Development of Sustainable HIV/TB Active Surveillance System in Swaziland – Protocol and Operational Plan

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The goal of the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program is to assure the availability of quality pharmaceutical products and effective pharmaceutical services to achieve desired health outcomes. Toward this end, the SIAPS result areas include improving governance, building capacity for pharmaceutical management and services, addressing information needed for decision-making in the pharmaceutical sector, strengthening financing strategies and mechanisms to improve access to medicines, and increasing quality pharmaceutical services.

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CONTENTS

ACRONYMS

ADE	adverse drug events
ADR	adverse drug reaction
AE	Adverse events
ART	antiretroviral treatment
ARV	antiretrovirals
ATC	Anatomical therapeutic chemical classification system
AZT	zidovudine
CEM	cohort event monitoring
CI	Confidence intervals
DCAT	Data collation and analysis tool
DTC	Drugs and Therapeutics Committee
DR TB	Drug resistant tuberculosis
EML	essential medicines list
FDA	US Food and Drug Administration
HAART	highly-active antiretroviral therapy
ICAP	International Centre for AIDS Care and Treatment Programs
IPAT	indicator-based pharmacovigilance assessment tool
MAH	marketing authorization holder
MedDRA	medical dictionary for regulatory activities
M&E	monitoring and evaluation
MSH	Management Sciences for Health
NTCP	National Tuberculosis Control Programme
PHP	public health program
PV	Pharmacovigilance
SIAPS	Systems for Improved Access to Pharmaceuticals and Services
SOP	standard operating procedure;
SNAP	Swaziland National AIDS Program
SPS	Strengthening Pharmaceutical Systems Program
TB	Tuberculosis
USAID	US Agency for International Development
WHO	World Health Organization
XML	extensible markup language

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EXECUTIVE SUMMARY

A pharmacovigilance system, through active surveillance in sentinel sites, is proposed to monitor the safety and tolerability of antiretroviral medicines (ARV) and anti-tuberculosis (TB) medicines at antiretroviral treatment (ART) clinics and TB clinics in Swaziland. The goal of this activity is to develop, implement, and demonstrate the local feasibility of a practical and sustainable pharmacovigilance system that could later be scaled up to monitor the safety of ARV and TB regimens throughout the country. The proposed system also has applicability for future active surveillance of other medicines, settings, and populations. The active surveillance activity, developed by the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program in consultation with the Swaziland National AIDS Program (SNAP), National Tuberculosis Control Programme (NTCP) and other partners, proposes to systematically document and quantify the presence or absence of ARV and anti-TB medicines-related adverse events, and to determine risk factors at sentinel sites. Systematically collecting information about medicines used in a defined population helps ensure that medicines have an acceptable safety profile and are used appropriately.

The active surveillance system will be a multi-center, prospective observational cohort activity designed to evaluate the incidence and identify risk factors for adverse drug events among HIV-infected patients newly placed on antiretroviral therapy and patients who are beginning the 1st or 2nd line TB treatment for the first time (or if their regimen is being changed). The proposed data collection strategy is based on data that SNAP and NTCP currently require the clinics to collect. The system will be implemented with 6 sites. For patients included in this activity, all suspected adverse drug reactions will be documented and evaluated, including mild to moderate events, reactions that result in substitution, switching, and stopping of regimen, occurrences of hospitalizations, and death. A Coordinating Center within the Ministry of Health Pharmacovigilance Unit will be established to provide data management and training support for the active surveillance sites. This activity will ultimately result in the development of a sustainable active surveillance system for longitudinally monitoring the safety of medicines in the country.

There is a clear and growing need to better understand the benefits and risks of ARVs and anti-TB medicines under conditions of actual use. Most questions of drug safety may only be answered by observing and analyzing the use and outcomes of therapy in large populations during the post-approval phase. The active surveillance system presented in this protocol will contribute to the knowledge-base, and help develop infrastructure for future active surveillance approaches. Results will also help inform future revisions to treatment guidelines and regulatory decisions. From the perspective of patient care, knowledge of factors that may affect the risk and management of adverse reactions, including other illnesses and conditions, the patient's other current medications, the availability of alternative regimens, and the patient's history of medication intolerance, may lead to improved outcomes.

BACKGROUND

The decade-long efforts of international health initiatives and commitment of national governments to provide life-saving treatments has resulted in an increased number of people with access to medicines in low- and middle-income countries. With increased access to newly introduced essential medicines, the importance of strong surveillance systems to monitor and promote their safety and effectiveness is becoming increasingly critical.

The burden of adverse events from poor product quality, adverse drug reactions (ADRs), and medication errors may affect achieving the full benefits of new medicines introduced to the market and pose great challenges to health care systems. Besides the impact of adverse drug events (ADEs) on morbidity and mortality and the direct cost of managing the events, ADEs also have other associated costs in terms of the loss of confidence in the health system, compromise of the success of public health programs, economic loss to the pharmaceutical industry, non-adherence to treatment, and development of drug resistance.

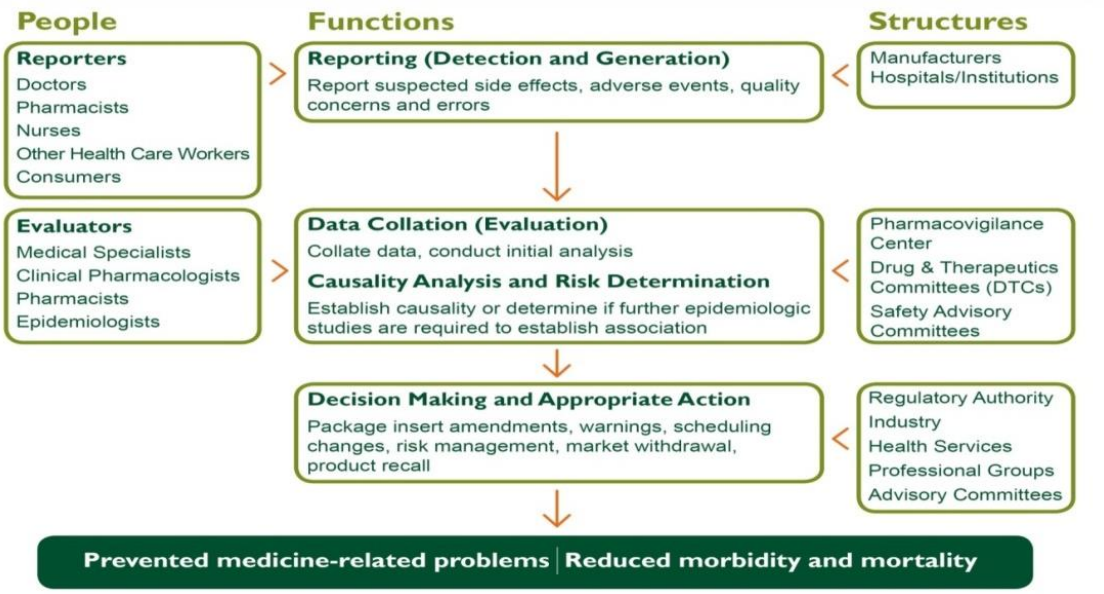
The World Health Organization (WHO) had defined pharmacovigilance as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems."[1] The pharmacovigilance system safeguards the public through efficient and timely identification, collection, assessment, and communication of medicine-related adverse events. A comprehensive pharmacovigilance system includes both active and passive surveillance methods, effective mechanisms to communicate medicine safety information to health care professionals and the public, collaboration among a wide range of partners and organizations, and incorporation of pharmacovigilance activities into the various levels of the health system, from the facility to the national levels.[2] As yet, few low- and middle-income countries benefit from having a functioning pharmacovigilance system to support medicine safety activities, and countries often lack evidence-based information to help guide treatment decisions and promote rational use—that is, safe, effective, and cost-effective—of medicines.[3,4,5]

To strengthen the capacity for monitoring the safety and effectiveness of medicines in these countries, a comprehensive pharmacovigilance system must be developed. Pharmacovigilance systems monitor the safety and effectiveness of medicines and other pharmaceutical products,

[1] WHO. 2004. WHO Policy Perspectives on Medicines (Pharmacovigilance: Ensuring the Safe Use of Medicines). Available at http://whqlibdoc.who.int/hq/2004/WHO_EDM_2004.8.pdf
[2] Strengthening Pharmaceutical Systems (SPS). 2009. *Supporting Pharmacovigilance in Developing Countries: The Systems Perspective*. Submitted to the US Agency for International Development by the SPS Program. Arlington, VA: Management Sciences for Health.
[3] Olsson et al. Pharmacovigilance activities in 55 low- and middle-income countries: A questionnaire-based analysis. *Drug Safety* 2010; 33 (8): 689-703
[4] Olsson, S., ed. 1999. *National Pharmacovigilance Systems*. 2nd ed. Uppsala: The Uppsala Monitoring Centre.
[5] Strengthening Pharmaceutical Systems (SPS) Program. 2011. *Safety of Medicines in Sub-Saharan Africa: Assessment of Pharmacovigilance Systems and their Performance.* Submitted to the US Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program. Arlington, VA: Management Sciences for Health.

related to product quality, medication errors, treatment failure, and previously known or unknown ADRs.

Figure 1. Pharmacovigilance Framework



Source: Center for Pharmaceutical Management. 2011. *Center for Pharmaceutical Management: Technical Frameworks, Approaches, and Results*. Arlington, VA: Management Sciences for Health.

The need for Pharmacovigilance of ARVs and anti-TB medicines in Swaziland

With the scale-up of antiretrovirals (ARVs) in Swaziland, 59,802 people were on ARV treatment in 2010[6] and this number is expected to increase due to the revision of the eligibility criteria. Swaziland also has one of the highest tuberculosis (TB) incidence rates (1,198 cases per 100,000)[7] and an alarmingly high prevalence of drug-resistant TB, which accounts for 7.7% of all new TB cases. More than 80% of TB patients are co-infected with HIV and TB is the leading cause of mortality among HIV-positive patients.[8,9] In the absence of comprehensive pharmacovigilance system in Swaziland, little is known about the epidemiology of toxicity profiles or risk benefits of ARVs and anti-TB medicines. Each country and setting has different patterns that may impact on the tolerability of high-risk medicines. Medicine use and its safety profile may be influenced by factors linked to the demographic and genetic and the presence of conditions such as malnutrition, use of traditional and/or alternative therapies, co-morbidity and the

[6] WHO. 2011. Progress report 2011: Global HIV/AIDS response. Available at http://www.who.int/hiv/pub/progress_report2011/en/index.html
[7] WHO. Global tuberculosis control 2011
[8] Médecins Sans Frontières. Fighting a dual epidemic: Treating TB in a high HIV prevalence setting in rural Swaziland January 2008 – June 2010
[9] Ministry of Health. 2011. ART Annual Report, MOH: Mbabane. Available at http://www.gov.sz/images/art_annualreport%202011.pdf

likelihood of medicine interactions.[10] Drug-related morbidity and mortality in TB and drug-resistant TB patients in Swaziland, especially those co-infected with HIV who are on highly-active antiretroviral therapy (HAART), has not been quantified and poses significant challenges to enhance treatment outcome. Given that ADRs are one of the most important factors affecting patient adherence, it is important to monitor, manage, and prevent adverse events.

Despite their life-saving and quality-of-life improving effects, ARVs have safety issues ranging from minor to serious ADRs, with both short- and long-term effects. Major adverse events associated with the use of ARVs affecting patient adherence and outcomes include lipodystrophy, neuropathy, hypersensitivity reactions, anemia, hepatic disorders, acute pancreatitis, osteopenia and osteoporosis, and lactic acidosis.[11,12] A sentinel-site based cohort study conducted in South Africa from 2007-2011 reported that 24% of patients enrolled in the study changed regimen due to ARV-related toxicity.[11] The most common opportunistic infection among patients infected with HIV is TB. In many countries including Swaziland, it is common that patients are taking both ARVs and anti-TB medicines. Other concurrent medicines that may be important to examine in patients on ARVs include antimalarial and antifungal medicines.

Many anti-TB medicines have been used for several decades and it is widely recognized by health workers that anti-TB medicines frequently cause ADRs. Long-term treatment and complex regimens increases the risk of ADRs. One study reported that two thirds of patients on treatment for drug-resistant TB had discontinued at least one medicine as a result of ADRs.[13] The common adverse events associated with first-line and second-line TB drugs include hepatitis, rash, arthralgia, hearing disturbances, visual disturbances, peripheral neuropathy, and nephrotoxicity.[14] Increasing use of complex regimens for drug-resistant TB, concomitant use of ARVs and anti-TB medicines in patients with HIV-associated TB, and introduction of new classes of medicines to treat TB calls for stronger pharmacovigilance systems.

Active Surveillance as a Tool for Pharmacovigilance in Public Health Programs

The need for active surveillance becomes recognized in identifying and quantifying important drug safety issues to complement spontaneous reporting.[15] A spontaneous report can generate a qualitative signal that provides new and important data, if the quality, completeness, and case causality are sufficient. In contrast, a quantitative signal can only be detected when an increase in frequency of its occurrence is observed from epidemiological studies, clinical trials, or cohort

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[10] Pirmohamed M., K.N. Atuah, A.N. Dodoo, P. Winstanley. 2007. ―Pharmacovigilance in developing countries.‖ *British Medical Journal*. 335(7618):462.

[11] Dube, N. M., R. Summers, K. Tint, G. Mayayise, A pharmacovigilance study of adults on highly active antiretroviral therapy, South Africa: 2007 – 2011. The Pan African Medical Journal. 2012;11:39.

[12] NACO. 2007. *Antiretroviral Therapy Guidelines for HIV-Infected Adults and Adolescents Including Post-exposure Prophylaxis*. New Delhi: NACO.

[13] Bloss E et al. Adverse events related to multidrug-resistant tuberculosis treatment, Latvia, 2000–2004. *International Journal of Tuberculosis and Lung Disease*, 2010, 14:275–281.

[14] WHO. 2012. A practical handbook on the pharmacovigilance of medicines used in the treatment of tuberculosis: enhancing the safety of the TB patient

[15] The Uppsala Monitoring Centre, WHO. 2002. Importance of Pharmacovigilance: Safe Monitoring of Medicinal Products. Geneva: WHO.

event monitoring (CEM).[16] Active surveillance involves methodically searching for exposures and health outcomes, often at sentinel site facilities. It consists of the on-going systematic collection, analysis, interpretation, and dissemination of data regarding one or more medicine-related outcomes using observational methods. Through active surveillance, potential safety problems and risk factors may be identified for specific patient populations. It also helps to understand, scope, and quantify adverse drug reactions by obtaining a denominator of persons exposed to medication(s) of interest. Wide range of approaches can be applied to detect and evaluate risks, such as CEM, registries, sentinel sites, epidemiological studies (case control study, cohort study, cross sectional study), and phase 4 clinical trials.[17]

The integration of pharmacovigilance, through active approaches to surveillance, can be crucial to the success of public health programs, such as HIV/AIDS, TB, and malaria programs.[18] It provides useful information for evaluating new medicines for mass treatment and making evidence-based decisions involving revision of treatment guidelines or developing risk management plans. Linking and coordinating pharmacovigilance activities in public health programs with national pharmacovigilance system can build a comprehensive and systematic medicines safety system and help facilitate the achievement of better program outcomes. In particular, where there is no established pharmacovigilance system, integrating pharmacovigilance as an essential component of public health programs can be an entry point to establish or develop fully functional pharmacovigilance system.

Expected Outcomes of Active Surveillance

Assessing the benefits and risks of medicines in a real life setting is becoming increasingly critical. Most of medicine safety issues may only be addressed by observing and analyzing the use and outcomes of treatment in large populations during the post-approval phase.[19,20] There are several examples in the region and beyond that can be alluded to. In Namibia, the Ministry of Health and Social Services (MoHSS) conducted an electronic record linkage study to investigate the risk of anemia associated with zidovudine (AZT) use and, as the result of this activity, treatment guidelines were revised and risk management plans were implemented for patients receiving AZT containing treatment.[21] Another example is the paper published from prospective, longitudinal multicenter cohort and case-control study in China that assessed the

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[16] Meyboom, R. H., A. C. Eqberts, I. R. Edwards, et al. 1997. Principles of Signal Detection in Pharmacovigilance. Drug Safety 16(6):355-65.

[17] Nwokike J., A. Stergachis, and P. Gurumurthy. 2011. *Development of Active Surveillance System for the Antiretroviral Program in Karnataka State — Protocol and Operation Plan.* Submitted to the US Agency for International Development by the Strengthening Pharmaceutical Systems Program. Arlington, VA: Management Sciences for Health.

[18] WHO. 2006. Safety of Medicines in Public Health Programs. Available from http://www.who.int/medicines/areas/quality_safety/safety_efficacy/Pharmacovigilance_B.pdf

[19] Institute of Medicine. 2007. Committee on the Assessment of the US Drug Safety System. *The Future of Drug Safety: Promoting and Protecting the Health of the Public*. Washington, DC: Institute of Medicine.

[20] Lang T., D. Hughes, T. Kanyok, J. Kengeya-Kayondo, V. Marsh, et al. 2006. ―Beyond registration—measuring the public-health potential of new treatments for malaria in Africa.‖ *The Lancet Infectious Diseases*. 6:46-52.

[21] Corbell, C., I. Katjitae, A. Mengistu, et al. 2011. Records linkage of electronic databases for the assessment of adverse effects of antiretroviral therapy in sub-Saharan Africa. *Pharmacoepidemiol Drug Saf.* 2011 Oct 19. doi: 10.1002/pds.2252 Available from http://onlinelibrary.wiley.com/doi/10.1002/pds.2252/abstract

incidences, prognoses, impacts, and risk factors of anti-TB drug induced adverse drug reactions.[22]

The active surveillance activities implemented in HIV and TB programs in Swaziland will contribute to building the knowledge base on safety and tolerability of ARVs, anti-TB medicines, and other frequently used products and help develop in-country infrastructure for future active surveillance approaches. In addition, results from this activity will help inform future revisions of national treatment guidelines and regulatory decisions. The prospective, observational approach will generate local data to provide better estimates of benefit-risk profiles and help prevent and minimized such risks.

Understanding the knowledge of factors that may affect the risk and management of adverse events from patient care perspective, including other illnesses and conditions, concomitant medications, availability of alternative regimens, and the patient's history of intolerance may lead to improved treatment outcomes. Well-integrated pharmacovigilance system in public health programs will ultimately lead to cost savings and improved outcomes through early recognition and management of these risks.

[22] Shang P., Y. Xia, F. Liu, et al. 2011. Incidence, clinical features and impact on antituberculosis treatment of anti-tuberculosis drug induced liver injury (ATLI) in China. *PLoS One* 2011, 6:e21836.

GOAL AND OBJECTIVES

Overall goal

The overall goal is to implement an active surveillance system in Swaziland to generate local, evidence-based information to improve patient care and safety through the identification, management, and prevention of medicine-related morbidity and mortality in patients on ART and anti-TB medicines. The active surveillance activity will improve the outcomes of the public health programs by systematically collecting and documenting information on the adverse events and implementing risk management plans to prevent identified risks and enhance patient safety.

Specific objectives

- Develop and implement procedures and tools for the active surveillance of ARVs and anti-TB medicines.
- Through active surveillance, prospectively determine the incidence of and risk factors for suspected adverse events in the treatment of naïve adults receiving ART and/or anti-TB medicines at sentinel ART clinics and TB clinics.
- Identify and assess signals of ADRs that are likely to affect adherence to treatment and patient outcomes.
- Demonstrate the feasibility of using active surveillance as a sustainable platform for assessing the safety and use of ARVs and anti-TB medicines to help support evidence-based decision making, including feedback to clinicians and review of standard treatment guidelines.

METHOD

Overview

A two year pilot active surveillance activity is proposed to systematically document and quantify the incidence rate of adverse events associated with ARVs, 1st and 2nd line anti-TB medicines, and to determine risk factors at selected sentinel sites in Swaziland. This active surveillance will be a multi-centre, prospective observational cohort activity. It aims to develop, implement, and demonstrate the local feasibility of a practical and sustainable pharmacovigilance system that could later be scaled up throughout the country.

Sentinel Sites

Sentinel surveillance is the collection and analysis of data by designated institutions selected for their geographic location, medical specialty, and ability to report high quality data.[23] It is proposed that the active surveillance system be implemented in 6 ART and TB clinics that will serve as the sentinel sites (Table 1). The following criteria are recommended to select the sentinel sites: geographical representation, number of patients expected, interest and commitment of the facility, and infrastructure support.

Table 1 Selected sentinel sites

	Mbabane hospital		**Raleigh Fitkin Memorial (RFM) hospital**		**Matsapa Community clinic (MSF)**		**Good shepherd hospital**		**Hlatikulu hospital**		**TB hospital**	
	ART clinic	TB clinic	ART clinic	TB clinic	ART Clinic	TB Clinic	ART clinic	TB clinic	ART clinic	TB clinic	ART clinic	DR TB
Region	Hhohho		Manzini		Manzini		Lubombo		Shiselweni		Manzini	
Staff												
No. of clinicians	4	1	5	1	3	2	2	2	2	1	6	
No. of pharmacists	1	N/A	Total 2		Total 1		Total 1		Total 1		Total 1	
No. of Nurses	10	4	12	3	5	3	9	5	3	3	>60	
No. of data entry clerks	3	0	2		2		1	0	2		1	
No. of patients/month*	147	50	100	64	120	40	150	100	20	15	29	30
Presence of automated records	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	Yes

[23] USAID. Sentinel Surveillance. www.usaid.gov/our_work/global_health/id/surveillance/sentinel.html

*Average No. of ARV treatment-naïve adult patients per month, No. of TB patients per month. These are based on monthly and quarterly reports from the ART and TB program.

Population and Inclusion/Exclusion Criteria

HIV positive patients newly placed on ART, patients who are beginning the 1st or 2nd line TB treatment for the first time (or if their regimen is being changed) at the selected sentinel sites will be recruited over a-6 months period and actively followed for 24 months. Patients who have previously been exposed to anti-TB medicines may also be recruited, but monitoring should begin at the commencement of a new course of treatment. To identify any risks or risk factors specific to paediatric or adolescent patients, patients under the age of 18 may be recruited and monitored.

Inclusion criteria

- Treatment-naïve HIV/AIDS patients who are enrolled for ART initiation
- Diagnosed TB or DR TB patients who attend outpatient clinic or hospitalized (for DR TB patients) and are enrolled for the 1st or 2nd line TB treatment initiation. Patients with HIV/AIDS co-morbidity will be monitored to determine any risks or risk factors specific to those with HIV-associated TB.
- Able and willing to provide adequate information.
- Resident in same location for at least 3 months and not intending to relocate out of the area for the duration of the active surveillance follow-up.

Exclusion criteria

- Treatment experienced HIV/AIDS patients (i.e., those with previous or currently on-going treatment with ARVs).
- Individuals with any condition that, in the opinion of the clinician, would make participation in the activity unsafe or interfere with achieving the activity's objectives.

Sample size estimation

Approximately 560 patients per month on ART, resulting in approximately 3360 new ART patients over 6 months, are expected to be enrolled in selected sentinel sites. An a priori criterion for site participating in this activity is the ability to maintain a loss to follow-up rate below 10% annually. A cohort of approximately 3000 patients on ART gives a 99.7 percent chance of identifying an adverse drug reaction that is expected to occur with an incidence of 1:500.

At least 300 patients per month on 1st and 2nd line TB treatment, resulting in approximately 1,800 patients over 6 months, are expected to be enrolled for the active surveillance activity. A cohort of 1,500 patients gives 99 percent chance of identifying a single event with a rate of 1:200 and 95 percent chance of identifying a single event with an incidence of 1:500.

Table 2 shows that larger sample size increases the likelihood of identifying less common or rare adverse events. WHO recommends a sample size of 10,000 patients for Cohort Event Monitoring to allow identification of rare and uncommon ADRs. However, the key expectation from this

activity is to provide the incidence rate, relative risk and risk factors that will allow for the characterization and quantification of known clinically significant adverse drug reactions.

While sample size of this magnitude may be achieved at a later stage by scaling up the active surveillance activity, piloting in a smaller, targeted sample will help to gain valuable experience with active safety surveillance and demonstrate the feasibility of the program. The key advantages of proposed active surveillance activity is to build a sustainable platform to continue the surveillance for the life of the treatment program, follow up patients as long as they remain on treatment, monitor newly introduced ARVs, and allow the investigation of adverse events with delayed onset and long-term toxicity.

Table 2 Relationship between simple size and probability of observing an adverse event (AE): Percent probability of observing at least one AE in the simple by expected incidence of AE

	Expected AE incidence: 1 event out of …patients						
Sample size	100	200	500	1000	2000	5000	10000
200	86.47	63.21	32.97	18.13	9.52	3.92	1.98
300	95.02	77.69	45.12	25.92	13.93	5.82	2.96
500	99.33	91.79	63.21	39.35	22.12	9.52	4.88
700	99.91	96.98	75.34	50.34	29.53	13.06	6.76
1000	100.00	99.33	86.47	63.21	39.35	18.13	9.52
1500	100.00	99.94	95.02	77.69	52.76	25.92	13.93
2000	100.00	100.00	98.17	86.47	63.21	32.97	18.13
3000	100.00	100.00	99.75	95.02	77.69	45.12	25.92

Source: WHO. 2012. A practical handbook on the pharmacovigilance of medicines used in the treatment of tuberculosis.

Data collection process

Table 3 presents the suggested minimum data set for the active surveillance activity. Several data elements are not systematically collected by the participating sites—concomitant medicines, adherence, adverse events, outcome of adverse events, and severity and seriousness of adverse event. Source of HIV transmission is not currently captured in ART clinics, although 97% are known to be sexually transmitted in Swaziland[24]. Included in the minimum data set is use of information from laboratory results that suggests non-symptomatic ADRs, i.e. elevation of liver enzymes, change in hemoglobin level.

Observations made during the mapping exercise and site visits conducted by SIAPS addressed that data required by SNAP and NTCP are not consistently documented. The active surveillance activity will provide extensive training to health workers to ensure that the data are collected and consistently documented. This will potentially benefit the programs with improved clinical documentation in the participating sites.

[24] Ministry of Health. 2011. ART Annual Report, MOH: Mbabane. Available at http://www.gov.sz/images/art_annualreport%202011.pdf

Table 3 Minimum Data Set for the Active Surveillance

Activity Type	Variable(s)	Currently Recorded?	Note
Patient data	Unique patient ID number	Yes	n/a
	Assigned code number	Yes	n/a
	Contact details	Yes	n/a
	Age/date of birth, gender, weight/height (BMI), pregnancy, other pre-existing conditions and medical history	Yes	n/a
	WHO clinical stage	Yes	n/a
	TB status, indication for TB treatment, prior exposure to anti-TB medicines	Yes	n/a
Medicine exposure data	ARV/TB regimen	Yes	n/a
	Date of treatment initiated and stopped	Yes	n/a
	Adherence to ARV treatment	No	Some sites are introducing pill count.
	Adherence to TB treatment	Yes	n/a
	Concomitant medications	No	Incomplete
Outcome data	Adverse drug event and outcome	No	Incomplete
	Classifications of seriousness and severity of outcome	No	n/a
	Laboratory values	Yes	n/a

In addition to the data described above, further description of the adverse event may be required for data analysis. The coordinator of the active surveillance activity may need to contact the participating sites to obtain such information, if necessary. The classification of adverse events and exposure to medicines will be standardized using the parameters in table 4.

Table 4 Additional data required for data analysis

Data	Description
Terminology for the adverse reaction	System Organ Class, medical dictionary for regulatory activities (MedDRA)
Classification of the medicines	Anatomical therapeutic chemical classification system (ATC)
Additional data on the ADR	how long the event lasted, challenge/rechallenge, outcomes of adverse event
Causality assessment	to determine if the event is associated with the regimen using the scales, such as WHO Scale and/or Naranjo's Algorithm
Seriousness	If any of these conditions occur; death, life-threatening, hospitalized,

	permanent disability, congenital anomaly
Severity grading	Severity grading by clinicians at the sentinel sites may be introduced, provided that it is acceptable and standardized and that the training is provided.
Predictability	Whether there is an effect from medication use that is related to the drug's known pharmacologic action or not. Unpredictable reactions include idiosyncratic, immunologic, allergic, carcinogenic, and teratogenic reactions.[25]
Preventability	Whether the events are preventable or not; If the events occur as a result of a medication error, a failure in the medication use process, such as prescribing, dispensing or administration of medicines, are considered to have been preventable.[26]

The data will be captured and collected at sentinel sites, building on existing data collection tools. All ART clinics selected as a sentinel site is currently using RxSolution for patient management, which can be adapted and used for active surveillance activity. TB clinics, in the absence of electronic tools, can either use paper-based data collection form or access-based data entry tool. Data collected at the sentinel sites will be transmitted to the Coordinating Center for collation and analysis (figure 2).

[25] Brown SD Jr, Landry FJ. Recognizing, reporting, and reducing adverse drug reactions. South Med J. 2001 Apr;94(4):370-3.

[26] Morimoto T, Gandhi TK, Seger AC, et al. Adverse drug events and medication errors: detection and classification methods. Qual Saf Health Care 2004;13(4):306-314.

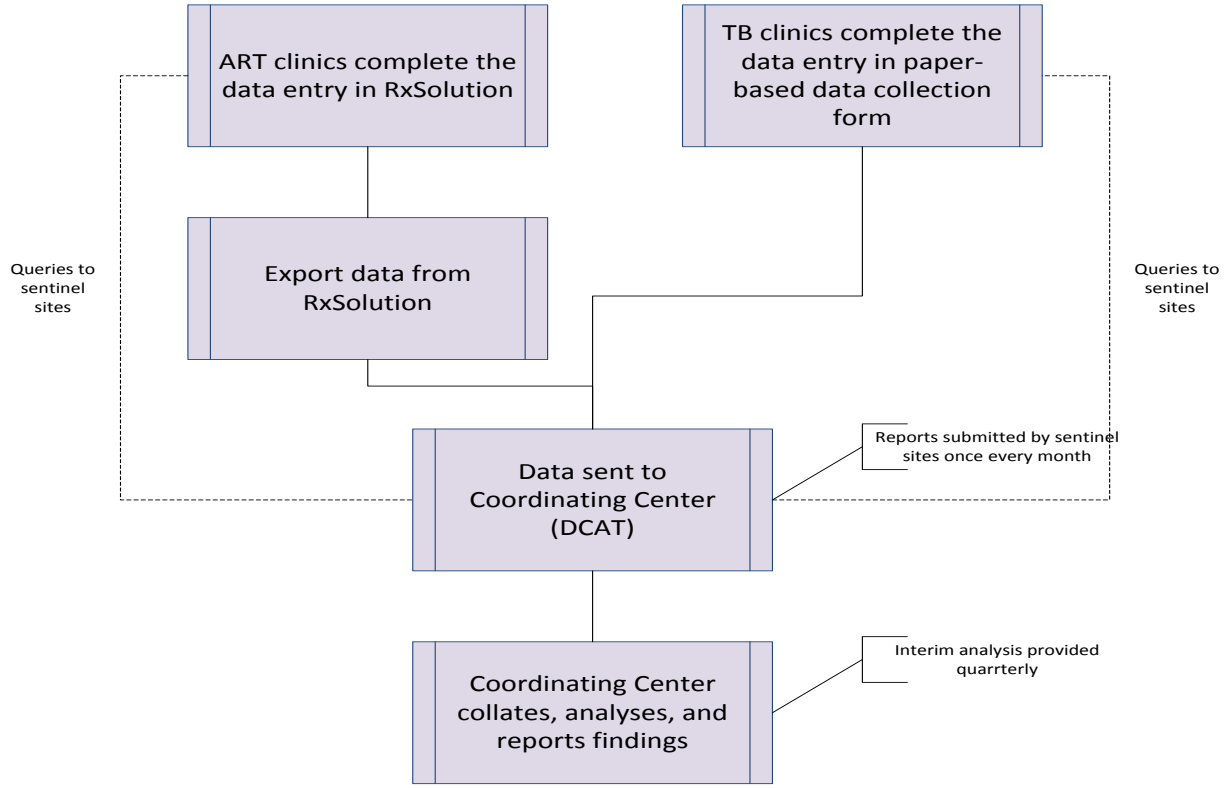


Figure 2 Data collection flow

Patient Outcome

The following outcomes should be recorded on the Active Surveillance Form: all ADRs and other adverse events (AEs), such as hospitalization, death, and suspected therapeutic failure. Clinicians or other health care staff should be asked to make no judgment on causality, and normal clinical terms or descriptions should be used. Specifically, health professionals will be asked to record the following types of events—

- All *new AEs* even if minor and expected
- Abnormal *changes* in laboratory tests compared with a previous examination (i.e. Hb, liver function tests, renal function tests)
- Suspected lack of *effectiveness*
- *Admission to hospital* with date and cause
- The first observation of *pregnancy* of any duration
- All *deaths* with date and cause
- Possible *drug interactions*

Data management and analysis

In the long-term, any existing information management tools and systems that are used in the clinics can be adapted to collect data for active surveillance activities and enhanced for

interoperability interface between DCAT and such tools. This is to avoid the duplication of efforts and the sustainability of the activities.

The Coordinating Center may be provided with a data collation and analysis tool (DCAT) for the active surveillance activity, which was developed by Strengthening Pharmaceutical Systems (SPS) program and used in Vietnam and South Africa. Sentinel sites will send their data on a monthly basis. The DCAT will be used to aggregate the data and conduct some analyses. The purpose of analysis is to identify the incidence rates, relative risks, and risk factors for the adverse drug events. The DCAT has the following features:

- Relevant dictionaries including MedDRA, ATC classification, International Nonproprietary Names (generic name), seriousness and severity scales, etc.
- Built-in causality analysis function
- Built-in function for other analyses, such as incidence rates, unadjusted and adjusted relative risk with 95% confidence intervals (CI), and risk factors
- Built-in function to generate the following reports:
    - Incidence of ADR (disaggregated by regimen, duration of treatment, gender, etc.)
    - Risk factors for each ADR (gender, concurrent medications, co-morbid conditions, adherence, CD4 at initiation, etc.)
    - Longitudinal data on cohort of patients experiencing ADRs
- Interoperability to facilitate exchange of standard XML (extensible markup language) with third party

As data accumulate, descriptive frequency tables for demographics, medicine use, and adverse drug events will be prepared periodically. As the program matures and more data accumulate, statistical analyses will be performed to understand and present various adverse event profiles, such as incidence rates, predictors of adverse events, and relative risks. Frequencies and risks of adverse drug events will be compared by medicine category. Multivariate models will be developed to identify predictors of adverse drug events taking into account potential confounders (table 5).

Table 5 Variables to be used in Analyses

Variable Name	Category	Type
ART regimen	Primary exposure	Categorical
TB regimen	Primary exposure	Categorical
Age	Confounder	Continuous
Gender	Confounder	Binary: male, female
BMI	Confounder	Continuous
Baseline CD4	Confounder	Continuous
Baseline hemoglobin	Confounder	Continuous
Baseline co-illnesses	Confounder	Categorical
Co-trimoxazole use	Confounder	Binary: yes, no
Baseline comorbidities	Confounder	Categorical
Other concomitant drugs	Confounder	Categorical
Previous exposure	Confounder	Categorical

Duration of regimen	Effect modifier	Continuous

The incidence rate of an event will be calculated as the number of events divided by the total number of patient-months of follow-up, for ADRs by type. Estimates will be given with 95 percent confidence intervals assuming a Poisson distribution. Regression models will be used to investigate factors associated with the occurrence of the endpoint events.

Trainings and supervisory visits

Personnel at all sentinel sites, including physicians, nurses, pharmacists, health workers, data entry clerks and counsellors, will be trained before the initiation of the active surveillance activity. Emphasis will be placed on what to report and how to report using the established system. The active surveillance data collection forms will be pre-tested and modified accordingly. To ensure credibility of results generated, quality assurance tools such as set of SOPs (Annex A) will be implemented.

Regular supervisory visits to the participating sites will be conducted by designated personnel from the Coordinating Center, SNAP, NTCP and SIAPS program. The supervisory visit is not meant to be an evaluation or audit of the sites. It is to provide on the spot support where possible and work with the key staff on ground to address some of their immediate concerns. The observations from the visit will be helpful in advising the Coordinating Center and programs on what challenges the sites have in implementing active surveillance activity and how to improve the capacity of the sites to ensure an appropriate and successful implementation of the relevant activities. The checklist will be developed based on the protocol and SOPs to support the supervisory visits. Some information obtained from supervisory visits may be transcribed to quantitative data and analyzed to measure the performance of the participating sites, which will be disseminated by regular progress report.

Data confidentiality and ethical considerations

A data privacy protection SOP will address safeguarding the confidentiality of the data. All personnel involved in the program will be trained on this SOP. Prior to sending data to the coordinating center, patients' personal information will be coded with unique, encrypted identification numbers.

Safety monitoring of ARVs and anti-TB medicines is an integral part of patient monitoring. The proposed active surveillance system will develop much-needed local data for better patient management, and build a safety network for comprehensive patient management. The proposed work will be presented to an ethics committee after necessary administrative approval from SNAP and NTCP. This active surveillance activity is not a clinical trial or research study and does not interfere with treatment in any way. It is a process of observation and data collection to guide decision making on the safety of ARVs and anti-TB medicines in the interests of public health.

The active surveillance system is an observational activity that has minimal risk. Information is collected from the patient and the clinical history of the patient, and without any intervention. All patient identifiers will be encrypted. Procedures will be established and maintained to ensure the confidentiality of data. Unauthorized persons will not have access to the data. The 2009 WHO *Practical Handbook on the Pharmacovigilance of Antiretroviral Medicines* (pages 85–87) states:

> Because it is essential to record personal identifiers, the security, privacy and confidentiality of personal data need to be strenuously maintained…should avoid attempting to obtain individual informed consent if at all possible because it will be time-consuming to try to explain the concepts of pharmacovigilance to each patient, will increase complexity and add to the cost, and could potentially compromise the validity of the results if many patients refuse to be enrolled. [It] is not a clinical trial or research study and does not interfere with treatment in any way. It is simply a process of observation data collection in the interests of public health.

Published data, including reports, will not contain any information that could identify patients.

Limitations

Data will only be collected from sentinel sites which may not be necessarily representative of the whole population of Swaziland. However, the sites were selected, to roughly represent the main geographical areas of Swaziland. The sample size and the duration of the follow-up are limited as there are time and financial limitations for conducting a longer prospective follow-up. However, the sample size and the duration of follow-up are sufficient for identifying all but rare adverse events, consistent with the national interest in this pharmacovigilance activity.

Disseminations

An interim report from the sentinel site activities will be included in the quarterly Medicines Safety Watch Newsletter. An annual report will be prepared including analysis of incidence, prevalence and risk factors and discussed with relevant stakeholders. Any emerging significant safety signals will be evaluated and discussed for next steps to be taken. The data will be used to inform the design of the risk management plan for patients on ARVs and anti-TB medicines.

OPERATIONAL PLAN

Strategic Framework

The operational plan for the implementation of active surveillance activity is based on the following strategic framework: leveraging existing monitoring and evaluation (M&E) structures; sustainability of the platform; stakeholder engagement; and use of the findings to inform treatment guidelines and regulatory decisions. The advantages of using existing M&E structures include cost efficiencies and improved documentation of clinical practices. As to sustainability, the operational framework will facilitate opportunities to institutionalize the active surveillance platform in SNAP and NTCP. The active surveillance activities will yield lessons on the safety and effectiveness of ARVs and anti-TB medicines from real-life experiences. The success of the active surveillance system will only be possible if all relevant stakeholders are engaged in the activity. The operational framework has several instruments which will ensure that lessons learned are used as evidence for action. Many countries experience challenges applying research findings in policy development and implementation. As shown in table 6 below, the operational framework will ensure that the opportunities are used.

Table 6 Framework For Active Surveillance in Developing Countries Approach

Approach	Benefits
Leverage existing M&E structures	• Improve efficiencies by leveraging existing M&E resources • Contribute to improved clinical documentation • A component of quality improvement activities
Build on sustainable platform	• Routine surveillance system, not a study • Robust platform contributes to other safety surveillance objectives
Engage all relevant stakeholders	• Government leadership • Local ownership and involvement
Use surveillance data for decision making	• Use of local data to improve treatment outcomes and inform disease control programs • Use of the findings reinforces the importance of the surveillance activity

Stakeholders' engagement, roles and responsibilities

The successful implementation of the active surveillance activity will involve the identification and engagement of all relevant stakeholders. In addition to providing overall leadership for the implementation of this activity, SNAP and NTCP will identify and engage other key stakeholders who will contribute to the success of the activity. The roles and responsibilities of other key stakeholders are described below.

Health Workers at ART and TB clinics

Health workers at the sentinel sites will have responsibilities for data collection and transmission, and for educating patients on anti-TB and ARV medicine use and possible adverse events. Table 7 lists the health workers and their recommended roles and responsibilities.

Table 7 Health workers roles and responsibilities at the sentinel sites

Title	Roles and Responsibilities
Facility Supervisor/In Charge	Provide overall responsibilities for monitoring the implementation of the active surveillance activity at the sentinel site; timely documentation and submission of data to the Coordinating Center; discussing information from the Coordinating Center through staff meeting
Clinician	Ensure proper case evaluation for possible adverse drug events, documentation of the suspected adverse drug events in the relevant fields in data collection form; additional description of the event.
Pharmacist	Provide counseling to patients as appropriate during dispensing with emphasis in both long and short term toxicities
Nurse	Provides support to clinicians during initial evaluation of patients. Assist in follow-up evaluation by conducting interviews on possible ADRs and documenting information in the patients' medical records for further evaluation by clinicians
Counselor	Provide patients with detailed information on possible ADRs of ARVs and anti-TB medicines and the importance of treatment adherence. Conducts follow-up interviews to identify possible ADRs; document information in the data collection tools and refer patients to the clinicians for further evaluation.
Data Entry clerk	Transcribe data from medical records to RxSolution and data collection form; ensure the completeness of data captured for the required fields; transmit data to the Coordinating Center

Advisory committee

Formation of an advisory committee to support the implementation of the active surveillance activity is recommended. The proposed roles and responsibilities of the Advisory Committee is to;

- Review reports, signals, and risk factors identified by the Coordinating Center
- Provide on-going and timely advice on current and emerging safety issues identified by active surveillance activity
- Develop recommendations related to clinical practice to address findings and safety issues generated by active surveillance activity
- Promote the dissemination and communication of priority public health recommendations emerging from the active surveillance activity to key decision makers and stakeholders.

Recommended members of the advisory committee are, but not limited to;

- ART Program Manager, SNAP

- Program Manager, NTCP
- ART Officer, SNAP
- Program Pharmacist NTCP
- WHO Officer (ART)
- Two clinicians from ART clinics with a minimum of 10 years of clinical and research experience in HIV care, treatment, and support. Experience treating HIV patients as both inpatients and outpatients is desirable.
- Two clinicians from TB clinics/hospital with a minimum of 10 years of clinical and research experience in TB care, treatment, and support.
- An epidemiologist with research experience in public health programs, especially in HIV or TB care, treatment, and support. Knowledge of bio-statistics is essential
- Pharmacovigilance focal point with an understanding of the principles of pharmacovigilance. This individual should have hands on experience in intensive monitoring or active surveillance and spontaneous reporting studies of adverse drug reactions.

Coordinating Center

The operational plan recommends the establishment of the Coordinating Centre within the Pharmacovigilance unit for active surveillance activity. The Centre will serve as the central data warehouse and will be responsible for data cleaning, aggregation, and analysis of all data. The proposed roles and responsibilities of the Coordinating Center include;

- Collation and analysis of all data transmitted from sentinel sites
- Follow up with sentinel sites for missing or incorrect data
- Causality assessment
- Analysis of signals
- Dissemination of progress update, interim findings, and annual analysis results
- Coordination of supervisory visit

Logistics and Budget

A budget for the implementation of the active surveillance activity should be developed and monitored. Table 8 provides an illustrative budget which may be used as a guide.

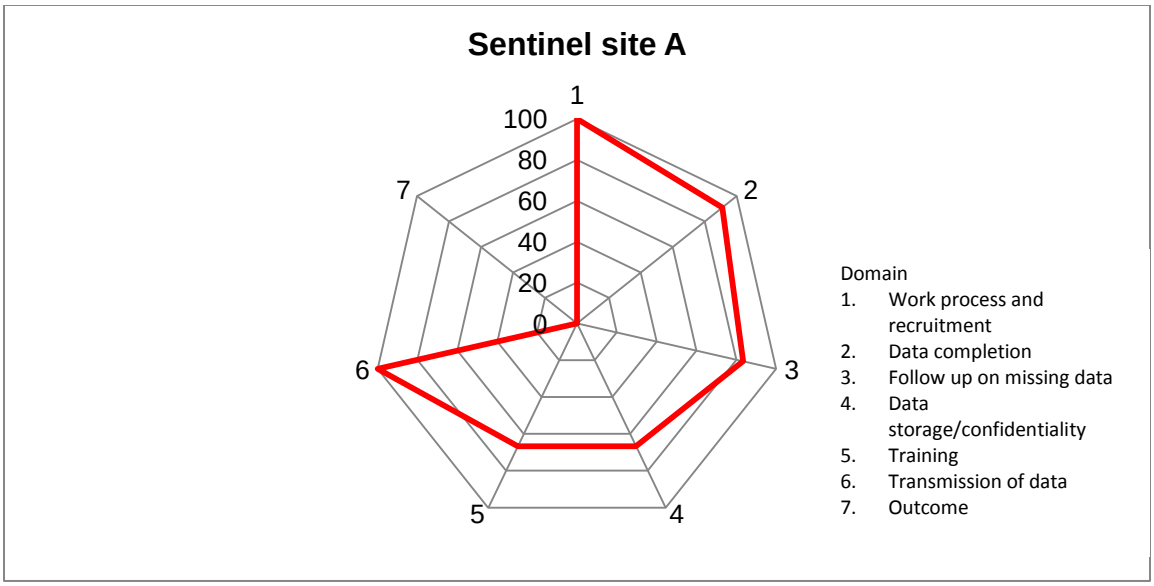
Table 8 Resource needs and budget

Category	Activity	Upfront cost for first year				Maintenance cost per year			
		Rate (per unit)	units	days	total	rate	units	days	total
Human resources at the Coordinating Center	Technical staff salary	E1,325.00	1	26	E34,450.00	E1,325.00	1	54	E71,550.00
	Data manager (TBD) salary	E946	1	60	E56,760.00	E946	1	45	E42,570.00
	Advisory committee meetings	E2,350.00	4	1	E9,400.00	E2,350.00	4	1	E9,400.00
Training of health workers in sentinel sites	Launch (including venue, accommodation, printing, refreshments, etc.) for 30 participants	E177,370.00	1	1	E177,370.00	n/a	n/a	n/a	n/a
	Supervisory visit (travel cost, per-diem) for 4 person	E530.00	4	2	E4240.00	E530.00	2	3	E3,180.00
Reference and IEC materials	Printing or photocopies (forms)	E0.95	4200	n/a	E3,990.00	E0.95	4200	1	E3,990.00
	Standard texts and references	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Data analysis	Allowance for biostatistician	n/a	n/a	n/a	n/a	E2,000.00	1	30	E60,000.00
Total					E286,210.00				E190,690.00

Workplan and monitoring the implementation of active surveillance activity

To ensure the timely implementation of the active surveillance activity, a work plan has been developed that is presented in table 9 below. The work plan defines the specific activities, products, output indicators, and timelines for the implementation of each activity.

Supervisory checklist can be used to measure performance of sentinel sites. Example of sites' performance is presented figure 3.



Figiure 4. Performance of sentinel sites

The following illustrative outcome indicators are provided for determining the success of the activity:

- Number of medicine safety decisions disseminated to inform clinical management
- Number of revisions to HIV/TB treatment guidelines informed by findings of the active surveillance activity
- Percent reduction in preventable adverse drug events
- Percent increase in spontaneous reporting (for serious adverse event)
- Percent improvement in documentation in patient records/files
- Percent reduction in low to follow up
- Percent improvement in adherence to treatment
- Percent improvement in health worker skills in prevention and management of ADRs
- Percent improvement in patient knowledge of ADRs

Table 9 Workplan

Activity	Products	Indicator	Accountable person/institution	2013				2014			
				Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Development of protocol, SOPs and tools	Protocols, SOPs and tools	Protocol approved, # SOPs developed	Coordinating center, SIAPS	√							
Establish the advisory committee	Terms of reference	Inauguration of the committee	Coordinating center, SIAPS		√						
Launch and trainings for health workers	Launch report	# of health workers trained	SIAPS, SNAP, NTCP		√						
Implement the tools and pilot test the data transfer	Pilot test results	Data management plan functional	Coordinating center, SIAPS		√						
Recruit patients as indicated in the protocol and SOPs	Status of recruitment report	# of patients recruited	Sentinel sites, Coordinating center		√	√	√	√			
Collect data as indicated in the protocol and SOPs	Status of data collection report	# of reports submitted per site	Sentinel sites, Coordinating center		√	√	√	√	√	√	√
Conduct interim data analysis	DCAT report	# of analysis report	Coordinating center			√	√	√	√	√	√
Disseminate progress reports, findings & lessons learned	Quarterly report	# of quarterly report	Coordinating center			√	√	√	√	√	√
Supervisory visit	Supervisory visit report	# of supervisory visit conducted	Coordinating center			√	√		√		√
Conduct advisory committee meeting	Meeting report		Coordinating center, advisory committee				√		√		√

ANNEX A: LIST OF STANDARD OPERATING PROCEDURES

SOPs 1-5 are recommended for the sentinel sites, SOPs 6 & 7 for the Coordinating Center and SOP 8 for the Advisory Committee.

1. **Guidelines for completing the data collection forms and interviewing patients on adverse events**: Provides detailed description of each field in the sentinel surveillance forms, provides direction on how to complete the forms, and how to interview patients on every visit to obtain information of adverse events

2. **Guidelines on work processes and patient recruitment for the sentinel site**: Provides information on the general workflow processes for patient recruitment and directions for the staff members that collects and enters data at the sites. This should include all the details about the process for obtaining the medical record, from whom, when, how, place, how long it takes to enter the record, etc.

3. **Guidelines for follow-up on missing data and providing additional information to the Coordinating Center**: Provides detailed description of what the coder at the facility level will need to do to obtain missing data from relevant healthcare worker or to confirm ineligible or presumably incorrect entries. Includes guidelines for interviewing clinicians, patients, and patient relatives to elicit missing information, and transmitting those information to the coordinating center

4. **Guidelines for orientation and training of new health workers recruited into the active surveillance activity**: Provides a brief outline of topics to cover during the orientation and training of new staff into the active surveillance activity

5. **Guidelines for the transmission of data from the sentinel sites to the Coordinating Center**: Provides details of the processes and quality assurance standards required for the transmission of data from the sites to the Coordinating Centers

6. **Guide for the use of dictionaries, terminologies and standard lists**: Provides the names/titles and contents of the dictionaries, codes, and standard lists that are relevant for data entry. This guide will describe how the list will be used, where it should be kept, etc

7. **Guidelines for the provision of preliminary reports from the active surveillance activity to relevant bodies and committees**: Provides details on how to develop and publish reports from the findings of the active surveillance activity and processes for the publication and sharing of those reports with the relevant committees and external audiences

8. **Guidelines for monitoring compliance to the protocols during the supervisory site visits**: Provides detailed checklist to support supportive supervisory visits to the sentinel sites by the Coordinating Center for the monitoring of compliance to the guidelines for the conduct of the active surveillance activity

ANNEX B: DATA COLLECTION FORM FOR TB PROGRAM

DATA COLLECTION FORM FOR TB PATIENTS (PART A INITIATION)

PATIENT DETAILS – COPY FROM RECORDS											
Patient ID Number:		**Serial Number:**			**Visit date:** DD/MMYYYY			**Date of Birth:** DD/MM/YYYY			
Interview site: □ Hospital TB clinic □ Health Center □ Phone interview □ Home Visit □ Other					**Facility name:** **Facility code:**			**Sex:** □ Male □ Female		**Age**: ____ yrs	
MEDICAL DETIALS											
Weight: _____kg					**Height:** _____cm						
Indication for treatment: □Pulmonary TB □Extra Pulmonary TB □ DR TB □ Prophylaxis											
HIV co-infection: □ Positive □ Negative	**WHO clinical Stage:** □ 1, □ 2			**Functional Stage:** □W □ A □B			**Pregnancy test:** □ Positive □ Negative				
TREATMENT REGIMEN							**LABORATORY TESTS**					
TB regimen	Dose		Frequency	Date Start			**Test**	**Date**	**Result**	**Test**	**Date**	**Result**
				DD/MM/YYYY			CD4 count			Lactic acid		
				DD/MM/YYYY			Viral Load			Lipase		
OTHER CLNICAL CONDITIONS	**CONCOMITANT MEDICINES (CURRENT AND WITHIN PAST MONTH)**						ESR			**Others**		
	Medicine	Dose	Frequency	Date Start	Date End	Continue	Total WBD					
				DD/MM/YYYY	DD/MM/YYYY	□	Hb					
				DD/MM/YYYY	DD/MM/YYYY	□	Creatinine					
				DD/MM/YYYY	DD/MM/YYYY	□	Creatinine Clearance					
				DD/MM/YYYY	DD/MM/YYYY	□	Glucose					
				DD/MM/YYYY	DD/MM/YYYY	□	TSH					
				DD/MM/YYYY	DD/MM/YYYY	□	ALT					
				DD/MM/YYYY	DD/MM/YYYY	□	AST					

DATA COLLECTION FORM FOR TB PATIENTS (PART B FOLLOW UP)

PATIENT DETAILS – COPY FROM RECORDS		
Patient ID Number:	**Visit date:** DD/MMYYYY	**Facility name:**
Interview site: □ Hospital TB clinic □ Health Center □ Phone interview □ Home Visit □ Other		**Facility code:**

MEDICAL DETIALS			
Weight: _____kg		**Height:** _____cm	
HIV co-infection: □ Positive □ Negative	**WHO clinical Stage:**	**Functional Stage:**	

TREATMENT REGIMEN							
TB regimen	dose	frequency	Date Start	Date End	Continue	Adherence	Reason for change
			DD/MM/YYYY	DD/MM/YYYY	□		
			DD/MM/YYYY	DD/MM/YYYY	□		

CONCOMITANT MEDICINES					
Medicine	Dose	Frequency	Date Start	Date End	Continue
			DD/MM/YYYY	DD/MM/YYYY	□
			DD/MM/YYYY	DD/MM/YYYY	□
			DD/MM/YYYY	DD/MM/YYYY	□

LABORATORY TESTS					
Test	**Date**	**Result**	**Test**	**Date**	**Result**
CD4 count			Glucose		
Viral Load			TSH		
ESR			ALT		
Total WBD			AST		
Hb			Lactic acid		
Creatinine			Lipase		
Creatinine Clearance					

ADVERSE EVENT						
Adverse event	Onset date	End date	Severity	ADR managemet	Outcome	Rechallenge
	DD/MM/YYYY	DD/MM/YYYY				
	DD/MM/YYYY	DD/MM/YYYY				
	DD/MM/YYYY	DD/MM/YYYY				
	DD/MM/YYYY	DD/MM/YYYY				

ANNEX C: DATA COLLECTION FORM FOR HIV PROGRAM

DATA COLLECTION FORM FOR HIV PATIENTS (PART A INITIATION)

PATIENT DETAILS – COPY FROM RECORDS			
Patient ID Number:	**Serial Number:**	**Visit date:** DD/MMYYYY	**Date of Birth:** DD/MM/YYYY
Interview site: □ ART clinic □ Health Center □ Phone interview □ Home Visit □ Other		**Facility name:** **Facility code:**	**Sex:** □ Male □ Female **Age**: ____ yrs

MEDICAL DETIALS		
Weight: _____kg	**Height:** _____cm	
WHO clinical Stage: □ 1, □ 2, □ 3, □ 4	**Functional Stage:** □W □ A □B	**Pregnancy test:** □ Positive □ Negative

TREATMENT REGIMEN			
ARV regimen	Dose	Frequency	Date Start
			DD/MM/YYYY
			DD/MM/YYYY

OTHER CLNICAL CONDITIONS	CONCOMITANT MEDICINES (CURRENT AND WITHIN PAST MONTH)					
	Medicine	Dose	Frequency	Date Start	Date End	Continue
				DD/MM/YYYY	DD/MM/YYYY	□
				DD/MM/YYYY	DD/MM/YYYY	□
				DD/MM/YYYY	DD/MM/YYYY	□
				DD/MM/YYYY	DD/MM/YYYY	□
				DD/MM/YYYY	DD/MM/YYYY	□
				DD/MM/YYYY	DD/MM/YYYY	□
				DD/MM/YYYY	DD/MM/YYYY	□

LABORATORY TESTS					
Test	**Date**	**Result**	**Test**	**Date**	**Result**
CD4 count			Lactic acid		
Viral Load			Lipase		
ESR			**Others**		
Total WBD					
Hb					
Creatinine					
Creatinine Clearance					
Glucose					
TSH					
ALT					
AST					

DATA COLLECTION FORM FOR HIV PATIENTS (PART B FOLLOW UP)

PATIENT DETAILS – COPY FROM RECORDS		
Patient ID Number:	**Visit date:** DD/MMYYYY	**Facility name:**
Interview site: □ ART clinic □ Health Center □ Phone interview □ Home Visit □ Other		**Facility code:**

MEDICAL DETIALS			
Weight: _____kg		**Height:** _____cm	
HIV co-infection: □ Positive □ Negative	**WHO clinical Stage:**	**Functional Stage:**	

TREATMENT REGIMEN							
ARV regimen	dose	frequency	Date Start	Date End	Continue	Adherence	Reason for change
			DD/MM/YYYY	DD/MM/YYYY	□		
			DD/MM/YYYY	DD/MM/YYYY	□		

CONCOMITANT MEDICINES					
Medicine	Dose	Frequency	Date Start	Date End	Continue
			DD/MM/YYYY	DD/MM/YYYY	□
			DD/MM/YYYY	DD/MM/YYYY	□
			DD/MM/YYYY	DD/MM/YYYY	□

LABORATORY TESTS					
Test	**Date**	**Result**	**Test**	**Date**	**Result**
CD4 count			Glucose		
Viral Load			TSH		
ESR			ALT		
Total WBD			AST		
Hb			Lactic acid		
Creatinine			Lipase		
Creatinine Clearance					

ADVERSE EVENT						
Adverse event	Onset date	End date	Severity	ADR managemet	Outcome	Rechallenge
	DD/MM/YYYY	DD/MM/YYYY				
	DD/MM/YYYY	DD/MM/YYYY				
	DD/MM/YYYY	DD/MM/YYYY				
	DD/MM/YYYY	DD/MM/YYYY				

eob