

Introduction of active tuberculosis drug-safety monitoring and management (aDSM) for new drugs and regimens



Acknowledgments

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Rationale

The rationale for the implementation of active TB drug-safety monitoring and management (aDSM) is anchored to the recent developments in drug-resistant TB (DR-TB) treatment, particularly the approval for use of the new drugs, bedaquiline (Bdq) and delamanid (Dlm) ahead of the completion of Phase III trials, the shorter treatment regimen (STR) for rifampicin-resistant (RR-)/multidrug-resistant (MDR-) TB patients, and the increased use of repurposed drugs. Such approaches need early and systematic detection, management, recording, and reporting of adverse events (AEs) that may occur.

High MDR-TB burden countries have expressed concerns that AEs would be a barrier to the introduction of new drugs and novel regimens. Stakeholders were also concerned that the introduction of new anti-TB drugs would be slowed down or even prevented due to a lack of capacity in countries to mount aDSM. Hence, in July 2015, WHO convened technical and funding agencies to discuss essential requirements for the implementation of active monitoring and proper management of AEs when introducing new anti-TB drugs or regimens.

Purpose of this document

Adapted from the WHO framework for aDSM implementation,¹ this document outlines the agreed essential activities for aDSM, and the key steps in implementing aDSM in patients on treatment for DR-TB. The key terms adapted to the specific context of aDSM are presented in **Annex 1**.

¹ World Health Organization. Active tuberculosis drug-safety monitoring and management (aDSM): Framework for implementation. WHO 2015, WHO/HTM.TB.2015. 28

Definition of aDSM

aDSM is defined as active and systematic clinical and laboratory assessment of patients while on treatment. It applies to patients on treatment with: a) new and repurposed anti-TB drugs, b) novel MDR-TB regimens, and c) regimens for extensively drug-resistant TB (XDR-TB).

Objectives of aDSM

The overall objectives of aDSM are to reduce risks from drug-related harm in patients on DR-TB treatment and to generate standardized aDSM data to inform future policy updates on the use of such medicines. aDSM seeks to detect, manage, and report suspected or confirmed drug toxicities.

Implications

Setting up aDSM for patients on treatment for DR-TB implies additional responsibility and resources. The implementation, management, and supervision necessary for aDSM should be systematically built into the PMDT component of the National TB program (NTP) and conducted integrally to other activities related to patient care and monitoring.

Collaboration between the NTP and national pharmacovigilance systems

Close coordination of aDSM activities between the NTP and the main pharmacovigilance (PV) center in the country is essential to avoid overlap and duplication of work, efforts, and resources, and for the purpose of sustainability.

Essential activities of aDSM

There are three essential activities of aDSM in order to achieve the objectives, namely:

- 1) Clinical monitoring
- 2) Clinical management, and
- 3) Recording and reporting.

1. Clinical monitoring: active and systematic clinical and laboratory assessment during treatment to detect drug toxicity and AEs. A sample of the laboratory assessment at baseline and during treatment is shown in **Table 1**.

Table 1. Baseline and routine monitoring of patients on MDR-TB treatment²

MONITORING EVALUATION	RECOMMENDED FREQUENCY
Serum creatinine	At baseline; then monthly if possible while receiving an injectable agent. Every one to three weeks in HIV infected patients, diabetics, and other high-risk patients.
Serum potassium	Monthly while receiving an injectable agent. Every one to three weeks in HIV infected patients, diabetics and other high-risk patients.
Serum magnesium and calcium	Check magnesium and calcium blood levels whenever hypokalaemia is diagnosed. At baseline and then monthly if on bedaquiline or delamanid. Repeat if any electrocardiogram (ECG) abnormalities develop (prolonged QT interval).
Thyroid stimulating hormone (TSH)	Every three months if receiving ethionamide/prothionamide and <i>p</i> -aminosalicylic acid (PAS). Every six months if receiving ethionamide/prothionamide or PAS, but not both together. TSH is sufficient for screening for hypothyroidism and it is not necessary to measure hormone thyroid levels. Monthly monitoring for clinical signs/symptoms of hypothyroidism is also necessary.
Liver serum enzymes (SGOT, SGPT)	Periodic monitoring (every 1–3 months) in patients receiving pyrazinamide for extended periods or for patients at risk for, or with symptoms of hepatitis. For HIV-infected patients monthly monitoring is recommended. For patients on bedaquiline, monitor monthly. For patients with viral hepatitis, monitor every one to two weeks for the first month and then every one to four weeks.
HIV testing	At baseline, and repeat if clinically indicated.
Pregnancy tests	At baseline for women of childbearing age, and repeat if indicated.
Haemoglobin and white blood cell count	If on linezolid, monitor weekly at first, then monthly or as needed based on symptoms; there is little clinical experience with prolonged use of linezolid. For HIV-infected patients on zidovudine, monitor monthly initially and then as needed based on symptoms.
Lipase	Indicated for work-up of abdominal pain to rule out pancreatitis in patients on linezolid, bedaquiline, D4T, ddl or ddc.
Lactic acid	Indicated for work up of lactic acidosis in patients on linezolid or anti-retroviral treatment (ART).
Serum Glucose	If receiving gatifloxacin, monitor fasting blood glucose at baseline and monitor monthly. Educate/remind patients on signs and symptoms of hypoglycaemia and hyperglycaemia monthly.
Audiometry (hearing test)	Baseline audiogram and then monthly while on an injectable agent. Ask patients about changes in hearing at every clinic visit and evaluate their ability to participate in normal conversation.
Vision tests	For patients on long-term ethambutol or linezolid perform at least a visual acuity test with Snellen charts and color vision test at baseline (as a small percentage of the population has color blindness). Repeat the test for any suspicion of change in acuity or color vision.
Educational, psychological and social consultation	At baseline by personnel trained in health education, psychological and social issues relevant to TB management; during treatment and repeat as indicated. Refer to social worker, psychologist or psychiatrist when indicated.
ECG	An ECG should be obtained before initiation of treatment with bedaquiline or delamanid, and at least 2, 4, 8, 12, and 24 weeks after starting treatment. Monitoring ECGs should be done monthly if taking other QT-prolonging drugs (i.e. moxifloxacin, clofazimine)

² World Health Organization. Companion Handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. WHO/HTM/TB/2014.11. WHO-Geneva. https://www.who.int/tb/publications/pmdt_companionhandbook/en/

Results of tests from clinical monitoring at baseline and during follow-up are to be recorded in a standard data collection form.

2. Clinical management: All AEs detected, whether mild or severe, should be managed in a timely manner to deliver the best possible patient care. The management of AEs is not within the scope of this document and the reader is referred to the PMDT Companion Handbook² or to the Challenge TB generic training module for the clinical management of common AEs (Module 3.2.2) in patients on new drugs and regimens.³

3. Data collection and reporting: Standardized data should be systematically collected and reported. aDSM reporting primarily targets serious adverse events (SAEs) (**Annex 2**) as a core requirement. Any other AEs emerging during the treatment that are deemed either of “special interest” to PMDT programs or are of “clinical significance”, may be reported as part of an extended aDSM approach. All SAEs are to be reported to the national authority responsible for PV in the country and assessed for causality. Eventually, these SAE reports and causality assessment results are to be reported to the Uppsala Monitoring Centre (UMC) and/or the WHO global aDSM database to enhance the detection of new signals and inform future updates of global policies on the use of new drugs and regimen. SAEs reported from patients using the new drugs, Bdq when procured via the USAID Bdq donation program and/or DIm are also to be reported to the Global Drug Facility (GDF).

Levels of monitoring in aDSM

There are three levels of monitoring in aDSM, (**Annex 2**) namely:

1. Core package: requires monitoring for and reporting of all SAEs
2. Intermediate package: includes SAEs and AEs of special interest
3. Advanced package: includes all AEs of clinical significance

All PMDT sites treating eligible patients with new and repurposed medicines, and novel MDR-TB regimens require, at least, the core aDSM package to be in place and functioning at the sites.

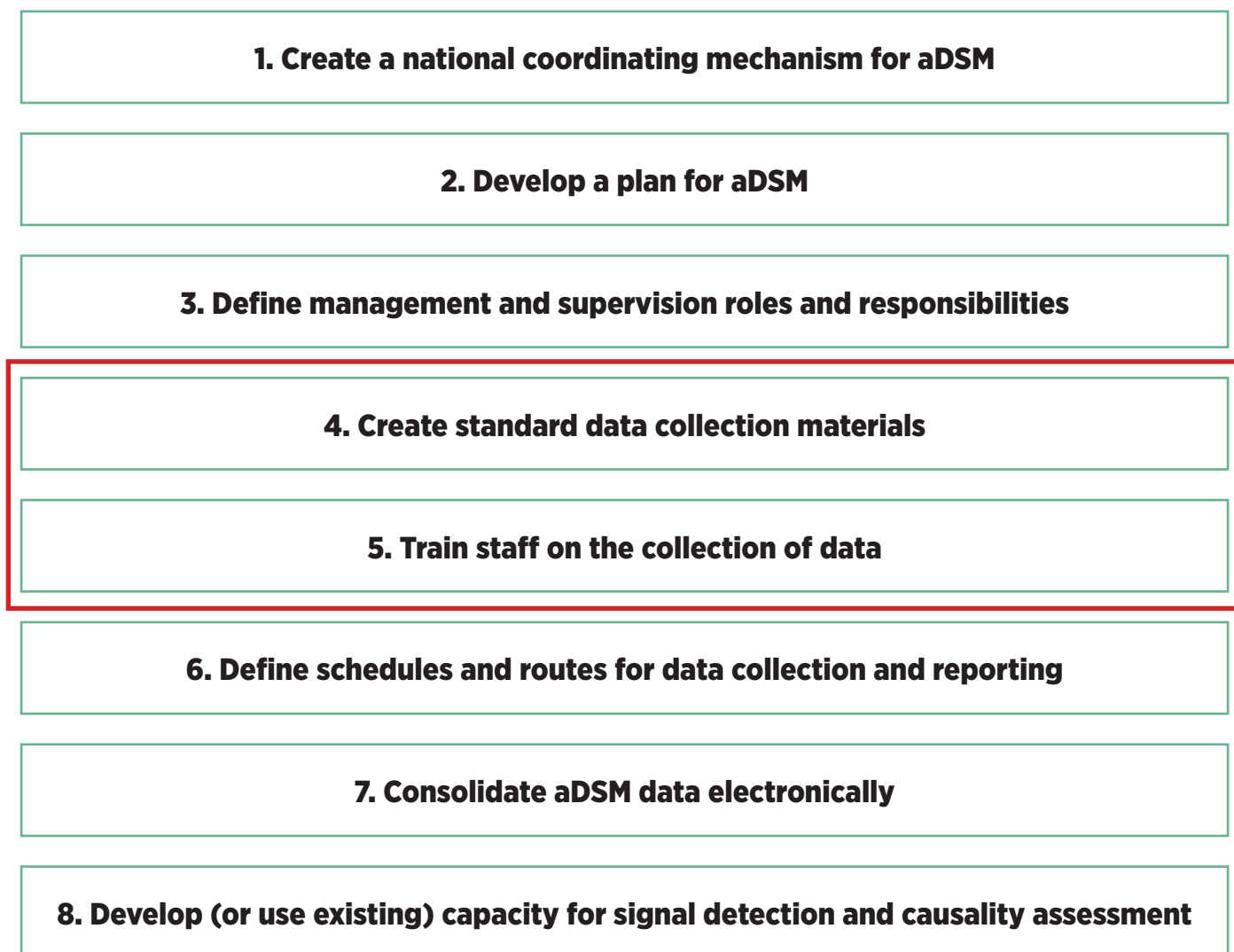
Implementing aDSM

Based upon the experience of successful implementation of other care and monitoring components of PMDT programs, eight key steps have been identified for programs to follow when introducing aDSM (**Figure 1**). Ideally all 8 steps should be in place before enrolling patients on new drugs and regimens, but as this is not always feasible, at least, two steps are deemed essential, namely:

- a) Create standard data collection materials, and
- b) Train staff on the collection of data.

³ https://www.challengetb.org/publications/tools/pmdt/Generic_NDandR_Training_Modules.zip

Figure 1. Key steps to implementing aDSM



1. National coordination mechanism for aDSM

The responsibility for the coordination of aDSM at the national level should be assigned to an existing TB expert body, such as the DR-TB consilium or the technical working group on new treatment regimens. Such a body should have scientific and clinical expertise for DR-TB care and drug-safety monitoring, as well as for the management and communication pertaining to funding, advocacy, and patient representation. The NTP also needs to assign a staff to coordinate the necessary aDSM activities.

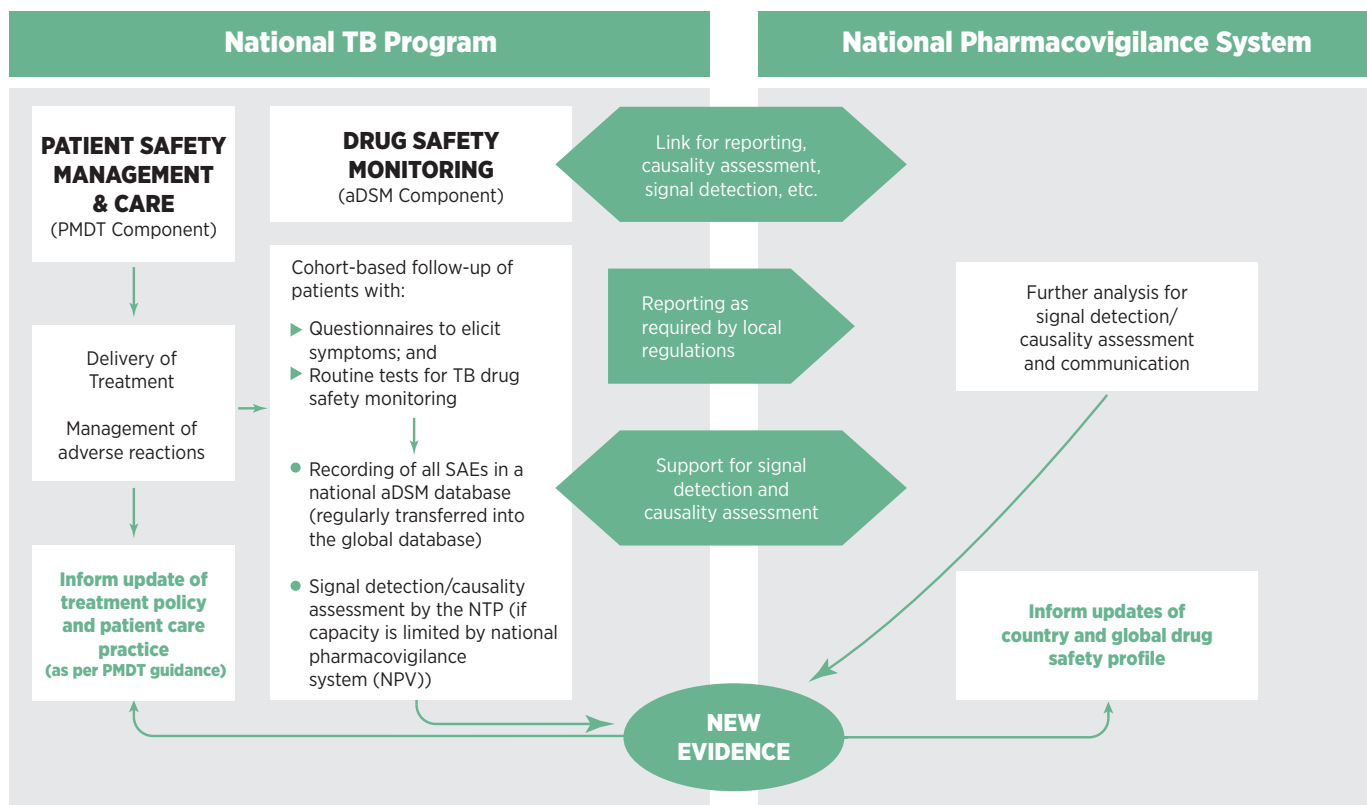
2. aDSM Plan

The aDSM plan should clearly define the activities and standard operating procedures including the plan for data collection, reporting of indicators, analysis, and communication. In addition, access to monitoring tests and ancillary drugs and the capacity building of health care workers on the diagnosis and management of AEs, should be included. Local and international experts in drug-safety and the national PV center should be engaged. The final document should be incorporated within the national TB or PMDT guidelines.

3. Roles and responsibilities

The roles and responsibilities for aDSM need to be discussed and shared among the different levels of the NTP (national, regional and facility level), the PV center, and other stakeholders, depending on the capacities of each, optimizing opportunities but avoiding duplication of efforts, time, and resources (**Figure 2**).

Figure 2. aDSM implementation to avoid the creation of parallel systems



4. Standard data collection materials

Data collection materials for the recording of clinical and laboratory test results should ideally be integrated into an expanded version of the PMDT Treatment Card. This would reflect both the baseline results prior to treatment initiation, and the follow-up results. The baseline results are recorded in this form before the start of treatment to document any abnormality which could otherwise later be confused with a drug-related AE. Follow-up test results during the treatment course are also recorded in same form (**Table 2**).

Table 2. Sample of a recording form for clinical monitoring⁴

Baseline and follow-Up investigations								
	Normal Values*	Date	Date	Date	Date	Date	Date	Date
Weight								
Smear								
Culture								
Hb	12-18 g/dl (M) 9-15 g/dl (F)							
WBC	4.0-11.0 x10 ⁹ /L							
PLT	150-400 x10 ⁹ /L							
Creatinine	97-137 µmol/L (M) 88-128 µmol/L (F)							
eGFR	>60 ml/min							
Potassium	3.6-5.2 mmol/L							
ALT (GPT)	0-49 U/L							
AST (GOT)	0-46 U/L							
Fasting Blood Sugar	2.5-6.2 mmol/L							
Albumin (if on DIm)	35-50 g/L							
Amylase/Lipase	25-86 U/L/0-160 IU/l							
TSH	0.27-5.0 mIU/l							
HIV								
CD4	500-1500 cells/mm ³							
Viral Load	<50 copies/ml							
ECG (QTcF)	<450 ms (M)/<470 ms (F)							
Audiometry	0-25 dB							
(Color) Vision Test								

* Normal ranges can differ for each laboratory
M=Male F=Female

The standard form (paper or electronic) for reporting (**Figure 3**) is intended for the core aDSM package which alerts the program when any SAE occurs at the facility level. The spontaneous reporting form (commonly referred to as the yellow form or yellow card) may be adapted for SAE reporting.

The SAE report form is sent to the designated PV center within an agreed period of time (ideally within 24 hours of detection, even upon suspicion of seriousness), even if not all details are available and regardless of certainty of association with any medicine. The essential details are the identifiers and the reporter, the name of the suspected medicine(s), and basic details of the SAE.

If more than one SAE occurred in the same patient, separate forms are to be sent for each event. All health care professionals are encouraged to report. Patients and relatives may also report. Every SAE will undergo a causality assessment. Upon receipt of the SAE report, the responsible authority will review the information and may contact the reporter and/or facility for more details. All information, including the identity of the patient and reporter will be handled in strict confidence.

⁴ADSM Training module for health workers involved in patients' treatment 2018. National Tuberculosis and Leprosy Control Program, Nigeria 2018

Figure 3. Sample alert form for serious adverse events

CONFIDENTIAL - To be sent even upon suspicion of a serious adverse event

IS THIS REPORT A NEW EVENT? YES NO

GIVE DATE WHEN PREVIOUS SAE FORM SENT: DD MM YEAR

1. PATIENT DETAILS

LAST NAME _____ FIRST NAME _____

SEX MALE FEMALE

DATE OF BIRTH DD MM YEAR
age in yrs if DOB unknown

PREGNANCY YES NO

ID NUMBER _____ PHONE NO. _____
ADDRESS _____

2. SUSPECTED and CONCOMITANT MEDICINE(S)

NAME (Brand name or Generic)	Total daily dose	Date started	Date stopped	Continues
				<input type="checkbox"/>
				<input type="checkbox"/>
				<input type="checkbox"/>
				<input type="checkbox"/>
				<input type="checkbox"/>

3. DETAILS OF SERIOUS ADVERSE EVENT

DATE EVENT STARTED _____ DATE EVENT STOPPED _____

DESCRIPTION OF EVENT _____

WHY IS THE EVENT CONSIDERED SERIOUS?

- Death
- Life-threatening event (specify: _____)
- Hospitalization or prolongation of hospitalization
- Persistent or significant disability (specify: _____)
- Congenital anomaly
- Other (specify: _____)

4. ACTIONS TAKEN

- Medicine withdrawn
- Dose increased
- Dose reduced
- Dose not changed
- Unknown

5. OUTCOME OF SERIOUS ADVERSE EVENT

- Recovered/Resolved
- Recovering/Resolving
- Recovered with sequelae
- Not recovered/Not resolved
- Died
- Unknown

6. REPORTER

NAME _____ POSITION _____

FACULTY/CLINIC _____

ADDRESS _____

EMAIL _____ PHONE NO. _____

SIGNATURE _____ DATE SENT: DD MM YEAR

For countries which used the USAID Bedaquiline Donation Program, SAEs for patients on Bdq-containing regimens, and Dlm-containing regimen are to be reported to the GDF within 24 hours, using a specific form.⁵

For countries implementing the intermediate or advanced package, AEs of special interest and those of clinical significance may be recorded in a form, and the data may be routinely entered into the national electronic database and analyzed together with other program data that are routinely collected. **Table 3** is a sample of an individual patient’s form where AEs of special interest and/or clinical significance may be recorded, and then encoded to the electronic database.

Table 3. Sample of an individual patient’s form for other AEs

Signs and Symptoms (Select in the list below*)	Date of appearance of signs and symptoms/ disappearance	Date of reporting on SAEs	Examinations confirming AEs (select in the list below**)	Suspected agent	Treatment scheme	AEs 1. Serious AE 2. AE of special interest	Measures taken to eliminate AE: 1. Dosage not changed 2. Dosage reduced 3. Temporary withdrawal of drug 4. Discontinuation of drug 5. Prescribing of auxiliary medicines 6. Additional examination	AEs management result 1. Resolved 2. Resolved with sequela(e) 3. Fatal 4. Resolving 5. Not resolved/persistent	Place of Treatment (level, facility)	If the agent was: 1. discontinued (de-challenged): 1a. AE disappeared 1b. AE remained 2. resumed (re-challenged): 2a. AE reappeared 2b. AE did not reappear	Comments

Example:

16	12/08/18	14/08/18	1	Cm	Cm, Lfz, Cs, Pto, PAS, Z	1	4, 5	1	National TB Center	2a	
22	01/02/18	01/02/18	7, 8	Z	Cm, Lfz, Cs, Pto, PAS, Z	2	4, 5	4	PHC Facility	1a	

***Signs/symptoms:**

1. Nausea/Vomiting
2. Diarrhea
3. Arthralgia
4. Vertigo/Loss of balance
5. Hearing loss
6. Headache
7. Sleep disturbance
8. Electrolyte disorders

9. Abdominal pain
10. Anorexia
11. Gastritis
12. Peripheral neuropathy
13. Depression
14. Tinnitus
15. Allergic reaction
16. Skin rash
17. Visual disturbances

18. Seizures
19. Hypothyroidism
20. Psychosis
21. Suicidal thoughts
22. Hepatitis
23. Renal failure
24. QT prolongation
25. Other

****Examinations confirming**

AEs:

1. General examination
2. Visual acuity
3. Determination of hearing
4. Audiogram
5. Examination for neurological and psychiatric abnormalities

6. Serum creatinine
7. ALT
8. AST
9. Bilirubin
10. Alkaline phosphatase
11. GGT (Gamma-glutamyl transferase)
12. ECG
13. Lipase

14. Amylase
15. Potassium
16. Magnesium
17. Calcium
18. Albumin
19. Complete blood count
20. Serum glucose
21. Thyroid stimulating hormone (TSH)
22. Other

⁵ <http://www.stoptb.org/gdf/drugsupply/bedaquiline.asp>

5. Training of staff

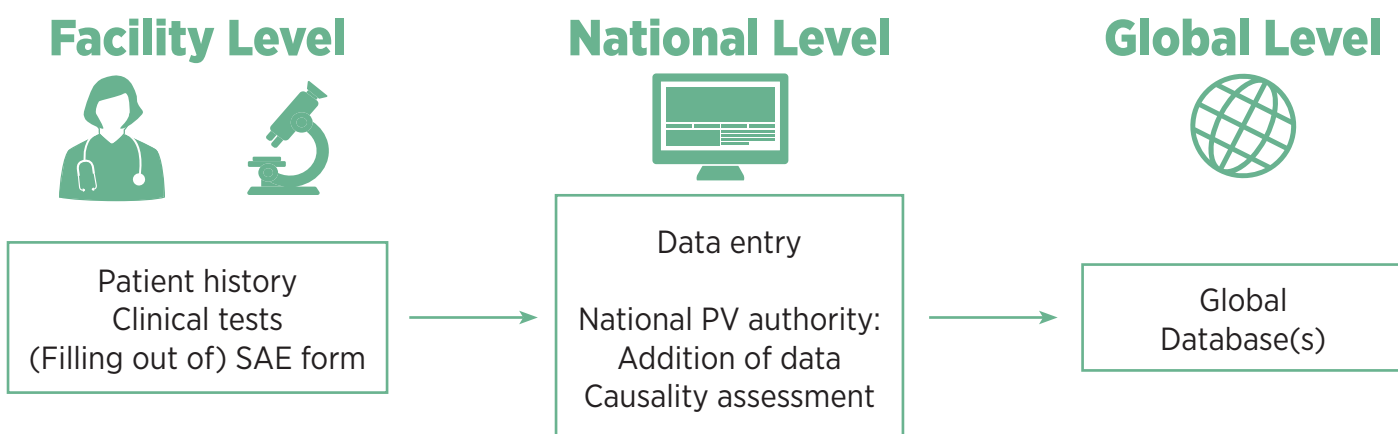
Ahead of any patient enrollment, the staff at different levels of health services should be trained on the use of the new drugs and regimen, patient treatment monitoring, early detection, management of AEs, and on the completion of the aDSM forms. This capacity building aims to ensure timely patient care and the proper and complete collection and reporting of information.

All detected AEs should lead to an appropriate and prompt response to limit potential harm to patients. Please refer to the PMDT Companion Handbook² or the Challenge TB aDSM Training Module for the clinical management of common AEs.³

6. Schedules and routes for data collection and reporting

Schedules and routes for data collection and reporting are to be agreed upon by the members of the national coordination committee. AE reports are filled out in the health facility as soon as the AE is detected, usually by the attending PMDT physician, and are sent via email, fax or phone, mobile application, or other means to the national level which can be an aDSM committee composed of many members. Depending on the agreement, reports are first sent from the facility to the NTP or to an aDSM committee for review and are then sent to the national PV center. In some countries, reports are sent directly to the national PV center where causality assessment is being done. AE data are then entered into the national aDSM database and then forwarded to the global database(s), the Vigibase of the UMC or the WHO aDSM global database. SAE reports of patients on Bdq-containing regimens procured through the USAID Bedaquiline Donation program, as well as Dlm-containing regimens are sent to GDF. **Figure 4** shows an example of the route of AE data reporting from the facility to the national level and then to the global level.

Figure 4. Flow of reporting from facility to the national and global levels



Note: Spontaneous AE reporting is a passive kind of AE reporting which is mandatory in most countries and collects AEs that may not be serious. Spontaneous AE reports are sent to VigiBase, the database in the Upsala Monitoring Center (UMC), which includes a large repository of drug-safety data collected from many parts of the world. UMC is the collaborating arm of the WHO – Program for International Drug Monitoring (PIDM) and is responsible for managing the technical and scientific aspects of WHO’s international PV network. aDSM reporting collects reports actively, and such reports may also be sent to UMC as “study reports”, a report type selected or clicked when entering SAEs in VigiBase. aDSM reports may also be sent to the WHO aDSM global database.

7. Electronic data consolidation

The creation of an electronic database, or preferably the adaptation of an existing TB patient database to accommodate the additional data fields required in aDSM, is an important step in aDSM implementation. Revisit existing data management systems to avoid duplication and ensure interoperability, consulting with local PV authorities and granting access rights to users for different data as needed. Entering paper-based data electronically on a regular basis ensures safekeeping and allows standardization through the use of codes. Electronic data entry to a national electronic database or to VigiBase will also facilitate the sharing of data and the generation of indicators and analysis. The electronic data may also be forwarded to the WHO global aDSM database. The full set of variables which can be made into an excel file for regular data entry, can be found at: http://www.who.int/tdr/research/tb_hiv/adsm/Global-aDSM-DB_List-of-variables.pdf

8. Causality assessment and signal detection

The ultimate purpose of data collection in aDSM is to enable causality assessment for AEs, determine their frequencies (or rates), and detect signals. Causality assessments may be done by physicians skilled in DR-TB management jointly with PV expert(s) attempting to assess relationships between medicines and AEs, and to take the appropriate clinical action. Local and/or international expertise in causality assessment needs to be sought by the program.

Annex 1. Definitions

active TB drug-safety monitoring and management (aDSM) is the active and systematic clinical and laboratory assessment of patients on treatment to detect, manage and report suspected or confirmed drug toxicities.

adverse drug reaction (ADR) is a response to a TB medicine which is noxious and unintended, and which occurs at doses normally used in humans.

adverse event (AE) is any untoward medical occurrence that may present in a TB patient during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with this treatment.

serious adverse event (SAE) is an adverse event which either leads to death or a life-threatening experience; to hospitalization or prolongation of hospitalization; to persistent or significant disability; or to a congenital anomaly. Serious events which do not result immediately in one of these outcomes but which might require an intervention to prevent it from happening are included. SAEs may require a drastic intervention such as termination of the drug suspected of having caused the event.

adverse event of clinical significance is an adverse event which is either serious, of special interest, leads to a discontinuation or change in the treatment, or is judged as otherwise clinically significant by the clinician.

adverse event of special interest is an adverse event documented to have occurred during clinical monitoring. The centers which offer the intermediate and advanced packages of aDSM will include all adverse events of special interest in their reporting.

causal relationship is a relationship between an exposure (A) and an event (B) in which A precedes and causes B. This may refer to the causal association between an exposure to a TB medicine and the occurrence of an adverse reaction.

causality assessment is the evaluation of the likelihood that a TB medicine was the causative agent of an observed adverse reaction.

signal is reported information on a possible causal relationship between an adverse event and a TB medicine, the relationship being unknown or incompletely documented previously or representing a new aspect of a known association.

drug-safety profile is a description of the benefits, risks and toxicity of a given TB drug or regimen, specifying any known or likely safety concerns, contraindications, cautions, preventive measures and other features that the user should be aware of to protect the health of a TB patient.

Annex 2. AEs of clinical significance or special interest

a. Serious adverse events: AEs that lead to:

- Death or a life-threatening experience
- Hospitalization or prolongation of hospitalization
- Persistent or significant disability
- Congenital anomaly

AEs that do not immediately result in one of the above but require an intervention to prevent them from happening are included.

b. Adverse events of special interest (suggested list):

- Peripheral neuropathy (paraesthesia)
- Psychiatric disorders and central nervous system toxicity (e.g. depression, psychosis, suicidal intention, seizures)
- Optic nerve disorder (optic neuritis) or retinopathy
- Ototoxicity (hearing impairment, hearing loss)
- Myelosuppression (manifested as anaemia, thrombocytopenia, neutropenia, or leukopenia)
- Prolonged QT interval
- Lactic acidosis
- Hepatitis (defined as increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\geq 5x$ the upper limit of normal (ULN), or increases in ALT or AST $\geq 3x$ ULN with clinical manifestations, or increases in ALT or AST $\geq 3x$ ULN with concomitant increase in bilirubin $\geq 1.5 x$ ULN)
- Hypothyroidism
- Hypokalaemia
- Pancreatitis
- Acute kidney injury (acute renal failure)

c. AEs leading to treatment discontinuation or a change in drug dosage

d. AEs not listed above but judged as otherwise clinically significant by the clinician

