The National Pharmacovigilance System in Tanzania:

a situational analysis at the start of the PAVIA and PROFORMA projects

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Part 2a

Tuberculosis Public Health programme (for PAVIA)

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List of abbreviations used in Part 2a of the report

ADR	adverse drug reaction
aDSM	active Drug Safety Monitoring and Management
DR-TB	drug-resistant tuberculosis(meaning: needing second-line anti-tuberculosis drugs for treatment)
EAC	East African Community
ETL	Electronic TB and Leprosy register
GDF	Global Drug Facility
GFATM	Global Fund to combat AIDS, Tuberculosis and Malaria
IPAT	Indicator-based Pharmacovigilance Assessment Tool
MDR	multi-drug resistant
MoH	Ministry of Health
NLTP	National Tuberculosis and Leprosy Programme
PHP	public health programme
PMDT	programmatic management of drug-resistant tuberculosis
PV	pharmacovigilance
SAE	serious adverse event
SSA	sub-Saharan Africa
TFDA	Tanzanian Food and Drug Authority
TB	tuberculosis
WHO	World Health Organisation
XDR	extensively-drug resistant

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Reading guidance

This report is an Annex to the general baseline situational analysis report of Tanzania for PROFORMA and PAVIA (called Part 1) and presents data specifically for the national tuberculosis and leprosy programme (NTLP) and its direct partners (tuberculosis treatment initiation sites), as the PAVIA project will start its efforts in strengthening the national pharmacovigilance (PV) system with the tuberculosis programme.
Being an Annex to the general report (Part 1), it is advised to read this report in conjunction with Part 1. However, we have tried to write it in such way that it can be read and understood independently.

Part 2a was prepared by and for the PAVIA project.

1. Introduction

1.1. PAVIA (Pharmacovigilance Africa)

In order for countries in Sub-Saharan Africa (SSA) to have more effective drug safety reporting mechanisms for new products introduced and to gain a better understanding of their safety profiles, PAVIA envisions to strengthen the PV systems in four SSA countries: Ethiopia, Nigeria, Eswatini and Tanzania. PAVIA's objectives are:
I) To strengthen governance of Pharmacovigilance (PV) systems, by strengthening regulatory and organizational structures and defining clear roles and responsibilities for all stakeholders
II) To improve efficiency and effectiveness of national surveillance systems, by strengthening active (sentinel) surveillance of adverse drug reactions and implementation of tools and technologies for their detection, reporting, analysis and dissemination
III) To build capacity and skills to sufficiently conduct safety-monitoring activities throughout the country
IV) To improve readiness of health systems within SSA, by improving performance assessment of PV systems allowing identification of enablers and barriers for implementation

PAVIA's strategy is to strengthen national PV systems in a collaborative effort with Public Health Programs (PHPs), building up medicines safety surveillance activities in the context of the introduction of new drugs for multi-drug resistant-tuberculosis (MDR-TB). Capacity at the national PV Centre/ national medicines regulatory authority will be built gradually taking the PV activities for TB as the "building and training ground" for a generic PV system including data collection, database entry, data analysis, signal identification and causality assessment. The results and lessons learned will be transferred by PAVIA to the PHP for HIV and malaria. Combined with identified enablers and barriers in addressing regional differences and needs, a blueprint will be developed that can guide other countries in strengthening their PV systems.

1.2. Pharmacovigilance

As explained in Part 1 of this report, PV as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems."[1]
There are several forms of pharmacovigilance monitoring, ranging from full cohort event monitoring, where all adverse events are systematically reported for a certain type of event, drug, or patient population for a limited number or patient and a limited time period, to targeted spontaneous reporting (soliciting reports for special adverse drug reactions(ADRs), or special patient groups) and spontaneous reporting (in which health care providers are encouraged to report any suspected ADR voluntarily). A special and new form of PV is aDSM for patients with drug-resistant (DR) forms of tuberculosis.

[1]WHO 2009, The importance of pharmacovigilance. Safety monitoring of medicinal products. Geneva.

1.3. TB / aDSM

Since 2013, after introduction of two new TB drugs (bedaquilline and delamanid), WHO recommends active TB-drug safety monitoring and management (aDSM) when using one of these drugs. aDSM is defined as the active and systematic clinical and laboratory assessment of patients on treatment with new TB drugs (part of which have not yet received full approval from international Food & Drug/Medicinal Authorities), novel MDR-TB regimens or extensively drug-resistant (XDR)-TB regimens to detect, manage and report suspected or confirmed adverse drug reactions. The overall objectives of aDSM are to reduce risks from drug-related harms in patients on treatment for drug-resistant TB and to generate data to inform future policy updates on the use of such medicines. aDSM is seen as an active and systematic way of patient monitoring to be incorporated in the programmatic management of patient with DR-TB. The WHO presents three different aDSM packages: in the core package, only serious adverse events (SAE) are to be reported. In the intermediate package, apart from the serious adverse events, also adverse events of special interest should be reported, and the advanced package targets all adverse events of clinical interest. Full cohort event monitoringis not deemed feasible for routine monitoring of DR-TB patients.

1.4. Treatment of drug-resistant tuberculosis and aDSM in Tanzania

The National PMDT technical working group (TWG), consisting of representatives from the NTLP and the DR-TB treatment sites, established a plan for the implementation of new drugs and regimens in June 2016. The plan includes a section on aDSM and was further refined following recommendations from focal persons at TFDA, the Central Tuberculosis Referral Laboratory (CTRL), the National Institute of Medical Research (NIMR), physicians of Muhimbili and Kibong'oto hospitals and international experts. Tanzania started to roll out the shorter DR-TB treatment regimen on the 22nd of January, 2018. In the first half year of 2018, 104 patients have been enrolled on the shorter treatment regimen (STR). Bedaquiline and delamanid were introduced in November 2017. Till end June 2018, five patients were initiated on these new drugs from the start (4 on bedaquiline-containing regimens and 1 on a regimen containing delamanid) and 20 DR-TB patients were shifted from other regimens to bedaquiline-containing regimens, mainly because of ototoxicity. Thus, in total, till the end of June 2018, there were 25 patients on regimens containing new drugs.

Currently, there are 75 DR-TB treatment facilities in the country, of which 45 are covered with all diagnostic resources for treatment monitoring; scale-up to include all 75 facilities was planned to conclude by the end of 2018, but due to funding issues, this deadline was not achieved (information of February 2019). All these 75 sites are treatment initiation sites. Once treatment is successfully initiated, patients are transferred to in- or outpatient facilities (depending on their condition) closer to their homes.

In July 2017, a pilot was done for aDSM in 9 DR-TB facilities. The pilot was gradually expanded through appointing regional aDSM focal persons. The regions covered so far are Kilimanjaro, Arusha, Tanga, Mbeya, Dar es salaam, Zanzibar, and Mwanza. Over 60% of the DR-TB treatment facilities are located in these regions. However, so far aDSM reports have been received from around 20 health facilities only. About 60% of DR-TB patients is being prescribed the STR while the other 40% is receiving individualized regimens. The STR is being rolled out to all DR-TB facilities in the country.

The Tanzanian Programme for the Management of Drug-resistant TB (PMDT) does achieve good treatment outcomes, with low loss-to-follow-up (<6% in 2015). This is achieved by paying much attention to patient counselling and education, provision of transportation allowances and stipends, training health care workers involved in DR-TB treatment, and the provision of free-of-charge laboratory tests needed for the monitoring of treatment including

adverse events. Patients are supposed to visit the clinic monthly. During such visits, monthly follow-up forms are being used, on which adverse events can be filled. Those patients who do not attend clinic visit are being followed by coordinators through phone or physical visit. However, adverse events are only reported by clinicians/aDSM committees during the monthly follow-up visits. This may result in both under- and overreporting of adverse events, e.g. if a patient forgets to mention an adverse event for which he/she sought treatment closer to his/her home, or if he/she reports the event and the event is being reported both through the aDSM and the passive system (Figure 1).
Tanzania has chosen to implement the intermediate aDSM package (see paragraph 4.3.1) for all patients receiving DR-TB treatment. So far, however, only part of the DR-TB treatment facilities do participate in aDSM; facilities that have not yet been trained do not report any adverse event through the aDSM system. Due to lack of funding, training of PV focal persons in DR-TB treatment sites has stopped. It is the plan to use TB ECHO for training purposes. TB-ECHO, started in August 2017, it is a learning network that connects DR-TB treatment sites using the Zoom platform (University of New Mexico, USA). The account is paid for by Challenge TB/KNCV. Trainings are provided by KNCV and staff from the National TB hospital Kibong'oto; and adverse events are being discussed.

2. Aim and objectives of the situational analysis

The aims and objectives of the situational analysis have been presented in detail in Part 1 of this report: to get a good understanding about the strengths and weaknesses of the current PV system in Tanzania, as well as to get a good understanding on training needs that can be addressed by the PAVIA project.

Part 2a of this report presents the situational analysis of the various aspects and needs of the PV systems regarding TB/aDSM at the start of the PAVIA project, including its strengths and gaps. Findings from this analysis will be used for developing a national PV roadmap, defining the steps needed and the desired 'end state' per country. A final assessment will be conducted at the end of the PAVIA project period, using the same methodologies as in the baseline situational analysis. The situation will be compared against the anticipated 'end state'. Lessons learned on how the true 'end state' was achieved will be defined, including how challenges were addressed and best practices identified. Also, challenges encountered that could not be overcome will be analysed for potential alternative approaches to address those in the future and in other settings. Lessons learned within PAVIA will be packaged in a practical blueprint for use in other SSA countries.

3. Methodology and team

3.1. Assessment strategy

A special PV indicator scoring form with standardized PV indicators was used to assess the integration of PV-related activities in the NTLP of Tanzania (see paragraph 3.2). This assessment was supplemented with interviews with key stakeholders from the NTP and key staff (clinicians, nurses, and pharmacists) of 14 of the health facilities which are now implementing new TB drugs and regimens to gain more insight into the current level of

implementation of aDSM/PV in the TB program, to ascertain training needs, and get recommendations for the future from these key stakeholders.

3.2. PV indicator assessment tool

The PHP indicator tool was based on a modified questionnaire developed and already used by the East African Community (EAC) which is based on the Indicator-based Pharmacovigilance Assessment Tool (IPAT)[2] and the WHO PV indicators[3]. The following elements were addressed: health system, policies, laws and financing, PV processes, capacity and infrastructure including training needs, stakeholder environment and communication/ dissemination opportunities. The indicator list for the PHP consists of 20 indicators addressing components two to five. The indicators tool for the NTP is attached as Annex 1.

3.3. Assessment team

The assessment was conducted by a team consisting of national staff and international consultants. See Part 1 of this report for a full overview.

3.4. Documents reviewed

For the NTLP, the following documents were reviewed:

- Annual operational plan of NTLP (2018)
- Guidelines for Management of Multi-Drug Resistant TB in Tanzania (2nd edition; 2018)
- aDSM roadmap (2018)
- DR-TB Training on aDSM: Facilitator's and Participant's Manual (drafted in 2018, published in 2019)
- aDSM SOP (as included in Training Manuals)
- aDSM form (as included in Training Manuals)

3.5. Sites assessed and stakeholders interviewed

The DR-TB wards and the pharmacy/PV unit were visited and assessed in each health facility included in the assessment, to assess the functioning of both aDSM specifically and of pharmacovigilance in general. SevenDR-TB facilities were visited during the week that the international team was in Tanzania:

- Amana hospital*
- Hindu Mandal hospital
- Mbagala Rangi Tatu hospital*
- Temeke Hospital*
- Vijibwemi dispensary

[2] Strengthening Pharmaceutical Systems (SPS) Program. 2009. *Indicator-Based Pharmacovigilance Assessment Tool: Manual for Conducting Assessments in Developing Countries*. Submitted to the U.S. Agency for International Development by the SPS Program. Arlington, VA: Management Sciences for Health.

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

- Sinza health centre*
- Mwananyamala hospital*

Additionally, seven other DR-TB facilities were visited after this week by a local team:

- Bagamoyo district hospital*
- Baobab dispensary
- Kerege health centre
- Kisarawe district hospital
- Mapinga dispensary
- Mkoani health centre
- Tumbi hospital

Six of the fourteen facilities visited have implemented aDSM, which is indicated by the *. The NTLP was also visited during the assessment (Annex 1).

3.6. Analysis of the indicator tool and interviews

All results are presented in Chapter 4 of this report.

3.7. Limitations

By the time the baseline assessment was conducted, there are 75 health facilities for DR-TB treatment in the country. In the current assessment, however, only 14 TB treatment facilities were visited and assessed (see paragraph 1.4). These may not represent the full spectrum of health care services offered in the country regarding DR-TB management. However, the team does believe that for (DR-)TB, sufficient information was collected to get a broad understanding of the issues regarding PV in Tanzania.

4.Results

4.1. Policy, law and regulations

The assessment tool did not contain any indicators in this area for PHPs. Indicators in this area are presented in Part 1 of this report.

4.2. Systems, structure and stakeholder coordination

In this area, six indicators were assessed at the level of the PHPs (Annex1).

4.2.1. Pharmacovigilance in the National TB Strategic Plan

Pharmacovigilance activities are included in the annual operational plan and there is budget allocated to these activities. There is a national aDSM committee that was officially appointed by the Ministry of Health. This national aDSM committee hosts representatives of NTLP with a background in PMDT and/or pharmacy, Kibong'oto Infectious Diseases Hospital, MSD, and TFDA, as well as the data manager of CTRL, the PV officer of PAVIA, and the technical officer

for PMDT of KNCV. The committee meets quarterly. The regional PV focal persons are expected to disseminate the information they receive in the national aDSM committee meetings to health care workers in their region. However, it is not clear to what extent they really do this.
The national TB treatment guidelines include PV, and evidence on safety data was considered when developing these guidelines.

4.2.2. National budget for PV tasks

The government allocates budget to the National TB Programme and the Programme itself divides the budget to its different activities. All budget for pharmacovigilance is available from external sources, namely the Global Fund to combat AIDS, tuberculosis and malaria (GFATM) and USAID (via the Challenge TB project),for a total of 842 million Tanzanian shilling (approx. 368,000 USD).

4.2.3. Pharmacovigilance training

The NTLP, with assistance from KNCV funded by USAID's Challenge TB project, has developed a 5-day aDSM training module for health care workers. The training materials include a manual for facilitators and for trainees (health care workers). Trainings-of-trainers are currently being conducted. Since July 2017 until June 2018, two trainings on aDSM have been given by NTLP staff, TB clinicians and PV staff. In total, 100 healthcare workers have been trained, including clinicians, pharmacists, lab personnel and nurses. NTLP staff has had training themselves but they feel that they need more training on causality assessment and signal generation, as well as on database management.
Out of the fourteen TB treatment facilities assessed, 8 had some staff that had received training on aDSM/PV. Most of the trained personnel were clinicians and pharmacists, but some nurses were also included. The number of trained people is not determined by the size of the facility.
Currently, aDSM activities are not supported by supportive supervision visits organized jointly by TFDA and NTLP.

4.2.4. Mechanisms to disseminate PV information

There is a TB program website (www.ntlp.go.tz) where PV data will be published once generated. There is also an aDSM WhatsApp group which is currently used for planning of meetings, sharing the minutes of these meetings and for dissemination of PV information.
The NTLP plans to include a PV component in the upcoming annual report.

4.3. Signal generation and data management

4.3.1. aDSM: data collection and reporting, data flow and management

Tanzania has adopted the aDSM intermediate package for all its DR-TB patients; i.e., health care providers treating DR-TB patients are supposed to report all SAEs and adverse events that have been pre-specified by the WHO as being of special interest[4].
The flow of information on adverse events is shown in Figure 1. NTLP has its own aDSM reporting form for MDR-TB treatment (Figure 2).

[4] These are 13 (groups of) AE that the WHO in its aDSM guidance document recommends to be reported if the "intermediate" aDSM package is chosen by the country. See: WHO, 2014. Active tuberculosis drug-safety monitoring and management (aDSM): Framework for implementation. Report no. WHO/HTM/TB/2015.28 Geneva: WHO. Available at: http://apps.who.int/iris/bitstream/handle/10665/204465/WHO_HTM_TB_2015.28_eng.pdf;jsessionid=212BF76DC2655FB575819CFBF1A50D89?sequence=1

Patients are supposed to visit the clinic monthly. During such visits, monthly follow-up forms are being used, on which adverse events can be filled. Patients visiting the clinic in-between their routine monthly follow-up visits are being attended based on their needs and as per medical practice. On such occasions, any information regarding adverse events is noted in their patient file. Those patients who do not attend clinic visit are being followed by coordinators through phone or physical visit. The patient is expected to report him/herself to the health facility's aDSM team in case of adverse events. The aDSM team of the facility consists of the laboratory manager, the chief pharmacist, the DOT nurse, and the treating DR-TB clinician, and is headed by the latter.

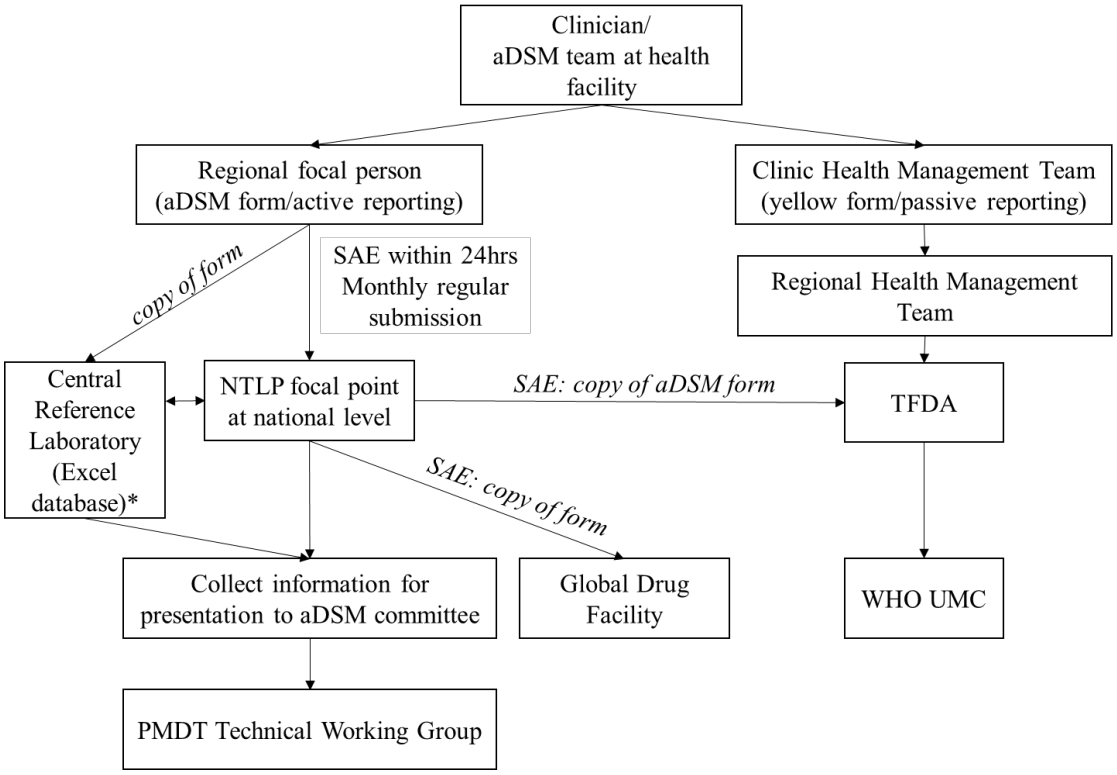

*Figure 1. Flow of information on adverse events from health care providers to the national PV centre (TFDA) and the Uppsala Monitoring Centre.**

* abbreviations used in this figure: aDSM: active drug safety management; SAE: serious adverse event; NTLP: National tuberculosis and leprosy programme; PMDT: programmatic management of drug-resistant TB; TFDA: Tanzanian Food and Drug Authority; UMC: Uppsala Monitoring Centre.

When TB treating clinicians suspect an adverse event that qualifies for reporting, they are supposed to fill out both the aDSM form as well as the yellow form. The first form is submitted to the Regional Focal Persons, who check the form and forward it to a data manager at the CTRL. Also, the Regional Focal Persons make a list of monthly treatment follow-up forms received and forward this list on a monthly basis to the data manager at CTRL. In case of an SAE, direct notice is being made to the NTLP focal person. The data manager at the CTRL compiles all data in a central Excel file. The CTRL data manager communicates directly with the NTLP focal person and reviews the data with the National aDSM Committee, of which the NTLP focal person is a member, each quarter. The aDSM committee discusses any important signals with the National PMDT Technical Working Group.

The yellow form is submitted to TFDA through their routine reporting channels, presented in Part 1 of this report (Figure 1).Following the aDSM guidance, DR-TB clinics' aDSM teams are supposed to actively report adverse events that should be reported under the intermediate package on aDSM forms to the NTLP while any other adverse event can be reported on

yellow forms if the clinician whishes so, but is not actively solicited. For serious adverse events, a copy of the form is sent to TFDA by the NTP focal person, to fulfill the legal obligation to report all SAEs to the TFDA.

Ministry of Health Community Development Gender Elderly and Children (MOHCGEC)
National Tuberculosis and Leprosy Programme
DRUG RESISTANT TB (DR-TB) aDSM FORM

The information collected will be kept confidentially

Patient name Initials: _____(Three) Treatment site_____

Birth Date___/___/_____ Sex ___ (M/F) DR-TB Reg. No. _____

Hospital File No.: _____Location (Patient address) _____Treatment Mo. _____

PREGNANCY ☐ YES ☐ NO ☐ N/A HEIGHT (cm) ☐ WEIGHT (kg) ☐

SAE or AE of special interest	☐ SAE ☐ AE of special interest

Serious adverse event(s) information		**SAE1**	**SAE2**	**SAE3**
Adverse event term				
Description of Adverse event				
Event onset date (*dd/mm/yyyy*)		____/____/_____	____/____/_____	____/____/_____
Event end date (*dd/mm/yyyy*)		____/____/_____	____/____/_____	____/____/_____
Duration if <1 day (*hrs/min*)		____/____	____/____	____/____
If SAE, seriousness category	**Death**	☐ *In case of death:* Death date: ____/____/_____ Autopsy: Yes ☐ No ☐	☐ *In case of death:* Death date: ____/____/_____ Autopsy: Yes ☐ No ☐	☐ *In case of death:* Death date: ____/____/_____ Autopsy: Yes ☐ No ☐
	Life-threatening	☐	☐	☐
	Hospitalization	Required ☐	Required ☐	Required ☐

Figure 2. aDSM reporting form.

4.3.2. Reporting tools

Currently, there is double reporting done by health care facilities; health care professionals are supposed to fill in:

- The aDSM form for NTLP (Figure 2) in case any adverse event arises that is reportable under aDSM; and
- The yellow form for TFDA for any adverse event

To reduce double reporting, TFDA and NTLP are discussing if the aDSM form could be used as the only reporting tool for adverse events from DR-TB facilities collecting such information. If possible, only electronic forms will be used in future.

The NTLP has agreed with the Global Drug Facility (GDF) that the aDSM form developed and used by NTLP can be used forfor reporting SAEs occurring in patients receiving bedaquiline or delamanid. Hereto, a copy of the form is submitted to GDF by the NTLP focal person for PV.

For MDR-TB treatment, a web-based adverse event reporting form (aDSM form) has been developed, which is coupled to a central database. However, the database is not yet functional and there is no connectivity with the TFDA database. Currently the regional PV focal persons enter data in an Excel database and send it to a data manager dedicated to the aDSM database, based at the CTRL. Possibilities for an improved database and automatic connectivity with the TFDA database will be explored by TFDA and NTLP in 2019. During the national aDSM meeting in August 2018, it was suggested to include adverse event information in the electronic patient file (Electronic TB register, ETL, available online to all clinicians treating patients with DR-TB) and extract the relevant information automatically to the TFDA database. This is indeed planned. However, in a recent meeting, TFDA and NTLP have agreed that the national aDSM database will be integrated into the electronic system of TFDA. The data entered in this integrated system will be accessible to both TFDA and NTP (using an online submission system – see above). An official request for this has already been sent to Ministry of Health (MoH).

4.4. Risk assessment and evaluation

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

4.4.1. Reporting of adverse events

The flow of data on adverse events has been explained in paragraph 4.3.1 and in Figure 1. From July 2017 – June 2018, NTLP received 114 reports of suspected adverse drug reactions from approximately 500 patients on DR-TB treatment[5], including 14 SAEs. These reports have been compiled in the KNCV/CTB report and the raw data have been entered in the national aDSM database.

There were no suspected quality issues reported, neither any reports on therapeutic ineffectiveness.

No active surveillance studies on TB drugs were performed in the past 3 years.

[5] The exact number of patients on treatment in this period was not available. Therefore, a rough estimation was made using the following information: Until 2018, DR-TB patients received 22-24 months of treatment, meaning that between July 2017 and June 2018, patients who started their DR-TB treatment in the second half of 2015, in 2016 and 2017, and in the first half of 2018, should still be receiving treatment if they had not did, got lost to follow-up, or failed treatment earlier. In 2015, 123 patients were put on DR-TB treatment, in 2016, 158, in 2017, 167 (data from WHO Global Burden of Tuberculosis reports, 2016-2018), and in 2018, 407 patients were starting DR-TB treatment (data through D. Lyakurwa, KNCV Tuberculosis Foundation, Tanzania). The treatment success rate for the cohort started in 2015 was 74% (data WHO Global Burden of Tuberculosis Report, 2018). The following formula was used for the estimation: $(N_{2015}/2)*0.74+N_{2016}*0.74+N_{2017}*0.74+N_{2018}/2=490$.

NTLP and TFDA so far have not communicated on risk management plans.

4.4.2. Reporting and feedback

All reports received were entered into the Excel file at the CTRL.
The procedure at TFDA has been described in Part 1 in this report. The focal point at NTLP does not send an acknowledgement of receipt to the reporters, but sometimes asks for additional information. Regional PV coordinators take part in the quarterly PV team reviews and are supposed to provide feedback on the reports to the reporters. It is not clear if this is really done.

4.4.3. Data analysis and causality assessment

Causality assessment is currently done by the National aDSM committee during quarterly meetings. Recently, it was agreed between NTLP and TFDA that TFDA will take the lead in causality assessment and be represented in all National aDSM Committee meetings. NTLP is responsible for organizing the meetings. Thus far, two meetings have been held (in July and September 2018) and five SAE of the total of seven SAE and 24 adverse events of special interest were discussed. Causality assessment was done for all five of these SAEs; four were possibly associated with kanamycin and one was probably related to pyrazinamide. If needed, the reporter of the adverse event is contacted to obtain additional information.

4.5 Risk management and communication

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

4.5.1. Management of adverse events of DR-TB patients

Most of the visited health care facilities have a Drugs and Therapeutic Committee, as per legal requirement, comprised of a Pharmacist, Heads of the Departments, the Medical officer in charge, Health Secretary in charge, and other relevant staff. At two DR-TB facilities, the Committee conducts regular meetings (monthly, quarterly). However, discussions focus on drug supply chain management (stock-outs, expiry), not on pharmacovigilance. For other facilities the committee does exist on paper, but has never met.
As per national protocol, monthly monitoring of DR-TB patients for treatment response and occurrence of adverse events is conducted at each DR-TB treatment site for the duration of treatment. During such visits, patients receive clinical, bacteriological and laboratory monitoring services. However, a monitoring mission by PMDT consultants of KNCV conducted just before the baseline assessment was started, indicates that clinical management of major adverse events, particularly nephrotoxicity and ototoxicity, was insufficient. Abnormal creatinine clearance was not picked up by clinicians, leading to further deterioration of renal function, profound hearing loss and hepatotoxicity. QT correction was not yet done properly, as staff training on this had just commenced.
Indeed, equipment to conduct monitoring for possible adverse events is not always available, from the 7 health facilities visited during the assessment mission, one facility had no equipment and one facility had only equipment for audiometry available, but not an ECG machine, and of the total of 14 visited DR-TB treatment facilities, ECG and audiometric equipment were only available in 6 (Annex 2), four of which have started implementing aDSM. One of these latter hospitals had only audiometry equipment available. One of the biggest challenges with ECG is the purchasing of ECG paper, which is not budgeted for by the hospital administration, nor by the funders (Global Fund for 10 sites, Challenge TB for 20 sites) that have donated the ECG machines. This has resulted in paper stock-outs. Monitoring tests and ancillary drugs to treat adverse events are usually provided free of charge for MDR-TB patients, but one of the facilities reported to charge patients for the both

the laboratory tests and ancillary treatment. Also in some sites, staff indicated that if any stock-outs in ancillary drugs occurred, the patients were requested to buy these drugs themselves elsewhere.
Until April 2018, patient coordinators had little understanding about the detection and management of adverse events, and necessary laboratory tests were often not available to detect some adverse events (e.g. increases in liver enzyme concentrations, increased QT-interval) timely. Due to a recent increase in attention to the detection and management of adverse events (following training of health care providers/patient coordinators), screening for adverse events has much improved, which is reflected in data from Dar es Salaam, where 60% of the country's TB patients are being managed.

4.5.2. Risk management

Even though most clinicians detect and treat the patient for adverse events, and ancillary drugs are provided for free, there is no routine of documenting and transmitting suspected ADRs to the PV centre. This is partly due to limited awareness of health care providers about the importance of reporting, lack of awareness about what type of adverse events should be reported and work overload. In spite of this, all health care providers interviewed agreed that aDSM contributes to improved patient care and thought it is time saving if the form is integrated to TFDA system of reporting so that they don't have to report twice.

4.5.3. Signal detection

So far, no signal or significant safety issues have been identified by the National aDSM committee. Up till now AE information is not routinely included in any newsletter(from NTLP, nor from TFDA) or other publication.
Though health care providers in the clinics visited reported that many medicine safety requests have come in by phone, the exact number remains unclear since no documentation is hold.

4.5.4. Communication

Fourteen health facilities caring for (DR) TB patients were visited during the assessment. Six of these are implementing aDSM. Some provide information on pharmacovigilance during morning clinical meetings and reported to educate patients in the TB clinic and when dispensing medicines. From only one facility, it was reported that both the patient and his/her relatives are trained on PV aspects (Annex 2).
No public or community education activities relating to medicine safety have been carried out.
Hospital pharmacies do receive and respond to medicine safety requests, but most pharmacies do not record these requests.

5.Recommendations and next steps

5.1. Respondents' recommendations

- Communication between NTLP and TFDA needs to be reinforced.
- The aDSM system and the TFDA electronic reporting system for ADR should be harmonized to share one common database. In a recent meeting with TFDA it was

decided that they will manage the national aDSM database (online submission). An official request has already been sent to MoH. TFDA will also take the lead in causality assessment and be present in the aDSM committee meetings.

- NTLP members should receive training on causality assessment and signal detection from TFDA

5.2. Visiting team's recommendations

Systems, structure and stakeholder coordination

- Communication between NTLP and TFDA should be reinforced, which can be done through regular meetings. The different roles and responsibilities (*e.g.* re. causality assessment) should be clearly described. It is recommended to perform joint supportive supervision visits (representatives from both NTLP and TFDA) to evaluate and support aDSM activities.

- It is important to make sure that at each health facility at least one health care worker is trained on aDSM, who could then train the other staff.

Signal generation and data management

- There should be one reporting tool instead of two for reporting adverse events, to decrease workload for healthcare workers.

- It is recommended to use an electronic database for capturing aDSM data, which preferably can be filled by the staff in the health facilities. Best option might be to add the information on adverse events in the already existing ETL database. Ideally, this electronic database should have an automatic linkage function to the TFDA database (Vigiflow) so that relevant reports can be automatically submitted to TFDA.

Risk assessment and evaluation

- It is important to increase awareness of AE reporting, to make sure all DR-TB facilities report their AE. Training of health care workers on PV reporting could assist in this, as well as feedback on AE reporting. Progressive and all-round training is needed for health care workers especially on what should be included in PV reporting.

Risk management and communication

- All DR-TB facilities should have the necessary equipment for patient monitoring. Detection and management of AE have improved in 2018 following training, and this process should be strengthened further. Also, clear guidelines on follow-up of patients who do not come for their monthly check-up are needed.

5.3. Next steps

After approval of this report by the Director General of TFDA, it will be disseminated to all key stakeholders. A stakeholder meeting to discuss the findings of this report and draft a PV strategic plan took already place before finalization of this report. However relevant information from this report was used as input during the stakeholders meeting.
TFDA and NTLP will meet and discuss the dataflow of adverse event reporting, harmonization of the adverse event reporting system and define responsibilities in causality assessment. These discussions should lead to a customized and clear aDSM guideline that outlines the time frame for aDSM and the roles and responsibilities of key stakeholders in aDSM, in which

reporting is efficiently and effectively organized for the reporters, the NTLP and the TFDA. Training plans include a training on causality assessment for NTLP staff and continued training on aDSM for healthcare workers (patient management, adverse event reporting).

Annex 1. PHP assessment tool

Indicator #	Indicator	Assessment Questions	Answer	Notes & additional comments	Information source
Component 2. Systems, Structures, and Stakeholder Coordination					
P2.1	PV activities included within the strategic and/or annual operational plans of PHPs	Are PV activities included within the strategic and/or annual operational plans of public health programs?	Yes	Included in annual operational plan. Also in global fund plan 2017-2022 (cannot be shared because salaries are also in there, has been translated in annual plan).	Annual operational plan
P2.2	Existence of a dedicated financial provision or statutory budget for the PHPs	Is there an annual budgetary allocation for PV activities for the PHP?	Yes	Global fund and KNCV	
		In the last fiscal year, how many funds were allocated by the MOH and donors for PV activities? *Please enter the amount and specify the currency*	842 mil	Tsh	
P2.3	Existence of a mechanism to disseminate PV information (including one or more of the following: newsletters, information bulletin, website or phone line for dissemination of pharmacovigilance information)	Is there a mechanism in place to disseminate PV information?	Yes	aDSM committee (national NTP team + regional PV focal persons) meets every quarter. Feedback to health care workers by PV focal persons, needs to be refined	
		Is there a newsletter or information bulletin for dissemination of PV information?	No	Looking forward to have a pharmacovigilance component in the annual TB report from next year	
		Is there a website for dissemination of PV information?	Yes	TB program website, if there is PV data it will be published here	www.ntlp.go.tz
		Is there a publicly advertised phone line to receive and provide medicine safety and PV information?	NO	they want to be linked to TFDA phone line	
		Is there another mechanism for dissemination of PV information? *Please describe the mechanism*	NO	aDSMwhatsapp group for organizing meetings and sharing minutes between the national team and focal point *currently not for sharing PV information*	
P2.4	Number of healthcare workers trained in pharmacovigilance in the previous calendar year through in-service training	How many healthcare workers has the center/program trained on PV in the previous calendar year (through **in-service** training)?	100	2 trainings with 50 people	
		- Clinicians / nurses		multidisciplinary training involving clinicians, pharmacists, some nurses etc	
		- Community health workers	0		
		How many training events/sessions were conducted in the previous calendar year?	2	training provided by NTLP, they have had some training themselves but feel they have a knowledge gap,not trained on all parts of aDSM, e.g. causality assessment and signal detection; database training	

P2.5	National treatment guidelines or protocols in use within the public health programs that consider pharmacovigilance	Who provided the training? PHP staff? PV staff? Joint training? What type of training was used Do the treatment guidelines or protocols in use in the PHP provide instruction for PV activities?	joint training, NTLP, TB clinicians, PV staff In class training Yes	NTLP TB treatment guidelines 2018 (2nd edition)	
P2.6	Evidence of consideration of safety data when developing and updating standard treatment guidelines or treatment policies	When developing standard treatment guidelines is evidence on safety data being described and taken into consideration?	Yes		
Component 3. Signal Generation and Data Management					
P3.1	PHPs use the national, standard ADR/AE reporting form	Does the PHP use the national, standard ADR/AE reporting form? *Request a copy of all existing reporting forms.*	Yes	aDSM form is used, HCW in MDR-TB fills in yellow form as well	
Component 4. Risk Assessment and Evaluation					
P4.1	Number and percentage of ADR/AE reports received by PHPs that were submitted to the national PV center in the previous calendar year	What is the number of AE reports received by the PHP in the previous calendar year?	114	Only covers the enrolled sites (July 2017 - June 2018)	
		What is the number of AE reports submitted by the PHP to the national PV center in the previous calendar year?	NA	all HCW also fill in yellow form which goes to PV center	
P4.2	Total number of ADR reports per 1000 individuals exposed to medicines in the PHP in the previous calendar year.	How many individuals received medicines under the PHP in question during the previous year?	500	estimate for July 2017 up to June 2018 including the patients administered with new drugs and shorter regimens (see footnote 5, paragraph 4.4.1)	
		How many ADR reports were received, referring to the exposed population?	NA	Database not able to specify in DR-TB, DS-TB, short regimen etc.	
P4.4	Number of suspected product quality issues detected through public health programs	What is the number of suspected product quality issues detected through the PHP in the previous calendar year?	0		
P4.5	Number of reports on therapeutic ineffectiveness in the previous year	What is the number of reports on therapeutic ineffectiveness received by the PHP in the previous calendar year?	0		
P4.6	Number of medicine-related hospital admissions per 1000 individuals exposed to medicines in the PHP in the previous year	What is the number of medicine-related hospital admissions of individuals exposed to medicines in the PHP in the previous year?	1	Between July 2017 and June 2018, based on number of SAEs leading to hospitalization.	
P4.7	Number of active surveillance activities initiated, ongoing or	How many active surveillance studies have been conducted in the last three years (36 months)?	0		

	completed during the past three years	Indicate what type (e.g. cohort event monitoring, targeted spontaneous reporting, etc.) and stage of completion (e.g. initiated, on-going or completed) for each study *Request research protocols*	NA		
P4.8	Functional collaboration/involvement in risk management plans with the PV centre	Do the PHP and PV centre communicate on risk management plans?	No	Both address the need for communication	
		How often have the PHP and PV center met to discuss risk management in the previous calendar year?	0		
Component 5. Risk Management and Communication					
P5.1	Average time lag between identification of safety signal of a serious ADR or significant medicine safety issue generated nationally and communication to health care workers and the public	How long does it take from when a safety signal or significant safety issue is identified to when it is communicated to health workers and the public? *Please enter your answer in days for each signal.*	NA	No signal / safety issue identified	
P5.2	Existence of a program-related newsletter that routinely features ADR or medicine safety information	Is there a program-related newsletter, bulletin or other publication that routinely features ADR or medicine safety information?	No		
P5.3	Number and percentage of medicine safety information requests addressed in the previous calendar year	How many requests for information about medicine safety were received in the previous calendar year?	?	not officially documented but (probably) often called by clinicians	
		How many requests for medicine safety information were addressed in the previous calendar year?	NA		
P5.4	Number of medicine safety issues of local relevance identified from outside sources (e.g., from another country or international sources) and acted on locally in the previous calendar year	How many medicine safety issues identified from outside sources were acted on locally in the previous calendar year?	NA	question was lacking on printed form	
P5.5	Number of public or community education activities relating to medicine safety carried out in the previous calendar year	How many public or community education activities relating to medicine safety were carried out by the PHP in the previous calendar year?	0		

Annex 2. Questions for (DR-)TB treatment facilities

Question	Amana Region Referral Hospital	Mwananyamala Hospital	Sinza Hospital	Hindu Mandal Hospital	Mbagala Rangi Tatu Health Centre	Temeke Regional Hospital	Vijibweni Hospital	Bagamoyo Hospital	Baobab Dispensary	Kerege Health Centre	Kisarawe Hospital	Mapinga Dispensary	Mkoani Health Center	Tumbi Regional Hospital
aDSM?	**Yes**	**Yes**	**Yes**	**No**	**Yes**	**Yes**	**No**	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**
Has staff been trained on PV / aDSM?	No	Yes (3 staff attended aDSM training)	No (no one attended aDSM training)	No	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes
By whom?		NTLP and TFDA	Attended PV training conducted by TFDA			By NTLP and KNCV	By TFDA, KNCV and MOH	By NTLP			No answer	TFDA /NTLP	By NTLP	By RTLC
is equipment (e.g. Audiometry, ecg machine) in place to monitor for possible ae?	Yes	Yes (only audiometry is available)	Yes	Yes	Yes	Yes - all bought by KNCV	No	Yes	No	No	No	No	No	No
If yes, is the equipment functioning?	Yes	No (users were trained recently on the use of these equipments however the equipment lack autoscopy)	No (users were trained recently on the use of these equipments and they are on the process of starting to use them)	Yes	Yes	Yes	Na	Yes	Na	Na	Na	Na	Na	Na
Have any problems with the equipment occurred?	No	Yes (lack autoscopy)	No	No	No (equipment was new)	No - equipment is new. Maintenance is done by kncv	Na	No	Na	Na	Na	Na	Na	Na
If yes, how did you solve these?	N/a	Not yet solved		N/a	N/a	But in case the equipment gets a problem, they would call the kncv technical office to repair the equipment	Na	Na	Na	Na	Na	Na	Na	Na

Question	Amana region referral hospital	Mwananyamala hospital	Sinza hospital	Hindu mandal hospital	Mbagala rangi tatu health centre	Temeke regional hospital	Vijibweni hospital	Bagamoyo hospital	Baobab dispensary	Kerege health centre	Kisarawe hospital	Mapinga dispensary	Mkoani health center	Tumbi regional hospital
Is treatment monitoring (lab tests, audiometry etc) provided free of charge to patients?	Yes	Yes (lab tests are provided free of charge to patients)	Yes (lab tests are provided free of charge to patients)	No (only sputum for smear is done free)	yes	All are free (provided by govt and kncv)	For MDR -TB patients these are free at the referral hospital	Yes	Yes	Yes	Yes	Yes	For MDR -TB patients these are free at the referral hospital(tumbi)	Yes
Are ancillary drugs available free of charge to patients who need it?	Yes	No	No	No (only pyridoxine is given free)	Yes-TB drugs are free (and the other drugs on the MoH list of essential drugs are free)	Essential drugs are all free. MDR-TB patients however buy drugs for other infections e.g malaria	No - if an MDR -TB patient gets malaria, they would buy. But the MDR-TB drugs are free (and the other drugs on the MoH list of essential drugs are free	Yes MDR-TB drugs are free (and the other drugs on the MoH list of essential drugs are free but if medicine are not available at the facility they would buy.	No	Yes	No	Yes	No - but the MDR-TB drugs are free (and the other drugs on the MoH list of essential drugs are free but medicine are not available at the facility, if an MDR -TB patient gets malaria, they would buy.	Yes MDR-TB drugs are free (and the other drugs on the MoH list of essential drugs are free but if medicine are not available at the facility they would buy.
Are AE/ADR reporting forms easily accessible for staff?	Yes	Yes	Yes	Yes - they are available at pharmacy.	Yes - they are available from the pharmacy and distributed to all points of the health care providers	Yes - the system is that a pharmacists provides them and if they get finished, the clinician makes a request	Yes - they are available from the pharmacy and distributed to all points of the health care providers	Yes	No	No	No	No	No (ADR reporting form were not available at the facility)	Yes
Are AE/ADR reporting forms electronically or paper-based?	Paper	Paper-based	Paper-based	Paper based	Paper based system - should be filled by the pharmacist and sent to TFDA (also enters them into a computer system)	MDR-TB is electronic (with an app also that can be used to report). Though the general hospital uses paper if they have to report)	Paper based system - should be filled by the pharmacist and sent to TFDA (also enters them into a computer system)	both	None	None	None	None	They report using TFDA phone application	both

Question	Amana region referral hospital	Mwananyamala hospital	Sinza hospital	Hindu mandal hospital	Mbagala rangi tatu health centre	Temeke regional hospital	Vijibweni hospital	Bagamoyo hospital	Baobab dispensary	Kerege health centre	Kisarawe hospital	Mapinga dispensary	Mkoani health center	Tumbi regional hospital
Do you receive feedback on ae reports?	Not informed	No (ae reports are submitted to hospital pharmacist)	(no ae report submitted to TFDA)	Never sent any report	Never sent any so no feedback.	No - but clinicians would be very interested in receiving feedback	Never sent any so no feedback.	No	N/a	N/a	N/a	N/a	No feedback	N/a
If yes: what type of feedback? (if available: ask for the documentation.)	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
Are AEs that require treatment change being discussed amongst MDR-TB experts/consilium before treatment change is made?	Yes	No	Yes (the AE report (psychosis) of patient on cycloserine was observed)	N/a	No ADR cases were observed all reactions were known/expected	Yes - every Wednesday there is a video conference call with the TB hospital experts (from Kibong'oto NTB hospital and difficult cases that need consultation are discussed	Yes - these are discussed but never reported. Only one case was reported to the Kibong'oto NTB hospital.	Yes	No	No	Yes	Yes	No. Only one case as reported to the Kibong'oto NTB hospital.(change of medicine were done at Kibong'oto)	Yes
How many health care workers have reported an ae in the previous calendar year?	None	No answer	No answer	None	None	No answer	None	Jan to Dec 2017 - 0,but Jan to Aug 2018 20 reports (after TFDA sensitization training)	None	None	None	None	1 HCW	None
How many ae reports have been submitted by the health facility?	None	2 AE reports	1 ae report (submitted to NTLPPV focal person)	None	None	4 in the last 3 months	None	20 reports	None	None	None	None	1 report	None
How many patients were started on TB treatment in the previous calendar year?	Jan to Dec 2017 - 546 patients	524 sensitive TB	701 DS-TB and 18 MDR-TB	Jan to Dec 2017 - 98 patients	Jan to Dec 2017 - 1350	In all Temeke region comprising of 2 districts (Jan - Dec 2017 - 4676 cases)	Jan to Dec 2017 - 96, Jan to June 2018 - 103	Jan to Dec 2017 - 502 for the whole Bagamoyo district and 375 for the Bagamoyo district hospital.	Jan to Dec 2017 - 18	Jan to Dec 2017 - 12	Jan to Dec 2017 - 207 for the whole district and 117 for Kisarawe district hospital	Jan to Dec 2017 - 21	Jan to Dec 2017 - 429 for the whole Kibaha district and 87 for the health center	Jan to Dec 2017 - 429

Question	Amana region referral hospital	Mwananyamala hospital	Sinza hospital	Hindu mandal hospital	Mbagala rangi tatu health centre	Temeke regional hospital	Vijibweni hospital	Bagamoyo hospital	Baobab dispensary	Kerege health centre	Kisarawe hospital	Mapinga dispensary	Mkoani health center	Tumbi regional hospital
Who supervises patient treatment at home?	Oriented family members	Relatives	Relatives	Oriented family members	Ex-TB patients help to supervise the on patients on on-going treatment. They are trained by clinician and nurses on PV	Former TB patients and current peer TB patients on treatment - these are trained by clinicians on how to support the patients	Ex-TB patients help to supervise the on patients on on-going treatment. They are trained by MoH on PV	treatment supporter and community volunteer help to supervise the on patients on on-going treatment. They are trained by clinician/ nurses	Treatment supporter. They are trained by clinician/nurses	Treatment supporter/ village health worker .they are trained by clinician/nurses	treatment supporter and community volunteer trained by kncv, clinician/nurses	treatment supporter/village health worker .they are trained by clinician/ nurses	relatives and friends help to supervise the on patients on on-going treatment. They are trained by clinician	treatment supporter help to supervise the on patients on on-going treatment. They are trained by clinician/nurses
Are they trained on pharmacovigilance?	No	No	Both patients and relative trained	No										
Other issues?					Yes[6]	Yes[7]	Yes[8]	Yes[9]	Yes[10]	Yes[9]	Yes[9]	Yes[9]	Yes[11]	Yes[12]

[6] Health workers they are not aware of a dedicated number to call at TFDA for ADR reporting, no specific person for pharmacovigilance,lack of electronic system for reporting of ADR,health workers seem they don't know how to differentiate between normal side effect and ADR

[7] - MDR-TB ADRs are reported through a special/separate system from the general Hospital (the MDR - TB has a dedicated PV focal person and the system is functional), For the other cases other than MDR-TB, the clinician who identifies the ADR is supposed to report to the Pharmacist who then reports to TFDA,; There has been no training on PV for clinicians in the past year, Only the PV focal person has received trainings; Few people have been trained to fill the forms and to use the reporting APP (even thePV focal person has not been trained to use the APP but has received other trainings by KNCV and TFDA

[8] There is a system for reporting ADRs - If found first call TFDA on the general office line, then fill the form and send to TFDA (they are not aware of a dedicated number to call at TFDA for ADR reporting, Also Pharmacist has never had any training

[9] The facility had forms for reporting ADRs and health workers are now reporting after being sensitized by TFDA on the ways and important of reporting ADR ,they are not aware of a dedicated number to call at TFDA TOLL FREE SERVICE NUMBER for ADR reporting

[10] The facility had no forms for reporting ADRs and were not aware of TFDA phone application for reporting of ADR ,they are not aware of a dedicated number to call at TFDA for ADR reporting

[11] The facility had no forms for reporting ADRs ,they are not aware of a dedicated number to call at TFDA for ADR reporting

[12] The facility had forms for reporting ADRs but health workers are not reporting ,they are not aware of a dedicated number to call at TFDA for ADR reporting