Active TB Drug-Safety Monitoring and Management (aDSM)

Manual for Tuberculosis Medicines and Regimens





National TB Programme
Department of Public Health
Ministry of Health and Sports
The Republic of the Union of Myanmar

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ABBREVIATIONS

ADR/AR	Adverse drug reaction/Adverse reaction
aDSM	Active TB Drug-Safety Monitoring and Management
AE	Adverse event
Bdq	Bedaquiline
CA	Causality assessment
Cfz	Clofazimine
Dlm	Delamanid
DR-TB	Drug-resistant tuberculosis
FDA	Food and Drug Administration
Gfx	Gatifloxacin
MDR-TB	Multidrug-resistant tuberculosis
Mfx	Moxifloxacin
NTP	National Tuberculosis Programme
PMDT	Programmatic Management of Drug-Resistant Tuberculosis
PV	Pharmacovigilance
SAE	Serious adverse event
SLD	Second-line drug
TB	Tuberculosis
UMC	Uppsala Monitoring Centre
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis

INTRODUCTION

Myanmar is one of the 30 high burden countries for TB, multidrug-resistant (MDR) TB and TB/HIV.[1] To implement an effective strategy to combat and control TB/MDR-TB, the NTP has developed a 5-year National Strategic Plan for Tuberculosis 2016-2020 (NSP)[2] that includes the programmatic management of drug-resistant TB (PMDT) as one of the key interventions. Management of drug-resistant TB (DR-TB) is challenging due to prolonged treatment duration, costly regimen, and side effects of the drugs that lead to poor treatment adherence. New and innovative strategies are needed to address these challenges.

Recently, WHO has approved the use of new anti-tuberculosis (TB) medicines, Bedaquiline (Bdq) and Delamanid (Dlm) under certain conditions.[3, 4] Moreover, a shorter regimen for MDR-TB that includes repurposed drugs, such as clofazimine (Cfz) and moxifloxacin (Mfx) has been approved and recommended by WHO in the Drug-resistant TB guidelines, 2016 update.[5] The introduction of new and repurposed TB medicines, some given at higher dosages than previously used, and some drugs with potentially additive toxicity given in combination, prompts the importance of active pharmacovigilance (PV) system for patients on TB treatment. Additionally, for HIV patients on treatment, some of the new TB drugs have been observed to manifest drug-drug interactions with certain anti-retroviral medicines.

To address this issue, the WHO Global TB Programme (WHO/GTB) and the Essential Medicines Products department drew on the input of technical partners to develop the concept of active TB drug safety monitoring and management (aDSM), defined as the “active and systematic clinical and laboratory assessment of patients while on treatment.” aDSM applies to patients on treatment with new anti-TB drugs, new MDR-TB regimens, including the shorter treatment regimen, and extensively drug-resistant TB (XDR-TB) regimens.[6] The purpose of aDSM is to detect, manage, and report suspected or confirmed drug toxicities in a timely fashion. A feedback mechanism to care providers needs to be in place for their knowledge and needed action for patient management.

[1] World Health Organization. WHO Global Tuberculosis Report, 2016. WHO-Geneva. WHO/HTM/TB/2016.13
[2] National Strategic Plan for Tuberculosis 2016-2020, National TB Programme, NTP, Myanmar.
[3] The use of bedaquiline in the treatment of multidrug-resistant TB WHO-Geneva. Interim Policy Guidance, WHO- Geneva, 2013. WHO/HTM/TB/2013.6
[4] The use of delamanid in the treatment of multidrug-resistant TB WHO-Geneva. Interim Policy Guidance WHO- Geneva, 2014. WHO/HTM/TB/2014.23
[5] WHO treatment Guidelines for drug-resistant tuberculosis, 2016 update. WHO- Geneva, 2016. WHO/HTM/TB/2016.04
[6] Active tuberculosis drug-safety monitoring and management: Framework for implementation. WHO- Geneva, 2015. WHO/HTM/TB/2015.28

Upon the request of the NTP, the Technical Officer, Technical Support Coordination (TSC) Global TB Programme (GTB), WHO (Geneva) conducted an aDSM mission on 2-6 May 2016.[7] The current national PV system in Myanmar for all diseases involves spontaneous reporting of adverse events (AEs) by voluntary reporting of health care workers. This has been managed by the Food and Drug Administration (FDA)/Drug control section although with limited human resources. An AE Reporting Form (in Myanmar language) is in place but with limited implementation, and with no TB-related AE reports submitted as of yet. Bdq and Dlm were introduced in the country in March 2016 through the EndTB project implemented by the NTP, Aung San TB Hospital and MSF-Holland. The PV system of the EndTB project is an advanced package with reporting of serious AEs (SAEs) plus AEs of special interest and clinical significance (see Definitions). While an advanced package is relevant in a project or research study context, programmatic aDSM implementation with a more simplified system is more appropriate in the NTP where resources are limited, in order to scale it up more widely.

[7] Active TB drug-safety monitoring and management (aDSM) for treatment of MDR/XDR-TB using new or repurposed drugs in Myanmar: Debriefing, aDSM mission, Myanmar 2-6 May 2016, WHO.

DEFINITIONS

1. **Active drug-safety monitoring and management (aDSM):** active and systematic clinical and laboratory assessment of patients while on treatment. aDSM applies to patients on treatment with (a) new anti-TB drugs, such as Bdq and Dlm; (b) new DR-TB regimens, such as the shorter (or 9-month) MDR-TB regimen; or (c) XDR-TB regimens on new/repurposed drugs, in order to detect, manage and report suspected or confirmed drug toxicities.
2. **Adverse event (AE):** 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.
3. **Adverse drug reaction (ADR):** a response to a TB medicine that is noxious and unintended, and which occurs at doses normally used in humans.
4. **Causality assessment:** the evaluation of the likelihood that a TB medicine was the causative agent of an observed adverse reaction.
5. **Serious adverse event (SAE):** an AE 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. SAEs that do not immediately result in one of these outcomes but which 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.
6. **AE of special interest:** AE documented to have occurred during clinical trials and for which the monitoring program is specifically sensitized to report regardless of its seriousness, severity or causal relationship to the TB treatment
7. **AE of clinical significance:** AE that is either a) serious (SAE), b) of special interest, c) leads to a discontinuation or change in the treatment, or, d) is judged as otherwise clinically significant by the clinician
8. **Signal:** 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

OBJECTIVES OF aDSM

The overall objectives of aDSM are to reduce risks from drug-related harms in patients on second-line (SL) treatment for DR-TB and to generate standardized aDSM data to inform future policy updates on the use of such medicines. aDSM aims to detect, manage, and report suspected or confirmed drug toxicities in a timely fashion.

PURPOSE AND SCOPE of the aDSM Manual

The purpose of this aDSM Manual is to provide a step-by-step guide to programmatically implement a sustainable aDSM system in line with the WHO-recommended aDSM Framework.[8] This Manual will be applicable to patients on **1) new and repurposed drugs, 2) new DR-TB regimens such as the shorter treatment regimen, and 3) XDR-TB regimens**. This document will describe the detection, active monitoring and management of DR-TB patients using clinical and laboratory assessment, as well as recording and reporting of SAEs.

ESSENTIAL ELEMENTS OF aDSM

There are three essential elements of aDSM to achieve the above objectives:

1. **Active and systematic clinical and laboratory assessment** during treatment to detect drug toxicity and AEs. There are ways to help health providers do this step.
    a. **Observe** and **listen** to patients. The detection of AEs is primarily dependent upon reporting from patients, nurses, doctors, counsellors, etc. At every DOT encounter, health workers should ask the patient and family members about clinical symptoms of common AEs including nausea, vomiting, peripheral neuropathy, skin rash, psychiatric disturbance (headache, anxiety, depression, irritability, behavior change), hearing loss, jaundice, vestibular toxicity (vertigo, ataxia, hearing loss), and symptoms of electrolyte wasting (muscle cramping, palpitations). All healthcare professionals involved must be trained on adverse event screening.
    b. Perform **routine** clinical assessments, e.g., for treatment adherence and tolerance, psychosocial support and consults with the psychiatrist, ophthalmologist, HIV specialist, etc. Clinical follow-up with the MDR-TB physician for all patients is at a minimum of 2 weeks after the start of MDR-TB treatment, then monthly until the treatment completion.
    c. Schedule regular laboratory screening, even if the patient has no specific complaints, e.g., creatinine, ECG, liver function tests, etc. Regular laboratory monitoring detects occult adverse effects. Laboratory tests and procedures related to treatment should be available and accessible to patients, free of charge.

[8] Active tuberculosis drug-safety monitoring and management: Framework for implementation. WHO- Geneva, 2015. WHO/HTM/TB/2015.28

Annex A shows the schedule of clinical and laboratory tests for patients on new and repurposed drugs and the shorter treatment regimen (STR). As Bdq and Dlm, Mfx, and Cfz may induce QT prolongation, ECG monitoring is essential. Challenge TB recently issued recommendations on the measurement of QT prolongation.[9]

2. **Management of AEs in a timely manner**. Early detection of signs and symptoms is key to **proper management** of AEs that significantly impacts patient well-being, overall treatment acceptance, and adherence. Management includes measures taken to alleviate the signs and symptoms of adverse reactions with careful individual case review, such as: a) reassurance, if AE is minor b) lowering the dose of the offending drug, c) stopping the drug, d) drug replacement; e) providing ancillary medications and f) other interventions (surgery, transfusion, psychological support, etc.). Ancillary medicines should be available and accessible to patients, free of charge.

   For AEs that need additional evaluation and/or medical treatment, a treatment decision algorithm or severity grading may help clinic staff in decision-making, allowing a more objective way of approaching symptoms **(Figure 1)** and laboratory test results **(Figure 2)**. The main sources of severity grading are the Division of Microbiology and Infectious Diseases *(DMID) and Common Terminology Criteria for AE (CTCAE)*.[10] A set of Severity Grading Scales using simple categories of Mild, Moderate, Severe and Life-threatening are provided in this document **(Annex E)** for selected common AEs *(taken from the end TB Guide for TB patient management[11])*.

Figure 1: Serverity grading of a symptom (vomiting)[10, 12]

Condition term	Grade 1	Grade 2	Grade 3	Grade 4
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	Physiologic consequences requiring hospitalization or requiring parementeral nutrition

[9] Guidance on requirements for QTc measurement in ECG monitoring when introducing new drugs and shorter regimens for the treatment of Drug-resistant Tuberculosis, ver 0.4, 25 Apr 2017. USAID, KNCV Tuberculosis Foundation, Challenge TB. http://www.challengetb.org/publications/tools/pmdt/Guidance_on_ECG_monitoring_in_NDR.pdf

[10] version 5.0; date, 14-Nov-2016, *DMID Nov 2007 and CTCAE v.4.03 14-Jun-2010*. https://www.google.com.ph/search?q=DMID+Severity+grading&oq=DMID+Severity+grading&aqs=chrome..69i57.18194j0j7&sourceid=chrome&ie=UTF-8 (accessed 4 Apr 2017)

[11] End TB clinical and programmatic guide for patient management with new TB drugs, ver 3.3, 25/11/2016. Partners in Health, IRD, MSF, UNITAID

[12] Clinical monitoring of AEs and management of adverse drug reactions, Multi-partner training package on active TB drug safety monitoring and management (aDSM), July 2016

Figure2. Severity grading of a laboratory test result (SGPT level)[10, 11]

Condition term	Grade 1	Grade 2	Grade 3	Grade 4
Alanine Aminotransferase (ALT or SGPT) Increased	1.1 - < 2.0 x ULN	2.0 - <3.0 x ULN	3.0 - 8.0 x ULN	>8 x ULN

General definitions apply for parameters not included in the given severity grading for specific signs and symptoms of the different organ systems in the DMID and CTCAE cited above.

Table 1. General definitions for parameters of AEs not provided in the DMID and CTCAE table[11]

Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	Grade 4 LIFE-THREATENING
Transient or mild discomfort (<48 hours) No medical intervention/ therapy required	Mild to moderate limitation in activity - some assistance may be needed No or minimal medical intervention/therapy required	Marked limitation in activity, some assistance usually required Medical intervention/therapy required, hospitalization possible	Extreme limitation in activity, significant assistance required Significant medical intervention/therapy required, hospitalization or hospice care probable

Certain references for clinical management of AEs are available. The PMDT Companion Handbook, 2014[13] contains comprehensive guidance on the management of various AEs commonly encountered during MDR-TB treatment. The relevant parts of the Handbook are enumerated below.

Table 2. Parts of the WHO Companion Handbook providing clinical guidance

2014 WHO Companion Handbook	Topic
Chapter 11	Management of adverse effects and pharmacovigilance
Annex A4.1.5	“How-to” guide on the use of Bdq in MDR-TB treatment Monitoring and managing patients receiving Bdq
Annex A4.2.5	“How-to” guide on the use of Dlm in MDR-TB treatment Monitoring and managing patients receiving Dlm
Annex 7	Management of electrolyte imbalance
Annex 8	Management strategy for hearing loss

[13] 2014 Companion Handbook to the WHO Guidelines for the programmatic management of drug-resistant TB. WHO-HQ. WHO/HTM/TB/@014.11 http://apps.who.int/iris/bitstream/10665/130918/1/9789241548809_eng.pdf

The EndTB clinical and programmatic guide for the patient management with new and repurposed TB drugs[14] also provides management guidance for peripheral neuropathy, myelosuppression, prolonged QT interval (example below), optic neuritis, hepatitis, hearing loss, acute kidney injury, hypokalemia, hypomagnesemia, and hypothyroidism.

Figure 3. Severity grading and management of QT prolongation[11, 13]

Severity grade	Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	Grade 4 LIFE-THREATENING
Prolongation of QTcF	QTcF 450-480 ms	QTcF 481-500 ms	QTcF>501ms on at least 2 separate ECGs	QTcF>501 or >60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia
Action	Monitor closely; at least weekly ECG until QTcF has returned to grade 1 or less	Monitor more closely; at least weekly ECG; check electrolytes and Replenish as needed	Stop the suspected causative drug(s). Hospitalize and replete electrolytes as necessary.	Stop the suspected causative drug(s). Hospitalize and replete electrolytes as necessary.

3. **Standardized data** should be systematically collected and reported for any detected SAE. These will eventually be used to characterize the types of SAEs, assess the safety of treatment, and inform future policy on the use of these medicines.

LEVELS OF aDSM MONITORING

There are three levels of aDSM monitoring that may be used in programs depending on the human resource capacity, namely:

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

* See above for definition

The NTP in Myanmar will implement **the core package of aDSM** and, therefore, will monitor and report **only SAEs**. However, as resources become available and as the NTP decides, aDSM may be expanded to include monitoring of other AEs that are of clinical significance or of special interest to the programme, as part of comprehensive aDSM.

[14] EndTB clinical and programmatic guide for the patient management with new TB drugs, version 3.3, 25/11/2016. Partners in Health, Medecins sans Frontieres, IRD, UNITAID

IMPLEMENTATION STEPS OF aDSM

There are 8 WHO recommended steps in the programmatic implementation of aDSM.[4] Ideally, all 8 steps are in place before patients are enrolled in treatment with new drugs and regimens including the shorter treatment regimen and the XDR-TB regimens. However, this may not always be feasible. Steps 4 and 5 are the most essential to be in place before any patient enrolment occurs.

Table 3. Key steps in implementing aDSM

1	Create a national coordinating mechanism for aDSM
2	Develop a plan for aDSM
3	Define management and supervision roles and responsibilities
4	Create standard data collection materials
5	Train staff for collection of data
6	Define schedules and routes for data collecting and reporting
7	Consolidate aDSM data electronically
8	Develop (or use existing) capacity for signal detection and causality assessment

1. Create a national coordinating mechanism for aDSM.

The National Core Committee for aDSM (NCCA) of Myanmar was created on 6th May 2016 during the WHO aDSM mission. It has the responsibility of oversight and coordination of aDSM activities at the national level. It is composed of members with scientific and clinical expertise for MDR-TB care and for management and communication, such as funding and advocacy. They will be trained on drug safety monitoring, including causality assessment.

Table 4. National Core Committee for aDSM (NCCA)

Agency	Representative(s)
1. Drug Control Section, Food and Drug Administration (FDA)	Director
2. Clinical Professors*	Professor & Head, Dept of Respiratory Medicine, University of Medicine 1, University of Medicine 2, University of Medicine Mandalay
3. NTP	National Program Manager
4. TB Specialist Hospitals – Department of Medical Services	Medical Superintendents of Aung San TB Hospital and Patheingyi Hospital
Partners*:	
5. MSF (Holland)	
6. WHO	
7. FHI360	

*Note: * The aDSM Workshop in March 2017 specified the clinical professors to include 2 from Yangon and 1 from Mandalay; FHI360 was added to the list of partners.*

2. Develop a plan for aDSM.

The **National aDSM Implementation Plan**[15] of Myanmar was drafted with the assistance of WHO following an assessment of the country situation and a wide consultation with all relevant stakeholders. It has been endorsed by the NTP and approved by the NCCA. The plan clearly described what should be done in each of the steps in aDSM implementation. Financial support for the implementation of the plan is through the NTP /FDA or other stakeholders.

3. Define management and supervision roles and responsibilities.

The NCCA will exercise national oversight and coordination of aDSM activities through regular coordination meetings among its members (6 monthly and ad hoc, when needed). A tentative pre-agreed schedule for meetings is recommended, e.g., the 3rd Wednesday of the month, so as to keep this in the calendar of the members. The NTP aDSM Focal Point with support from CTB or any other partners will arrange the NCCA meetings including sending of invitations to members and providing minutes of the meeting.

With NTP being a lead member of the NCCA, the **NTP Program Manager** will designate an **NTP aDSM Focal Person** to coordinate aDSM activities together with partners, and ensure that the key steps are in place prior to the start of patient enrolment. The **FDA**

[15] Annex 3. National aDSM Implementation Plan of Assessment on Drug safety monitoring and management for the treatment of DR-TB using new and repurposed drugs Myanmar, 2-6 May 2016, WHO.

Director will likewise designate an **FDA aDSM Focal Person** to work together with the NTP aDSM Focal Person in coordinating aDSM activities. The current NTP and FDA aDSM Focal Persons have been trained on PV during the Asia-Pacific PV Course in India in January 2017.Other opportunities for training should further strengthen the capacity of NCCA members.

The **Clinical Professors** who are members of the National DR-TB Expert Committee, and other designated members, will provide clinical advice for AEs that cannot be managed in the MDR-TB Centres, and will be responsible for causality assessment, after undergoing training by experts in this field.

Monitoring and supervision of the programmatic implementation of aDSM is an important task for the NCCA. The committee will oversee the monitoring of the two essential indicators out of four aDSM indicators suggested by WHO (**Annex B**). The two essential indicators, namely a) coverage (rate of enrolled patients covered by aDSM); and b) SAE rate among patients treated and monitored for aDSM will be used to monitor aDSM programmatic implementation given the current limited resources.

4. Create standard data collection materials

WHO, the Clinton Health Access Initiative (CHAI), and other partners will provide support in data collection and M & E.

The forms related to aDSM are as follows:

a. Modified NTP MDR-TB Treatment Card (DR-TB Form 01) (Annex C)

The six-page NTP MDR-TB Treatment Card, based on the WHO recommended template, is the standard card used for all DR-TB patients enrolled in treatment. For aDSM purposes, some revisions have been made on the original Treatment Card, which are as follows:

- Page 1: Added abbreviations for new and repurposed drugs; modified table for DST
- Page 2: Provided 4 columns for liver function tests (LFT) [bilirubin, alkaline phosphatase, aspartate aminotransferase (AST) and alanine aminotransferase (ALT)]
- Page 3: Provided separate tables; the first table (as continuation of the table on page 2), 3 columns for electrolytes, added columns for albumin and lipase, and a new table for ECG/ QTc, and audiometry for follow-up.
- Page 4: added one column for follow-up month and year (mm-yy).

- Page 5: Updated the column heading with new and repurposed drugs; a new table to record the issues, discussion and decision by Expert Panel.
- Page 6: Included a comment box, outcome categories with new categories (moved to either conventional regimen or individualized regimen); added a table to record patients' information during 2 years after completion of treatment.

b. Form for Reporting of Serious Adverse Event

This form is a simplified version of the MSF SAE Form developed by WHO with inputs from the NCCA members, and is now being used by the focal MSF-H doctor for the EndTB Project in Aung San TB Specialists Hospital (ASTSH). This form is to be filled out by the MDR-TB Hospital physician every time an SAE is detected during the course of treatment. This form will be used to alert the NTP and the NCCA, and will also be sent to the Region/State DR-TB Committee for their information and clinical inputs. The Reporter/ the attending (on duty) clinician from the Hospital / MDR-TB centre will enter all available information at the time of reporting, and will submit the form within 24 hours from SAE detection. All other missing information in this form will be filled out and transmitted to the NCCA within 72 hours.

For now, all data collection forms are paper-based, and should be kept on-site, and filed for electronic data entry in the future (when an aDSM electronic database is developed).

5. Train staff for collection of data

The training will cover, most importantly, data collection (which happens both in the hospital when the patient is still confined, and in the out-patient setting after discharge), reporting flow, as well as the basics of aDSM, clinical monitoring and management, causality assessment, and signal detection. Training participants will include those involved in direct patient care, in providing clinical advice, performing causality assessment and signal detection, and in supervision and monitoring of both hospitalized and ambulatory phases of treatment.

6. Define schedules and routes for data collection and reporting

Under the core aDSM package, reporting is mainly for SAEs detected and identified while on treatment either in the MDR-TB hospital or in the community during the ambulatory phase.

A. The hospital or MDR-TB Centre submits the SAE Reporting Form **(Annex D) within 24 hours of SAE detection** by email to the following:

a. Region/State DR-TB Committee: This is to inform the Committee of the SAE, and to seek technical assistance, be it for programmatic or clinical management purposes.

b. NCCA: The NTP Program Manager needs to know the SAE, and will supervise the NTP aDSM Focal Point (who is copy furnished with the SAE Form) in quickly reviewing the entries of the SAE Form for completion, consistency and accuracy.

B. The NTP aDSM Focal Point verifies with the hospital reporter any unclear information. Within **72 hours**, all information in the SAE Form must have been completed and received by the NTP aDSM Focal Point.

C. The NPT aDSM Focal Point will forward the completed SAE Form by email to the following:

a. Clinical Professors who are members of the NCCA and the National DR-TB Expert Committee and to the other members of the NCCA for their information, their review and clinical inputs, if and when necessary.

b. All members of NCCA

c. The FDA Director with a copy furnished to the FDA aDSM Focal Point. The Director and/or the FDA Focal Point may ask questions or clarification to the NTP aDSM Focal point about the SAE.

d. The Department of Medical Services

D. The NTP aDSM Focal Point will then schedule and convene a meeting among the Clinical Professors to perform causality assessment on the SAE **within 15 days** from SAE detection.

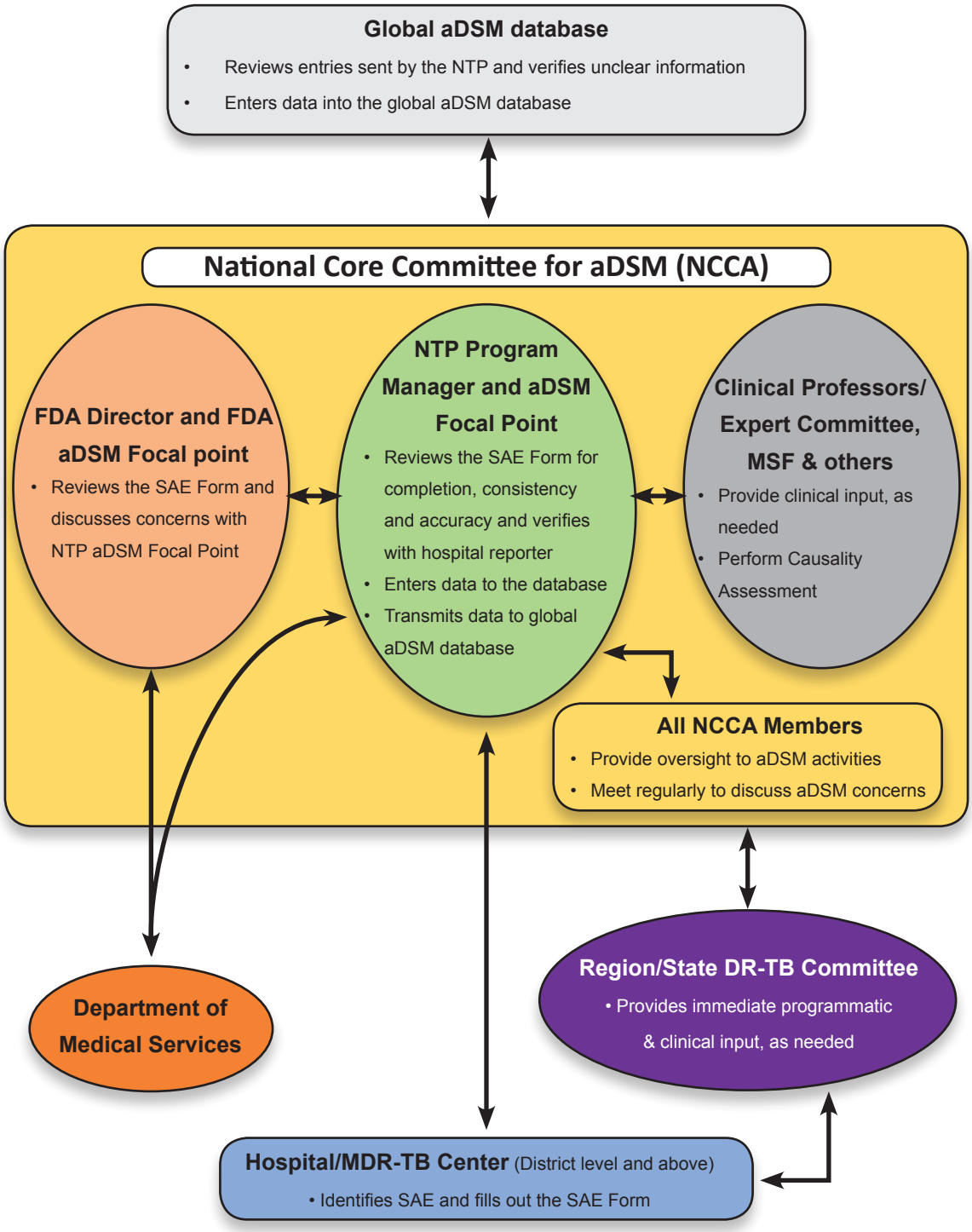
E. The NTP aDSM Focal Point enters the data to the National aDSM Database within 72 hours as soon as all details are verified from the hospital or MDR-TB Center.

F. The NTP aDSM Focal Point transmits the data to the Global aDSM Database in WHO to aDSM-database@who.int within 30 days of SAE detection.

G. The Global aDSM team will make verifications to the NTP aDSM Focal Point, as need, and will enter the data to the Global Database. Feedback will be given to the country, after a certain agreed period of time.

H. Two-way communication is maintained between the FDA and the Department of Medical Services, and between the NTP and Department of Medical Services.

Figure 4. Reporting Flow for SAE, Myanmar



7. Consolidate data electronically

The Clinton Health Access Initiative (CHAI) for DR-TB patients is assisting the NTP in creating a national electronic database for DR-TB patients. The elements of the aDSM database are to be incorporated into this DR-TB Database, rather than be developed independently as a separate one. The creation of the electronic aDSM database should not duplicate the work being done for the existing databases, and should be interoperable with the existing data management system. The electronic aDSM database will ensure standardization and safekeeping of data.

The paper-based SAE Form received by the NTP should be entered regularly to the National Database by the NTP Focal Point in a format linked with the Global aDSM Database sharing the same key variables to facilitate data transmission and contribution of the data from the country to the Global Database.

A list of key variables to be collected for the WHO central aDSM database and a data dictionary may be found at http://www.who.int/tdr/research/tb_hiv/adsm/en/. It collects anonymized individual patient data for all SAEs from PMDT. WHO and CTB are helping facilitate the link between the group working on the National Database with the Global Database.

Management of data in electronic form is necessary and will facilitate sharing of data as well as generation of indicators and analysis that will be useful to assess the coverage of aDSM activities and to summarize the overall AE experience of monitored patients.

8. Develop capacity for signal detection and causality assessment

The ultimate purpose of systematic data collection within aDSM is to enable causality assessment for the SAEs, determine the frequency and rates of occurrence and detect signals. Clinical experts in M/XDR-TB management may attempt to establish relationships between drugs and ADRs; however, performing causality assessment is a separate process requiring expertise. The physicians involved in M/XDR care will undergo training on causality assessment which will enable them to conduct causality assessment for every SAE reported. Signal detection will be a function that will be requested from external experts.

ROLES AND RESPONSIBILITIES

The roles and responsibilities in aDSM focus on key stakeholders involved in the clinical management and public health management for DR-TB patients at the national, regional and hospital levels. These are discussed in Step #2 above and summarized in the next 2 tables.

Table5. Responsibilities for aDSM implementation

aDSM Component	Lead responsibility
Formation of national aDSM coordination mechanism	NTP, FDA, Expert Committee
Development of the aDSM Implementation Plan	NTP with support from WHO
Tools for data collection	NTP with support from WHO
Development of aDSM Manual	NTP with support from FHI360
Training plan for all staff involved in aDSM	NTP with support from FHI360
Collection of data	Hospital sites/ MDR-TB centres
Communication, coordination and follow up of all data collected from the sites	NCCA (NTP aDSM Focal Point)
Data review	NCCA (NTP aDSM Focal Point)
Transfer of cleaned and validated data to Global Databases	NTP aDSM Focal Point
Causality assessment	NCCA (Clinical Professors)
Analyse data and provide feedback to health centres and clinicians	NCCA through causality assessment, and NTP

The table below summarizes the steps and timelines for SAE reporting in Myanmar

Table 6. Summary of steps and timelines for SAE reporting, Myanmar

STEP	Event description	Action taken	Responsible party	Forms sent to	Time frame
STEP 1	SAE event detected	SAE Form filled out and submitted	Hospital (treating) physician	NTP aDSM Focal Point adsm.ntp.myanmar@gmail.com (to send to NTP Program Manager)	Within **24 hours or 1 working day** of SAE detection
STEP 2	SAE Report Form received at the national level	SAE Form completed with all details, upon verification with the hospital/ MDR-TB Centre reporter; meeting for CA scheduled	NTP aDSM Focal Point	Clinical Professors and all members of the NCCA including FDA, and to the Department of Medical Services	Within **72 hours** of SAE detection for initial reporting, then follow-up
STEP 3	SAE entry to National Database	All entries of SAE Form entered to National aDSM Database	NTP aDSM Focal Point	National aDSM Database	Within **72 hours** of SAE detection
STEP 4	Clinical Professors' meeting and causality consensus	Meeting conducted for CA, and Causality consensus made	NCCA Clinical Professors and other designated partners	NTP	Within **15 days** of SAE detection or during monthly meeting
STEP 5	CA report completed	Feedback to the NTP and the hospital	NTP aDSM Focal Point	WHO Global aDSM database aDSM-database@who.int	Within **30 days** of SAE

CAUSALITY ASSESSMENT

Causality assessment (CA) is an integral part of clinical management. In TB, evaluating the likelihood that a TB medicine was the causative agent of an observed adverse reaction forms part of clinical evaluation. While the details of the systematic method of conducting CA may not be familiar to the practitioner, the overall approach is not too different from the clinical practice followed when evaluating any patient on treatment.[16]

CA involves making an attribution or describing the relationship between the AE and an exposure by a physician or any other health care professional with the right expertise which forms part of clinical monitoring and management. This determination must be recorded both in the patient's medical record as well as in a case report form. For aDSM, CA should be made primarily at the country level and by consulting the relevant data sources close to where the event occurred. Attributing a relationship requires a systematic process and is one of the main reasons why data are collected in aDSM. CA once done attributes a level of certainty between the event and the exposure, ranging from certain to unrelated.

CA is conducted by the Clinical professors of the NCCA, who also comprise the National DR-TB Expert Committee, with the participation of other designated members. CA should be conducted using a systematic tool provided later in this section, involving inputs from the panel of experts beyond the treating physician. The steps in doing CA are as follows:

- The hospital site provides all details relevant to the SAE to the national level (within 24 hours to the NTP and FDA aDSM focal points)
- The hospital site will forward all other details to the NTP aDSM Focal Point (within 72 hours from SAE detection) in the Case Summary section of the SAE Form, including the following key data elements:
    a) medical history (including concomitant disease),
    b) other risk factors (social factors, alcohol use, substance abuse, etc.),
    c) details of drugs taken: names, doses, routes,
    d) start and stop dates and indications for use,
    e) description of adverse event, including clinical description, baseline, monthly and ad hoc laboratory results, and date of onset / end and
    f) evolution of event, severity, seriousness, and outcome.
- The NTP aDSM Focal Point forwards the completed SAE Form to the Clinical Professors and all who are involved in CA, and other NCCA members

[16] aDSM training package (training slides prepared by KNCV Tuberculosis Foundation, Management Sciences for Health (SIAPS), Médecins sans Frontières, World Health Organization / Global TB Programme Special Programme for Research and Training in Tropical Diseases (TDR) at WHO Headquarters, July 2016 http://www.who.int/tdr/research/tb_hiv/adsm/training_adsm/en/ ((accessed on 2 Feb 2017)

- The NTP aDSM Focal Point schedules a CA meeting within 15 days from SAE detection.
- Prior to the meeting, each member of the CA team will individually review the SAE Form guided by the WHO-Uppsala Monitoring Centre (UMC) Causality Algorithm or the Naranjo ADR probability scale.
- During the CA meeting, the individual CAs will be considered until a **NCCA Causality Consensus** is arrived.

The goal for CA is to decrease inter-individual differences in the assessment of a given event, classify the likelihood of a relationship between the drug and the event, and improve scientific evaluation. CA cannot prove the connection between the drug and the AE, nor can it quantify the contribution of a drug to the development of the AE. AEs are rarely specific to the drug, and often case reports involve suspected adverse drug reactions that may never be proven.

Some questions to ask to guide the process of CA include the following:

1. Is there a convincing relationship between the medicine and the event?
2. Did the medicine actually cause the event, or was it caused by other TB medicines, or medicines for other diseases, or by drug-drug interaction?
3. Is the AE the effect of the TB disease itself or of a co-morbidity?

Some of the criteria to guide the process of CA include the four below:

1. The association in time between the drug administration and the event.
2. The pharmacology and pharmacokinetics: including previous knowledge of side effects, features of the event, site of reaction, dose-response effects (dose reduction; effect of re-exposure); as well as known actions of the drug.
3. Medical plausibility: including characteristic signs and symptoms, laboratory tests, pathological findings
4. Likelihood or exclusion of other causes

There are instruments for the systematic performance of CA, namely the **WHO-Uppsala Monitoring Centre (UMC) algorithm (Table 7) and the Naranjo ADR probability scale, but country preference is the UMC algorithm**.

The **WHO-UMC algorithm** has been developed as a practical tool for the assessment of case reports, and is basically a combined assessment taking into account the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation. Since PV is particularly concerned with the detection of unknown and unexpected adverse reactions, other criteria such as previous knowledge and statistical chance play a less prominent role in the system. The various causality categories are listed in **Table7**.[17]

[17] The use of the WHO-UMC system for standardised case causality assessment. The Uppsala Monitoring Centre https://www.who-umc.org/media/2768/standardised-case-causality-assessment.pdf (accessed 20 May 2017)

Table 7. The WHO-UMC Classification System for causality assessment

Causality term	Definition	Assessment criteria*
Certain	**Clearly caused by the exposure** *There is **clear** evidence to suggest a causal relationship and other possible contributing factors can be ruled out.*	• Event or laboratory test abnormality, with ***plausible time*** relationship to drug intake • ***Cannot*** be explained by disease or other drugs • Response to withdrawal ***plausible (pharmacologically, pathologically)*** • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) • Re-challenge ***satisfactory***, if necessary
Probable/Likely	**Likely to be related to the exposure** *There is evidence to suggest a **likely** causal relationship and the influence of other factors is unlikely.*	• Event or laboratory test abnormality, ***with reasonable time*** relationship to drug intake • ***Unlikely*** to be attributed to disease or other drugs • Response to withdrawal ***clinically reasonable*** • Re-challenge ***not required***
Possible	**May be related to the exposure** *There is **some** evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).*	• Event or laboratory test abnormality, with ***reasonable time*** relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	**Doubtfully related to the exposure** *There is **little** evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study regimen). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).*	• Event or laboratory test abnormality, ***with a time to drug intake that makes a relationship improbable*** (but not impossible) • Disease or other drugs provide ***plausible explanations***
Conditional or Unclassified	**There is insufficient information** about the ADRs to allow for an assessment of causality.	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable or Unclassifiable	There is insufficient information about the ADRs to allow for an assessment of causality and **NO MORE is expected**.	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

*All points should be reasonably complied with

SIGNAL DETECTION

A signal is a reported information on a possible causal relationship between an AE and a TB medicine. Either the relationship was *previously unknown* or incompletely documented (e.g. a new aspect of a known association)

Signal detection is an important process to improve knowledge on the new TB medicines and complete the safety profile of a new drug. When monitoring AEs, it is important to look beyond already known adverse reactions and biological pathways. Previously unknown or rare associations may occur, especially for new and repurposed drugs. Reports of AEs to the global aDSM Database is expected to improve the likelihood of picking up more signals.

A signal is worth investigating when the data quality is reliable, several reports show a credible and strong relationship between event and drug, and the event is of sufficient importance or interest (either to require regulatory action, to require advice to prescribers, or for scientific / clinical purposes).

The features of a signal include the following: a) usually >1 event with a similar, strong relationship to a medicine (“certain” or “probable “). Events coded as “possible” can be used as supporting evidence; b) a cluster of unexpected deaths coded as “possible” forms an exception to the general rule and will need to be taken seriously; c) occasionally, a single event (“certain” or “probable”) - notable for its severity, seriousness or distinctiveness.

Signal detection can add knowledge to the drug safety profile of an agent which describes 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.

ANNEXES

ANNEX A –Monitoring schedule (Clinical, bacteriological and laboratory) during M-/XDR-TB treatment on new and repurposed drugs and the shorter regimen[18]

	Evaluation/Test	Baseline	Intensive phase (IP)	Continuation phase (CP)	Follow-up after treatment completion for 2 years
CLINICAL	Clinical evaluation (symptoms, side effects &PE)	√	Daily at every DOT encounter; monthly by MDR physician	Monthly	Months 3, 6 & 12, and as needed
	Weight	√	Monthly	Monthly	Months 6 & 12
	Audiometry	√	Monthly while on injectable	Monthly while on injectable; 3 & 6 month post-injectable	No need
	Visual (Snellen's and Ishihara chart)	If on long-term E and/ or Lzd	When indicated	When indicated	No need
	12-lead ECG	√	Week 2,4, then monthly, and ad hoc[1]	Monthly, and ad hoc if on Bdq or Dlm,Mfx and Cfz[1]	No need
			Note: Special attention in patients receiving more than one QT prolonging drugs (Bdq, Dlm, Mfx, Lfx, Cfz) or with low albumin (<3,4g/dl)		
	Chest X-ray	√	Every 6 month, and ad hoc	Every 6 month, and ad hoc	Months 6 & 12, and as clinically indicated
BACTERIOLOGIC	Smear	√	Monthly		Months 6 & 12
	Culture	√	Monthly		Months 6 & 12
	Xpert® MTB/Rif	√			If clinically indicated
	SL-LPA	√	In case of + culture after conversion, and baseline showed no resistance to FQ and SLI		When culture + and RR-TB by Xpert or MDR-TB by DST
	DST (H, R, Mfx, Lfx, Km, Am, Cm), if culture positive	√	In case of + culture by month 3 of treatment, or reversion	In case of reversion	When culture +

[18] Generic programmatic and clinical guide for the introduction of new drugs and shorter regimens for the treatment of multi-/extensively drug-resistant tuberculosis, ver 0.19, 20 Feb 2017 (USAID, KNCV, Challenge TB)

	Evaluation/Test	Baseline	Intensive phase (IP)	Continuation phase (CP)	Follow-up after treatment completion for 2 years
LABORATORY	Hemoglobin, White blood cells	If on Lzd	If indicated. If on Lzd, weekly on month 1, then monthly or if indicated. If on Zidovudine, monthly initially then if indicated		If indicated
	Platelets	If indicated, especially if on Lzd			
	Creatinine[5]	√	Monthly while on injectable Every 1-3 weeks in HIV-infected, diabetics and other high-risk patients		If indicated
	Potassium[5]	√	Monthly while on injectable Repeat if any ECG abnormalities develop while on Bdq or Dlm Every 1-3 weeks in HIV-infected, diabetics and other high-risk patients		If indicated
	Serum magnesium and calcium	If hypokalemia is present If on Bdq or Dlm	If hypokalaemia is present. Monthly if on Bdq or Dlm. Repeat if any ECG abnormalities develop		When indicated
	Liver enzymes (AST/SGPT, ALT/ SGOT) [2]	√	Monthly and as clinically indicated for DM	At least quarterly and as clinically indicated for DM	If clinically indicated
	Glucose	√	Monthly if elevated at baseline and if receiving Gfx		If indicated
	Thyroid-stimulating hormone (TSH) [3]	√	At months 3 and 6, if with Eto (with or without PAS), then if clinically indicated		
	Serum albumin	√	Every 2 months if on Dlm	When indicated	When indicated
	Serum Lipase/amylase	Special attention to patients receiving Bdq, Lzd, D4T, ddI or ddc, and based on risk factors			
	Lactic acid	When indicated	For work up of lactic acidosis in patients on Lzd and ART or Lzd and Metformin		
	HbsAg and anti-HCV	If risk factors are present			
	HIV	√	Repeat, if indicated	Repeat, if indicated	
	CD4 count (if HIV +)	√	According to National AIDS Program guidelines		
	Pregnancy test (for childbearing women)	√	Repeat, if indicated	Repeat, if indicated	

[1] ECG - ad hoc for suspected rhythm and conduction disturbances
[2] LFTs- Periodic monitoring (every 1-3 months) for patients on prolonged Z, and patients at risk of, or with symptoms of hepatitis. Monthly if HIV-positive, and if on Bdq. Monitor every 1-2 weeks for the first month, then every 1-4 weeks for patients with viral hepatitis. Discontinue suspected drug if LFTs are >3X the upper limit of normal LFTs, and 2X the upper limit of bilirubin.

ANNEX B – Programmatic indicators for aDSM (WHO Guidelines, 2014)

CLASS	IMPOR-TANCE	INDICATOR NUMBER AND NAME	CALCULATION	STRATIFICATION	EXPRESSED AS	DATA SOURCES	LEVEL	PERIOD OF ASSESSMENT	NOTES
Coverage (process)	Essential	1) Target RR/ MDR-TB patients included in cohort event monitoring	Numberator: Number of TB cases started on target treatment included in aDSM during the period of assessment. Denominator: Number of TB cases started on target treatment during the period of assessment and who were eligible for a aDSM.	None	Absolute numbers, proportion	Numberator: aDSM register. Denominator: Second-line TB treatment register.	National: NTP and national pharma covigilance centre (NPV)	3 months	To be computed durinng the period of recruitment but not in the post-treatment observation phase
Completeness (process)	Optional	2) Time to stopping target drug	The different in days between the date of start of treatment with a target drug and the date of the stopping the target drug. The calculation is done for each member of the cohort.	Reason for stopping	Number of patients included in the calculation; median interval and interquartile range in days	aDSM register	National: NTP & NPV	12 months	Stratify by reason for stopping (e.g. success, died, treatment failed, loss to follow up, exclusion criterion developing after start of treatment such as pregnancy).
Serious adverse events	Essential (but Stratifica-tion optitonal)	3) RR-/MDR-TB patients included in aDSM with any serious adverse event	Numberator: Number of TB cases included in aDSM during the period of assessment with one or more serious adverse events. Denominator: Number of TB cases included in aDSM during the period of assessment.	By organ group; by outcome	Absolute numbers, proportion	Numberator: aDSM register. Denominator: aDSM register.	NTP & NPV	3 months	To be computed during the period of patient recruitment and during the post treatment observation phase. Indicate outcome (deaths, hospitalisations, disability)

CLASS	IMPOR-TANCE	INDICATOR NUMBER AND NAME	CALCULATION	STRATIFICATION	EXPRESSED AS	DATA SOURCES	LEVEL	PERIOD OF ASSESSMENT	NOTES
Adverse reactions associated with target treatment	Optional	5) Time to development of ADRs associated with the target treatment	The difference in days between the date of start of the target treatment and the date of the first detected onset of the ADR attributed to it	By organ group	Number of ADRs included in the calculation; median interval and interquartile range in days	aDSM register	aDSM centre	6 months	To be computed during the period of patient recruitment and during the post-treatment observation phase. The calculation is done for each reaction attributed to the target treatment; the same patient may have several ADRs computed (the unit of measurement is the ADR and not the patients); if a particular ADR recurs in the same patient during the aDSM it is not calculated again. Only to be reported after causality assessment (e.g. dechallenge, rechallenge) suggests the target treatment as the causative agent (certain, probable or possible).

ANNEX C-MDR-TBTreatment Card (DR-TB Form 01) including new drugs, and new regimens

NATIONAL TUBERCULOSIS PROGRAMME

(DR-TB Form 01)

MDR-TB Treatment Card

Name: _____

Sex: ☐ M ☐ F

Age: _____ Date of birth: _____/_____/_____

Initial weight (kg): _____ Height (cm): _____

Site: ☐ Pulmonary ☐ Extra-pulmonary ☐ Both

If extra-pulmonary, specific site: _____

Address: _____

_____

_____

phone: _____

MDR-TB Initiation Center: _____

DC Site/Center: _____

Name of DOT Provider: _____

DOT Supervisor: _____

Date of X-pert Result : _____

No	Registration group
1	New
2	Non-converter ☐ IR ☐ RR
3	Treatment after loss to follow up ☐ IR ☐ RR
4	Treatment after failure of treatment ☐ IR ☐ RR
5	Relapse ☐ IR ☐ RR
6	Treatment after MDR-TB treatment 6.1 Standard Regimen ☐ LFU ☐ Failure ☐ Relapse 6.2 Other Regimen ☐ LFU ☐ Failure ☐ Relapse
7	Others (a. Unknown regimen/outcome of previously treated TB b. patient who does not fit in registration group 1-6)

HIV information
HIV testing done: ☐ Y ☐ N ☐ unknown
Date of test ___/___/____ Results:
Started on ART: ☐ Y ☐ N Date ___/___/____
Started on CPT: ☐ Y ☐ N Date ___/___/____

ART= antiretroviral therapy;

CPT = co-trimoxazole preventive therapy

Diabetes Mellitus	☐ Yes	☐ No

X-pert result:

N	I	T	RR	TI

N = No MTB, **I** = Invalid / No result, **T** = MTB detected, **RR** = Rif resistant,
TI = MTB (+)/but Rif resistant is invalid or No result

Date	S	H	R	E	PZA	Pto/Eto	Km/ Amk	Cm	Fq( )			

R=resistant, S=susceptible, C=contaminated

MDR TB registration number:_____

Date of registration: ___/___/____

Previous tuberculosis treatment episodes

Previous Township TB No./township	Start date (if unknown, put year)	Regimen (in drug abbre -viations)	Outcome

Used second-line drugs previously? ☐ Yes ☐ No

If yes, specify: _____

Drug abbreviations

First-line drugs

H= Isoniazid
R= Rifampicin
E= Ethambutol
Z= Pyrazinamide
S= Streptomycin
(Th= Thioacetazone)

Second-line drugs

Am= Amikacin
Cm= Capreomycin
Ipm = Imipenem
Mpm = Meropenem
Lfx= Levofloxacin
Mfx= Moxifloxacin
Eto= Ethionamide
Cs= Cycloserine
PAS = P-aminosalicylic Na
Bdq = Bedaquiline
Dlm = Delamanid
Lzd = Linezolid
Cfz = Clofazimine
Amx/Clv = Amoxicillin/Clavulanate

Standard Treatment Regimen

☐ 6-8 (Amk Z Lfx Eto Cs)/ 12-14 (Z Lfx Eto Cs)
☐ 6-8 (Amk Z Lfx Eto Cs PAS)/ 12-14 (Z Lfx Eto Cs PAS)
☐ Other Regimen
(Specify……..……)

Month No.	Sputum Smear Microscopy			Culture			Urea	Serum Creatinine	Liver Function Test				CP	Serum Uric Acid	TSH
	Date	Sample No.	Grading	Date	Sample No.	Grading			Bilirubin	Al Phos	AST	ALT			
Diagnosis															
1															
2															
3															
4															
5															
6															
7															
8															
9															
10															
11															
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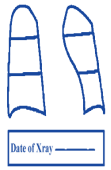
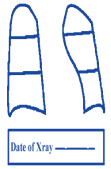
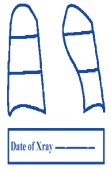
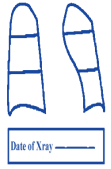
26															

CXR Results









Month No.	Date	Serum Electrolytes			Blood Sugar	Albumin	Lipase
		K^+	Mg^{++}	Ca^{++}			
Diagnosis							
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
21							
22							
23							
24							
25							
26							

Week No.	Date	ECG findings	QTc (ms)	Audiogram Findings	
				Rt Ear	Lt Ear
Diagnosis					
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
25					
26					

ADMINISTRATION OF DRUGS (one line per month):

Mth No.	mm-yy	Days																													Weight (kg)
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	
1																																	
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Mark in the boxes: √ = directly observed, N = not supervised, Ø = drugs not taken

MDR-TB REGIMEN (date treatment started and dosage (mg), frequency of dose, change of dosage, and cessation of drugs):

Date	H	Z	E	S/Am/ Cm	FQ( )	Eto	Cs	Lzd	Cfz	Bdq	Dlm	PAS	Imp/ Mpm	Amx/ Clv	Comments, SAE (Y/N)

(od = Once a day, bd = 12 hourly: morning and evening doses)

DR-TB Committee/ Panel Discussion and Decisions

Date	Issues and Discussion	Decision

Comments

Outcome (circle one)	Date
Cured	
Completed	
Failed	
Died	
Lost to follow up	
Not evaluated	
Moved to conventional Regimen	
Moved to individualized Regimen	

6th month Follow up after completion of treatment				
Date	Smear	Culture	CXR	Clinical
12th month Follow up after completion of treatment				
Date	Smear	Culture	CXR	Clinical
18th month Follow up after completion of treatment				
Date	Smear	Culture	CXR	Clinical
24th month Follow up after completion of treatment				
Date	Smear	Culture	CXR	Clinical

ANNEX D – NTP Form for Reporting Serious Adverse Event (SAE)

National Tuberculosis Program
Ministry of Health and Sports (MYANMAR)

Form for Reporting of Serious Adverse Event

Date of Report (/ /) **All dates must be filled in as (dd/mm/yyyy)**

Is this report a new event? Yes No Give date when initial SAE form sent (/ /)

Give date of follow-up SAE form last sent (/ /)

1. Patient Details

Full Name _____ Age (yrs) _____ Date of Birth (/ /)

pre/XDR/MDR -TB registration number _____ Sex M / F Is patient pregnant Yes No

Treatment Center _____ Weight (Kg) _____ Height (cm) _____ LMP (/ /)

Address and phone number

2. Details of Serious Adverse Event **Provisional Diagnosis** .....

Date Event Started - (/ /)

Description of Event

Why is the event considered serious?

◯ Death Life Threatening Hospitalization OR prolongation of hospitalization OR ICU/HDU

◯ Persistent/ Significant disability ◯ Congenital Abnormality Others (specify)……

3. Suspected Medicine (s)

Name (Generic name)	Total daily dose	Date started	Date stopped	Continues √

4. Action Taken	Responsible Drug	5. Outcome of Serious Adverse Event	Date
◯ **Medicine withdrawn**		◯ Recovered/ resolved	
◯ **Dose reduced**		◯ Recovering/ resolving	
◯ **Dose not changed**		◯ Recovered with sequelae	
◯ **Dose interupped**		◯ Not recovered/ not resolved	
◯ **Unknown**		◯ Died	
		◯ Unknown	

National Tuberculosis Program
Ministry of Health and Sports (MYANMAR)

6. Details of suspected drug	Drug 1	Drug 2	Drug 3
Brand Name (formulation/ dosage form)			
Generic Name			
Name of manufacturer, country of origin			
Batch No			
MM Reg: no			
Expiry Date			

7. Co-morbidities

◯ IHD Hypertension Other Heart Disease (specify)..... DM Renal disease

◯ Viral Hepatitis Alcoholic Hepatitis Other Liver Disease (specify)..... Peptic Ulcer/ Gastritis

◯ HIV Opportunistic Infection(s) (specify)..... Last CD4/VL & date .....

◯ Bronchial Asthma COPD Other Lung Disease (specify)..... Other (specify) .....

◯ None

8. Concomitant Medicine (s)

Name (Generic name)	Total daily dose	Date started	Date stopped	Continues √

9. Relevant Laboratory/ Investigation Results(s) - Clinical

Laboratory Test	Date done	Normal Value (unit)	Patient's result (unit)	Comment

10. SOURCE OF REPORT

Name of Reporter .....

Address .....

Designation ..... **email** .....

Signature ..... Date ..... Tel no. .....

Annex E - Severity grading scales and suggested action for common AEs

Severity grade	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life- threatening
1. Peripheral neuropathy **Possible anti-TB drug causes:** Lzd,Cs,H,S,Km,Cm,H,FQ,Pto/Eto,E. **Possible other causes:** d4T, ddI				
Paresthesia (Burning, tingling, etc.)	Mild discomfort; no treatment required; and/or BPNS (Brief Peripheral Neuropathy Screen) subjective sensory neuropathy score 1-3 on any side.	Moderate discomfort; non-narcotic analgesia required; and/or BPNS subjective sensory neuropathy score 4-6 on any side.	Severe discomfort; or narcotic analgesia required with symptomatic improvement; and/ or BPNS subjective sensory neuropathy score 7-10 on any side.	**Incapacitating; or not responsive to narcotic analgesia**
Action	Stop Cs and Lzd. If symptoms improve, consider restarting these drugs. Consider restarting Lzd at a lower dose (300 mg daily or 600 mg thrice weekly). If Cs is not essential to the regimen consider suspending the drug.	Stop Cs and Lzd. If symptoms improve, consider restarting Cs. Do not reintroduce Lzd. Provide symptomatic relief	Same as Grade 2.	**Same as Grade 2.**
2. Myelosuppression (anemia, thrombocytopenia, or neutropenia) **Possible anti-TB drug causes:** Lzd. **Possible other causes:** AZT, cotrimoxazole				
Anemia	10.5 - 9.5 g/dL	9.4 - 8.0 g/dL	7.9 - 6.5 g/dL	**< 6.5 g/dL**
Platelets decreased	75,000 – 99,999/mm³	50,000 – 74,999/mm³	20,000 – 49,999/mm³	**< 20,000 /mm³**
Absolute neutrophil count low	1500 - 1000/mm3	999 - 750/mm3	749 - 500/mm3	**<500/mm3**
Action	Monitor carefully, and consider reduction of dose of Lzd (300 mg daily or 600 mg thrice weekly).	Monitor carefully, and consider reduction of dose of Lzd (300mg daily or 600 mg thrice weekly); in case of Grade 2 neutropenia, stop Lzd immediately. In case of Grade 2 anemia, consider erythropoietin (EPO). Restart at reduced dose once toxicity has decreased to Grade 1.	Stop Lzd immediately. In case of Grade 3 anemia, consider EPO. Restart at reduced dose once toxicity has decreased to Grade 1.	**Stop Lzd immediately. Consider hemotransfusion or EPO. Restart at reduced dose once toxicity has decreased to Grade 1.**

Severity grade	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life- threatening
3. Prolonged QT interval **Possible anti-TB drug causes:** Cfz, Bdq, Mfx, Dlm, and Lfx (a mild QT prolonging drug) **Possible other causes:** Other drugs, e.g., erythromycin, clarithromycin, quinidine, ketoconazole, fluconazole, antipsychotics (all have some risk, including haloperidol, chlorpromazine and risperidone), many anti-nausea drugs (ondansetron/granisetron, domperidone), methadone, and some anti-retrovirals); genetic causes such as long QT syndrome; hypothyroidism				
Prolonged QTcF	QTcF 450 – 480 ms.	QTcF interval 481 – 500 ms.	QTcF>= 501 ms without signs/ symptoms of serious arrhythmia.	**QTcF>= 501 or >60 ms change from baseline and one of the following: Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia.**
Action	Monitor more closely; at least weekly ECG until QTcF has returned to less than grade1. Replete electrolytes as necessary.	Monitor more closely; at least weekly ECG until QTcF has returned to less than grade 1. Replete electrolytes as necessary.	Stop the suspected causative drug(s). Hospitalize and replete electrolytes as necessary.	**Stop the suspected causative drug(s). Hospitalize and replete electrolytes as necessary.**
4. Optic nerve disorder (optic neuritis) **Possible anti-TB drug causes:** Lzd,E,Eto/Pto,Cfz,rifabutin,H,S. **Possible other causes:** ddI				
Optic nerve disorder	Asymptomatic; clinical or diagnostic observations only	Limiting vision of the affected eye (20/40[6/12] or better)	Limiting vision in the affected eye (worse than 20/40[6/12] but better than 20/200[6/60])	**Blindness (20/200[6/60] or worse) in the affected eye**
Action	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart it.	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart it.	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart it.	**Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart it.**
5. Hepatitis **Possible anti-TB drug causes:** Z,Lzd,Cfz,Bdq. **Possible other causes:** unknown				
ALT (SGPT)	1.1 – 3.0 x upper limit of normal (ULN)	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	**>20.0 x ULN**
AST (SGOT)	1.1 – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	**>20.0 x ULN**
Action	Continue treatment regimen. Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.	Continue treatment regimen. Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.	Stop all drugs, including anti- TB drugs; measure LFTs weekly. Treatment may be reintroduced after toxicity is resolved.	**Stop all drugs, including anti-TB drugs; measure LFTs weekly. Treatment may be reintroduced after toxicity is resolved.**

Severity grade	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life- threatening
6. Acute kidney injury **Possible anti-TB drug causes:** S,Km,Am,Cm. **Possible ART causes:** Tenofovir (TDF)- rare				
Acute kidney Injury	Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0 x above baseline	Creatinine 2 - 3 x above baseline	Creatinine >3 x baseline or >4.0mg/dL; hospitalization indicated	**Life-threatening consequences; dialysis indicated**
Action	Consider stopping injectable until creatinine has returned to baseline. Consider restarting the injectable at lower frequency (e.g., MWF).	Stop injectable until creatinine has returned to baseline. Consider restarting the injectable at lower frequency (e.g., MWF) or substitute with a non-nephrotoxic drug.	Stop injectable until creatinine has returned to baseline. Consider restarting the injectable at lower frequency (e.g. MWF) or substitute with a non- nephrotoxic drug.	**Stop injectable until creatinine has returned to baseline. Consider restarting the injectable at lower frequency (e.g. MWF) or substitute with a non- nephrotoxic drug.**
7. Hypokalemia and hypomagnesemia **Possible anti-TB drug causes:** Cm,Km,Am,S. **Possible ART causes:** TDF(rare)				
Hypokalemia	3.4 - 3.0 mEq/L	2.9 - 2.5 mEq/L	2.4 - 2.0 mEq/L or intensive replacement therapy or hospitalization required	**< 2.0 mEq/L or abnormal potassium with paresis, ileus or life-threatening arrhythmia**
Action	Continue injectable. Start oral potassium replacement therapy. Check serum magnesium and replace if necessary.	Continue injectable. Start aggressive oral potassium replacement therapy. Replace magnesium as necessary.	Continue injectable. Start IV potassium replacement therapy in addition to oral. Replace magnesium and other electrolytes as necessary.	**Stop injectable temporarily. Start IV potassium replacement therapy in addition to oral. Replace magnesium and other electrolytes as necessary.**
Hypomagnesemia	0.60-0.70 mmol/L	0.45-0.59 mmol/L	0.30-0.44 mmol/L	**<0.30 mmol/L**
8. Hypothyroidism **Possible anti-TB drug causes:** Eto/Pto, PAS. **Possible ART causes:** d4T				
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting iADL (instrumental activities of daily living) *	Severe symptoms; limiting self-care ADL* hospitalization indicated	**Life-threatening consequences; urgent intervention indicated**
Action	Continue anti-TB drugs.	Continue anti-TB drugs. Start thyroxine.	Continue anti-TB drugs. Start thyroxine.	**Stop all anti-TB drugs. Start thyroxine.**

*https://www.payingforseniorcare.com/longtermcare/activities-of-daily-living.html#title2

Severity grade	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life- threatening
8. Hearing loss **Possible anti-TB drug causes:** S,Km,Am,Cm,Clr. **Possible other causes:** none.				
Hearing loss	Adult enrolled in monitoring program (on a 1,2,4,3,6 and 8 kHz audiogram): threshold shift of 15 - 25 dB averaged at 2 contiguous test frequencies in at least one ear or subjective change in the absence of a Grade 1 Threshold shift. Pediatric (on a 1, 2, 4,3, 6 and 8 kHz audiogram): threshold shift >20 dB at 8 kHz in at least one ear.	Adult enrolled in monitoring program (on a 1,2,3,4,6 and 8 kHz audiogram): threshold shift of >25 dB averaged at 2 contiguous test frequencies in at least one ear. Adult not enrolled in monitoring program: hearing loss but hearing aid or intervention not indicated; limiting instrumental ADL. Pediatric (on a 1,2,3,4,6 and 8 kHz audiogram): threshold shift >20 dB at 4 kHz and above in at least one ear.	Adult enrolled in monitoring program (on a 1,2,3,4,6 and 8 kHz audiogram): threshold shift of >25 dB averaged at 3 contiguous test frequencies in at least one ear; therapeutic intervention indicated. Adult Not enrolled in monitoring program: hearing loss with hearing aid or intervention indicated; limiting self-care ADL. Pediatric (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): hearing loss sufficient to indicate therapeutic intervention, including hearing aids): Threshold shift >20 dB at 3 kHz and above in at least one ear; additional speech-language related services indicated.	**Adults: profound bilateral hearing loss (Threshold >80 dB HL at 2 kHz and above); non-serviceable hearing** **Pediatric: audiologic indication for cochlear implant and additional speech-language related services indicated.**
Action	Continue injectable.	Consider decreasing injectable frequency if further hearing loss is a concern. Initiate discussion with patient about risks and benefits of the injectable. Consider replacing injectable agent with a non- ototoxic TB drug. Do NOT substitute a single drug replacement if the treatment is failing, add additional TB drugs.	Consider stopping or decreasing injectable frequency (e.g. MWF). Discuss with patient the risks and benefits of further injectable use. In most cases of Grade 3 hearing loss the injectable should be stopped and replaced with a non-ototoxic TB drug. Do NOT substitute a single drug replacement if the treatment is failing, add additional TB drugs.	**Consider continue injectable if tolerated by the patient. (In cases of complete hearing loss, some clinicians will continue the injectable agent as the damage is already done). Consider suspension of the injectable if ongoing use contributes to worsening tinnitus or vestibular disturbances (or if some hearing might be still preserved). Add additional TB drugs as needed.**

Source: End TB Clinical and Programmatic Guide for patient management with new TB drugs, ver 3.3, 25/11/2016, Partners in Health, IRD, MSF and UNITAID

WHO Classification grading scale for hearing loss

40dB Slight/Mild	41-60 dB Moderate	61-80 dB Severe	Over 81 dB Profound
Difficulty hearing and understanding soft speech, speech from a distance, or speech against a background of noise	Difficulty hearing regular speech, even at close distance.	May only hear very loud speech or loud sounds in the environment, such as a fire truck siren or a door slamming. Most conversation speech is not heard.	**May perceive loud sounds as vibrations**

In the case of moderate hearing loss, the range for children is 31-60 dB.


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TOT on Active Drug-safety Monitoring and Management (aDSM)

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