Protocol for Treating MDR-TB/RR-TB with Shorter Treatment Regimen (STR)

Edited By:

Dr. Abdul Ghafoor (National Technical Advisor MDR-TB, Pakistan)

Dr. Raja Muhammad Ayub (Manager, MDR- TB, NTP, Pakistan)

Dr. Zafar Iqbal Toor (National MDR-TB Coordinator, NTP, Pakistan)

Abdullah (Surveillance Data Manager)

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Acronyms

aDSM	Active TB drug safety monitoring and management
AE	Adverse drug event
Am	Amikacin
BDQ	Bedaquiline
CBC	Complete Blood Cell Count
Cm	Capreomycin
CXR	Chest X Ray
DLM	Delamanid
DOT	Directly observed therapy
E	Ethambutol
ECG	Electro-cardiogram
Eto	Etionamide
FQ	Fluoroquinolone
H	Isoniazid
Km	Kanamycin
LFU	Loss to follow up
LPA	Line probe assay
LTR	Longer treatment regimen
MDR TB	Multi-drug resistant tuberculosis
Mfx	Moxifloxacin
M&E	Monitoring and evaluation
MSF	Medecines Sans Frontieres
ND	New drug
NTP	National tuberculosis program
PMDT	Programmatic management of drug resistant TB
PV	Pharmaco-vigilance
RR-TB	Rifampicin resistance tuberculosis
SAE	Serious/Severe adverse drug event
SLI	Second-line injectable
SID	Second-line drugs
STR	Shorter treatment regimen
TB	Tuberculosis
WHO	World Health Organization
XDR TB	Extremely drug resistant tuberculosis
Z	Pyrazinamide

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1. Introduction

Longer MDR TB treatment regimen that requires 20-24 month treatment duration is lengthy and toxic, resulting not only difficult to complete treatment successfully for the individual patient but also contributing to higher prevalence of disease and acquisition of amplified drug resistance. Moreover, it is resource intensive programmatically. In an attempt to overcome those challenges, international experts, organizations, academic institutions and national programs have been putting tremendous effort to develop novel treatment regimens for MDR-TB treatment which will be shorter, safer, cheaper and patient friendlier.

WHO has released its recommendation on the programmatic use of the short-course regimen for MDR TB cases (9-11 months duration) under specific conditions ***without needing an observational study or operational research*** in June 2016. The validation was made after analyzing data of 1116 patients treated with shorter treatment regimen under observational studies in 14 countries and based on the comparative analysis results of treatment outcomes amongst patients treated with shorter MDR TB treatment regimen (STR) and those treated with longer MDR TB treatment regimen or longer treatment regimen (LTR) that requires 20-24 months duration. The analysis showed that overall treatment success rate in STR group was statistically-significant higher than that of LTR group either on individualized or standardized treatment regimen, 89.9% vs. 78.3% respectively when success was compared with treatment failure/relapse/death and 83.4% vs. 61.7% when compared with treatment failure/relapse/death/loss to follow-up. Relapse risk was very low <1%. In the stratified analysis made between the two groups associated with additional resistance to pyrazinamide, treatment success rate was 88.8% vs 81.4% in STR and LTR respectively (WHO guideline 2016 update). If additional resistance was associated with both Pyrazinamide and Fluoroquinolone, treatment success rate was 67.9% for STR and 59.1% for LTR.

In addition to individual patient and programmatic benefit (medicine cost alone for STR is as much as four times more cost-effective than LTR), a modeling study in Uzbekistan has shown that the use of shorter treatment regimen for MDR-TB patients a context where a program can allow rapid enrollment of cases soon after diagnosis may decrease the disease transmission rate (Trauer et. al, 2016). Therefore overall benefits outweigh risk if STR is implemented under programmatic conditions

undertaking proper MDR-TB diagnosis, selection of eligible patients for STR properly, regular treatment monitoring as well as programmatic evaluation. However, continuing longer treatment regimen and optimizing longer treatment regimen with the use of new anti-TB drugs (Bedaquiline and Delamanid) are essential to obtain maximum results and to mitigate the potential harm that would compromise TB control effort.

2. Selection of MDR-TB/RR-TB patients for Shorter Treatment Regimen

2.1. Eligibility criteria for a shorter treatment regimen

- Confirmed MDR TB cases with no resistance to second-line drugs
- No previous exposure to 1 or more second-line medicines in the shorter MDR-TB regimen for >1 month
- No intolerance to 1 or more medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)
- Pulmonary TB
- Children

2.2. Exclusion criteria for shorter treatment regimen

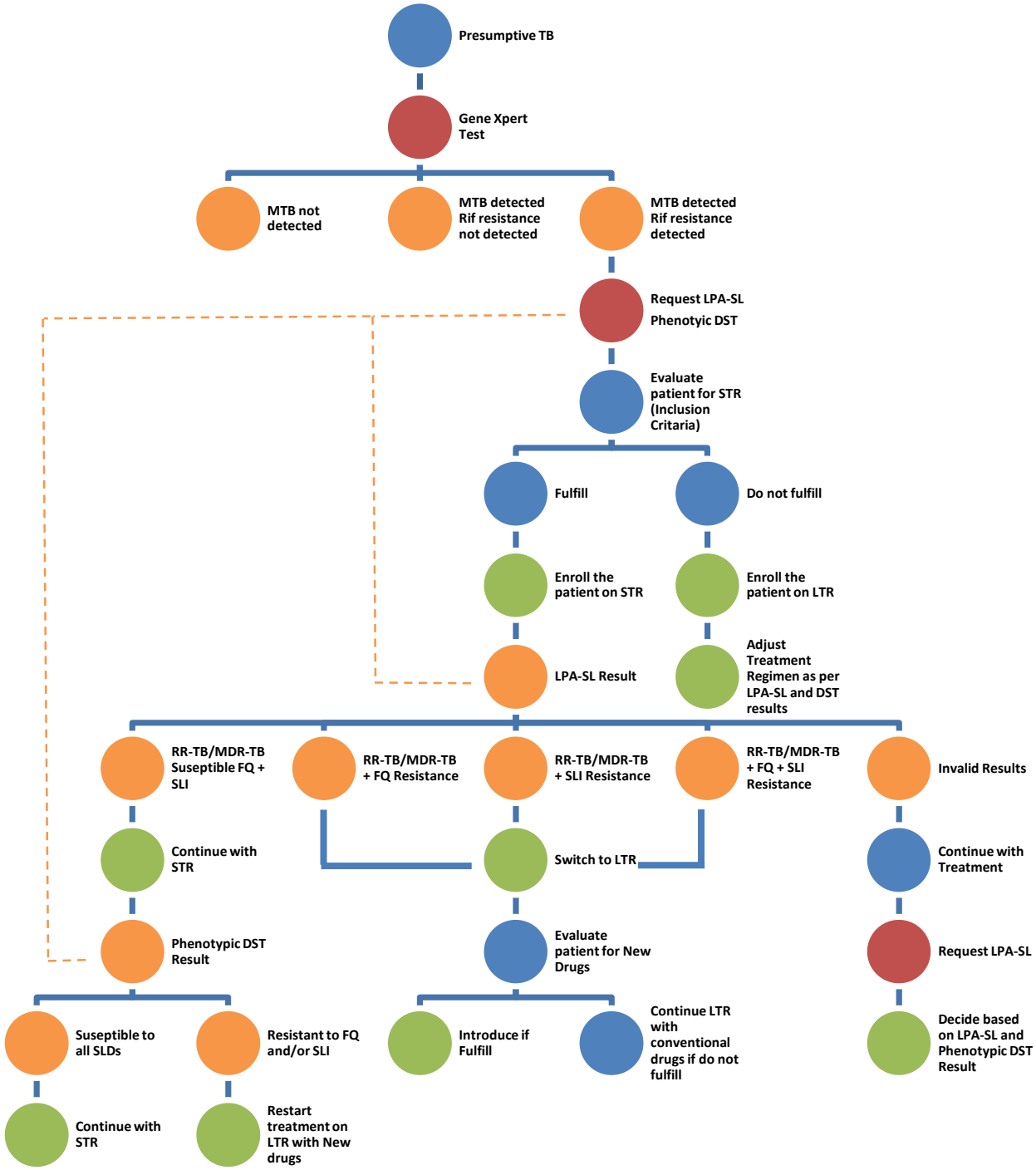
- MDR-TB/RR-TB cases with resistance to second-line drugs
- MDR-TB/RR-TB cases without second-line DST results
- Past history of exposure to one or more of second-line drugs in the shorter treatment regimen for > 1 month
- Clinically severe cases or disseminated TB cases
- Advanced pulmonary disease with extensive Parenchymal lesions
- Clinically diagnosed MDR TB cases
- Intolerance to one or more drugs in the shorter MDR-TB regimen or risk of toxicity;
- QTc >500ms
- ALT/AST > 5 time of UNL
- Creatinine > 2 times of UNL or Creatinine clearance <50 ml/min

- HIV co-infected
- Extra-pulmonary TB
- Pregnant women

Note: Treating contact cases of MDR TB and RR TB with STR without proven microbiological diagnosis is not yet recommended by WHO. They may have a different drug-resistant pattern from index cases especially in high prevalence settings where community transmission of the disease is occurring.

3. When to start treatment

Immediately after having a confirmed microbiological diagnosis of Rifampicin resistance after screening by inclusion and exclusion criteria as in above (see algorithm below). However, sending sputum sample for LPA and culture and phenotypic DST testing should be done promptly. It is highly suggested using the same sputum sample of Gene Xpert Rif Resistant for LPA testing in order to shorten turn-around time for LPA-SL DST as much as possible and to ensure availability of phenotypic DST result.


Presumptive TB
Gene Xpert Test
MTB not detected
MTB detected Rif resistance not detected
MTB detected Rif resistance detected
Request LPA-SL Phenotyic DST
Evaluate patient for STR (Inclusion Critaria)
Fulfill
Do not fulfill
Enroll the patient on STR
Enroll the patient on LTR
LPA-SL Result
Adjust Treatment Regimen as per LPA-SL and DST results
RR-TB/MDR-TB Suseptible FQ + SLI
RR-TB/MDR-TB + FQ Resistance
RR-TB/MDR-TB + SLI Resistance
RR-TB/MDR-TB + FQ + SLI Resistance
Invalid Results
Continue with STR
Switch to LTR
Continue with Treatment
Phenotypic DST Result
Evaluate patient for New Drugs
Request LPA-SL
Suseptible to all SLDs
Resistant to FQ and/or SLI
Introduce if Fulfill
Continue LTR with conventional drugs if do not fulfill
Decide based on LPA-SL and Phenotypic DST Result
Continue with STR
Restart treatment on LTR with New drugs

4. Shorter treatment regimen as recommended by WHO

The shorter treatment regimen is a standardized treatment regimen for a selected patient group as mentioned in eligibility and exclusion criteria with total treatment duration of 9-11 months.

4-6 Am-Mfx-Eto-Cfz-Z-Hhigh-dose-E / 5 Mfx-Cfz-Z-E

The intensive phase that includes injectable is generally 4 month. If there is delayed in smear 9microscopy) conversion by month four of treatment, the intensive phase is to prolong up to six months, **but not more than six months.**

Continuation phase is fixed at 5 months after injectable has been stopped.

5. Some issues that would arise during shorter treatment course

Table 1: Issues and comments surrounding STR

Issue	Comment
Change of treatment duration	Treatment duration for intensive phase and continuation phase, which are 4-6 months and 5 months respectively are not to shortened or prolonged than the defined period. WHO does not recommend changing the treatment duration based on treatment response.
Missed doses: < 2 continuous months of treatment interruption and on treatment for >1month 2 continuous month or more of treatment interruption and on treatment for >1 month	Compensate the missed doses Declare the case as "Loss to Follow Up" and re-start with longer treatment regimen (design treatment regimen in consideration of likely working drugs and DST results and may need to use of group C drugs and new drugs; Bedaquiline, Delamanid)
*Lack of smear conversion by 6 months of treatment or clinical deterioration despite treatment and having a good adherence to	Declare the case as "Failure". Re-start with longer treatment regimen (design treatment regimen in consideration of likely working drugs and DST

treatment	results and may need to use of group C drugs and new drugs; Bedaquiline, Delamanid)
Discrepancy between LPA and phenotypic DST result of Fluoroquinolone and second-line injectable	Very occasionally there can be a discrepancy between LPA and phenotypic DST results because of variation of sensitivity of LPA performance of drug susceptibility testing (DST) for second-line anti-TB drugs in smear-positive samples though high specificity results. The sensitivity of Fluoroquinolone in direct LPA testing amongst MDR TB patients was 86.2% (74.6%-93.0%, CI of 95.0%) and the specificity was 98.6% (96.9%-99.4%, CI of 95.0%). That of second-line injectable was 87.0% (38.1%-98.6%, CI of 95.0%) and 99.5% (93.6% - 100%, CI of 95.0%) respectively for sensitivity and specificity. In case if a discrepancy occurs between the two results of LPA and phenotypic DST, take Phenotypic DST result. Review the case and switch to longer treatment regimen [also in consideration of using new drugs (Bedaquiline, Delamanid)] if phenotypic DST result shows resistance to Fluoroquinolone/s and/or second line injectibles (Amikacin, Kanamycin, Capreomycin).
A woman becomes pregnant while on treatment with STR	Should consider case by case basis to continue STR or switch to the longer treatment regimen. Medicines in longer treatment regime have same safety profiles as that of in STR (mainly for fetus, hearing, teratogenic and discolouration side effects). If it is known only in late 2nd trimester or 3rd trimester, STR may continue.

*Although smear microscopy result is taken for a clinical management decision, culture result is taken for defining treatment outcomes.

6. Dosage of anti-TB drugs in STR

Table 2: Drug dosing by weight band for adult

Drugs	<30 kg	30-50 kg	>50 kg
Moxifloxacin/Gatifloxacin	400 mg	600 mg	800 mg
Ethionamide/Prothionamide	250 mg	500 mg	750 mg
Clofazamine	50 mg	100 mg	100 mg
Ethambutol	800 mg	800 mg	1200 mg
Pyrazinamide	1000 mg	1500 mg	2000 mg
Isoniazid	300 mg	400 mg	600 mg
[a]Amikacin/Kanamycin	15 mg/kg body weight (maximum 1 G)		

[a] For >59 years old, the dose will be reduced to 10 mg/kg body weight (maximum 750 mg).

It is to give 7 days per week dosing without any drug holiday/s for injectable or oral drugs

Table 3: Drug dosing for children < 30 kg

Drugs	Daily dosage (mg/kg)
Moxifloxacin	7.5-10 mg (max 400mg)
Ethionamide/Prothionamide	15-20 mg (split into two doses/day)
Clofazamine	Safety in children with the use of 1 mg/kg has been reported.
Ethambutol	15 mg (max 1200mg)
Pyrazinamide	30-40 mg (max 2000 mg)
High dose Isoniazid	16-20 mg (max 600mg)
Amikacin	15-22.5 mg (max 1000 mg)
Kanamycin	15-30 mg (max 1000 mg)
Capreomycin	15-30 mg (max 1000 mg)

In children, doses of all drugs, including the fluoroquinolones, should be at the higher end of the recommended ranges. Wherever possible, except Ethambutol. Ethambutol should be dosed at 15 mg/kg, and not at 25 mg/kg as sometimes Used in adults with DR-TB, as monitoring for optic neuritis is more difficult in children.

7. Treatment monitoring and adverse drug event management

Table 4: Schedule of treatment monitoring during treatment with STR and post-treatment follow-up

	Baseline	Intensive phase	Continuation phase	Post-treatment follow up
Clinical assessment (including Bodyweight)	X	Monthly	Monthly	6 monthly for 2 years
Audiometry	X	Monthly		
Vision test	X	Monthly	Monthly	
Adverse event	X	Monthly	Monthly	
Microbiological				
Smear & Culture	X	Monthly	Monthly	If clinical and CXR suspicious
Gene Xpert	X			
LPA	X	If smear/culture remains positive at 4 months or failure (microbiological/clinical), culture reversion/return after loss to follow up/relapse		If clinical and CXR suspicious
DST	X			
Laboratory tests				
CBC	X	If required		
Urea & Creatinine	X	Monthly		
Electrolyte (K+, Mg+, Na+, Cl-)	X	Monthly		
AST, ALT, Bilirubin	X	Monthly	Monthly	
TSH	X	Every 3 month		
Blood glucose	X	As clinically indicated		
HIV, HBV, HCV	X	If clinically indicated		
CD4, Viral Load if HIV (+)ve	X	Every 6 month		
Pregnancy test	X	Monthly		
ECG	X	Monthly	Monthly	
CXR	X	End of intensive and continuation phase		Every 6 month

The periodicity of examining and testing for above parameters including clinical follow up is for regular and routine schedule. More frequent follow up (clinical and laboratory workup) will be required in case a patient experiences adverse drug events or clinically deteriorated. The profile of adverse drug events is same as that of the longer treatment regimen. Please refer management of adverse events to the national MDR TB treatment guideline and the companion handbook for WHO guidelines for programmatic management of drug-resistant TB (2015).

Though there may be some concern with cardio-toxicity (QTc prolongation) with the combined use of high dose of Moxifloxacin and Clofazimine, the risk of developing Torsade de Pointes or polymorphic ventricular tachycardia is very low. In case of QTc prolongation > 500ms or >60 ms from baseline, check electrolyte and correct if abnormal. Also check concomitant treatment with other drugs which have potential QTc prolonging side effect such as antidepressant, psychotropic's, anti-emetic and may consider stopping them if conditions are controlled and may switch to drugs with a least cardio-toxic side effect. If QTc is > 500 ms or >60 ms from baseline and after verification of other causes that would contribute to QTc prolongation (e.g. electrolyte imbalance, no other ancillary drugs that have potential QT prolonging effect, decreasing Mfx dose to 400 mg will be the first option. *If decreasing Mfx to 400 mg does not correct QTc prolongation, substitution with a high dose of Levofloxacin may consider instead of substituting to the longer treatment regimen.* However, approach to further treatment with such cases should be discussed with PTP and NTP MDR TB clinical responsible persons.

Another concern may be hepato-toxicity due to high dose Isoniazid. WHO analysis showed no increased risk in adults and children were also well tolerated to high dose isoniazid. Pyridoxine prophylaxis dose of 50 mg in children and 100 mg in adult for potential peripheral neuropathy side effect may consider for some risk groups such as malnourished, diabetes and HIV. In case of peripheral neuropathy, the dose of Pyridoxine should be increased to 100 mg daily dosage.

8. Treatment outcome definitions for shorter treatment regimen

Outcome	Definition
Cure	Treatment completed as recommended by the national policy without evidence of failure and three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
Treatment completed	Treatment completed as recommended by the national policy without evidence of failure BUT no record that the three consecutive cultures taken at least 30 days apart are negative after the intensive phase.

Failed	Anyone of the following:
	- Treatment terminated or need for permanent regimen change of at least one anti-TB drug because of:
	  - Lack of evidence of at least two negative cultures* (and not followed by a positive culture) by the end of an extended intensive phase (6 months) of the shorter regimen; or
	  - Positive sputum smear (confirmed by two consecutive samples) after ≥ 6 months of treatment,
	  - Culture reversion** in the continuation phase after conversion to negative
	  - Evidence of additional acquired resistance to an FQ or an SLI,
	  - Adverse drug reaction

Died	A patient who dies for any reason during the course of treatment
Lost to follow-up* **	A patient whose treatment was interrupted for ≥2 consecutive months
Not evaluated	A patient for whom no treatment outcomes are assigned. (This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown.

** Perform culture from two specimens every month during the intensive phase*

*** Culture reversion (to positive) after an initial conversion; two consecutive cultures were taken at least 30 days apart are found to be positive during the continuation phase.*

Remark – in all other situations when failure is suspected the possible causes, patient management strategy and registration of outcome will be discussed by the expert committee

**** If a patient has received the STR for more than a month, and returns for treatment after an interruption of 2 consecutive months or more, he is not restarted on the STR but on a longer MDR-TB regimen which is individualized based on the medicines most like to be effective. If the interruption is less than 2 months, e.g., medical indication in case of adverse events (AE), or patient's decision, then the STR can be continued and the missed doses added to the rest of the treatment.*

9. Post-treatment outcomes

Recurrent TB is defined as 1) two consecutive positive cultures, after cure or treatment completion, or 2) one positive culture with clinical signs and symptoms and/or radiographic deterioration after cure or treatment completion. An isolated positive smear or culture without clinical deterioration after treatment completion provides insufficient evidence to define recurrent tuberculosis.

The following outcomes are possible after the declaration of cure or treatment completed:

- **Reinfection:** recurrent TB disease in a successfully treated individual who becomes culture-positive within 6 to 12 months after cure or treatment completion, with an MTB strain that is different from the baseline MTB strain recovered before starting treatment based on molecular fingerprinting.
- **Relapse:** recurrent TB disease in a successfully treated individual who becomes culture-positive within 6-12 months after cure or treatment completion, with an MTB strain that is identical to the baseline MTB strain recovered before starting treatment based on molecular fingerprinting.
- **Undetermined:** there is insufficient information to determine whether the recurrent episode is due to relapse or reinfection.

10. Pharmacovigilance and recording/reporting

- As per WHO aDSM guidelines, all side effects/adverse events should be recorded regardless of frequency and nature of the event.
- Whenever any minor to a major side effect (severe/serious) is detected or reported to MDR TB physician/treatment coordinator, this should be recorded on the already provided Performa in DR TB register.
- **Reporting of SAE to aDSM focal in NTP/DRAP is mandatory in a specific form which allows collecting sufficient information for causality analysis**.
- Each adverse event should be reported to pharmaco-vigilance (PV) monitoring committee.
- Establishment of the pharmaco-vigilance committee is mandatory at PMDT site and provincial level, involving federal MDR TB unit.
- AE/SAEs should be reviewed and analyzed quarterly.

11. Patient/family education and support

The same interventions for patient and family education and psycho-social support providing to MDR TB/RR TB patients on longer treatment regimen will be applied since 9-12 month treatment regimen is still long and the issues of pills burden and adverse events are yet unavoidable. DOT by treatment supporter and/or healthcare worker remain the same important role in ensuring treatment adherence.

It is not mandatory to take patient's consent for enrolling patients on STR. However, it should clearly inform patients and families that the switch to the longer treatment regimen is possible in case if phenotypic DST result shows resistance to any of second-line drugs, in case of failure or clinically worsening clinical condition and in case of severe intolerance to one or more of drugs in STR.

12. Recording, Reporting and Monitoring & Evaluation

- For individual patient recording, the same treatment card, Drug Gram and adverse event monitoring forms that are being used for longer treatment regime are to be used.
- Routine quarterly case finding a report of PMDT will continue but with differentiation of MDR TB and RR TB cases put on a longer standard treatment regimen, shorter treatment regimen and individualized treatment regimen with new drug added regime should be reported.
- Six monthly reports on interim treatment outcomes will be continued the same way. But the results should show differentiation for 3 main different treatment regimen groups.
- The annual report will include treatment outcomes of a cohort from the previous year (i.e. report of 2017 cohort is produced by the end of 2018).
- Any occurrence of relapse should be recorded and reported 6 monthly.

13. References:

1. The use of molecular line probe assays for the detection of resistance to second-line antituberculosis drugs, WHO Policy Guidance, 2016
2. WHO treatment guidelines for drug-resistant tuberculosis, 2016 update
3. Companion Handbook to the WHO guidelines for programmatic management of drug-resistant TB, WHO 2015
4. Frequently asked questions about the implementation of the new WHO recommendation on the use of shorter MDR-TB regimen under programmatic condition, WHO 2016
5. Key issues surrounding shorten treatment regimen, e-mail communication with Manson Unit, MSF-UK