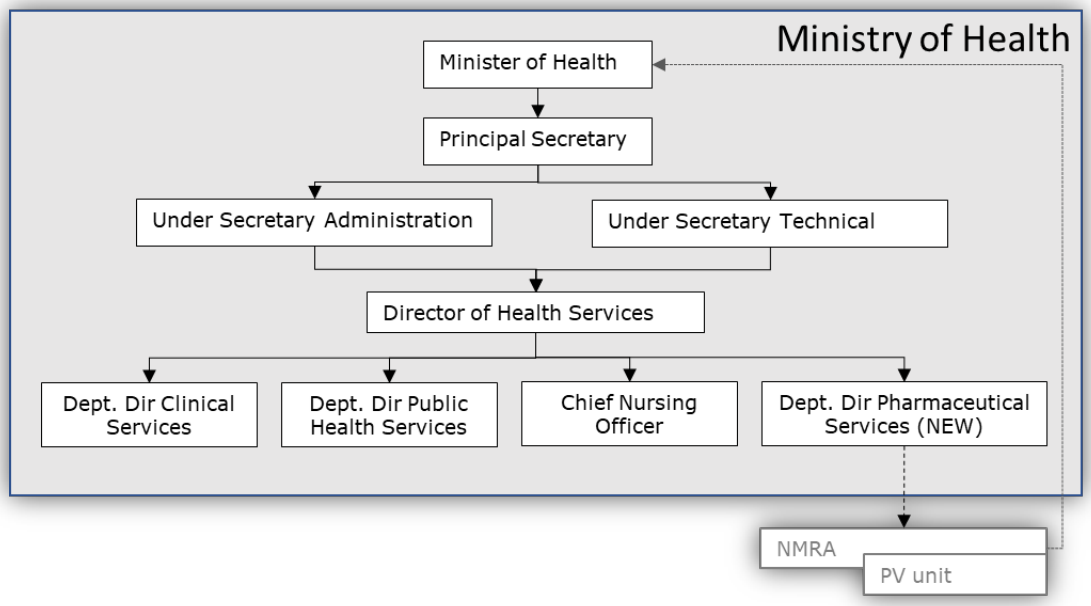

Figure 2. Organogram of the Ministry of Health, with proposed place of NMRA with PV unit (not yet established).

4.2.2. Role of non-governmental organizations

The TB and HIV program of Eswatini are mainly supported by four non-governmental organizations: Baylor/SC-PASS, EGPAF, ICAP, and URC. These partners support the MoH in implementing TB and HIV activities in the country. A regional model for implementing these activities is utilized, *i.e.,* each partner is responsible for implementing the activities in the different regions as shown in Figure 1 above. Some partners are however also provide technical support to the implementation of certain programs at a national level *e.g.*, ICAP is responsible for supporting the NTCP to implement the TB program, and URC is responsible for supporting the SNAP to implement the HIV program at the national level. All non-governmental organizations (NGOs) receive mainly funding from PEPFAR for these activities.

PV activities are currently mainly funded through SC-PASS, a PEPFAR-funded project. SC-PASS has taken over the activities from Management Sciences for Health (MSH), Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Project, which was active in

country till March 2018. Other NGOs, like MSF, also have some activities involving PV, but these are not connected to the national system.
SC-PASS supports spontaneous reporting (referred to as "passive PV") on yellow forms by 1) printing and distributing the paper reporting forms and 2) entering PV reports received in an Excel sheet, which is regularly forwarded to the PV focal person of the MoH. Also, SC-PASS supports "active PV", which essentially is CEM for all patients on TB and/or HIV medication. This was started in 7 sites throughout the country, but is currently actively implemented at three sites (Raleigh Fitkin Memorial Hospital, National TB Hospital, and Hlathikulau Hospital).
Other NGOs play a minor role in supporting PV: EGPAF includes a module on PV in their trainings, discussing possible side effects per drug and its management and stressing the importance of reporting these; the Institute for Health Measurement (IHM) Southern Africa is supporting the CMIS system (see below) of which implementation is done by the Strategic Information Department (SID) of the MoH. In CMIS some adverse event information can be entered, but it has no functionality for automated creation of PV reports for the PV unit. ICAP reportedly does not conduct any activities regarding PV at the moment.

4.2.3. National budget for PV tasks

Although the MoH pays the salaries of PV staff from Consolidated Funds, currently PV funding is mainly donor-driven (MSH through Systems for Improved Access to Pharmaceuticals and Services (SIAPS) previously, now SC-PASS) (Table 2). This makes the national PV work vulnerable to international donors' focus areas and threats its long-term sustainability.
Using the example of the requirement to have "active PV" when introducing new drugs and regimens for TB, one of the interviewees illustrated how systems are being pushed by donors and NGOs to absorb new interventions without the necessary structures being present or suitable to incorporate the intervention, which leads to 'Band-Aid solutions'.

4.2.4. Pharmacovigilance training

Preservice training

At the University of Swaziland (UNISWA, http://www.uniswa.sz/), there is a faculty of Health Sciences that offers a bachelor's degree in nursing sciences, but there is no training offered for other health care professionals such as medical doctors or pharmacists.
The Swaziland Christian University's (http://scu.ac.sz/Pharmacy.html) Health Science Faculty offers bachelor's degrees in nursing sciences and in pharmacy. They started operating in 2013 and the first students graduated in July 2018. The bachelor's degree comprises of five disciplines which include pharmaceutical chemistry, pharmacology, pharmacognosy, and pharmacy practice.
The Southern Africa Nazarene University in Manzini has a Faculty of Health Sciences http://www.sanu.ac.sz/healthsciences/pharmacy/ that offers a Diploma of Pharmacy and delivers pharmacy assistants/technicians and nursing degrees. Since inception in 2012 until February 2018, 21 students had graduated with a certificate in pharmacy and 8 with a diploma in pharmacy. Fifty pharmacy personnel graduated from this university with different qualifications (i.e., diplomas and certificates) and are currently working in the public and private pharmaceutical sectors.[15]
For none of these degrees is it clear how much these involve training on the reporting, assessment and analysis of adverse drug reactions.

[15] SIAPS Swaziland Final Report (2011-2018). Submitted to the USA Agency of International Development by the Systems for Improved Access to Pharmaceuticals and Services (SAPS) Program. Arlington, VA: Management Sciences for Health.

Table 2. PV activities by funding source. Activities specifically targeting PV are highlighted in blue*.

Partner	Salaries	Procurement	Trainings and meetings	TA	Budget
MoH	• national PV staff • doctors and nurses • laboratory staff • Pharmacy personnel	• Laboratory reagents • Laboratory equipment • Ancillary drugs			Not provided
Global Fund	• 8 regional DR-TB doctors • 12 regional DR-TB nurses laboratory personnel national audiologist	• for audio screening: ○ 8 kuduwaves ○ 4 titan machines for children • 11 ECG machines	training of doctors and nurses on audiology and ECGs		Not provided
Baylor/ SC-PASS	• data entry clerks for SSASSA (CEM) and Excel (spontaneous reporting)	• printing of spontaneous reporting forms, job aids and SOP, printing PV guideline is planned • transportation of data clerks & supervisors	PV training module for doctors, nurses and pharmacists	Tech-nical assis-tance to PV unit	80,750 USD for the fiscal year 2018/2019
ICAP	• PMDT technical advisor seconded to NTCP who assists coordinating TB PV activities • laboratory staff • regional clinical advisors and mentors supporting PV activities in Manzini region	calibration of audio equipment	• quarterly DR-TB expert meeting-forum to discuss PV issues • Funding for consultant cardiologist to train doctors and support ECG training • Regional TB trainings for HCWs in Manzini region		Not provided
URC	• regional clinical advisors and mentors to support PV activities in Lubombo region • regional clinical advisors and mentors to support PV activities in Lubombo region		Regional TB trainings for HCWs in Lubombo region		Not provided
EGPAF	Salaries for regional clinical advisors and mentors to support PV activities in Hhohho region		Regional TB trainings for HCWs in Hhohho region		Not provided
MSF	• Salaries for regional clinical advisors and mentors to support PV activities in Shiselweni region • laboratory personnel in Nhlangano lab • doctors and nurses working in Shiselweni and Manzini region	• laboratory equipment and reagents in Nhlangano lab • ECGs and audio equipment for other facilities in Manzini and Shiselweni	Regional TB trainings for HCWs in Shiselweni region		Not provided

* Abbreviations used in table: see List of Abbreviations (p. 3)

In-service training

Although the clinical management of adverse events is addressed, the formal and standardized TB and HIV training curriculum does not include a specific section for PV (see Annex 3 for the training curriculum). SC-PASS supports MoH to provide annual training on pharmaceutical services. Training is provided to pharmacists, nurses and pharmacy personnel and sometimes also to physicians. In this training, PV is a 30-minute module which contains the importance of PV, definitions, reporting, how to fill in the ADR reporting forms and why it is important to report.

Two pharmacists (the PV focal person and the pharmacist at Piggs Peak Hospital) have received PV training in Ghana. The PV focal person has also been trained at the UMC.

4.2.5. National patient safety monitoring committee

The NPSMC consist of approximately 14 persons, representing the following organizations:

1. National PV Unit
    a. Deputy Director Pharmaceutical Services
2. WHO
3. ENAP
4. NTCP
5. National Malaria Control Programme
6. Expanded Programme on Immunisation (EPI)
7. National TB Hospital Senior Medical Officer
8. URC

The aim of this committee is to provide technical assistance to the PV unit on data analysis and validation including causality assessment, risk assessment, risk management, case investigation and, where necessary, crisis management. From quarter 2 of 2018 onwards the committee will meet quarterly. The NPSMC coordinates all PV activities in country.

4.2.6. Consumption and prescriptions of medicines

For some PHPs consumption data is collected under the respective Logistics management Information system (HIV, TB, family planning, malaria). The data is not publicly available but used by MoH for decision making only (*e.g.* supply chain). There is no data on private sector sales, although some private facilities have memorandums of understanding with the government do provide data from their laboratory, medical and commodity information system to the MoH.

4.2.7. Mechanisms to disseminate PV information

A PV newsletter, titled 'Swaziland Medicine Safety Watch' is published by the PV unit, the most recent one dating from September 2017. PV information is also disseminated during trainings of health care workers (HCW) or data dissemination activities. There is no website for dissemination of PV information.

4.3. Signal generation and data management

In this area, six indicators were assessed at the level of the NMRA (Annex 1), and one indicator at the level of the PHPs (Annex 2).

4.3.1. Collection of PV data, data flow and management

Spontaneous reporting (passive surveillance)

Spontaneous reporting, referred to as "passive surveillance' in country, was implemented in Eswatini in 2010 and resulted in receiving around 30 ADR reports per year[16]. The reporting form was available in all health facilities visited during the assessment. The form is based on the CIOMS form (Annex 4).

During the time of the assessment, in some facilities the forms were kept at an easily accessible location in the TB unit as well as in the pharmacy, but this was not the case in other health facilities.

The forms should be filled in by the clinicians or nurses and then be forwarded to the pharmacy. In some facilities the clinicians and nurses thought that it was the responsibility of pharmacy personnel to fill the forms. In other facilities the clinicians were aware that they themselves are responsible for completing the forms.

[16] SIAPS, 2018. SIAPS Swaziland Final Report (2011-2018). Submitted to the USA Agency of International Development by the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program. Arlington, VA: Management Sciences for Health.

The pharmacist collects all forms from the health facility and then sends these to the CMS using the routine medicines transportation system, where they are passed on to the PV focal person. The PV focal person checks the reports for completeness and consistency, and then forwards the reports to data entry clerks based at SC-PASS for data entry. The reports entered in an Excel sheet which currently serves as the national PV database. Selected reports are then entered by the PV focal person in VigiFlow, which serves as the national PV database. Only in 2015, reports have been entered in VigiFlow and submitted to VigiBase at the UMC.

There is no dedicated computer available for the national PV database. VigiFlow data are stored in the cloud, but those reports that are entered in Excel and not also entered in VigiFlow are stored on one person's laptop only, and no back-ups are made.

Between June 2016 and May 2017, the PV focal person received 224 reports; most reports were received from clinicians (Table 3). Three health facilities submitted more than 10 reports.

Table 3. Number of yellow forms received by the National PV Unit between June 2016 and May 2017, by type of reporter.

Reporter	Number of reports received	%
Clinician	110	49.1
Nurse	42	18.8
Pharmacist	19	8.5
Pharmacy technician	46	20.5
Not available on report	7	3.1
Grand Total	**224**	**100.0**

In three of the five health facilities visited, there was little awareness about the importance of reporting ADRs.

In one facility, there was good awareness. In this facility, the pharmacist actively encourages clinicians to report ADRs. She asks patients collecting medicines in the facility's pharmacy about their health, if they experienced any adverse event, and checks if their medication involves ancillary drugs. If such is the case, she informs the clinician and encourages him/her to report this adverse event. Until recently, she would fill in a form herself, but recently she has trained clinicians and nurses in filling the forms and has shifted this responsibility to them. In this facility, also frequent updates are provided on safety of medicines, PV, and importance of reporting.

Active PV projects (Cohort Event Monitoring)

CEM, called "active surveillance" in Eswatini, involves all TB and HIV patients in sentinel sites. In other countries, CEM is drug specific and conducted during a certain period of time or until a certain cohort size has been obtained. In Eswatini, the CEM is not drug specific, but disease specific and it is not time- or cohort size limited. The CEM was initiated by SIAPS in collaboration with the NTCP and the ENAP in 6 health facilities (five hospitals and one clinic) in 2013, with specific reporting forms and an electronic database available on-site.[17] Currently, CEM is still being conducted in four of these 6 health facilities.

Paper-based data collection forms are available in the patient files so as to remind clinicians about filling these for each patient encounter. At the start of treatment, baseline information

[17] SIAPS, 2018. SIAPS Swaziland Final Report (2011-2018). Submitted to the USA Agency of International Development by the Systems for Improved Access to Pharmaceuticals and Services (SAPS) Program. Arlington, VA: Management Sciences for Health.

about the patient (demographics, risk behaviour, concomitant medication and comorbidities) is collected on the treatment initiation form. The occurrence of adverse events is recorded on follow-up forms, to be filled at each follow-up visit. There is also a separate form for recording the laboratory results and treatment changes. The forms are to be filled by the TB and HIV clinicians. The filled forms are collected on regular basis by data entry clerks supported by SC-PASS (previously: SIAPS) and entered into the SSASSA[18] database on-site. The SSASSA database captures all CEM data and is maintained by SC-PASS. The database is available on the laptops of the data entry clerks and there is one central database in one laptop at the SC-PASS office in Mbabane, but no regular backups are made. The Swaziland Medicines Safety Watch report of October 2016 published results of 4210 patients enrolled in CEM, reporting 1224 adverse events altogether.[19]
Since there was no funding available for PV activities supported by SIAPS after February 2018, the active surveillance was transitioned to SC-PASS in the first quarter of 2018.

4.3.2. Reporting tools

In Eswatini two official adverse event reporting forms exist, a spontaneous reporting form and an active reporting form for TB drugs or antiretroviral treatment (ART). Spontaneous reporting forms are available to all health facilities that request them. They were available in each health facility visited. In some facilities, different versions of the spontaneous reporting forms were used.
Some facilities also had unofficial adverse event reporting forms, which were still available from studies previously performed on site. Nearly all clinicians interviewed found the active reporting form long and it requires copying patient data which is a barrier to filling out the form.
The reporting tools are paper-based, and all persons interviewed mentioned that an electronic reporting system would facilitate reporting adverse event. CMIS currently contains some fields for reporting adverse event. The CMIS team agreed on elaborating the possibilities of including adverse event reporting in the system. The use of electronic reporting means such as app could be a possibility since smart phone use is quite high, however since reporters pay for a data bundle themselves, they would probably not be very keen on using their private data bundle for professional purposes. Also, the limited availability of computers within health facilities is a limitation. In one of the visited facilities, for example, the computer in the TB consultation room was already out of order for 6 months and had never been repaired. In other facilities, not all consultation rooms had a computer available. CMIS was available in different facilities. In one facility, health staff organized step-down trainings using CMIS itself, as no training module was available. They did not realize that any changes made in CMIS would be stored and reported later as 'real' changes.

4.4. Risk assessment and evaluation

In this area, twelve indicators were assessed at the level of the NMRA (Annex 1), and eight indicators at the level of the PHPs (Annex 2).

4.4.1. Reporting of adverse events

In all five health facilities visited, clinicians check for known side effects of TB treatment at each visit and management of side effects was done accordingly. Adverse events are recorded in the patient file, but only in two of the facilities there is a strong reporting practice. In interviews, most clinicians mentioned high workload and copying of patient information prevents reporting to be a priority.

[18] SSASSA=Sentinel Site-based Active Surveillance System for Antiretroviral and anti-TB medicines
[19] Swaziland Medicines Safety Watch 5(2); 2016.

There are no data for a full calendar year, but between June 2016 and May 2017, spontaneous surveillance yielded 224 adverse event reports received by the PV unit, all regarding adverse drug reactions. No reports were received on suspected medication errors, therapeutic ineffectiveness, suspected misuse, adverse events following immunization (AEFI) or suspected counterfeit drugs. All reports were reviewed by the PV centre and entered in the national database (Excel file). In 2017, none of the ADRs were submitted to Vigibase (in 2015, 27 adverse event reports had been submitted to Vigibase, which were the last reports received by UMC).
For active surveillance, it is not known if any reports were received but not entered in the SSASSA database. Such may have happened during the transition period early in 2018.

Table 4. Number of adverse event reports received in 12 months and expected reports.

Population exposed	Number of adverse event reports		Comments
	Observed	Expected	
Total population	224*	120	Using 100 reports per million population
Patients on TB treatment	27**	**# AE reports per 1,000 patients**	
MDR/XDR-TB	19	59.7	Based on 318 patients on treatment in 2017
non-MDR-TB	4	1.24	Based on 3226 patients on treatment in 2017
Isoniazid preventive treatment (for TB)	4	0.14	Based on 29,155 PLHIV on treatment in 2017***

* Reporting period: June 2016-May 2017. ** Reporting period: Calendar year of 2017. *** PLHIV: persons living with HIV. Source: Annual HIV Report, 2017.

4.4.2. Reporting and feedback

In most health facilities reports of adverse event are collected monthly. Acknowledgement of receipt is not given consistently. Feedback is not given on individual reports, but summaries of adverse events and signals are presented through different platforms like the PV newsletter, DR-TB expert group meetings, and emails. The PV newsletter (Swaziland Medicines Safety Watch) is in principle published twice per year and was published once in 2017 (October).

4.4.3. Data analysis and causality assessment

For data obtained through CEM, causality assessment was done by PV experts. The last causality assessment meeting happened towards the end of 2016 and took into account mostly reports about serious ADRs. It was conducted by the NPSMC, supported by external experts from MSH and the WHO collaborating Centre for Tropical Clinical Pharmacology and Therapeutics in Accra, Ghana. No causality assessment has been done for spontaneous reporting so far. In conclusion, there is a lack of resources and capacity for data analysis and causality assessment, both were last done in 2016. The NPSMC discusses the management of adverse events but is not very active in driving causality assessment.

4.5 Risk management and communication

In this area, ten indicators were assessed at the level of the NMRA (Annex 1), and five indicators at the level of the PHPs (Annex 2).

4.5.1. Management of adverse events

All ART and TB medicines being procured by the country are from WHO prequalified suppliers. Within the TB and HIV program, increasing attention is given to the management of adverse events. This is also reflected in the standard training curriculum (trainings #6 and #9, see Annex 3). Before introduction of new drugs and regimens, all laboratories and hospital services have been updated to make sure that adequate patient management could be performed. There is a national PMDT expert hired at the NTCP to coordinate activities related to PV in the DR-TB sites, and there are regional clinical advisors that can assist clinicians on the management of adverse events. Clinicians and nurses at the visited sites were aware of the occurrence and treatment of adverse events. Also, the laboratory staff flag abnormal laboratory values and call clinicians if values are out of the normal range.
After starting DR-TB treatment, a treatment observer is assigned at patient's preference and the treatment is monitored on at least a monthly basis by a community nurse. Also, the nurse is aware of the possibility of adverse events happening; open questions about ADRs are asked during the check-up visits and there is a tick list available listing the most common adverse events, which can be ticked when adverse events occur. Treatment observers are trained on their task (observing medicine intake), but also about adverse events. If an adverse event is suspected, the treatment observer can phone the community nurse. The community nurse can contact a clinician if the adverse event needs treatment or observation.

The most commonly mentioned adverse event in the DR-TB sites visited was hearing loss associated with kanamycin. Despite increased vigilance, the proportion of DR-TB patients experiencing any hearing loss did not decrease since 2015 (Figure 3).

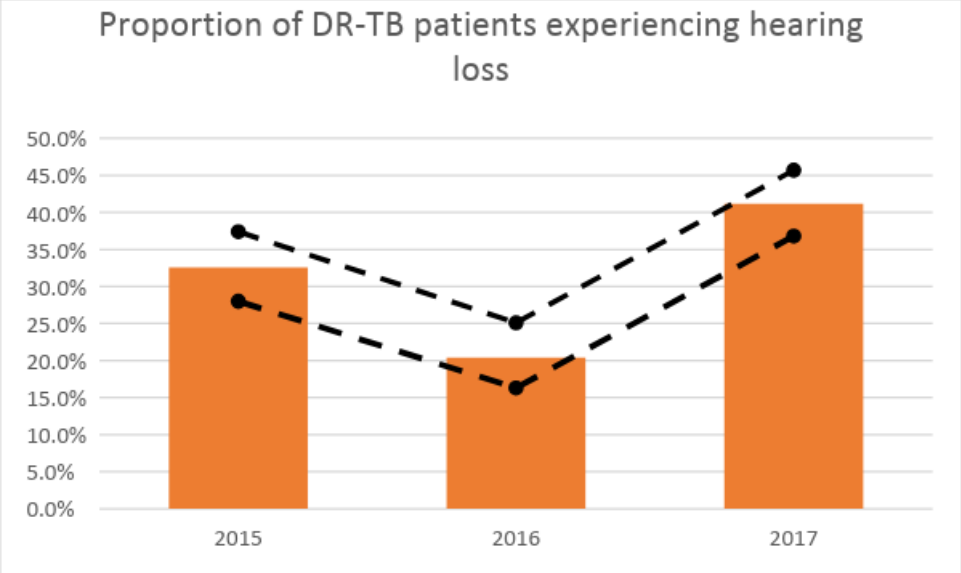

Figure 3. proportion of patients facing hearing loss, per year (2015-2018). Bars present percentages, dotted lines the 95% uncertainty ranges.

4.5.2. Risk management

Since there is no NMRA, it is the MRU within the MoH that acts if signals arise internally (Eswatini) or externally (through WHO alerts). Dolutegravir (DTG, for persons living with HIV) roll out will start in October 2018, in the preparation it was planned to use DTG in all patients who were initiating ART treatment. With the recent warning about probable congenital abnormalities it was decided to change the treatment guidelines and exclude women of reproductive age from DTG treatment until further evidence is available.

4.5.3. Signal detection

There is no signal detection process in place. In the past 5 years two signals were detected by the PV centre, one through spontaneous reports from health facilities and the other driven by WHO information but confirmed by own reports. It takes approximately 3 months from identification of a safety signal till it is communicated to all health workers and the public.

4.5.4. Communication

WHO alerts are forwarded to key stakeholders via email or WhatsApp. The PV unit planned to publish a PV newsletter twice a year, in 2017 one newsletter was published. During interviews with clinicians many reported they had never seen the newsletter.

5. Conclusion: strengths and weaknesses of the PV system in Eswatini

Strengths

1. The political goodwill of government is a great strength for the growth of PV in Eswatini coupled with the enthusiasm of the available personnel
2. The legal framework envisaged is likely to position PV and integrate it into the healthcare system
3. The extant Law though not activated provides a potential enabling environment and a substrate for various facets of PV to build on

Weaknesses

1. A great weakness and limitation relates to the personnel disposition in numbers and expertise. Despite being a small country there are too few personnel to deal with the PV activities at the Centre and around the country
2. The lack of resources to facilitate the growth of PV is a hindrance that have to be addressed
3. The lack of training platforms for PV locally and the inability to fully factor into external opportunities is yet another weakness
4. The country also lacks basic infrastructure to provide visibility for PV providing space to allow for PV function.

6. Recommendations and next steps

6.1. Respondents' recommendations

During the interviews respondents gave suggestions and recommendations for improvement of the PV system. Below are the most recommendations, some responses were given more than once.

- NMRA needs to be put in place to enforce regulations
- A way to obtain more sustainable funding for PV activities could be to charge fees and retain these for PV. Fees could be obtained from importation of drugs, and from licensing of importers, pharmacies, health facilities and drugs, i.e. a user-fee based structure
- For the PV program to work well, enough human resources (regarding both time and capacity) are needed

- Incorporation of PV in pre-service curricula can be important in creating greater PV awareness
- PV should be part of in-service trainings of health care workers
- It is important to concurrently strengthen PV in both the TB and HIV/AIDS PHP because there are a lot of TB-HIV co-infections and doctors/nurses often treat both diseases. TB and HIV/AIDS programs are working together in most facilities
- It would help to have a dedicated clinical therapeutic committee (like the Pharmacy Therapeutics Committees within health facilities) that discusses any problems with drug interactions
- Electronic adverse event reporting forms connected to electronic patient file would facilitate reporting by reducing the administrative burden (copying names and patient info on every form and in each registration book)
- Training on how to use the adverse event reporting form would facilitate reporting
- Receiving feedback on reports would stimulate reporting and help to better understand adverse events
- TB treatment supporters could monitor for, detect and report adverse events

6.2. Visiting team's recommendations

Policy, law and regulations

It is recommended that the Medicines and Related Substances Control Act is enforced as soon as possible. This is an essential first step to facilitate the development of PV. Once it is enforced a NMRA can be established and PV regulations can be drafted. The establishment of an NMRA to drive the pharmaceutical sector in the country is paramount.

The operationalization of the ACT is key to ensuring that all necessary regulations are put in place; and procedures for funding and providing logistics are established. There is essentially the need to have the complement of staff and establish some collaboration and linkages with more established organs and settings which can provide the expertise to facilitate the operationalization exercise.

Systems, structures and stakeholder coordination

A clear mandate for the PV unit can be obtained after the NMRA is established. Possibilities for obtaining more sustainable funding for PV activities should be explored, *e.g.* charge fees and retain these for PV, from importation of drugs, and from licensing of importers, pharmacies, health facilities and drugs, *i.e.* a user-fee based structure. To better coordinate PV activities in the country, including activities of different donors, the NMRA with the MoH should take a central coordinating role in PV.

Establishment/strengthening of training curricula on PV for both pre-service and in-service training can improve PV awareness and knowledge and thereby increase reporting of adverse events. Also training of PV staff on causality assessment and signal detection is important.

Methodology of data collection

It is recommended to evaluate what is learnt from the current active surveillance, if it fits the current information needs. Also, feasibility of active surveillance should be considered (regarding human resources and human capacity), since data analysis and causality assessment were last done in 2016.

Data collection tools

Developing an electronic adverse event reporting form could reduce workload and thereby facilitate reporting. Availability of computers in health facilities and internet access should be considered.

Data management

It is advisable to use one national secured PV database including a secured back-up system which communicates with Vigibase and to avoid duplicate entry of data into a national database and Vigibase.

Adverse event reporting

Possibilities to increase adverse event reporting should be explored, like an electronic adverse event reporting form, providing training or mentoring to HCW, providing feedback on reports and strengthening the reporting infrastructure.

Data analysis, causality assessment and signal generation

Increased human resources and capacity for data analysis, causality assessment and signal generation are needed. Improve the process of signal detection and communication.

6.3. Next steps

After approval of this report by the senior management team of the MoH it will be disseminated to all key stake holders. This will be followed by a stakeholder meeting to discuss the findings and draft a PV strategic plan to strengthen the PV system in the upcoming years.

Annex 1. NMRA assessment tool

Indicator #	Indicator	Assessment Questions	Answer	Notes & additional comments	Information source
Component 1. Policy, Law, and Regulation					
1.1	Existence of a policy document that contains essential statements on pharmacovigilance or safety of medicines, health products and technologies (stand alone or as a part of some other policy document)	Is there a national policy on pharmacovigilance or medicine safety, or a more general medicines policy that contains essential statements?	No	MoH responsible for providing safe, efficacious & quality medicines, but no PV policy; refer to health policy	Interview & documentation (National health policy (art. 4.27))
		When was the policy last reviewed?	NA	National health policy last updated March 2011	
1.2	Existence of specific legal provisions for pharmacovigilance in the national medicines legislation or similar legislation	Are there legal provisions for pharmacovigilance or medicine safety in the medicines act or law?	No	Not comprehensive; not explicit; no specific section on PV legislation or post-marketing surveillance	Interview & documentation (Medicines and related substances control act, 2016)
1.3	Legal provisions for Marketing Authorization Holders to monitor and report the safety and quality of their products	Is it mandatory by law or regulations for MAHs to:		No MAHs in country. No risk management plans post-marketing. No license authority. Legislation in process. Act has passed, but regulations have not yet passed. New parliament expected Oct/Nov 2018. Regulations need to go through parliament (probably after Nov 2018). To be provided for in the regulations based on Section 72 of the Medicines & Related Substances Control Act	Interview & documentation
		- conduct post marketing safety activities?	No		
		- report adverse drug reactions/medicine safety related issues?	No		
		- regularly submit periodic safety update reports (PSUR) or periodic benefit-risk evaluation reports (PBRER)?	No		
1.4	Existence of legal provisions empowering the national regulatory authority to require Marketing Authorization Holders to submit proof of their proactive pharmacovigilance planning as part of an application for product licensing	Does the national regulatory authority have the power to require MAH to submit any of the following documents prior to product licensing?		No registration active - process in preparation – to be provided for in the regulations based on Section 72 of the Medicines & Related Substances Control Act	
		I. Pharmacovigilance plan	No		Interview
		II. Risk management plan	No		Interview
		III. Risk minimization/mitigation plan	No		Interview

		Are MAHs required to adapt the plans to the particular risk situation of the population in the country?	No	international alerts are forwarded to wholesalers/importers by MoH. If drug needs to be taken off market, importer will be notified.	Interview
1.5	Existence of national pharmacovigilance guidelines developed or reviewed within the past 5 years	Does a national guideline for PV (or a related document) exist?	No	Only In-service training for HCW	Interview
		Has the national PV guideline been developed or reviewed within the past 5 years?	NA		
		When were the guidelines last reviewed?	NA		
1.6	Regulations and guidelines encourage distributors, importers exporters, health- care institutions, other stakeholders and consumers to report ADR and/or AE to the MAH and/or NRA	Do regulations and guidelines encourage distributors, importers exporters, health- care institutions, other stakeholders and consumers to report ADR and/or AE to the MAH and/or NRA	No	Regulations to be drafted so that incoming parliaments consider them together with the rest of draft regulations	Interview
1.7	The legal provisions and/or regulations allow NRA to require manufacturers and/or MAHs to conduct specific studies on safety and effectiveness under specific conditions	Does the national regulatory authority have the mandate to require manufacturers and/or marketing authorization holders to conduct and present results from specific studies addressing identified safety concerns?	No	Regulations to be drafted so that incoming parliaments consider them together with the rest of draft regulations	Interview
1.8	Legal provisions, regulations and/or guidelines require manufacturers and/or marketing authorization holders to designate a Qualified Person responsible for vigilance.	Do legal provisions, regulations and/or guidelines require manufacturers and/or marketing authorization holders to designate a Qualified Person responsible for vigilance?	No	Regulations to be drafted so that incoming parliaments consider them together with the rest of draft regulations	Interview
1.9	Existence of updated National Essential Medicines List that was reviewed with consideration of medicine safety information	Is there an essential medicines list in use?	Yes	As section b in the standard treatment guidelines and essential medicines list	Interview & documentation
		Does the essential medicines list selection committee consult medicine safety information?	Yes	National Essential Medicines Committee also reviews safety information. Chair person is Se. Shabangu (National TB Hospital), secretary is F. Bhembe (Deputy Director Pharmaceutical Services)	Interview
		When was the list last reviewed?	06-Mar-12	First version 2012, last meeting March 2016	Interview

1.10	Existence of a medicines regulatory authority or agency	Is there a drug regulatory authority or agency?	No	Unit within MoH implements some regulatory functions of medicine. Medicines and related substances control Act aims to establish NMRA. Though the Act has passed, it is not yet functional since it awaits ministerial action. The Act has general provisions, but the details of the implementation of the Act will come with the Regulations.	Interview & documentation
1.11	Existence of official records of licensed medicinal products	Is there an official source of information on medicinal products that are licensed for use in the country?	No	Eswatini does not license drugs, importers of medicines are required to register with MoH and the products they bring in need to have official registration, no marketing license for products.	
1.12	Accreditation of private health facilities includes requirements for the existence of a pharmacovigilance system	Does the public authority responsible for accreditation of private health facilities require that a pharmacovigilance system is in place?	No	Nursing Council for private nurses and Medical and Dental Council for accreditation of private health facilities; private pharmacy needs trading license from Ministry of Commerce, Industry & Trade. For this, the pharmacy will need a letter of approval from MoH (Dept Dir Pharm Services). MoH will ensure quality of pharmacy (inspection of premises, check if pharmacist is registered, current practice licensed, etc)	
Component 2. Systems, Structures, and Stakeholder Coordination					
2.1	Existence of a national pharmacovigilance centre with a clear mandate and structure	Is there a National PV centre or any other body assigned the responsibility of monitoring safety of medicines?	Yes	PV unit within MoH	Interview
		Is there a clear mandate and organizational structure for the pharmacovigilance centre?	Yes	Mandate is clear but is not on paper. Before 2018, there was one PV focal person only. PVU reports to Dept Dir Pharmaceutical services. Current mandate: data analysis. Any decisions need to go through MoH.	Interview
2.2	The pharmacovigilance centre has designated, qualified human resources to carry-out its functions	How many staff members (full-time equivalent) does the PV centre or system have who are specifically responsible for carrying out its functions (technical and administrative)?	<1	1 part-time staff, who does PV work next to other tasks, % of work on PV not specified. PV unit works hand in hand with SC-PASS	Interview

2.3	Existence of a dedicated financial provision or statutory budget for the pharmacovigilance centre	Is there an annual budgetary allocation for PV activities or for the PV Centre?	No		Interview
		In the last fiscal year, how many funds were allocated by the government and donors for pharmacovigilance activities? *Please specify the amount & currency*	not clear	No direct donations to PV unit, MSH /SC-PASS hires data clerks providing technical assistance to PV unit, printing PV forms	Interview
2.4	Existence of a functional national medicine safety advisory committee	Does a national medicine safety advisory committee exist with the responsibility to provide technical advice on the safety of medicines to the regulatory authority?	Yes	National patient safety monitoring committee.	Interview & documentation (Terms of Reference)
		Has the national medicine safety advisory committee met at least twice in the previous calendar year?	No	From Q2 2018 onwards, there will be quarterly meetings	Interview
2.5	Existence of standard operating procedures (SOPs) for conducting pharmacovigilance activities	Does the NMRA / PV centre have SOPs for pharmacovigilance activities?	Yes	for active reporting for TB and HIV and for spontaneous reporting. SOPs on ADR reporting, monitoring compliance, reports etc.	Interview & documentation (SOPs)
		When were the SOPs last reviewed? *Date.*	09-May-13	No dates in document, drafted 9 May 2013. Seems to be the first version	Documentation
2.6	Existence of a source of data on consumption and prescription of medicines	Are there any sources of information on sales or consumption of medicines on a national, regional or local level?	Yes (for some PHPs)	No data on private sector sales; public sector: consumption data collected under different PHPs Logistics management Information System (HIV, TB, family planning, malaria) = stock management form in which facilities are reporting on the movement of products within their facilities (medicines are part of that)	Interview
		Are they publicly available?	No	used for MoH decision making only (*e.g.* supply chain)	Interview
2.7	Existence of a library or other reference source for drug safety information	Does the PV centre have access to a library or electronic sources providing up-to-date information on medicine safety and the progress of scientific knowledge in the domain?	No		Interview
2.8	Existence of a mechanism to disseminate pharmacovigilance information (including one or more of the following: newsletters, information bulletin, website or phone line for dissemination of pharmacovigilance information)	Is there a communication plan in place to disseminate PV information?	No		Interview
		Is there a newsletter or information bulletin for dissemination of PV information?	Yes		Interview & documentation
		How many issues of the medicine safety bulletin are supposed to be published per year	2	bi-annually (2x/year)	Interview

		How many issues of the medicine safety bulletin were published in the previous calendar year?	1	September 2017	Interview & documentation
		Is there a website for dissemination of PV information?	No		Interview
		Is there a publicly advertised phone line to receive and provide medicine safety and PV information?	No	Emergency preparedness response program of MoH executes an emergency line: 977. Reporting may also include reporting of AE. EPI & malaria program have linked in to this program.	Interview
		Are findings published in national/international journals?	No		Interview
		Is there another mechanism for dissemination of PV information?	Yes	PV information disseminated during presentations at HCW trainings, data dissemination activities.	Interview
2.10	Existence of harmonized pharmacovigilance curricula for key healthcare workers - **In-Service**	Is there a pharmacovigilance training module, manual, or curriculum for **in-service** training of health care workers?	No	ad-hoc presentations provided during trainings, not a PV curriculum. Trainings mostly provided by implementing partners (PHPs).	Interview
2.11	Number of healthcare workers trained in pharmacovigilance in the previous calendar year through in-service training program	How many healthcare workers has the centre/program trained on PV in the previous calendar year (through **in-service** training)?		Pharmaceutical Management training for pharmacists, pharmacy technicians and nurses that oversee pharmacy activities, which had a 1-hour PV training slot. 104 HCW trained	
		a. Health professionals	0	see comment above	Interview
		b. Community health workers	0		Interview
		How many training events/sessions were conducted in the previous calendar year?		No formal PV training, presentations at several platforms (data dissemination meetings, MDR-TB expert meeting, NARTIS, Hospitals clinical meetings (upon request))	
		a. Health professionals	0	1 training on pharmaceutical management including 1-hour on PV	Interview
		b. Community health workers	0	0	Interview
2.12	Adoption and use of harmonized web-based pharmacovigilance training tools	Are web-based PV training tools available?			
		a. For health professionals	No		Interview
		b. For the general public	No		Interview

2.13	Existence of a functioning platform, mechanism or strategy for the coordination of pharmacovigilance activities - **National Level**	Does a platform, mechanism or strategy for the coordination of pharmacovigilance activities (such as PV technical working group, forum or regularly scheduled meetings) exist among **national stakeholders**?	Yes	NPSMC committee coordinates all PV activities in country	Interview
		Have the key **national stakeholders** convened at least once in the previous calendar year?	No		Interview
2.16	Submission of AE reports by health-care facilities in the previous year	From how many health facilities were AE reports received in the previous calendar year?	at least 15	There were also reports received that had no details for the reporter.	
		How many health facilities are there in the country?	450	Approximately 450 (national health policy document)	
		How many health facilities submitted >10 reports to the PV centre in the previous calendar year?	3		
2.17	Evidence of consideration of safety data when developing and updating standard treatment guidelines	When developing standard treatment guidelines is evidence on safety data being described and taken into consideration?	Yes	HIV guideline does use safety evidence for updating guidelines. TB ND & STR guideline as well.	Interview & documentation
2.18	National PV centre is a full or associate member of the WHO Program for International Drug Monitoring	Is the national pharmacovigilance centre a full or associate member of the WHO Program for International Drug Monitoring?	Full member	since 2015	Interview
Component 3. Signal Generation and Data Management					
3.1	Existence of a national database for pharmacovigilance information	Does a central database exist for managing PV data?	Yes	Spontaneous: VigiFlow but backlog and partially in Excel sheet; CEM: SSASSA/DCAT	Interview
		Does the central database contain data from various PV sources and methods (including PHPs?)	Yes	Spontaneous: includes different PHPs (TB, HIV) CEM: TB & HIV	Interview
		Is there a dedicated computer for pharmacovigilance activities?	No	CEM: stored in 1 single laptop (not at MoH); Spontaneous: different computers (at different organizations)	Interview
		Does the computer have internet access?	Yes	laptops - see previous comment	Interview
		Is data stored on a cloud/server?	see comments	CEM: No (previously: Yes) Spontaneous: Partly (VigiFlow)	Interview
		Is there a back-up system?	see comments	CEM: No (previously: Yes) Spontaneous: Partly (VigiFlow), but not for Excel sheet	Interview
3.2	Evidence of a process or mechanism for sharing information with other regulatory functions, other regulatory agencies and global databases	Has information in the database been shared (either electronically or via report) with other regulatory functions, other regulatory agencies and/or global databases?	Yes	CEM: Presentations at conferences incl. reg. authorities; Spontaneous: Yes - via reports and partly electronically with UMC	Interview

3.3	Existence of a standard adverse event (AE) reporting form and subset indicators	Is there a standard AE reporting form?	Yes	There are different versions of the official forms in use in different facilities; there are also different forms in use from different programs	Interview & documentation
		How is the reporting form offered? (e.*g.* paper form, web, app)	paper form	Spontaneous and CEM: paper	Interview
		Are there relevant fields in the standard AE form (or a separate form) to report:			Interview & documentation
		- adverse drug reactions?	Yes	Standard AE reporting form	
		- Suspected medication errors?	Yes	Partly covered on standard AE form - not under/over dosing	
		- therapeutic ineffectiveness?	No		
		- misuse, abuse and/or dependence on medicines?	No		
		- suspected/ observed poor quality issues?	Yes	Separate form: Product complaint form for CMS - not under PV program	
		- adverse events following immunization?	Yes	Separate form	
		- medical devices and diagnostics?	Medical devices: Yes Diagnostics: No	Separate form: Product complaint form for CMS - not under PV program	
3.4	Existence of a form or mechanism for the public to report AEs (Patient reporting system)	Is there a standard reporting form for the general public to report AEs?	No		Interview
3.5	Existence of electronic AE reporting system that complies with international reporting format standards	Is there an electronic AE reporting system?	Yes	However, CEM data entered in SSASSA in 4 sites by data entry clerks, not by clinicians themselves. No direct uploading of results into central database.	
		If yes, please provide technical details.		see above	
		Is the system compliant with the international reporting standards (E2B)?	see comments	CEM: no Spontaneous: Yes (VigiFlow) and No (Excel)	
3.6	A process is in place for collection, recording and analysis of ADR reports	Is there a process in place for collection, recording and analysis of ADR reports?	Yes	Not standardized and not implemented at all relevant levels	
Component 4. Risk Assessment and Evaluation					
4.1	Number of registered products with a PV plan and/or a risk management strategy	How many registered products with a pharmacovigilance plan and/or a risk management strategy from market authorization holders exist in the country?	NA	No MAHs in country	

4.2	Total number of AE reports received in the previous calendar year (also expressed as number of AEs per 100 000 persons in the population). And number of reports of sub-indicators	What is the total number of AE reports received in the previous calendar year? Of the total, what is the number of reports of:	224	Data for June 2016-May 2017; between Oct 2016 - March 2017 216 valid ADR reports received	
		- ADR?	224	Data for June 2016-May 2017; between Oct 2016 - March 2017 216 valid reports received, all ADR	
		- suspected medication errors?	0		
		- therapeutic ineffectiveness?	0		
		- suspected misuse, abuse, dependence?	0		
		- AEFI?	0	not received any reports from EPI, working on the collaboration	
		- medical devices and diagnostics?	0		
		- suspected counterfeit / substandard drugs?	0		
		What is the total population of the country?	1.2 million	Approx. 1.2 million	census of 2017
4.3	Number and percentage of total AE reports received by the national pharmacovigilance centre in the previous calendar year from:	What is the number of AE reports received by the national pharmacovigilance centre in the previous calendar year from:			
	- Marketing Authorization Holders	- Marketing Authorization Holders	0	0	
	- PHPs	- PHPs	0		
	- Health care providers	- Health care providers	224	all, June 2016-May 2017.	
	- Patients	- Patients	0	0	
	-Distributors	-Distributors	0	0	
	-Suppliers	-Suppliers	0	0	
4.4	Number and percentage of total AE reports received that are entered in the national database in the previous calendar year	What is the total number of AE reports received that have been entered in the national database in the previous calendar year?	224	Reporting period: June 2016 – May 2017	
4.6	Number and percentage of total AE reports acknowledged and/or issued feedback in the previous calendar year	What is the total number of AE reports acknowledged/issued feedback in the previous calendar year?	0	No consistent acknowledgement and feedback given. Feedback is given in the newsletter and in presentations during trainings and meetings	
4.7	Number and percentage of AE reports subjected to causality assessment in the previous calendar year	What is the total number of AE reports subjected to causality assessment in the previous calendar year?	0	Last done in 2016	Interview
4.8	Number and percentage of AE reports submitted to Vigibase in the previous calendar year	How many of the AE reports received at the national PV centre were submitted to Vigibase in the previous calendar year?	0	27 for 2015, 2016 not posted, 2017 none	Interview

4.9	Average completeness score of quarterly reports submitted to Vigibase in the previous four quarters (= one year)	What was the average completeness score of quarterly reports submitted to Vigibase in the previous calendar year? *Consult quarterly reports from VigiGrade for completeness scores of submitted reports*	0.47	First & last reports submitted in 2015 (Q4) (n=27) with completeness score of 0.47	Documentation
4.10	Number of active surveillance activities initiated, ongoing or completed during the previous three years	How many active surveillance studies have been conducted in the last three years (36 months)?	2	CEM for TB and HIV in 4 sites implemented by SIAPS/SC-PASS since 2015, but implemented as a system rather than a study MSF has implemented efficacy and safety study for the STR 2014-2016, results not shared with PV Unit	Interview
		Indicate what type (e.g. cohort event monitoring, targeted spontaneous reporting, etc.) and stage of completion (e.g. initiated, on-going or completed) for each study.		CEM, ongoing, safety and efficacy study was completed in 2016, for the CEM study there is no research protocol made	Interview
4.11	Number and percentage of total AE reports received at the national pharmacovigilance centre in the previous calendar year from healthcare providers by type of provider	What is the number of AE reports received in the previous calendar year submitted by:		Reporting period: June 2016 – May 2017	
		- doctors?	110	for 7 reports, the type of reporter was unknown	
		- nurses or midwifes?	42		
		- pharmacists?	65		
		- manufacturers and pharmaceutical companies?	0		
		- dentists?	0		
		- the general public?	0		
		What is the total number of AE reports received in the previous calendar year?	224	Reporting period: June 2016 – May 2017	
4.12	Evidence of supervision visits to marketing authorization holders by NMRA that address PV	Does the NMRA conduct supervision visits of MAHs that address PV?	NA	No MAH in country. The Medicine Regulatory Unit, MRU, within the ministry of health mandates that importers of drugs are registered with the Ministry. The registration must be renewed annually. The medicines and related substances act gives the unit the mandate to conduct inspections and import license can be revoked.	Interview
		How many supervision visits have been conducted in the previous calendar year?	0	At the moment there is not enough capacity (no human resource, knowledge is available)	Interview

Component 5. Risk Management and Communication

5.1	Number of regulatory actions taken in the previous calendar year as a consequence of national pharmacovigilance activities. *Request documentation to verify*	How many regulatory actions were taken in the previous calendar year as a consequence of pharmacovigilance activities that resulted in:		Despite the absence of the NMRA, the MRU within the MoH takes action if internal (within Eswatini) or external (through WHO alerts) signals arise. A topical corticosteroid was restricted in sales (points where it can be sold) since patients had experienced adverse drug reaction.	
		- product label changes (variation)?			Interview
		- safety warnings on medicines to health professionals?		Safety warnings from WHO alerts are shared with health care providers within country if applicable through e-mail system	Interview
		- safety warnings on medicines to the general public?		Because at the moment the general public is not involved in PV	Interview
		- withdrawals of medicines?		NMRA is not existing but MRU has the right to ban import and force the MAH to withdraw from the market, there is provision for it in the act.	Interview
		- treatment guideline/policy changes?	1	DTG roll out will start in October 2018, in the preparation it was planned to use DTG in all patient who were initiating ART treatment. With the recent warning about probable congenital abnormalities it was decided to change the treatment guidelines and exclude women of reproductive age from DTG treatment until further evidence is available.	Interview
		- other restrictions on use of medicines?	0		Interview
5.2	Number of signals detected in the past 5 years by the pharmacovigilance centre	How many signals were detected in the past 5 years by the pharmacovigilance centre?	2		Interview
		If any signals were detected, which ones and how were they identified?	see comments	Stavudine and gynecomastia, through spontaneous reports from health facilities, stavudine and lipoatrophy, also driven by WHO information, but also confirmed through own reports. Gynecomastia signal (2016) was discussed with HIV programmes, and this also coincided with the phasing out of the drug in the programme.	Interview

5.3	Average time lag between identification of safety signal of a serious ADR or significant medicine safety issue generated nationally and communication to health care workers and the public	How long does it take from when a safety signal or significant safety issue is identified to when it is communicated to health workers and the public?	3 months	Within 3 months since newsletters were produced quarterly	Interview
5.4	Number of suspected product quality issues detected through the pharmacovigilance system	What is the number of suspected product quality issues detected through the pharmacovigilance system in the previous calendar year?	NA	Since product quality is separated from the PV system. It is not considered to be PV and more related to supply chain.	Interview
5.5	Percentage of planned issues of the medicine safety bulletin (or any other health-related newsletter that routinely features ADR or medicine safety issues) published in the previous calendar year	How many issues of the medicine safety bulletin are supposed to be published per year?	4		Interview
		How many issues of the medicine safety bulletin were published in the previous calendar year?	1	PV unit delivers the content, SC-PASS prints it.	Interview
5.6	Number of products voluntarily withdrawn by marketing authorization holders because of safety concerns in the previous calendar year	How many products were voluntarily withdrawn by marketing authorization holders because of safety concerns in the previous calendar year?	NA	No MAH in country.	Interview
5.7	Number and percentage of medicine safety information requests addressed in the previous calendar year	How many requests for information about medicine safety were received in the previous calendar year?	0	Drug information is included in the proposed structure for the NMRA.	Interview
		Of the total received, how many requests for medicine safety information were addressed in the previous calendar year?	NA		Interview
5.8	Number of summaries of product characteristics updated by MAH because of safety concerns in the previous year	In the previous calendar year, how many summaries of product characteristics were updated by MAH because of safety concerns?	NA	No MAH in country	Interview
5.9	Number of medicine safety issues of local relevance identified from outside sources (e.g., from another country, from region or international sources) and acted on locally in the previous calendar year	How many medicine safety issues identified from outside sources were acted on locally in the previous calendar year?	2		Interview
5.10	Number of public or community education activities relating to medicine safety carried out in the previous calendar year	How many public or community education activities relating to medicine safety were carried out in the previous calendar year?	1	during the pharmacy week - last year on antimicrobial resistance (but seems focus was on how to take these, not on safety)	Interview

Annex 2. PHP assessment tool

Indicator #	Indicator	Assessment Questions	Answer	Notes & additional comments	Information source
Component 2. Systems, Structures, and Stakeholder Coordination					
P2.1	PV activities included within the strategic and/or annual operational plans of PHPs	Are PV activities included within the strategic and/or annual operational plans of public health programs?	Yes	NTP strategic plan 2015-2020.	Documentation
P2.2	Existence of a dedicated financial provision or statutory budget for the PHPs	Is there an annual budgetary allocation for PV activities for the PHP?	Yes	2 fte (national audiologist and pharm. technician) and audiology and ECG equipment all on Global Fund budget	Interview
		In the last fiscal year, how many funds were allocated by the MoH and donors for PV activities?	NA	MoH: lab reagents Global Fund: ECG equipment and some audiometers + salaries as above. Partners do not have specific budget line	Interview
P2.3	Existence of a mechanism to disseminate PV information (including one or more of the following: newsletters, information bulletin, website or phone line for dissemination of pharmacovigilance information)	Is there a mechanism in place to disseminate PV information?	Yes	see below	Interview
		Is there a newsletter or information bulletin for dissemination of PV information?	No		Interview
		Is there a website for dissemination of PV information?	No		Interview
		Is there a publicly advertised phone line to receive and provide medicine safety and PV information?	No		Interview
		Is there another mechanism for dissemination of PV information?	Yes	Quarterly DR-TB clinical expert meetings - sensitization about PV. Also, adverse events are discussed when patients are discussed	Interview
P2.4	Number of healthcare workers trained in pharmacovigilance in the previous calendar year through in-service training	How many healthcare workers has the centre/program trained on PV in the previous calendar year (through **in-service** training)?			
		- Clinicians / nurses	125-150	Mainly on clinical management of ADR & ADR monitoring	Interview
		- Community health workers	120		Interview
		How many training events/sessions were conducted in the previous calendar year?	See comments	1 for pharmacists (PV slot during a training) 5 for clinicians/nurses 4 for community health workers	Interview
P2.5	National treatment guidelines or protocols in use within the public health programs that consider pharmacovigilance	Do the treatment guidelines or protocols in use in the PHP provide instruction for PV activities?	Yes	The bedaquiline and delamanid treatment guideline contains this information. Including AE identification, management and reporting	Documentation, bedaquiline and delamanid guideline 14 April 2016

P2.6	Evidence of consideration of safety data when developing and updating standard treatment guidelines or treatment policies	When developing standard treatment guidelines is evidence on safety data being described and taken into consideration?	Yes	relative and absolute contra-indications included, possible drug-drug interactions (TB & ART), use in children	Interview and documentation
Component 3. Signal Generation and Data Management					
P3.1	PHPs use the national, standard ADR/AE reporting form	Does the PHP use the national, standard ADR/AE reporting form?	Yes	Both spontaneous and active reporting forms are used, developed by the PV unit. However, some facilities also use other forms which are developed by other organizations (*e.g.* MSF study form)	Interview and documentation
Component 4. Risk Assessment and Evaluation					
P4.1	Number and percentage of ADR/AE reports received by PHPs that were submitted to the national PV centre in the previous calendar year	What is the number of AE reports received by the PHP in the previous calendar year?	NA	Reports are forwarded directly to the PV system	Interview
		What is the number of AE reports submitted by the PHP to the national PV centre in the previous calendar year?	NA	Only once (just recently) a report was forwarded	Interview
P4.2	Total number of ADR reports per 1000 individuals exposed to medicines in the PHP in the previous calendar year.	How many individuals received medicines under the PHP in question during the previous year?	702	DR-TB initiated on Tx: 318 in 2017, 384 in 2016 - so on Tx in 2017 702; 2017 3226 TB cases identified. In 2017 165 (276 - 111) patients started on new TB drugs, some already on new TB drugs but started in 2016 (or 2015)	
		How many ADR reports were received, referring to the exposed population?	19	17 for MDR-TB and 2 for XDR-TB. For other TB cases 8 ADR reports.	
		Total number of ADR reports per 1000 individuals exposed to medicines in the PHP in the previous calendar year	27	DR-TB 19/702*1000 = 27 ADR reports per 1000 population on treatment	
P4.3	Percentage of patients in public health programs for whom drug-related, serious unexpected/unknown adverse events were reported in the previous calendar year	What is the total number of patients receiving medicines under the PHP?	3226	All TB cases notified in 2017: 3226 of which DR-TB 318	
		What is the total number of patients receiving medicines in the PHP who experienced drug-related, serious, unexpected adverse events?	NA	Data not available	
		How many of those were reported to the national PV centre?	NA		
P4.4	Number of suspected product quality issues detected through public health programs	What is the number of suspected product quality issues detected through the PHP in the previous calendar year?	1	specific batch of Kanamycin: injection painful and causing abscesses at injection site, but no actions taken by regulatory authority. Kanamycin newly ordered by hospitals.	Interview
P4.5	Number of reports on therapeutic ineffectiveness in the previous year	What is the number of reports on therapeutic ineffectiveness received by the PHP in the previous calendar year?	0		Interview

P4.6	Number of medicine-related hospital admissions per 1000 individuals exposed to medicines in the PHP in the previous year	What is the number of medicine-related hospital admissions of individuals exposed to medicines in the PHP in the previous year?	NA	Data not available	
P4.7	Number of active surveillance activities initiated, ongoing or completed during the past three years	How many active surveillance studies have been conducted in the last three years (36 months)?	1	Effectiveness and safety of a simplified short regimen for Multidrug Resistant Tuberculosis treatment in Manzini Region, Swaziland. (MSF)	Interview and documentation
		Indicate what type (e.g. cohort event monitoring, targeted spontaneous reporting, etc.) and stage of completion (e.g. initiated, on-going or completed) for each study		CEM	
P4.8	Functional collaboration/involvement in risk management plans with the PV centre	Do the PHP and PV centre communicate on risk management plans?	No	There are no risk management plans	Interview
		How often have the PHP and PV centre met to discuss risk management in the previous calendar year?	NA		
Component 5. Risk Management and Communication					
P5.1	Average time lag between identification of safety signal of a serious ADR or significant medicine safety issue generated nationally and communication to health care workers and the public	How long does it take from when a safety signal or significant safety issue is identified to when it is communicated to health workers and the public?	NA	No safety signals generated	Interview
P5.2	Existence of a program-related newsletter that routinely features ADR or medicine safety information	Is there a program-related newsletter, bulletin or other publication that routinely features ADR or medicine safety information?	No	There is no TB newsletter	Interview
P5.3	Number and percentage of medicine safety information requests addressed in the previous calendar year	How many requests for information about medicine safety were received in the previous calendar year?		Not recorded Kanamycin (see above); Bedaquiline and delamanid: need to ask advice for giving this to patients outside original target groups (children)	Interview
		How many requests for medicine safety information were addressed in the previous calendar year?		Not recorded	
P5.4	Number of medicine safety issues of local relevance identified from outside sources (e.g., from another country or international sources) and acted on locally in the previous calendar year	How many medicine safety issues identified from outside sources were acted on locally in the previous calendar year?	0		
P5.5	Number of public or community education activities relating to	How many public or community education activities relating to medicine	0		

	medicine safety carried out in the previous calendar year	safety were carried out by the PHP in the previous calendar year?			

DR TB/HIV MANAGEMENT TRAINING CURRICULUM

	MODULE	DESCRIPTION	OBJECTIVES	TIME	LEARNING OUTCOMES	METHODS/ MEDIUM
1	Epidemiology of TB and DR-TB	This Module seeks to create awareness on the epidemiology of TB and DR-TB in Swaziland.	- Comprehend the basics of TB epidemiology - Evaluate the impact of MDR-TB on TB control - Discuss the epidemiology MDR-TB and XDR TB	1 hour	By the end of the module, participants should: - be aware of the global, regional and national burden of TB (DS- and DR-TB) - understand the impact of the emergence of drug resistant forms of TB on TB control strategies	Participatory lectures using power point slides and or flip charts.
2	Introduction to TB and TB/HIV	This module seeks to describe the causation, risk factors and clinical aspects TB and TB/HIV co-infection	-Describe what tuberculosis (TB) is and its causes -Describe ways in which TB is transmitted -Describe ways in which TB could be prevented -Explain risk factors for TB transmission -Differentiate between TB infection and TB disease -Differentiate the types of TB -Demonstrate an understanding of the clinical presentation of TB -Describe the relationship between TB and HIV	1.5 hours	By the end of this module, participants will be able to: -define TB disease and TB infection -understand the modes of TB transmission and prevention measures -understand the clinical presentation of different forms of TB -appreciate TB and HIV correlation	Participatory lectures using power point slides and or flip charts.
3	Introduction to DR-TB	This module seeks to define the terminology, and describe the mechanisms of development of resistant forms of TB	-Define the different types of drug-resistance (Mono-drug, Poly-drug, Multi-drug and Extensive-drug resistance) -Classify and describe the mechanisms of development of Drug-resistance in TB -Describe the risk factors for developing drug-resistant TB	2 hours	By the end of this module, participants should be able to: -Define Mono-drug resistant, Poly-drug resistant, Multi-drug resistant and Extensively-drug resistant TB -Understand the mechanisms by which drug resistance develops -Risk factors for developing drug-resistant TB (natural resistance; among new cases, previously treated cases; health system related and patient related risk factors)	Participatory lectures using power point slides and or flip charts.
4	Diagnosis of DR-TB	This module seeks to improve the knowledge on the clinical and laboratory diagnosis of DR-TB, and to prescribe the use of the DR-TB diagnostic algorithm.	-Classify and define the risk groups for suspecting Drug-resistant TB (medium risk v/s high risk) -Realize the importance of contact tracing in controlling community transmission of DR-TB (especially children under 5) -Demonstrate proper sputum sample collection techniques, packaging, storage and transportation -Review the science behind TB diagnostic tests -Demonstrate ability to interpret TB laboratory results (GeneXpert, smear microscopy, culture, LPA and DST – 1st line and 2nd line)	2 hours	By the end of this module the participants will: - know how to identify medium and high risk DR-TB groups - demonstrate competency in proper sample handling and proper use of the diagnostic algorithm. -be able to interpret laboratory results -be aware of the need to screen all household contacts especially children under 5 years old and PLWHA	Participatory lectures using power point slides and or flip charts Practical exercise on proper specimen handling and interpretation of laboratory results. Print out of the TB diagnostic algorithm
5a	DR-TB management: *Principles of DR-TB management*	This sub-module seeks to make aware the principles of DR TB management, and emphasize the adherence to the National treatment	- Classify anti- tuberculosis drugs into the 5 groups -Understand the different types of WHO regimens used for treating TB -Design a Category 4 treatment regimen for	1 hour	By the end of this module the participants will be able to: - Know the different classes of anti-tuberculosis drug -Understand the principles of designing a	Participatory lectures using power point slides and or flip charts. Distribution of the National Drug-resistant TB

		guidelines.	drug-resistant TB - Describe the Standard regimens for MDR and XDR-TB in Swaziland		Category 4 treatment regimen. -Understand the National Standardized treatment regimens for MDR-TB and XDR-TB	Guidelines
5b	DR-TB management: *Second Line Anti TB drugs*	This sub-module seeks to expand on the knowledge about the pharmacology of anti-tuberculosis drugs	-Review the pharmacology of 1st line and 2nd line drugs	1.5 hours	By the end of this module the participants will be able to: -Name and describe the modes of action of all 1st and 2nd line anti-tuberculosis drugs -know the dosages of all anti-tuberculosis drugs -know the major adverse effects of each of the anti-tuberculosis drugs	Participatory lectures using power point slides and or flip charts. Side-effect card matching exercise.
5c	DR-TB management: *New and repurposed TB medications*	This sub-module seeks to introduce participants to the pharmacology and clinical uses of new and re-purposed anti-tuberculosis drugs	-Review the ongoing clinical trials on the use of new agents in TB treatment -Review the clinical use of new and repurposed drugs in the programmatic management of drug-resistant TB	1 hour	By the end of this module the participants will be able to: -Name and describe the modes of action of the new and re-purposed anti-TB medications -know the dosages of all the new and re-purposed anti-tuberculosis drugs currently in use in the country -know the major adverse effects of each of the anti-tuberculosis drugs	Participatory lectures using power point slides and or flip charts. Building treatment regimen for patients with Pre-XDRTB and XDR-TB.
6	Clinical monitoring of DR-TB treatment	The module seeks to impart knowledge on the clinical presentation of drug-related adverse effects and their management.	-Demonstrate an understanding of the adverse effects related to TB chemotherapy, and their management -Discuss the type, purpose and frequency of laboratory investigations requested during patient follow-up - Prescribe ancillary medications for the treatment adverse effects	1 hour	By the end of this module the participants will be able to: -identify treatment-related adverse effects early and manage them appropriately -understand when to use patient monitoring investigations (laboratory, Audiometry, X-Ray) -understand drug-drug interactions	Participatory lectures using power point slides and or flip charts.
7	Management of DR-TB in special situations	The module seeks to increase awareness on the special circumstances surrounding the management of DR-TB in the presence of a co-morbid condition (HIV, Diabetes Mellitus, Liver disease, Kidney disease) and in special groups of patients (Pregnant women and Children)	-Understand the relationship between DR-TB and HIV -Apply the principles of DR-TB and HIV co-management. -Identify the special situations surrounding the management of DR-TB in pregnant women. -Understand the management of DR-TB in children, including empirical treatment. -Identify the special approach to the management of DR-TB in Diabetic patients, and patients with Chronic kidney and liver disease	2 hours	By the end of this module, the participants should be able to: -demonstrate understanding of the complex co-management of DR-TB and HIV (drug-drug interactions, synergistic adverse effects and pill burden) -appreciate the specialist approach to the management of TB in pregnant women. -diagnose, treat and follow-up children with confirmed or suspected DR-TB (symptomatic contacts of a confirmed index case) -demonstrate understanding of individualized approach to managing DR-TB in diabetic patients and chronic kidney and liver disease patients	Participatory lectures using power point slides and or flip charts.
8	Infection and Prevention control	This module describes the different levels of infection control in relation to TB and MDR TB in health facilities and other congregate settings. It places emphasis on the low cost, evidence-based best practices that minimize contamination and infection transmission.	1. Identify all levels of infection control measures 2. Distinguish between primary and secondary prophylaxis 3. Ensure there is satisfactory administration of BCG vaccinations and TB tests 4. Assess different settings at risk for M. tuberculosis transmission 5. Apply appropriate procedures for sputum collection and patient education 6. Evaluate infection interventions	1 hour	By the end of the module, participants will; - Have basic knowledge about IPC practices - Have an understanding of the three levels of infection control - Understand the basic concept of TB IPC - Be able to implement the basic IPC measures to prevent TB infection.	Participatory lectures using power-power point slides , video and or flip charts.

			7. Describe ventilation and ventilation systems 8. Understand the role of surgicalmasks and respirators in respiratory protection			
9	Introduction to Audiology	The module seeks to increase awareness on the importance of audiology in DRTB treatment and the importance of hearing screening in the monitoring of ototoxicity in DRTB patients.	-Understand the role of an audiologist. -Understand the role of an audiology department in the DRTB unit. -Understand the anatomy of the ear and physiology of hearing. -Understand the different types of hearing loss. -Understand how TB medication affects the ear. -Understand ototoxicity. -Know how to conduct otoscopy and audiometry procedures. -Know to interpret an audiogram. -Be able to classify hearing loss. -Management of hearing loss	1 hour	By the end of this module, the participants should be able to: -Demonstrate an understanding of the audiology department in the DRTB unit. -Recognize an audiogram and the results. -Demonstrate an understanding on the different types of hearing loss. -Understand the procedures conducted in hearing screenings -Understand how to manage a patient's hearing whilst they are on DRTB treatment,	Participatory lectures using power point slides and or flip charts.
10	Psychosocial support	The module seeks to increase awareness on the importance of psychosocial support in DRTB treatment and the importance of adherence and motivating of patients through family involvement and support. Also the importance of linking patients with resources/support that will aid their adherence.	-Psychosocial support improvesDRTB treatment outcomes and treatment adherence. -The Importance of conducting a psychosocial assessment in DRTB. -Understand the definition of adherence. -Factors affecting adherence in DRTB. -Strategies to address adherence in DRTB. -Why is support for DRTB patients needed -Monitoring and assessment of adherence in DRTB.	2 hours	By the end of the module the participants will be able to: -Understand the importance of psychosocial support and care to DRTB treatment and outcomes -Identify barriers towards adherence and address them. - Recognize that addressing a patient's needs and expectations, and fostering a relationship of mutual respect between patient and provider are key elements in promoting treatment adherence -Understand that patients present with more than a set of medical problems, thus psychological or social factors may affect their adherencewith treatment. Understand that adherence is a process thus monitoring it is key.	Participatory lectures using power point slides and or flip charts.
11	Monitoring and Evaluation	The module seeks to introduce the participants on the basic M&E concepts , importance of M&E, importance of Data Quality and overview of DR-TB Recording and Reporting Tools.	• Introduce basic M&E concepts • Outline the importance of M&E • Overview of TB indicators • Ensuring data quality • Orientation on Reporting and Recording Tools	1 hour	By the end of the module participants will be able to: Understand basic M&E concepts Understand the importance of M&E for TB Program To have and understanding DR-TB Indicators To be able to use DR-TB Recording and Reporting tools.	Participatory lectures and presentations and discussions.

MINISTRY OF HEALTH

Adverse Drug Reactions (ADR) Report Form

Report can be returned to Central Medical Stores by fax 25186279 or 25186642
Email swazilandpharmacovigilance@gmail.com or mnshongwe@gmail.com or
Post to: Adverse Drug Reaction, Central Medical Stores, P. O. Box 72, Kwaluseni
For Further inquiries, please contact the Pharmacist (Pharmacovigilance) at Central Medical Stores at 25184111 or 25187255

Section (A): Patient Information

Patient initials or ref. no.: ----------Sex: □ M □ F: Pregnant? No □ Yes □ Unknown □
Weight (if known): ____ kg Date of birth: (dd/mm/yyyy) / / or age (at last birthday):____

Section (B): Medication History

All Drug Therapies/Vaccines Prior to ADR (Please use trade names and circle the suspected drug.)	**Batch number**	**Daily Dosage**	**Route**	**Date Begun**	**Date Stopped**	**Indication for Use**

Allergies or other relevant history (including medical history, liver/kidney problems, smoking, alcohol use etc)

_____

Section (C): About the Adverse Drug Reaction

Date of onset of ADR: (dd/mm/yyyy) / /
Description of event: ----------

Category of ADR (please tick)

□ Suspect minor/major reaction from a drug (e.g. allergic reaction)
□ Adverse Event (e.g. congenital defects)
□ Product Use Error (e.g. use of antibiotic instead of NSAID)

Severity (can tick more than one if appropriate):

□Life threatening
□ Hospitalized (dd/mm/yyyy) / /
□Hospitalization NOT required

Relevent Laboratory result:_____

Section (D): Treatment & Outcome

Treatment of ADR: □ No □ Yes. Details (including dosage, frequency, route, duration) ----------
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Outcome:

□ Recovered on: (dd/mm/yyyy) / /

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□ Not yet recovered
□ Unknown
□ Died on: (dd/mm/yyyy) / /
□ Persistent disability
□ Birth defect
□ Medically significant events
Details: _____

Section (E): Reporter Details

Name:_____ Sector of service: _ Private _Public
Occupation: _Doctor _Dentist _Pharmacist _Nurse _Others_____
Correspondence Address:_____
Tel. no.: _____Fax. no.: _____Email: _____
Also report to: _Manufacturer _Distributor/Importer _Others_____ Date of this report:_____

FOR OFFICIAL USE ONLY

Report to: Manufacturer □ Distributor/Importer □ Other □_____

Reported by: _____ Capacity_____

Instructions/ Notes

1. ADR can be briefly described as a noxious and unintended response to a drug or vaccine when the normal dose is used.
2. This report form is used for voluntary reporting of all suspected ADR.
3. There is no need to put down the full name of the patient.
4. Please provide information to every section. Information of individual reporter will be treated with strict confidence.
5. Please use another page for additional information if necessary.
6. Where date is required write in this format DDMMYYYY

"Completion of this form is not an admission of guilt or negligence"

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Annex 5. Active reporting form TB

DATA COLLECTION FORM
TUBERCULOSIS PATIENTS (PART A INITIATION)

PATIENT DETAILS – COPY FROM RECORDS			
Patient number:	**Visit date:**	**Date of Birth:**	
Facility name:	**Facility center number:**	**Sex:** □ Male □ Female	**Age:**

MEDICAL DETIALS	
Weight:	**Height:**
Indication for treatment: □Pulmonary TB □Extra Pulmonary TB □ DR TB □ Prophylaxis	
HIV co-infection: □ Positive (old) □ Negative	**Prior exposure to TB medicines:** □ Yes □ No
Pregnancy test: □ Positive □ Negative	

OTHER CONDITIONS			
Condition*	**Date start**	**Date end**	**Note**

OTHER MEDICINES (CURRENT AND WITHIN PAST MONTH)					
Medicine*	**Dose**	**Frequency**	**Date Start**	**Date End**	**Continue**
					□
					□
					□
					□
					□

TREATMENT REGIMEN			
Regimen	**Dose**	**Frequency**	**Date start**

LABORATORY TESTS (PLEASE RECORD RESULTS ON THE LABORATORY TESTS DATA COLLECTION FORM)					
Test	**Date**	**Result**	**Test**	**Date**	**Result**
Sputum smear			AST		
Sputum culture			ALT		
DST			Lactic acid		
GeneXpert			Lipase		
TSH			CD4		
Hb			Viral Load		
Creatinine			Total WBC		
Creatinine Clearance			ESR		
Glucose			Others (specify)		

NEXT APPOINTMENT DATE

DATA COLLECTION FORM: TB PATIENTS (PART B FOLLOW UP) **Patient Number:** _____

I. VISIT DATE_____

MEDICAL DETIALS				TREATMENT REGIMEN		
Weight: kg	Pregnancy test: □ Positive □ Negative	HIV co-infection: □ Positive □ Negative	If HIV positive, WHO clinical Stage: □ 1, □ 2, □ 3, □ 4	If HIV positive, Functional Stage :□W □A □B	TB Regimen	Dose and Frequency	Date Start

ADVERSE EVENT						
Adverse event*	Onset date	End date	Severity*	Seriousness*	ADR management*	Outcome*

OTHER MEDICINES							
Medicine	Dose and Frequency	Date Start	Date End	Medicine	Dose and Frequency	Date Start	Date End

II. VISIT DATE_____

MEDICAL DETIALS				TREATMENT REGIMEN		
Weight: kg	Pregnancy test: □ Positive □ Negative	HIV co-infection: □ Positive □ Negative	If HIV positive, WHO clinical Stage: □ 1, □ 2, □ 3, □ 4	If HIV positive, Functional Stage :□W □A □B	TB Regimen	Dose and Frequency	Date Start

ADVERSE EVENT						
Adverse event*	Onset date	End date	Severity*	Seriousness*	ADR management*	Outcome*

OTHER MEDICINES							
Medicine	Dose and Frequency	Date Start	Date End	Medicine	Dose and Frequency	Date Start	Date End

III. VISIT DATE_____

MEDICAL DETIALS				TREATMENT REGIMEN		
Weight: kg	Pregnancy test: □ Positive □ Negative	HIV co-infection: □ Positive □ Negative	If HIV positive, WHO clinical Stage: □ 1, □ 2, □ 3, □ 4	If HIV positive, Functional Stage :□W □A □B	TB Regimen	Dose and Frequency	Date Start

ADVERSE EVENT						
Adverse event*	Onset date	End date	Severity*	Seriousness*	ADR management*	Outcome*

OTHER MEDICINES							
Medicine	Dose and Frequency	Date Start	Date End	Medicine	Dose and Frequency	Date Start	Date End