Generic programmatic and clinical guide for the introduction of new drugs and shorter regimens for the treatment of Multi/Extensively Drug-Resistant Tuberculosis

USAID FROM THE AMERICAN PEOPLE

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CHALLENGE TB

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This document describes the steps necessary to implement the shorter regimen and the new drugs for drug-resistant TB treatment including diagnosis and bacterial confirmation of drug resistance, treatment regimen design, monitoring of treatment efficacy and safety, and programmatic evaluation.

Countries that will introduce a shorter regimen and new drugs will need to follow this programmatic and clinical guide (guide) and adapt to their local settings. Highlighted text displays the sections that minimally require additions and adaptations of the guide.

The guide is also valid for countries that will introduce the new drugs but not the shorter regimen for M/XDR-TB treatment or vice versa; they may take out the text sections related to the shorter regimen or the new drugs, respectively.

Generic programmatic and clinical guide for the introduction of new drugs and shorter regimen for treatment of Multi/Extensively Drug-Resistant Tuberculosis

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This generic guide is developed by Challenge TB through the technical support of KNCV Tuberculosis Foundation and uses elements from the Médecins Sans Frontières protocol for the shorter regimen, the Union/Global Drug-resistant TB Initiative generic protocol for the shorter regimen [1], the endTB Project protocols, and the Philippines bedaquiline protocol.

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List of Abbreviations

ADR	Adverse drug reaction
aDSM	Active drug safety monitoring and management
AE	Adverse event
ALAT	Alanine aminotransferase
Am	Amikacin
Amx/Clv	Amoxicillin/Clavulanate
ASAT	Aspartate aminotransferase
ART	Anti-retroviral therapy
Bdq	Bedaquiline
BMI	Body mass index
Cfz	Clofazimine
Cm	Capreomycin
CrCl	Creatinine Clearance
Cs	Cycloserine
Dlm	Delamanid
DRS	Drug Resistance Surveillance
DR-TB	Drug-resistant TB
DST	Drug susceptibility testing
E	Ethambutol
ECG	Electrocardiogram
EMA	European Medicines Agency
FDA	Food and Drug Administration
FLD	First-line Drugs
FQ	Fluoroquinolone
GDF	Global Drug Facility
Gfx	Gatifloxacin
H	Isoniazid
H^{HD}	Isoniazid high dose
HIV	Human Immunodeficiency Virus
Imp/Cln	Imipenem/Cilastatin
Km	Kanamycin
Lfx	Levofloxacin
LPA	Line probe assay
Lzd	Linezolid
MDR-TB	Multidrug- resistant tuberculosis
Mpm	Meropenem
Mfx	Moxifloxacin
MGIT	Mycobacteria Growth Indicator Tube
MOH	Ministry of Health
ND&R	New Drugs and Regimens
NRL	National TB Reference Laboratory
NTP	National Tuberculosis Program

Ofx	Ofloxacin
PAS	Para aminosalicylic acid
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency of Japan
PMDT	Programmatic Management of Drug Resistant Tuberculosis
Pto	Prothionamide
PV	Pharmacovigilance
R	Rifampicin
RR-TB	Rifampicin resistant TB
S	Streptomycin
SAE	Serious adverse event
SLD	Second-line drugs
SLI	Second-line injectable
SL-LPA	Second-line line probe assay
TB	Tuberculosis
Trd	Terizidone
TSH	Thyroid stimulating hormone
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis
Z	Pyrazinamide

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Summary of the guide

Recent international experience demonstrates that for rifampicin-resistant (RR) tuberculosis (TB) patients without additional resistance or intolerance to key second line drugs (SLD), i.e. fluoroquinolones (FQ) and second line injectables (SLI), the treatment duration can be substantially shortened, thereby reducing the burden for the patients and TB programs. In May 2016, the World Health Organization (WHO) issued a recommendation on the use of a shorter drug – resistant TB (DR-TB) treatment regimen [2]. For patients with resistance to FQ and/or SLI, early initiation of treatment regimens containing new and repurposed drugs could improve treatment outcomes.

This document describes the steps necessary to implement the shorter regimen and the new drugs for DR-TB treatment, including diagnosis and bacterial confirmation of drug resistance, treatment regimen design, monitoring of treatment efficacy and safety, and programmatic evaluation. These steps are detailed within an M/XDR Patient Triaging Approach. This approach entails:

a. Availability of drug resistance test results (and periodic test results to monitor treatment) based on optimized diagnostic algorithms for early detection of RR and resistance to FQ and SLI. Algorithms should be adapted over time when new diagnostic tests become available
b. Provision of treatment regimens for RR-TB patients depending on the additional resistance detected or suspected and/or intolerance to either FQ and/or SLI in compliance with WHO recommendations
c. Routine data collection on patients diagnosed with RR-TB in accordance with WHO guidelines on programmatic management of drug-resistant TB (PMDT), new drugs, and active drug safety monitoring and management (aDSM) guidelines [3]
d. Patient management before, during and after treatment in accordance with WHO guidelines on PMDT [4] and WHO guidelines on the introduction of new drugs [5]
e. Monitoring and supervision visits to support high-quality programmatic implementation of the MDR/XDR-TB Patient Triaging Approach.

Routine data collection and programmatic monitoring and supervision visits will allow for monitoring of implementation of this Triaging Approach and evaluation of effectiveness, safety and feasibility of its programmatic implementation. Programmatic indicators on effectiveness and safety include:

Effectiveness

1. Distribution of patients in DR-TB treatment regimen groups allocated through the diagnostic algorithm
2. Treatment outcomes by DR-TB regimen group: interim (6-month culture conversion) and final treatment outcomes including the number and proportion of patients requiring a change of regimen due to the occurrence of adverse drug reactions or lack of efficacy of the regimen
3. Frequency of relapse at 6 and 12 months after successful treatment completion by DR-TB regimen group
4. Frequency and timing of smear and culture conversion, by each DR-TB regimen group.

Safety

5. Frequency of serious adverse events (SAE), by DR-TB regimen group
6. Frequency of adverse events of special interest, by DR-TB regimen group.

If NTP or MoH of a country decides to add indicators or research questions that require information beyond what is routinely collected, this may require a formal study. Such study protocol will need to be developed separately from this guide, and may require approval from an ethical committee as well as from the donor agency.

Introduction

General background

In 2014, 9.6 million people developed tuberculosis (TB) and 1.5 million died, ranking with HIV as an equally major cause of death by a single infectious agent worldwide [6]. Of the 480,000 cases of multidrug-resistant TB (MDR-TB) estimated to have occurred in 2014, only 123,000 were detected and reported. A total of 111,000 people started MDR-TB treatment in 2014 while 190,000 MDR-TB patients were estimated to have died, largely due to lack of access to effective treatment. The approaches currently used for DR-TB management require a very lengthy treatment period (at least 20 months), great financial and human resources and are therefore difficult to implement. MDR-TB treatment success rates remain unacceptably low at 50% overall (WHO 2015 Global TB report).

Recent international experience demonstrates that for MDR-TB patients without additional resistance or intolerance to key second-line drugs (SLD), i.e. fluoroquinolones (FQ) and second line injectables (SLI), the treatment duration can be substantially shorter, thus reducing the burden for the patients and National TB Programs. In May 2016 WHO issued a recommendation on the use of a shorter MDR-TB regimen [2]. One of the main requirements for successful introduction of shorter MDR-TB treatment regimens is an ability to rule out resistance to key SLD, given the dependence of the shorter regimen on these drugs.

Bedaquiline (Bdq) developed by Janssen Pharmaceuticals, is the first new bactericidal TB drug in more than 40 years. Bdq has been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). WHO has included Bdq on its Essential Medicines List and by the end of April 2016 it has been used in more than 3,000 MDR-TB patients globally. USAID launched a Bdq donation program for the treatment of patients with MDR-TB. The program will provide 30,000 treatment courses of Bdq to patients in more than 100 countries.

Delamanid (Dlm), developed by Otsuka Pharmaceuticals, is another new TB drug recently approved by the European Medicines Agency (EMA) and the Pharmaceuticals and Medical Devices Agency of Japan (PMDA). It has also been included in the WHO's Essential Medicines List. Dlm is available through the Stop TB Partnership's Global Drug Facility (GDF) for all countries that are Global Fund eligible. Both drugs will be critical additions to country and program strategies for treating DR-TB.

The WHO has published interim policy guidance on the use of Dlm and Bdq in adult MDR-TB patients [7][8]. Both drugs, when used according to WHO guidance and in combination with existing medications, provide new hope for DR-TB patients with limited treatment options.

Rapid, molecular tests are available for early detection of RR and resistance to key SLDs. Yet these tests have not been sufficiently scaled-up in countries. Often existing instruments are underutilized, infrastructure challenges limit their use, and results are not consistently used to influence treatment decisions. The implementation of **appropriate diagnostic** and **treatment algorithms** allows for the early allocation of the best DR-TB treatment regimen to rifampicin-resistant tuberculosis (RR-TB) patients, considering the additional resistance to second line drugs (SLD) detected or suspected (e.g. based on previous treatment with SLDs, or close contact with an RR-TB patient that has additional resistance to FQ and/or SLIs). Patients without resistance to SLI and/or FQ will be allocated to the

shorter DR-TB treatment regimens. Patients with more extensive resistance to SLD will be allocated to standard-length treatment (20-24 months) with addition of new and/or repurposed drugs to the regimen.

Country-specific background

[Describe here (max 1 page):

1) epidemiology of TB, including
    a. TB burden
    b. case finding strategy
    c. outcome of treatment of TB
    d. prevalence of DR-TB among new and previously treated cases
    e. prevalence of fluoroquinolone- and second-line injectable resistance among RR-/MDR-TB cases
2) current capacity to diagnose TB and DR-TB
    a. diagnostic algorithm for TB and DR-TB, including DST for first- and second-line drugs,
    b. current TB laboratory capacity for diagnosis of TB and DR-TB: describe the current lab network (including SRL), tests available and coverage, referral links (sample transportation and reporting of results) and linkage to treatment
3) MDR TB treatment:
    a. DR-TB regimens currently used in the country
    b. Current management of patients with SLD resistance or intolerance
    c. treatment enrollment rate for patients diagnosed with RR-/MDR-TB
    d. outcomes of rifampicin-resistant patients enrolled on treatment
4) Rationale for the introduction of the new approach
    a. summarize what the new approach will look like: diagnostic and treatment algorithms to be used].

Implementation sites

[Describe here (max 1 page) the implementation sites with background on number of TB/DR-TB patients diagnosed and treated per year, number of beds, etc. and parameters used for site selection. Provide timeline for pilot sites to start the implementation and then for a country scale up]

Note that the parameters advised to use for initial site selection are:

1) Implementing PMDT for 2 years or more
2) Ability to follow-up all patients, including after hospital discharge
3) Existing reliable mechanisms to refer samples (and receive results) for FLD and SLD susceptibility testing, e.g. including the use of rapid molecular tests such as Xpert MTB/RIF and second-line line probe assays (SL-LPA)
4) Access to other required tests such as blood chemistry, ECG, radiographic test, etc.

DST and Diagnostic Algorithm

When countries introduce the shorter DR-TB regimen, they must have a diagnostic algorithm that will ensure access to quality SL DST for all potentially eligible patients. CTB partners should be evaluating current capacity and implementing interventions to strengthen in-country testing for drug resistance. Although NTPs may have access to SL molecular or SL phenotypic DST outside of the country, this will

add to the delay to receive results and excessive expenses. Each country should have a plan to optimize SL DST depending on their current capacity for molecular and phenotypic DST including both availability and quality of testing.

The appropriate algorithm for SL DST will depend on the laboratory capacity currently existing in the respective country. Namely:

1. SL LPA and SL phenotypic DST capacity are both available in country. In this scenario, NTP and partners should ensure testing is performed under quality and safe conditions, supplies are accessible and referral mechanisms are functional to ensure timely testing and results
2. SL LPA is available but SL phenotypic DST is not available. In this scenario, referral mechanisms to an outside laboratory must be available, and in-country phenotypic DST should be implemented after proper situational analysis
3. SL LPA is not available but SL phenotypic DST is available. In this scenario, a thorough analysis with involvement of SRL must be done to determine the best options to ensure access to SL genotypic DST (e.g. LPA) depending on prevalence of DR-TB in the country, e.g. referral testing at an outside laboratory, installation of SL LPA locally or implementation of forthcoming innovations
4. No SL DST is available both molecular and conventional. In this scenario, an urgent review of the diagnostic network should be made by experts with recommendations on the best options for building SL DST capacity with the following implementation.

The referral options for each country based on the current availability and quality of SL LPA and phenotypic DST, are summarized in Table 1.

Table 1. Referral options for countries with different access to SL LPA and phenotypic DST

In-country capacity			**Referral options**
SL LPA	**FL DST**	**SL DST**	
Yes	Yes	Yes	• Transport specimen to the national reference or other appropriate laboratory(ies) for SL LPA and phenotypic DST
No	Yes	No	• Transport specimen to the national reference or other appropriate laboratory(ies) FL phenotypic DST • Transport sample(s) to an external laboratory for SL LPA and phenotypic SL DST
No	Yes	Yes	• Transport specimen to the national reference or other appropriate laboratory(ies) for phenotypic DST • Transport specimen to an external laboratory for SL LPA if results can be ensured within 2 weeks
No	No	No	• Transport sample(s) to an external laboratory for SL LPA and for phenotypic DST

Options for shipment of samples for testing

Depending on the capacity of a country or an external laboratory and national regulations on shipment of biological materials, the following samples can be transported:

- Specimen (a preservative, e.g. CPC or Omnigene, can be added depending on requirements of a reference laboratory; i.e. CPC is not compatible with MGIT960), or
- Live culture isolate with viable bacilli (for phenotypic DST), or
- Specimen or culture isolate with inactivated bacilli (for LPA).

CTB experts in collaboration with SRL and NTP will advise countries on algorithms, based on background epidemiological information and assessment of the situation on the ground. Together they will come to the optimal combination and sequence of diagnostic tests based on the simplified concept. CTB partners together with NTP and SRL will plan and implement the necessary support for optimal diagnostic algorithms.

Currently, individual specimens are not tested for resistance to Bdq or Dlm before patients are initiated on regimens that include either drug. This is based on the assumption that Bdq- or Dlm-resistant strains are not yet circulating through the general MDR/XDR-TB patient population and because Bdq and Dlm DST testing is not yet available as a validated test. Ongoing studies will assess the level of Bdq or Dlm resistance that can be expected among treated patients, and inform drug resistance monitoring and future placement of Bdq and Dlm resistance testing in diagnostic algorithms. Countries should be advised and facilitated to store the strains from patients using new drugs in order to test afterwards when testing is needed in case of failure (for instance by SNRL) and/or when testing becomes available in country. Therefore capacity for storage of isolates should be assessed and developed accordingly.

[Describe here in detail the diagnostic algorithm to be used.]

[Describe here the situation on the ground in selected implementation sites with regard to access to diagnostics, specimen transportation, laboratory feedback, etc.]

Eligibility criteria for MDR/XDR-TB treatment

Patients (adults and children) with confirmed rifampicin resistance

All patients enrolled in care in the implementation sites who have been diagnosed with RR-TB and who do not have contraindications to treatment or documented intolerance (e.g. drug-drug interactions, cardiotoxicity) with one or more of the anti-tuberculosis drugs used in the treatment regimens, are eligible for the DR-TB treatment options as described in this guide.

Patient at high risk for rifampicin resistant TB to be considered for enrollment

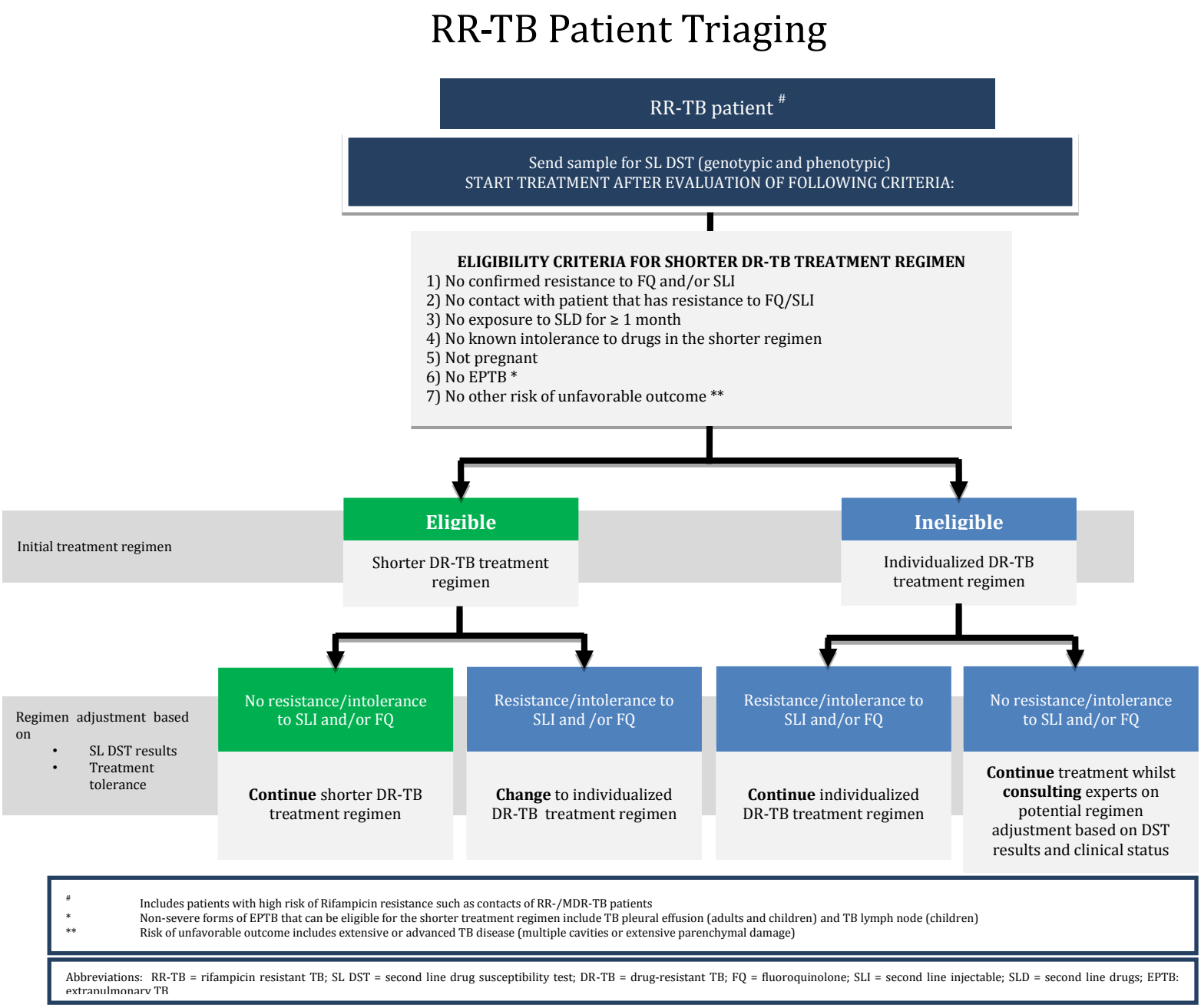
Children and HIV infected patients with clinically diagnosed TB who have been in close contact with patients with DR-TB should also be considered for enrollment for the treatment options as described in this guide. Molecular tests should be used for both children and HIV-infected to confirm clinical diagnosis. The absence of confirmation should not, however, determine them ineligible for the treatment.

[Describe here how eligibility for DR-TB treatment based on a presumptive diagnosis of DR-TB will be determined.]

Patient Triage Approach

The treatment regimen design for patients with RR-/MDR-TB will differ according to whether there is a risk or proof of resistance to an FQ and/or SLI and/or intolerance of FQ and/or SLI.

Figure 1. Patient triage flowchart (for adaptation to country specific situation)



1. For patients with confirmed RR-TB or MDR-TB, a systematic approach must be followed to determine if the patient should be treated with the shorter DR-TB regimen or an individualized DR-TB regimen. The approach includes clinical evaluation to determine the individual's risk of resistance or intolerance to FQ and/or SLI, and bacteriological testing of a pre-treatment specimen to determine the strain's resistance to FQ and SLI drugs (see next section on DST and Diagnostic Algorithms). Molecular and phenotypic drug susceptibility testing will inform the appropriate treatment regimen at different times in the triage approach therefore it is important to have clear decision pathways: Molecular DST for FQ and SLI resistance can identify resistance to FQ and/or SLI before treatment initiation.

2. Phenotypic DST can confirm the molecular DST results and offer drug-specific resistance results to confirm or revise the treatment regimen.

Since the capacity of a country to reliably test for drug resistance varies, both molecular and phenotypic DST results must be considered in context of the individual's clinical evaluation and risk of resistance or intolerance to FQ and SLI drugs.

If there is no risk of intolerance and/or resistance for FQ and/or SLI based on the clinical evaluation and/or the molecular DST, the patient will start with the shorter regimen. If there is risk of intolerance/resistance to FQ and/or SLI and/or bacterial confirmation of drug resistance or other risk factors for poor treatment outcome (such as severe TB disease), the patient shall start with an individualized treatment regimen.

Once the phenotypic DST results become available, the initial treatment regimen has to be re-evaluated. In this case there are 5 options (see Figure 1):

1. For patients that started with the shorter regimen and phenotypic DST results reveal no additional resistance to FQ and/or SLI, the shorter regimen can be continued;
2. For patients that started with the shorter regimen and phenotypic DST results show additional resistance to FQ and/or SLI, the patient should switch to (starting from the beginning of the treatment duration) an individualized treatment regimen based on the phenotypic DST results;
3. For patients that started with an individualized regimen based on resistance for FQ and/or SLI which is confirmed by the phenotypic DST results, they should continue the individualized treatment regimen; and
4. For patients that started with individualized regimen based on intolerance to FQ and/or SLI, the regimen should be re-evaluated and adjusted if needed based on the phenotypic DST results; and
5. For patients that started with an individualized regimen based on resistance for FQ and/or SLI which is not confirmed by phenotypic DST results, they should continue the treatment whilst consulting expert on potential regimen adjustment based on DST results and clinical status.

Ideally, all DR-TB patients are to be tested for resistance to FQ and/or SLI before starting any DR-TB treatment and efforts should be made to ensure that rapid molecular DST for FQ and SLI is available for all DR-TB patients. However, for those countries which do not yet have access to rapid, quality molecular DST, initiation of the shorter regimen should be guided by the clinical evaluation of the patient and recent representative surveillance data from the area.

Regimens

[Include here a description of regimen formulations: adapt the generic guidance provided below]

Shorter DR-TB regimen

Eligible patients

RR-TB patients who have not been previously treated with SLD and with low risk of or with DST results excluding additional resistance to FQ and/or SLI and fit the other criteria shown in Figure 1, will be eligible for treatment with the shorter DR-TB treatment regimen.

Children and HIV infected patients with clinically diagnosed TB, who have not been previously treated with SLD and with low risk of additional resistance to FQ and/or SLI, and who have been in close contact with patients with RR-/MDR-TB, should also be considered for treatment with a shorter regimen as described in this guide.

Exclusion criteria

1. Confirmed resistance to FQ and/or SLI
2) Contact with patient that has resistance to FQ/SLI
3) Exposure to SLD for ≥ 1 month
4) Known intolerance to drugs in the shorter regimen
5) Extrapulmonary TB
6) Other risk of unfavorable outcome
7) Pregnancy.

Other considerations

Patients already on treatment with a conventional DR-TB treatment regimen, cannot be switched to the shorter DR-TB treatment regimen.

Patients with high risk of treatment failure, such as severe TB disease (e.g. multiple cavities, extensive parenchymal damage), should be treated with the individualized treatment regimen.

Regimen design[1]

1) Unlike the longer MDR-TB regimen, the shorter MDR-TB regimen has been studied as a fairly standardized intervention. It is not advised to shorten the duration of the intensive or continuation phase. Likewise, changes to the regimen composition other than those which were allowed in the studies (refer to 5) may have an unpredictable impact on its effectiveness and are therefore not recommended. For further guidance please refer to the "Frequently asked questions about the implementation of the new WHO recommendation on the use of the shorter MDR-TB regimen under programmatic conditions" published by the WHO in June 2016;
2) Standard duration of the intensive phase will be at least 4 months of *Km (Am, Cm), Mfx (Gfx), Cfz, Z, E, H_{HD}, Pto (Eto)* given daily;
3) The intensive phase shall be extended to a maximum of six months until sputum smear conversion. If a sputum smear conversion is not achieved within four months Km (Am or Cm) will be given thrice-weekly from the fourth month onwards;
4) The continuation phase consists of *Mfx (Gfx,) Cfz, E, Z* for a fixed duration of five months;
5) The shorter TB regimen is a standard regimen. There are a few exceptions that could be adapted in the local guide:
    a. Pto could be replaced with Eto

[1] Dosages of medicines are provided in Table 3.

   b. Km could be replaced with Am or Cm
   c. Mfx could be replaced with Gfx.
6) If the patient remains smear positive and/or is still culture positive at 6 months, the patient will be declared as a failure. Failure declaration and a switch to an individualized treatment will be considered earlier in patients with clear lack of response (clinically, smear grading, culture); and
7) In case of diagnosis of any resistance to FQ and/or SLI or AEs requiring change of 2 drugs, the patient will be registered as treatment failure and an individualized regimen will be designed (not shorter regimen).

Note

- Low risk of additional resistance to FQs and/or SLIs – patients without known contact with pre-XDR-/XDR-TB patient and/or without previous exposure to SLDs for more than one month
- Specific recommendations on extrapulmonary TB (EPTB) cannot yet be made by WHO as studies were limited to patients with pulmonary disease. Inclusion of patient with EPTB for treatment with the shorter DR-TB regimen is upon the respective NTP's discretion. It is suggested that non-severe forms of EPTB such TB pleural effusion (adults and children) and TB Lymph Nodes (children) could be eligible for treatment with the shorter DR-TB regimen
- Based on experience from MSF project in Uzbekistan in settings with high risk of resistance to E and Z, Pto could be used throughout the treatment to limit the risk of failure and amplification of resistance
- In countries where the private sector treats large proportion of TB patients, further discussion of the eligibility of these patients should be considered.

Individualized DR-TB regimens

Eligible patients

RR-TB patients with high risk of or confirmed resistance and/or intolerance to SLI and/or FQ or with high risk of treatment failure.

Children and HIV infected patients with clinically diagnosed TB, who have been in close contact with patients with confirmed DR-TB and who are not eligible for the shorter regimen, should also be considered for treatment with regimens containing new and repurposed drugs as described in this guide.

Regimen design

1) Standard duration of the intensive phase will be at least 8 months and duration of the continuation phase will be at least 12 months;
2) The duration of the injectable agent, and hence the intensive phase, may then be extended according to the patient's response to treatment and confidence in the drugs in the treatment regimen;
3) The regimen will be designed based on the patient's most recent DST results and history of previous drug use and/or exposure (see Table 1);
4) The regimen will consist of at least 5 drugs with confirmed or high likelihood of susceptibility from the following list: Bdq or Dlm, Lfx (Mfx), Km (Am, Cm), Pto (Eto), Lzd, Cfz, Cs, Z, E, H_{HD}, PAS, Imipenem, Amx/Clv;

5) Bdq or Dlm will be used for 6 months. The use of Bdq or Dlm can be extended by MDR-TB expert committee in cases where the remaining regimen is insufficient (less than 3 effective drugs) and treatment tolerability is good.

Note

- For patients enrolled for treatment with regimens containing new drugs (Bdq or Dlm) informed consent should be obtained as per WHO guidelines [4]
- For HIV-infected patients, ART will be prescribed within the first eight weeks of DR-TB treatment initiation. For patients on ART, Dlm (if available) should be used instead of Bdq
- If indicated, Dlm or Bdq can be used also for children with proper safety measures. However, for children <12 years of age Dlm should be the drug of choice [9]
- The patient will be provided with materials in local languages that explain DR-TB treatment procedures
- Additional information on contraindications and precautions for SLDs is provided in Annex B
- High risk of additional resistance to FQ and/or SLI: contact with pre-XDR-/XDR-TB patient and/or previous use of SLDs for more than one month.

Table 2. Steps to design a treatment regimen and medicines used in treatment of drug-resistant TB (individualized regimen)

STEP 1	**Choose new drug**	**Bdq or Dlm**
STEP 2	**Choose a fluoroquinolone**	**Lfx** **Mfx** **Gfx**
	In addition to determining strain susceptibility to ofloxacin, every attempt should be made to specifically determine susceptibility also to moxifloxacin and levofloxacin. • If only ofloxacin DST is known (and resistant) use levofloxacin unless thought to be compromised (previous use in failing regimen or known contact with a patient with levofloxacin resistance); • If resistance has specifically been shown to ofloxacin and/or levofloxacin, and moxifloxacin is susceptible, consider adding moxifloxacin to the regimen; • Moxifloxacin should be used only as a last resort and under carefully monitoring. In such case, the potential benefit of moxifloxacin should be weighed against the additive toxicity of prolongation of interval between Q wave and T wave in the heart's electrical cycle (QT) with bedaquiline; • If resistance shown to all FQs, exclude FQs from regimen; and • Be aware that Bdq has a long half-life and replacing Lfx with Mfx after the Bdq has stopped could still result in cardiac toxicity.	
STEP 3	**Choose an injectable [2]**	**Km** **Cm**

[2] Drugs are listed in order of priority until a total of at least 5 drugs deemed effective are included, including Z.

		Am • If patient's strain is still susceptible to one of the injectable drugs, include this in the regimen; and • If resistant to all injectable drugs, consider using one that the patient has never received.
STEP 4	**Other core SL agents**	**Pto (Eto)** **Lzd** **Cfz** **Cs (Trd)** • Add all drugs thought to meet the criteria of an effective drug; and • If a drug is considered not to be effective or it has induced severe toxicity, do not include it in the regimen; and • If effectiveness is difficult to judge, the drug can be added to the regimen, but should not be counted as one of the effective second-line drugs.
STEP 5	**First line drugs**	**Z** **E** **High-dose isoniazid (H_{HD})** Z is routinely added in most regimens
STEP 6	**Add on agents**	**PAS** **Amx/Clv** **Imp/Cln** **Meropenem** **Thioacetazone** Add one or more drugs if the regimen does not yet contain at least 5 effective drugs

Initial individualized regimen will be initiated based on risk of resistance to FQs and SLIs or based on SL LPA test results while awaiting phenotypic SL DST results. Examples of regimens are as follows:

1) For patients with risk of resistance to FQ and/or SLI treatment with ***Bdq (Dlm), Lfx (Mfx), Cm, Lzd, Cfz, Pto*** will be initiated;
2) For patients with no risk of resistance to FQ and/or SLI where individualized regimen is indicated due to other reasons (such as severe TB) treatment with ***Bdq (Dlm), Lfx, Km (Cm, Am) Pto, Cfz, Z*** will be initiated***.***

The treatment regimen design for pregnant patients:

- Most pregnant patients should be started on treatment as soon as the diagnosis is made. However, since the majority of teratogenic effects occur in the first trimester, treatment may be delayed until the second trimester when the patient is very stable with minimum disease. ***Treat with three or four oral second-line anti-TB drugs*** which are likely to be highly effective against the infecting strain ***plus pyrazinamide***
- The regimen should be reinforced with an injectable agent and other drugs as needed immediately postpartum
- Avoid injectable agents. Aminoglycosides can be particularly toxic to the developing fetal ear. Cm may also carry a risk of ototoxicity but is the injectable drug of choice if an injectable agent cannot be avoided because of an immediate life-threatening situation resulting from

DR-TB. The option of using capreomycin thrice weekly from the start can be considered to decrease drug exposure to the fetus

- Avoid Pto (Eto) as it can increase the risk of nausea and vomiting associated with pregnancy, and teratogenic effects have been observed in animal studies
- Despite limited data on safety and long-term use of ***FQ, Cs, PAS and Amx/Clv*** in pregnancy, they are considered the drug of choice for DR-TB treatment during pregnancy
- There may not be a clear transition between the intensive phase and continuation phase, and the injectable agent can be given for three to six months postpartum even in the middle of treatment. Alternatively, if the patient is doing well and past the normal eight-month period for the injectable agent, it need not be added.

Dosage and administration

Table 3. Weight-based oral anti-TB drug daily dosing in adults ≥30 kg [4]

DRUGS	DAILY DOSE	30–35 KG	36–45 KG	46–55 KG	56–70 KG	>70 KG
Pyrazinamide	20–30 mg/kg once daily	800 mg	1000 mg	1200 mg	1600 mg	2000 mg
Ethambutol	15–25 mg/kg once daily	600 mg	800 mg	1000 mg	1200 mg	1200 mg
Levofloxacin	750–1000 mg once daily	750 mg	750 mg	1000 mg	1000 mg	1000 mg
Moxifloxacin	400 mg once daily	400 mg	400 mg	400 mg	400 mg [3]	400 mg [3]
Ethionamide	500–750 mg/day in 2 divided doses	500 mg	500 mg	750 mg	750 mg	1000 mg
Prothionamide	500–750 mg/day in 2 divided doses	500 mg	500 mg	750 mg	750 mg	1000 mg
Cycloserine	500–750 mg/day in 2 divided doses	500 mg	500 mg	500 mg	750 mg	750 mg
p-aminosalicylic acid	8 g/day in 2 divided doses	8 g	8 g	8 g	8 g	8–12 g
Bedaquiline	400 mg once daily for 2 weeks then 200 mg 3 times per week					
Delamanid	100 mg twice daily (total daily dose = 200 mg)					
Clofazimine	200–300 mg daily (2 first months) then reduce to 100 mg daily (alternative dosing 100 mg daily)					
Linezolid	600 mg once daily	600 mg	600 mg	600 mg	600 mg	600 mg
Amoxicillin/clavulanic-acid 7/1	80 mg/kg/day in 2 divided doses	2600 mg	2600 mg	2600 mg	2600 mg	2600 mg
Amoxicillin/clavulanic-acid 8/1	80 mg/kg/day in 2 divided doses	3000 mg	3000 mg	3000 mg	3000 mg	3000 mg
High-dose isoniazid	10mg/kg, maximum 600mg/day	300mg	400mg	500mg	600 mg	600mg

[3] Good results for patients on shorter DR-TB treatment regimens were obtained under program condition with Mfx 400 mg regardless of weight. In the STREAM trial, Mfx 800mg is used under clinical trial conditions. Until results on the safety of Mfx 800 mg are shared, CTB does not recommend this high dose of Mfx.

Imipenem/cilastatin	1000mg imipenem/1000 mg cilastatin twice daily
Meropenem	1000mg three times daily (alternative dosing is 2000 mg twice daily)

Table 4. Weight-based injectable anti-TB daily dosing in adults ≥30 kg [4]

DRUGS	DAILY DOSE	30–33 KG	34–40 KG	41–45 KG	46–50 KG	51–70 KG	>70 KG
Kanamycin	15–20 mg/kg once daily	500 mg	625 mg	750 mg	875 mg	1000 mg	1000 mg
Amikacin	15–20 mg/kg once daily	500 mg	625 mg	750 mg	875 mg	1000 mg	1000 mg
Capreomycin	15–20 mg/kg once daily	500 mg	600 mg	750 mg	800 mg	1000 mg	1000 mg

Table 5. Weight-based drug dosages for children (up to the age of 14 years): see Annex for details about drugs dosages in children [9] [10] [11]

Drug name	Daily pediatric dose in mg/kg (max dose in mg)
Bedaquiline [4]	300mg daily for 2 weeks, then 200mg 3 times a week
Delamanid	20 – 34kg 50mg twice daily, for 24 weeks >35kg 100mg twice daily, for 24 weeks
Fluoroquinolones	
Levofloxacin	7.5 – 10 (750)
Moxifloxacin	7.5 – 10 (400)
Second-Line Injectable	
Kanamycin	15 – 30 (1000)
Amikacin	15 – 22.5 (1000)
Capreomycin	15 – 30 (1000)
Other core second-line agents	
Ethionamide/protionamide	15 – 20 (1000) 2x daily
Cycloserine/terizidone	10 – 20 (1000) 1x/2x daily
Linezolid	10mg/kg/dose twice daily for children < 10; 300mg daily for children ≥ 10 years of age (600)
Clofazimine	2 – 3 (200)
Add on agents	
Pyrazinamide	30 – 40
Ethambutol	15 – 25
Isoniazid	7 – 15
PAS	200 – 300
Amoxicillin – clavulanate	80 (4000 amoxicillin and 500 clavulanate)
Meropenem	20 – 40 (6000)

Administration of new drugs

- Bdq is recommended for a maximum length of 24 weeks (6 months) from the start of treatment and comes in tablets of 100mg. The six-month dosing schedule in adult of the medication is as follows:
  - Week 0-2: bedaquiline 400 mg (4 tablets of 100 mg) daily (six days per week)

[4] Currently there is no WHO recommended dose for bedaquiline in children. Hence the dosage suggested above in Table 5 is based on current clinical experience from Belarus for children between 11 to 14 years of age.

  - Week 3-24: bedaquiline 200 mg (2 tablets of 100 mg) 3 times per week (with at least 48 hours between doses) for a total dose of 600 mg per week.
- Bdq pharmacokinetics (PK) and safety has not been formally evaluated in children. Persons under the age of 18 years were not included in the phase IIb Bdq trials, but part of this was due to the chellenges of obtaining ethical approval and consent for this population. Adolescents aged 12 years and above generally have similar PK paramaters to adults for most medications, and even stringent regulatory agencies have agreed that adult dosing recommendation can be extrapolated for this population. Multiple TB programs are already giving Bdq for adolescents as young as 12 years at the same dose as recommended for adults, after carefull consideration of the risk and benefits
- All children treated with Bdq should undergo close clinical monitoring and there should be careful documentation of the treatment experience and results
- Dlm is recommended for a maximum duration of 24 weeks (6 months), and children aged 15 years and above should receive the standard 100 mg twice daily dose
- Dlm can be given to children with DR-TB between the ages 6 – 14 years and their weight is 20kg or more, as pharmacokinetic (PK) and safety data to guide optimal dosing is available for this population. Children between the ages of 6 to 14 years should receive 50mg twice daily.

Note

For the management of DR-TB in selected special conditions and situations, such as pregnancy, breastfeeding, renal insufficiency please consult the WHO PMDT Companion Handbook and NTP protocols.

Organization of patient management

DR-TB expert committee

The DR-TB expert committee ensures the evaluation of eligibility, treatment regimen design, registration of each DR-TB patient and analyzes treatment monitoring results at the minimum every two months after treatment initiation during the intensive phase including at the time of completion of the intensive phase of treatment, at the minimum quarterly during the continuation phase and at the time of treatment completion. In the event of any complications and reversion during the treatment, each patient can be additionally considered by the DR-TB expert committee.

Table 6. Objectives for DR-TB expert committee review and timing of review per

Time from treatment initiation	Objective
Treatment enrollment («month 0»)	Assessment of eligibility criteria, evaluation of the patient's condition, treatment regimen design
2 months after treatment initiation	Evaluation of the treatment response (test results, clinical improvement), safety monitoring, regimen adjustment based on DST results, evaluation by surgeon (based on the table with indications for adjuvant surgery)
4, 6 months after treatment initiation	Evaluation of the treatment response, adverse events, decision on transition to the continuation phase
3, 6, 9, 12 months after initiation continuation phase	Evaluation of the treatment response, adverse events, decision on treatment completion or extension if needed
Additional review	In case of serious and severe AEs, TB complications and any other clinical situations

Initiating treatment

[Describe here the treatment enrollment procedures (max 1 page)]

All patients enrolled in care in the implementation sites and diagnosed with DR-TB will be evaluated for eligibility and regimen allocation by the DR-TB expert committee. The DR-TB Expert Committee will also evaluate the eligibility of patients with a high risk for RR-/MDR-TB, such as children who have been in close contact with a confirmed RR-/MDR-TB patient. After the DR-TB Expert Committee has decided on the treatment regimen most appropriate for the patient, the patient will be provided with information on DR-TB treatment. Informed consent will be obtained for patients enrolled in treatment with new drugs. (See informed consent procedure below).

At baseline, i.e., before initiation of treatment, a clinical evaluation as described in Annex A will take place. This includes an assessment of medical history, weight, height, vital signs, chest X-ray, laboratory examinations, HIV status, and other co-morbidities.

Laboratory examinations will include sputum smear, culture, molecular (if available) and phenotypic DST and in addition basic parameters (full blood count, liver transaminases, electrolytes, TSH, audiometry, glucose, serum creatinine and potassium), as well as HIV parameters if applicable. Pregnancy testing will be performed systematically for pre-menopausal women, and contraception will be recommended to female patients during the whole treatment period. Additional tests (e.g. ECG, viral hepatitis B and C, glomerular filtration) and consultations (e.g. psychiatrist, neurologist) may be applied depending on the treatment regimen and patient's history.

Note

If for whatever reason clinicians in a site are not able to decide which patients can initiate shorter regimen within 1-2 working days after a diagnosis is made, e.g. the DR-TB Expert Committee cannot meet so often, the clinician may decide that patients eligible according to the inclusion/exclusion criteria will be started on shorter regimen immediately, with evaluation by the DR-TB Expert Committee afterwards.

Hospitalization criteria

[Describe details here, based on bacteriology results, clinical condition, TB complications, adverse events, adjuvant surgery, etc. (max 0.5 page)]

Note

WHO does not require the hospitalization for patients on either shorter regimen or new drugs. Countries need to follow their standard protocols for this and try to reduce the hospitalization up to a maximum of 2 months.

Hospital discharge criteria

[Describe details here. (max 0.5 page)]

Community management

[Describe details here of the ambulatory treatment model(s), including DOT arrangements, detection and treatment of AEs, treatment monitoring arrangement, etc. Include details on what to do in case of missed doses. (max 1 page)]

Treatment support

Support for adherence will be provided according to standard guidelines. Although not part of this guide, TB programs should aim to support patients to the best of their abilities to help overcome financial, psycho-social and socio-economic barriers that could negatively affect treatment adherence and threaten the patient's ability to complete treatment. This is even more vital for DR-TB patients, given the longer and more toxic treatment required to be successfully treated. Contact tracing activities are to be implemented to prevent and control further spread of (DR-)TB.

[Describe details here on how support is provided to help overcome financial, psycho-social and socio-economic barriers that could negatively affect treatment adherence and threaten the patient's ability to complete treatment (max 0.5 page)]

Monitoring treatment response

Monitoring during treatment

- Patients should be monitored closely for signs of treatment failure
- Monitoring response to treatment is done through regular history taking, physical examination, chest radiograph and laboratory monitoring. For children, height and weight should be measured monthly to ensure that they are growing normally. For adults, weight should be recorded monthly (height is only recorded at the start of treatment)
- Chest radiographs should be taken at least every six months to document progress and to use for comparison if the patient's clinical condition changes
- The most important evidence of improvement is conversion of the sputum culture to negative.
- Drug susceptibility testing (DST) can be repeated for patients who remain smear and culture positive or who are suspects for treatment failure
- A key component of monitoring the progress of treatment is patient-centered directly observed therapy (DOT). All treatment should be given under direct observation and DOT providers should be trained on the signs of treatment failure.

[Describe here the clinical monitoring schedule and how examinations and consultations to monitor treatment efficacy are organized in practice at each site (which clinic and laboratory will perform which test, etc.). This should include a description of management of patients not responding to treatment, including signs and time points when to switch to regimens, and when to extend the treatment duration. (max 1.5 pages)]

Table 7. Activities for monitoring treatment response [4]

Monitoring & Evaluation	Recommended frequency
Evaluation by clinician	There will be clinical follow up with a doctor for all patients at 2 weeks after DR-TB treatment initiation and then monthly until treatment completion. During the continuation phase: Monthly assessments unless there is a medical necessity to see the patient more often. The DOT supporter sees the patient daily between consultations and signals any concerns to the clinician.
Treatment adherence and Tolerance	Daily at every DOT encounter by the DOT provider.
Sputum smears and culture	Monitoring smears and culture monthly throughout treatment. (Note: programs with limited resources may choose to do monthly smears and cultures until conversion and then monthly smears with every other month cultures.)
Weight	At baseline, then every two weeks for first three months and then monthly.
Height	At start of treatment for all (to be able to assess BMI throughout treatment); monthly for children (to assess growth).
Drug susceptibility testing	At baseline for first- and second-line anti-TB drugs. Repeat DST for patients who remain culture-positive or revert after month four
Chest radiograph	At baseline, and then every six months.

Note

The baseline assessment and clinical monitoring schedule is under the responsibility of the National TB Programs in each country and may slightly vary. It is based on WHO recommendations (PMDT Companion Handbook and generic WHO protocol for shorter regimen) and WHO recommendations for the introduction of new anti-TB drugs. All recommended examinations and consultations are presented in Annex A. All examinations should be performed in quality assured laboratories at recommended frequency and should be free of charge for patients.

Follow-up after treatment completion

All patients will be followed up until 12 months after the DR-TB treatment has ended. A follow-up visit will be planned at 6 months after treatment completion (or at any time earlier in case of re-occurrence of symptoms) for clinical assessment and a final visit will take place at month 12 post-completion.

Note

The aim is to follow up all patients at least 12 months after end of treatment, but at the minimum there should be 12 months post-treatment follow-up for patients who are successfully treated.

Recording of treatment effectiveness

Data on **effectiveness** will be collected from routinely used electronic recording and reporting systems (i.e. eTB manager) or from routine registers (laboratory registers, TB registers) and patients' medical records as necessary. If needed, patient treatment cards will be updated so they are in accordance with WHO's PMDT and aDSM guidelines [3].

Each country will collect individual patient data to enable programmatic analysis on the indicator data. Standard variable definitions will be used as much as possible across countries to allow for multi-country analysis. A list of minimal data elements in line with WHO's PMDT and aDSM guidelines to be collected is included in Annex C.

The routinely collected **baseline information** for all patients diagnosed with RR-/MDR-TB or with presumptive MDR/XDR-TB includes:

- Demographic data (age, sex, height, weight, etc.)
- TB treatment history
- DR-TB contact history
- Laboratory test results (smear, culture, DST, Xpert MTB/RIF, Genotype®MTBDR*plus*, etc.) at diagnosis of RR-TB, with date of collection of the sample(s) and date of test result
- Chest X-ray results
- TB treatment initiation date and regimen initiated, and
- HIV-status and other co-morbidities.

The routinely collected information on treatment **effectiveness** for all patients diagnosed with RR-/MDR-TB or with presumptive MDR/XDR-TB and started on DR-TB treatment, includes:

- Follow-up laboratory test results (smear, culture, DST, etc.)
- Any adjustment to the treatment regimen including reasons for adjustment and date of adjustment
- Treatment outcome, and
- As already is standard practice in most countries and in accordance with WHO PMDT guidelines, post-treatment follow-up visits will be conducted at 6 and 12 months after the end of treatment when a clinical examination and sputum smear microscopy and culture will be performed. At those visits data will be recorded on long term treatment outcome (relapse, no relapse).

Active drug safety monitoring and management (aDSM)

Clinical monitoring and management of adverse events (AE) [5]

- AEs should be monitored in a systematic and timely manner. At every DOT encounter, health workers should ask the patient about clinical symptoms of common AEs including skin rashes, gastrointestinal disturbances, psychiatric disturbance (headache, anxiety, depression, irritability, behavior change), jaundice, vestibular toxicity (nausea, vertigo, ataxia), peripheral neuropathy and symptoms of electrolyte wasting (muscle cramping, palpitations). Ototoxicity (hearing loss) needs particular attention
- A set of laboratory tests will be performed according to schedule (see annex A)
- Laboratory monitoring outlined in Annex A should be performed to detect occult adverse effects. As Mfx (Gfx), Cfz, and the new drugs, Bdq and Dlm, may induce QT prolongation, monitoring of ECG is essential and required for all countries under this guide
- There will be clinical follow up with a doctor for all patients at a minimum at 2 weeks after DR-TB treatment initiation and then monthly until treatment completion. At each visit, clinical assessment with evaluation of treatment efficacy and AEs will be conducted. Treatment safety will be assessed by the doctor and/or nurse with a specific data collection form (either the one already in use routinely or if not available, introduced at the implementation sites)
- Any relevant clinical event (adverse events or reactions) and any required additional diagnostic testing and/or therapy will be recorded
- Management of AEs should take patient safety and treatment need into consideration. For minor AEs, re-assurance to enhance adherence is needed. For AEs that need additional evaluation and/or medical treatment, a treatment decision structure (consultation back-up for DOT provider), additional tests and ancillary medicines should be available and accessible, free of charge
- If drug(s) thought to cause the AE need to be removed from the regimen, replacement might be required, especially in the intensive phase when the bacillary load is high. Replacement of drugs should take the clinical condition and bacteriological status of patients into account. Follow as much as possible the steps outlined in table 1, and ensure at least 4 medicines with known effective drugs. Any decision must be made on the basis of careful case review.

[Describe here how AEs will be managed, including which examinations will be done in which laboratory and when, how consultation back-up for DOT nurses is established, which AEs should be discussed in consilium, when drug or whole treatment should be stopped, etc. (max 2 pages)]

Note

A table on Management of AEs with ancillary drugs should be based on WHO recommendations (Companion Handbook Table 11.4, page 166) [4].

Recording and reporting of AEs

Like the data on effectiveness, data on **safety** will be collected from routinely used electronic recording and reporting systems (i.e. eTB manager) or from routine registers (laboratory registers, TB registers)

[5] **Adverse event** is any untoward medical occurrence that may present in a TB patient during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship wiith this treatment (refer to Annex C and Reference 3).

and patients' medical records as necessary. If needed, patient treatment cards will be updated so they are in accordance with WHO's PMDT and aDSM guidelines [3].

Each country will collect individual patient data to enable programmatic analysis on the indicators. Standard variable definitions will be used as much as possible across countries to allow for multi-country analysis. A list of minimal data elements in line with WHO's PMDT and aDSM guidelines to be collected is included in Annex C.

Routine data collection on **safety** of the DR-TB regimens includes registration of all SAEs and AEs of special interest – in line with the intermediate aDSM package. For all patients who started on DR-TB treatment who experience an SAE or AE of special interest the following information will be recorded:

- meDRA or WHO-ART code
- Type of SAE (congenital anomaly or birth defect; persistent or significant disability; death; required hospitalization; prolonged hospitalization; life threatening)
- Type of AE of special interest
- Onset date of adverse event
- Clinical action taken (including provision of ancillary drugs, rechallenge), and
- Result of the causality assessment (whether the SAE is attributable to one or more anti-TB or concomitant drugs).

Note

- Countries may decide to implement the advanced aDSM package with recording and reporting of all AEs of clinical significance. In that case the same information will be recorded for those AEs, including type of AE of clinical significance.

[Describe here for which adverse events (i.e. SAE and AEs of special interest, or also other AEs of clinical significance) data will be specifically registered and reported, how collaboration with pharmacovigilance (PV [6]) authorities will be established to ensure that data on the adverse events collected also will be available to the pharmacovigilance authorities, that causality assessment will be done in an expert committee existing of at least DR-TB and PV experts, and that conclusions on causality assessment will be available to the NTP and for analysis.]

[Describe here how this will be organized - shown in Annex A with suggestion to incorporate schedule of follow-up for short and individualized regimens. (max 2 pages)]

Programmatic monitoring and evaluation

Routine recording and reporting data on RR-TB patients according to WHO's PMDT and aDSM guidelines, and standardized quality-improvement information collected during programmatic monitoring and supervision visits will allow for monitoring of implementation and programmatic evaluation of effectiveness and safety. Monitoring on enrollment, safety and (interim) treatment outcomes will be done quarterly at the site, and in case of several implementing sites, also at the regional or national level.

[6] WHO defines pharmacovigilance as the"science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem"

Recording and reporting

At each implementation site, clinicians or their medical assistants need to make sure that all data are completely, appropriately and consistently collected according to the guidelines.

Facility level data will be managed and monitored by the NTP. TA partners will assist with quarterly data monitoring, including data quality checks and analyses, while building in-country capacity. Listings of missing or incorrect data based on quarterly data quality checks will be sent to the sites along with monitoring reports, and corrections will be done directly in the database and registers on site.

[Describe here the electronic data capture system(s) that will be used for recording and reporting of patient and treatment data. If no routine electronic TB registration system is in use, describe if an electronic database will be developed specifically to record data not yet included in the routinely used database (provide name of software). Describe archiving procedures at the sites, or refer to where this already has been described. (max 1 page)]

All relevant data for patient management will be entered in the patient's medical file. Data quality procedures are to be put in place to ensure data accuracy and completeness at the primary data source (patient file). Routine data management procedures are to be put in place to ensure quality transfer of data from paper records into the electronic registers (e.g. reports of missing and out-of-range values, consistency checks).

[Summarize the process of data capture and refer to the corresponding SOP (max 0.5 page)]

At national level, the NTP is responsible for monitoring the data collected and reported by the participating sites (see monitoring and supportive supervision).

The NTP is responsible for sharing relevant AE data with the pharmacovigilance authorities. The AE reporting form is included in Annex E.

[Describe how data will be exchanged between the NTP and the national PV authorities to allow for causality assessment of serious adverse events. (max 0.5 page)]

Note

- Each implementation site will maintain its own electronic database. If an electronic data recording and reporting system is in place, adaptations can be made to include missing data elements related to drug safety monitoring and management, including PV data elements. This is preferred above creating a separate (interim) recording and reporting system for aDSM. Sites that currently do not have a functional electronic data recording and reporting system are encouraged to develop their own system with assistance of partners
- If possible, data should be entered directly into a case-based electronic data collection system (i.e., a patient management system) by the clinician. This is not possible in most countries. In that case, data will be collected routinely on the existing forms and registers, and regularly entered in the database. Data need to be updated regularly for each patient, e.g. bacteriology results becoming available during treatment and AE data. When treatment outcome is declared, a final check is needed to confirm that all data are entered

- The AE form in annex D is an example form, listing all data elements to be included. Include the reporting form to be used locally
- If possible, a data management system to allow exchange of pharmacovigilance data between NTP and the pharmacovigilance authorities will be established to allow for reporting of SAEs and inclusion of causality assessment results into the NTP data collection system
- If a country decides to add indicators or research questions that require information beyond what is routinely collected, this may require a formal study. Such a study protocol will need to be developed separately from this guide, and may require approval from an ethical committee.

Programmatic indicators on effectiveness

The programmatic indicators on effectiveness – to be reported based on routine patient data recorded- are:

1. Distribution of patients in DR-TB regimen groups allocated through the diagnostic algorithm
2. Treatment outcomes by DR-TB regimen group: interim (6-month culture conversion) and final treatment outcomes including the number and proportion of patients requiring a change of regimen due to the occurrence of adverse drug reactions or lack of efficacy of the regimen
3. Frequency of relapse at 6 and 12 months after successful treatment completion by DR-TB regimen group
4. Frequency and timing of smear and culture conversion, by each DR-TB regimen group.

Note

For patients diagnosed with RR-/MDR-TB who are not started on any DR-TB treatment regimen, the reasons for not starting DR-TB treatment will be registered in their patient file, e.g., critical condition, death, drugs not available to form an appropriate regimen, etc.

Programmatic indicators on safety

The programmatic indicators on safety – to be reported based on routine patient data recorded- are:

1. Frequency of serious adverse events (SAE[7]), by DR-TB regimen group
2. Frequency of adverse events of special interest,[8] by DR-TB regimen group.

Monitoring and supportive supervision

Programmatic monitoring and supervision visits will promote adherence to the diagnostic and treatment algorithms, to promote clinical monitoring before and during treatment according to the guidelines used, and to ensure recording and reporting is complete. Furthermore, monitoring and supervision will identify difficulties that need resolving.

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[7] **Serious adverse event (SAE)** is 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 (refer to Annex C and Reference 3).

[8] **Adverse event of special interest** is an 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. The centers that offer intermediate and advanced packages of aDSM will include all AEs of special interest in their reporting (refer to Annex C and Reference 3).

NTP and partners providing technical assistance organize supportive supervision. Especially during the first period after starting enrollment this is important to trouble shoot and provide additional on-the-job learning where needed to optimize quality of care and quality of data collection. Therefore, verify for at least the first 20 patients enrolled adherence to the algorithms, clinical guidelines and data recorded and reported in hard-copy and soft-copy to ascertain barriers to implementation, further training requirements, and other difficulties that may be encountered in the field.

[Describe how supportive supervision will be organized including roles, responsibilities, frequency etc.]

Information will be collected using standardized checklists filled during monitoring and supportive supervision visits. The collected information will be used for continuous quality improvement.
During supportive supervision visits at all different levels, the monitoring and supportive supervision checklist. (**Table *8***) will be filled to track implementation.

Table 8. Monitoring and supportive supervision checklist

Components	Follow up on recommendations from previous visit	Status	Strengths	Weaknesses	Changes made	Recommendations for further solutions and follow-up
1. Planning (site preparation)						
2. Training and capacity building						
3. Application of diagnostic algorithm						
4. Regimen design/adherence						
5. Psycho-socio-economic patient support						
6. Clinical monitoring on effectiveness (bacteriological follow-up)						
7. Clinical monitoring and management on safety (AEs)						
8. Pharmacovigilance (reporting of AEs)						
9. Drug supply and management						
10. Recording and reporting						

To assess adherence to the guide actual procedures will be compared with activities described in this guide through review of records, using the assessment checklist (**Table *9***).

During the visit, at least 10 treatment cards of patients on treatment in the last month are reviewed to assess compliance to the guide and to compare recording and reporting on hard-copy and soft-copy.

Table 9. Assessment checklist

Critical Steps	Implemented according to guide/guidelines *	Not implemented according to guide /guidelines^	If not according to guide/guidelines, why?	Changes made	Recommendations for further solutions and follow-up
1. Diagnostic algorithm					
2. Treatment initiation					
3. Clinical monitoring of effectiveness					
4. Clinical safety monitoring and management					
5. Pharmacovigilance (reporting to PV center and causality assessment)					
6. Recording and Reporting[#]					

* yes/no/partially

^ if not or only partially implemented, list what was not conducted according to the guide/guidelines

[#] based on comparison of recording and reporting on hard-copy and soft-copy of at least 10 treatment cards of patients on treatment in the last month

Partnership, implementation team and coordination

[Describe how the implementation will be coordinated, monitored, what are the roles and responsibilities of different partners, what kind of trainings and for whom these will be provided, etc.]

[Describe here names, organizations and roles and responsibilities of all staff involved in the implementation and patient care]

[Describe here the initial and potential future implementation sites for implementation with background on number of TB/MDR-TB patients diagnosed and treated per year, number of beds, etc. (max 1 page)]

Ethical Considerations

Considering that this guide describes how to programmatically implement PMDT care in accordance with WHO guidelines and the indicator data utilize only anonymized and routine data collected in accordance with WHO guidelines for quality patient care will be used, ethics approval would not be required according to international regulations. However, if required by national standards, regulatory approval will be obtained from national authorities and if needed, from local authorities.

[Describe here whether and if yes, from which ethics committee(s) and other regulatory authorities' approval will be sought (max 0.5 pages)]

Informed consent

Informed consent needs to be obtained for patients treated with the new anti-TB drugs Bdq and Dlm [4]. Once eligibility for DR-TB treatment is established, the site physician will discuss the details of the treatment regimen, monitoring and follow-up procedures, and the risks and benefits. The patient will be given adequate time to answer all questions, and an opportunity to ask questions, which the site physician will address accordingly.

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7. WHO. The use of bedaquiline in the treatment of MDR TB. 2013 Interim guidance.

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Annexes

A. Baseline & Follow-up examinations for monitoring of DR-TB treatment efficacy and safety
B. List of essential data elements to be recorded
C. Definitions
D. Adverse event reporting form
E. List of Standard Operating Procedures to be developed per site
F. Weight based dosing of SLDs in children
G. Contraindications and precautions for medicines used for treatment of DR-TB

Annex A. Baseline & Follow-up examinations for monitoring of DR-TB treatment efficacy and safety

Examination	Baseline (at start of MDR/XDR-TB treatment)	Intensive phase	Continuation phase	Follow up after treatment completion	Remarks
Clinical evaluation					
Treatment adherence and tolerance		Daily at every DOT encounter by the DOT provider			
Evaluation by clinician	√	Every day during the first weeks if hospitalized and at least every week if treated as outpatient, until the treatment is well tolerated. Once stable, the patient is seen twice a month or once a month	Monthly assessments unless there is a medical necessity to see the patient more often.	At months 6 and 12	DOT supporter sees the patient daily between consultations and signals any concerns to the clinician.
Educational, psychosocial and social consultation	√	Repeat when indicated	Repeat when indicated	Repeat when indicated	Including highlights from the informed consent, provide new information when available about medicines and regimens
Psychiatrist/HIV specialist/ narcologist etc.	When indicated	When indicated	When indicated	Repeat when indicated	

Weight	√	Monthly	At least quarterly	At months 6 and 12	More frequent for children to adjust drug dosage to the bodyweight
Height	√	Monthly for children	Monthly for children		More frequent for children (to assess growth and BMI)
Neurological examination	When indicated	When indicated	When indicated	When indicated	Special attention to patients receiving Lzd
Audiometry	√	Monthly while on injectable	Monthly while on injectable	When indicated	
Chest X ray	√	Every 6 months	Every 6 months	At months 6 and 12	
Electrocardiogram	Recommended for all. Mandatory for patients receiving Bdq or Dlm	At weeks 2, 4, 8, 12 and 24 after starting treatment with Bdq or Dlm. Monthly if other QT prolonging drugs other than Bdq or Dlm are used	Monthly if taking Bdq or Dlm		Special attention in patients receiving more than one QT prolonging drug (Bdq, Dlm, Mfx, Lfx, Cfz) or with low albumin (<3,4g/dl)
Visual acuity test with Snellen charts and color vision	For patients on long-term ethambutol or linezolid	When indicated	When indicated	When indicated	
Bacteriological testing					
Smear	√	Monthly	Monthly	At months 6 and 12	Programs with limited resources may choose to do monthly smears and cultures until conversion and then monthly smears
Culture	√	Monthly	Monthly	At months 6 and 12	

					with every other month cultures
Phenotypic DST to second line drugs	√	When indicated: if patient remains culture-positive or reverts after month 4 of treatment	When indicated: if patient reverts after conversion	When culture-positive	Repeat DST for patients who remain culture-positive or revert after month four. This includes also DST to new drugs (Bdq and Dlm) if they are part of the regimen
Laboratory testing					
Hemoglobin and white blood count	√	Monthly	At least quarterly	When indicated	If on Lzd monitor weekly at first month, then monthly or as needed based on symptoms. For HIV-infected patients on zidovudine, monitor monthly initially and then as needed based on symptoms
Platelets	When indicated	When indicated	When indicated	When indicated	Indicated for patients using Lzd
Serum creatinine	√	Monthly while on injectable	Monthly while on injectable	When indicated	Every 1-3 weeks in HIV-infected patients, diabetics and other high-risk patients
Serum potassium	√	Monthly while on injectable	Monthly while on injectable	When indicated	Every 1-3 weeks in HIV-infected patients, diabetics and other high-risk patients
Serum magnesium and calcium	When indicated	When indicated	When indicated		Check magnesium and calcium levels whenever

					hypokalaemia is diagnosed. At baseline and then monthly if on Bdq or Dlm. Repeat if any ECG abnormalities develop
Liver enzymes (ALAT/SGOT, ASAT/SGPT)	√	Monthly	At least quarterly	When indicated	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. For patients with viral hepatitis monitor every 1-2 weeks for the first month, then every 1-4 weeks.
Thyroid stimulating hormone (TSH)	When indicated	When indicated	When indicated	When indicated	Close monitoring if receiving Eto / Pto and/or PAS. Every 3 months if on both drugs, every 6 months if on one of the drugs.
Serum albumin	√	Every 2 months for patients on Dlm	When indicated	When indicated	
Lipase/amylase	When indicated	When indicated	When indicated	When indicated	Special attention to patients receiving Bdq, lzd, D4T, ddI or ddc, and based on risk factors

Lactic Acid	When indicated	When indicated	When indicated	When indicated	For work up of lactic acidosis in patients on Lzd and ART
Serum glucose	√	When indicated	When indicated	When indicated	If receiving Gfx, measure fasting blood glucose at baseline and monthly
Pregnancy test	√	When indicated	When indicated	When indicated	
HIV	√	When indicated	When indicated	When indicated	Repeat if clinically indicated; should consider to test bi-yearly in high HIV-burden settings
Glomerular filtration	When indicated	When indicated	When indicated	When indicated	Based on risk groups (elderly, diabetes, receiving nephrotoxic drugs etc.)
Viral hepatitis serology (B and C)	When indicated	When indicated	When indicated	When indicated	Based on risk factors

Annex B. Overview of essential data to be collected on the effectiveness and safety indicators

A. Data collected at start of DR-TB treatment (orange ones are not essential but preferable)

Data element	**Categories or values (*when applicable*)**
Facility information	
Consultation/examination date	DD-MMM-YYYY
Facility name and address	free text /drop-down list
Patient information	
Patient ID	TBD
Patient name	free text
Date of birth	DD-MMM-YYYY
Sex	M; F
Height (cm)	###.#
Weight (kg)	###.#
Cavities on baseline chest x-ray	U (unilateral); B (bilateral); N; U
Site of TB	PTB only; PTB+EPTB; EPTB only; Unknown
Extrapulmonary TB site	List of possible locations (can include >1 site) with free text for 'other'
TB patient category	[standard list of patient categories: in most countries at least: new, relapse, after loss to follow-up, failure after FLD treatment, failure after SLD treatment, other]
Previous TB treatment?	Y; N; U
Previous TB treatment: last regimen before current treatment	Cat I; Cat II; MDR-TB; other (specify)
Outcome of previous TB treatment (last regimen)	[standard list of outcomes]
Date of outcome of previous TB treatment (last regimen) – from register.	DD-MM-YYYY (If date is unknown: enter 1st day of month and year or year only (take 1 July))
Documented contact with MDR-TB or XDR TB patient?	Y; N; U
Injecting Drug Use	Y; N; U

Excessive alcohol use	Y; N; U
Any concomitant diagnoses or events	free text (List all current medical conditions including pregnancy)
Documented HIV infection	Y; N; U
IF HIV-infected: On anti-retroviral therapy	Y; N; U
If HIV-infected: using cotrimoxazole	Y; N; U
For pre-menopausal female patients result of baseline pregnancy test	Negative, Positive, Unknown
DR-TB treatment initiated after confirmed rifampicin resistance or as presumptive DR-TB patient	Confirmed RR-TB; presumptive MDR-TB; presumptive XDR-TB; other (specify)
Smear microscopy result(s) at baseline	
Date of sample collection for smear microscopy for diagnosis of TB	DD-MM-YYY *(repeat for sample 1-3 depending on local situation)*
Sample number	
Result of smear microscopy	1-9AFB; 1+; 2+; 3+; negative; positive (no grading); not done *(repeat for sample 1-3 depending on local situation)*
Date of smear microscopy result	DD-MM-YYYY *(repeat for sample 1-3 depending on local situation)*
Culture result(s) at baseline	
Date of sample collection for culture for diagnosis of (DR-)TB	DD-MM-YYY *(repeat for sample 1-3 depending on local situation)*
Sample number	
Date of inoculation on culture for diagnosis of (DR-)TB	DD-MM-YYY *(repeat for sample 1-3 depending on local situation)*
Culture method	Solid; Liquid; Unknown
Result of culture	1-9CFU; 1+; 2+; 3+; no growth; positive (no grading) MTB; NTM; contaminated; not done *(repeat for sample 1-3 depending on local situation)*
Date of culture result	DD-MM-YYYY *(repeat for sample 1-3 depending on local situation)*

Drug susceptibility by any laboratory test(s) result(s) at baseline	
Drug name	Anti-TB drug abbreviation from the list [Name] *(repeat per drug tested for)*
Laboratory test method	Xpert MTB|RIF; Genotype®MTBDR*plus*; liquid culture DST; solid culture DST other *(country specific tests, repeat per test used)*
Date of sample collection for drug susceptibility/resistance marker test	DD-MM-YYYY
Sample number	
Date of test result	DD-MM-YYYY
Test(s) result(s) (baseline)	SUSCEPTIBLE; RESISTANT; INDETERMINATE; UNKNOWN

DR-TB treatment regimen	
Date of DR-TB Expert Committee decision to start MDR/XDR Treatment	DD-MM-YYYY
Initial DR-TB treatment regimen start date	DD-MM-YYYY
Initial DR-TB treatment regimen group	Shorter DR; Pre-XDR/XDR; Conventional regimen
Adjusted DR-TB treatment regimen group	Shorter DR; Pre-XDR/XDR; Conventional regimen (leave blank if not adjusted)
Adjusted DR-TB treatment regimen start date	DD-MM-YYYY
Drug name	Anti-TB drug abbreviation from the list [Name] *(repeat for all drugs in the regimen; may choose to include standard regimens)*
Daily Dose	####
Unit of dose	Mg
Days/week	#
TB drug start date	DD-MMM-YYYY
TB drug end date	DD-MMM-YYYY
Reason for changing/stopping TB drug	End of intensive phase; lack of effectiveness; drug resistance; AE; other

B. Repeatedly collected data on treatment effectiveness

Data element	**Categories or values (*when applicable*)**
Smear microscopy result(s) during DR-TB treatment follow-up	
Date of sample collection for smear microscopy during follow-up	DD-MM-YYY *(repeat for sample 1-3 depending on local situation)*
Sample number	
Result of smear microscopy	1-9AFB; 1+; 2+; 3+; negative; positive (no grading); not done *(repeat for sample 1-3 depending on local situation)*
Date of smear microscopy result	DD-MM-YYYY *(repeat for sample 1-3 depending on local situation)*
Culture result(s) during DR-TB treatment follow-up	
Date of sample collection for culture during follow-up	DD-MM-YYY *(repeat for sample 1-3 depending on local situation)*
Sample number	
Date of inoculation on culture during follow-up	DD-MM-YYY *(repeat for sample 1-3 depending on local situation)*
Culture method	Solid; Liquid; Unknown
Result of culture	1-9CFU; 1+; 2+; 3+; no growth; positive (no grading) MTB; NTM; contaminated; not done *(repeat for sample 1-3 depending on local situation)*
Date of culture result	DD-MM-YYYY *(repeat for sample 1-3 depending on local situation)*
Drug susceptibility by any laboratory test(s) result(s) during DR-TB treatment follow-up	
Drug name	Anti-TB drug abbreviation from the list [Name] *(repeat per drug tested for)*
Laboratory test method	Solid culture DST; Liquid culture DST; Hain SL; other *(country specific tests, repeat per test used)*
Date of sample collection for drug susceptibility/resistance marker test	DD-MM-YYYY
Sample number	
Date of test result	DD-MM-YYYY *(repeat for sample 1-3 depending on local situation)*

Test(s) result(s) (baseline)	SUSCEPTIBLE; RESISTANT; INDETERMINATE; UNKNOWN *(repeat for sample 1-3 depending on local situation)*

C. repeatedly collected data on DR-TB treatment safety

Data element	**Categories or values (*when applicable*)**	
Adverse Events (AEs) including new events or changes in pre-existing conditions for SAEs and other AE of special interest selected for recording and reporting		
Patient ID	free text	
Reporter (person filling out paper form)	free text / drop-down list	
AE MedDRA/WHO-ART numeric code**	free text	
Onset date	DD-MMM-YYYY	
AE category	SAE, AE of special interest, other	
If SAE, indicate type of SAE	A congenital anomaly or birth defect	Y; N
	Persistent or significant disability	Y; N
	Death	Y; N
	Required hospitalization	Y; N
	Prolonged hospitalization	Y; N
	Life Threatening	Y; N
If AE of special interest, indicate the type of AE	[list of AEs selected by site for recording and reporting]	
If 'Other AE' registered	Free text / drop-down list with 'other' option	
The following data should be collected at least for SAE and AE of special interest		
Result of rechallenge^	No rechallenge done; Recurrence of event; No recurrence; Result unknown	
Clinician action taken with regard to TB drug suspected causing AE (for each suspected drug)^	Dose not changed; Dose reduced; Drug interrupted; Drug withdrawn; Not applicable	
Ancillary drug provided^	Y; N; UNKNOWN	

If “yes”, which ancillary drugs were used	Free text
Concomitant Drug Name^	free text *(repeat per concomitant drug)*
Concomitant drug start date^	DD-MMM-YYYY *(repeat per concomitant drug)*
Concomitant drug end date^	DD-MMM-YYYY *(repeat per concomitant drug)*
Was the AE attributed to one or more anti-tuberculosis or concomitant drugs? ^ **	Y; N; UNKNOWN
Select the first most likely drug that the AE may be attributed to ^ **	Anti-TB drug abbreviation from the list [Name]
Causality grade	Drop-down list: certain, probable, possible, unlikely, unclassified, un-assessable
Select the second most likely drug that the AE may be attributed to ^ **	Anti-TB drug abbreviation from the list [Name]
Select the third most likely drug that the AE may be attributed to ^ **	Anti-TB drug abbreviation from the list [Name]
Outcome (Status of the AE) ^	Resolved; Resolved with sequelae; Fatal; Resolving; Not resolved; Unknown
If resolved, provide resolution date ^	DD-MMM-YYYY

^ to be filled in case of an SAE or an AE of special interest

*If the AE is due to an abnormal laboratory test or clinical examination result, indicate the AE type (e.g., “anaemia”) and enter the value of the test result with units (e.g. “Hemoglobin 4.9 mmol/L”).

**Done by national PV committee or at PV Centre.

D. Repeatedly collected data in case of changes in pregnancy status

Pregnancy status (in case of changes)	
Pregnancy Status	Y; N; U; NA
Pregnancy Status recording date	DD-MMM-YYYY
If pregnant, gestation week	##

E. Data collected at end of DR-TB treatment

Data element	**Categories or values (*when applicable*)**
Interim outcome of current treatment episode, at 6 months of treatment	Culture converted; Culture not converted; Culture reverted after earlier culture conversion; Died; Lost to follow-up; Not evaluated; Not assessable
6-month interim treatment outcome date	DD-MMM-YYYY
Outcome at end of current treatment episode	Cured; Treatment completed; Treatment failed; Died; Lost to follow-up; Not evaluated
End-of-treatment outcome Date	DD-MMM-YYYY
Date of follow-up visit (6 months)	DD-MMM-YYYY
Status at follow-up at 6 months	Relapse; No relapse; Unknown
Date of follow-up visit (12 months)	DD-MMM-YYYY
Status at follow-up at 12 months	Relapse; No relapse; Unknown

Annex C. Standard definitions

Adverse event (AE): Any untoward medical occurrence that may present during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with this treatment.

Adverse events of special interest: (suggested list from aDSM document):

- Peripheral neuropathy (paraesthesia);
- Psychiatric disorders and central nervous system toxicity (e.g. depression, psychosis, suicidal intention, seizures);
- Optic nerve disorder (optic neuritis) or retinopathy;
- Ototoxicity (hearing impairment, hearing loss);
- Myelosuppression (manifested as anaemia, thrombocytopenia, neutropenia or leukopenia);
- Prolonged QT interval (Fredericia correction; see (8));
- Lactic acidosis;
- Hepatitis (defined as increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥5x the upper limit of normal (ULN), or increases in ALT or AST ≥3x ULN with clinical manifestations, or increases in ALT or AST ≥3x ULN with concomitant increase in bilirubin ≥1.5 x ULN);
- Hypothyroidism;
- Hypokalaemia;
- Pancreatitis;
- Phospholipidosis; and
- Acute kidney injury (acute renal failure).

Adverse events leading to treatment discontinuation or change in drug dosage: Results in a temporary interruption, permanent discontinuation, or change in the dose of one or more drugs directed by the doctor

Adverse events not listed above but judged as otherwise clinically significant by the treating clinician

Acquisition of additional resistance: in vitro resistance to one or more drugs used in treatment, observed after treatment initiation and not at baseline, with no molecular evidence of mixed or re-infection. (This requires storage of baseline strains, and genotyping of baseline and follow-up samples with extended drug resistance.)

Culture conversion: Two cultures found negative from two samples taken at least 30 days apart. The specimen collection date of the first negative culture is used as the date of conversion.

Culture reversion: After an initial conversion, two cultures found positive from two samples taken at least 30 days apart.

Drug dose change: Change in the dose of a drug. Changes can be related to a change in patient weight, an AE or any other reason.

Extension of additional resistance: in vitro resistance to one or more drugs used in treatment, observed after treatment initiation and not at baseline. Ideally extension would be determined in a supranational reference laboratory.

Medication error: unintended mistakes in the prescribing, dispensing and administration of a medicine that could cause harm to a patient (e.g. wrong drug prescribed, overdose).

Multidrug resistance (MDR): Resistance to at least both isoniazid and rifampicin.

Not related AE: an AE is considered not related to one or more TB drug(s) in the situations where there is no reasonable possibility that the drug(s) caused the AE. This implies that there is a plausible alternative cause for the AE that better explains the occurrence of the AE or that significantly confounds the causal relationship between the drug(s) and the AE.

Regimen change: Change between DR-TB regimen group or change of at least two drugs within one DR-TB regimen group.

Related AE: an AE for which a causal relationship with one or more TB drug(s) is at least a reasonable possibility. All AEs for which there is insufficient information to fully assess the causal relationship with the TB drug(s) will be conservatively considered related to the drug(s) as a convention.

Serious adverse events: Any untoward medical occurrence that, at any dose or frequency:

- Results in death.
- Is life-threatening; life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.
- Requires inpatient hospitalization or prolongation of hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly or a birth defect.
- Is otherwise medically significant; medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above.
- Suspected transmission of an infectious agent (e.g. pathogenic or non-pathogenic) via drug is always considered an SAE.

Relapse: Relapse will be considered six and 12 months after successful treatment completion and is defined as:

- Relapse-free: A DR-TB patient who meets the criteria of cured or completed short course of treatment and remains asymptomatic.

- Relapse: A DR-TB patient who meets the criteria of cured or completed short course of treatment and at any time within the first year after treatment completion is subsequently diagnosed with at least one sample of bacteriologically positive DR-TB by culture and DST.

Smear conversion: Two smears found negative from two samples taken at least 7 days apart. The specimen collection date of the first negative culture is used as the date of conversion. The smear will be the primary means of determining the duration of the intensive phase as described above. For patients who remain smear positive, then culture results will also be taken into account.

Treatment/Drug discontinuation: Permanent discontinuation of a regimen/drug. This can be due to a declared treatment outcome (i.e. cured, treatment completed, failed, lost to follow up or died) or an AE.

Treatment/Drug interruption: Temporary discontinuation of a regimen/drug by the patient or clinician.

Treatment Outcomes:
Cured: Treatment completed as recommended by the national policy without evidence of failure AND 3 three or more consecutive cultures take 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 three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.

Treatment failed: Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of:

- Lack of conversion by the end of intensive phase; or
- Bacteriological reversion in the continuation phase after the conversion to negative; or
- Evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs; or
- Adverse drug reactions (ADRs).

Died: A patient who dies for any reason during the course of treatment.

Lost to follow-up: A patient whose treatment was interrupted for two consecutive months or more.

Not evaluated: A patient for whom no treatment outcome is assigned (this includes cases ‘transferred out' to another treatment unit and whose treatment outcome is unknown).

Treatment success: The sum of *Cured* and *Treatment completed*

Favorable outcomes: the sum of patients declared Cured or Treatment completed
Unfavorable outcomes: the sum of patients declared Treatment failed, Lost to follow-up and Died.

Annex D. Adverse event reporting form (to report SAEs and other AEs selected for recording and reporting

Case number: ……..

SERIOUS ADVERSE EVENT (SAE) AND ADVERSE EVENT (AE) REPORT FORM		
Initial report: ☐	**Follow-up report:** ☐	**Date of report:** ___ / ____ / _____ (dd/mm/yyyy)

Patient information					
Patient n°:	**Initials:**	**Date of birth:** ___ / ____ / _____ (*dd/mm/yyyy*)	**Gender:** M ☐ F ☐	**Height:** …….. cm	**Weight:** …….. kg

Serious adverse event(s) information		**SAE 1**	**SAE 2**	**SAE 3**
Adverse event term *(drop down list, incl. option other)*		……	……	……
Description of Adverse event (free text)		……	……	……
Event onset date **(*dd/mm/yyyy*)**		___ / ____ / _____	___ / ____ / _____	___ / ____ / _____
Event end date **(*dd/mm/yyyy*)**		___ / ____ / _____	___ / ____ / _____	___ / ____ / _____
Duration if <1 day **(*hrs/min*)**		___ / ____	___ / ____	___ / ____
SAE or AE of special interest		☐ SAE ☐ AE of special interest	☐ SAE ☐ AE of special interest	☐ SAE ☐ AE of special interest
SAE	**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 / prolonged	required ☐ prolonged ☐	required ☐ prolonged ☐	required ☐ prolonged ☐
		Hospitalization dates: Admission: ___ / ____ / _____ Discharge: ___ / ____ / _____	*Hospitalization dates:* Admission: ___ / ____ / _____ Discharge: ___ / ____ / _____	*Hospitalization dates:* Admission: ___ / ____ / _____ Discharge: ___ / ____ / _____
	Persistent or significant disability / incapacity	☐	☐	☐

	Congenital anomaly / birth defect	☐	☐	☐
	Otherwise medically important	☐	☐	☐
If SAE, seriousness category		Mild ☐ Moderate ☐ Severe☐	Mild ☐ Moderate ☐ Severe☐	Mild ☐ Moderate ☐ Severe☐

Event outcome	Fatal	☐	☐	☐
	Not resolved	☐	☐	☐
	Resolved	☐	☐	☐
		If resolved: Resolution date: ___ / ____ / _____	*If resolved:* Resolution date: ___ / ____ / _____	*If resolved:* Resolution date: ___ / ____ / _____
	Resolved with sequelae	☐	☐	☐
		If resolved: Resolution date: ___ / ____ / _____	*If resolved:* Resolution date: ___ / ____ / _____	*If resolved:* Resolution date: ___ / ____ / _____
	Resolving	☐	☐	☐
	Unknown	☐	☐	☐

Suspected drug(s) ***including all TB drugs & any other drug****	**1st most like drug**	**2nd most likely drug**	**3rd most likely drug**	**4th most likely drug**	**5th most likely drug**	**6th most likely drug**	**7th most likely drug**
Suspected drug name (INN)	…….	…….	…….	…….	…….	…….	…….
Dose & route							
Frequency	__ times/wk	__ times/wk	__ times/wk	__ times/wk	__ times/wk	__ times/wk	__ times/wk
Batch number							
Treatment start	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____

Treatment stop	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____

Action taken in response to the event							
Dose maintained (None)	☐	☐	☐	☐	☐	☐	☐
Dose reduced	☐	☐	☐	☐	☐	☐	☐
New dose							
New frequency	__ times/wk	__ times/wk	__ times/wk	__ times/wk	__ times/wk	__ times/wk	__ times/wk
On							
On	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____
Drug permanently withdrawn	☐	☐	☐	☐	☐	☐	☐
On	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____
Drug interrupted, temporary stop	☐	☐	☐	☐	☐	☐	☐
From	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____
To	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____	___ / ____ / _____
Not applicable	☐	☐	☐	☐	☐	☐	☐
Event diminished after drug stopped / dose reduced?	☐ Yes ☐ No ☐ N/A	☐ Yes ☐ No ☐ N/A	☐ Yes ☐ No ☐ N/A	☐ Yes ☐ No ☐ N/A	☐ Yes ☐ No ☐ N/A	☐ Yes ☐ No ☐ N/A	☐ Yes ☐ No ☐ N/A
Event reappeared after drug/dose reintroduction?	☐ Yes ☐ No ☐ N/A	☐ Yes ☐ No ☐ N/A	☐ Yes ☐ No ☐ N/A	☐ Yes ☐ No ☐ N/A	☐ Yes ☐ No ☐ N/A	☐ Yes ☐ No ☐ N/A	☐ Yes ☐ No ☐ N/A

**Please list all TB drugs (suspected by default) and any other treatment you think may have contributed to the event(s). Decide on the causal relationship in the next table.*

Causality assessment	**SAE 1**	**SAE 2**	**SAE 3**
1st most likely drug Drug name: _____	☐ not related ☐ probable ☐ doubtful ☐ very likely ☐ possible	☐ not related ☐ probable ☐ doubtful ☐ very likely ☐ possible	☐ not related ☐ probable ☐ doubtful ☐ very likely ☐ possible
2nd most likely drug Drug name: _____	☐ not related ☐ probable ☐ doubtful ☐ very likely ☐ possible	☐ not related ☐ probable ☐ doubtful ☐ very likely ☐ possible	☐ not related ☐ probable ☐ doubtful ☐ very likely ☐ possible
3rd most likely drug Drug name: _____	☐ not related ☐ probable ☐ doubtful ☐ very likely ☐ possible	☐ not related ☐ probable ☐ doubtful ☐ very likely ☐ possible	☐ not related ☐ probable ☐ doubtful ☐ very likely ☐ possible
4th most likely drug Drug name: _____	☐ not related ☐ probable ☐ doubtful ☐ very likely ☐ possible	☐ not related ☐ probable ☐ doubtful ☐ very likely ☐ possible	☐ not related ☐ probable ☐ doubtful ☐ very likely ☐ possible
5th most likely drug Drug name: _____	☐ not related ☐ probable ☐ doubtful ☐ very likely ☐ possible	☐ not related ☐ probable ☐ doubtful ☐ very likely ☐ possible	☐ not related ☐ probable ☐ doubtful ☐ very likely ☐ possible
Other causal factors (incl. med history, procedure, etc.)	……	……	……
Event description Provide a clear description of the sequence of events, diagnosis, relevant investigation results (ECG, CT scan, etc.), corrective treatments and evolution.			
Relevant laboratory tests			
Laboratory tests done?	No ☐ Yes ☐ *If yes, provide details below* ☐ Don't know		

Test	Date (*dd/mm/yyyy*)	Result (unit)	Reference range
	___ / ____ / _____		
	___ / ____ / _____		
	___ / ____ / _____		

Concomitant medications

Concomitant medication provided? No ☐ Yes ☐ *If yes, provide details below* ☐ Don't know

Drug name (INN)	Daily dose and route	Indication	Treatment start date (*dd/mm/yyyy*)	Treatment stop date (*dd/mm/yyyy*)	Continued
			___ / ____ / _____	___ / ____ / _____	☐ Yes ☐ No
			___ / ____ / _____	___ / ____ / _____	☐ Yes ☐ No
			___ / ____ / _____	___ / ____ / _____	☐ Yes ☐ No
			___ / ____ / _____	___ / ____ / _____	☐ Yes ☐ No
			___ / ____ / _____	___ / ____ / _____	☐ Yes ☐ No

Relevant medical history Indicate relevant medical history, including prior diagnoses, past laboratory investigations, X-ray, ECG prior to treatment, previous procedures, and relevant past drugs.	

Reporter

Name of reporter:	**Role in trial/program:**	**Date of event's awareness:** *ALL SAEs to be reported within 24 hrs of awareness* ___ / ____ / _____	**Address:** **Email:** **Phone:**	**Date and signature:** ___ / ____ / _____

Further information on this SAE expected?	**Yes** ☐ **No** ☐ *If yes please send a follow-up report once new information is available*	**Any annex to this document?** (e.g. discharge summary, autopsy report, lab results)	**Yes** ☐ **No** ☐ *If yes, list the annexes:*

Annex E. List of potential Standard Operating Procedures (SOPs) to be developed

- SOP on diagnostic process:
    - Describe process for patients who enter 1st level facility, 2nd level facility, 3rd level facility as their first place of seeking care
    - When and where are sputum samples taken
    - When are patients / samples referred for further testing
    - This SOP should describe how we suggest that the flow goes, not necessary what is currently done
    - Appendix in this SOP with for each rayon/facility where they should send samples/patients when?
    - Feedback/information exchange between clinic and laboratory
    - Sample storage (if)/ packing/ sending turn-around- time (if as per guidelines) has to be mentioned.

- SOP on estimation, calculation of laboratory consumables (needs, procurement, timing, roles/responsibilities)

- SOP on estimation, calculation of TB and ancillary drugs (needs, procurement, timing, roles/responsibilities)

- SOP on eligibility for different treatments
    - Include flow chart that describes on lab test results to which treatment regimen patients should be allocated
    - Include eligibility /exclusion criteria for enrollment for each regimen.
    - In fact, for patients you need to do 2 checks: first check their resistance pattern, second check base on in-/exclusion criteria
    - Describe process of treatment decision of the consilium/DR-TB Committee.
        - Describe who is giving information to patient, and when

- SOP on evaluation, decision making by expert committee
    - Evaluation
    - Enrollment
    - Clinical decisions
    - Special situations
    - Extended consilium
    - Frequency of interim evaluation (table for short and XDR regimens)

- SOP on informed consent procedure
    - Describe what information should be given to the patients and who should sign the informed consent (patient and/or parents)

- SOP for the lab
    - Describe which tests should be done when
    - Reporting of results to treating facilities

  - Recording of results in eTB manager? (not sure if the lab already fills in the data directly in eTB manager).

- SOP on treatment monitoring during hospitalization phase
  - Which monitoring tests need to be done when
  - How to do DOT
  - What to do when test is not available
  - What to do when there is an AE refer to SOP on reporting AE.

- SOPs for roles and responsibilities of different project team members

- SOP on treatment monitoring during ambulatory phase
  - See above
  - Include list of facilities that have monitoring tests available in order to know where to refer patients to for clinical monitoring.

- SOP for reporting and recording of AE and SAE
  - Where the AEs should be recorded
  - To whom reported
  - Causality assessment
  - Feedback from PV department.

- SOP for quarterly/monthly/weekly/regular monitoring and supervision by monitoring and supervision group
  - Checklists – update, development
  - List with minimum items that they should monitor
    - Time between Xpert result and start treatment regimen
    - Time between full DST results and change in regimen (when needed)
    - Recording of AEs
    - Completeness of lab data in eTB manager
    - Check in-exclusion criteria?
    - Monitor how many patients are not enrolled and reasons why (did patient not agree, was site not ready, did doctor not ask….)
    - Monitor drug stock (on a monthly basis in the beginning of the project?)
    - Monitor availability of lab tests (Xpert cartridges and BACTEC reagents, on a monthly basis in the beginning of the project?)
    - Monitor treatment adherence of enrolled patients.

- SOPs or algorithms or instructions for nurses. In hospitals or outpatient facilities – DOT, side effects, adherence to treatment, infection control for both (patients and staff)

- SOP for monitoring team- what is TAT for data analysis, to whom they present data, what do they do with data, who to contact etc.

Annex F Weight based dosing of SLDs for children [4] [10] [11]

A. Fluoroquinolones

Levofloxacin				
5 years and under		7.5-10mg/kg twice daily		
Over 5 years and up to 14 years		7.5-10mg/kg once daily		
Kg	250mg tablet		25g/ml suspension	
1.0-2.9	*Not recommended*			
3.0-4.9	0.25	Tab	2.5	mL
5.0-8.9	0.50	Tab	5	mL
9.0-11.9	0.75	Tab	7.5	mL
12.0-16.9	1	Tab	10	mL
17.0-24.9	1.50	Tabs	15	mL
25.0-29.9	2	Tabs	20	mL

Moxifloxacin				
7.5-10mg/kg				
Kg	400mg tablet		20g/ml suspension	
1.0-2.9	*Not recommended*			
3.0-3.9	*Not recommended*		1.5	mL
4.0-4.9			2	mL
5.0-7.9			2.5	mL
8.0-13.9			5	mL
14.0-14.9	0.5	Tab	5	mL
15.0-19.9	0.5	Tab	7.5	mL
20.0-26.9	0.5	Tab	10	mL
27.0-29.9	0.5	Tab	12.5	mL

B. Second Line injectable agents

Drug	Daily dose	Maximum daily dose
Amikacin	15-20 mg/kg once daily	1000 mg
Kanamycin	15-20 mg/kg once daily	1000 mg
Capreomycin	15-20 mg/kg once daily	1000

C. Other core second-line agents

Drug	Daily dose	Maximum daily dose
Clofazimine	2-3 mg/kg once daily (if child is >25kg give 100 mg every second day)	200 mg
Linezolid	10 mg/kg twice daily for children < 10 years of age; 300mg daily for children ≥ 10 years of age. Also give vitamin B6	600 mg

Prothionamide / Ethionamide		
15-20 mg/kg		
Kg	250mg tablet	
1.0-2.9	*Not recommended*	
3.0-4.9	0.25	Tab
5.0-8.9	0.50	Tab
9.0-11.9	0.75	Tab
12.0-16.9	1	Tab
17.0-24.9	1.50	Tabs
25.0-29.9	2	Tabs

Cycloserine / Terizidone				
15-20mg/kg				
Kg	250mg capsule		1 capsule in 10ml water	
1.0-2.9	*Not recommended*			
3.0-4.9	0.25	Cap	2.5	Ml
5.0-8.9	0.50	Cap	5	Ml
9.0-11.9	0.75	Cap	7.5	Ml
12.0-16.9	1	Cap	10	Ml
17.0-24.9	1.50	Caps	15	Ml
25.0-29.9	2	Caps	20	Ml

D. Add on agents *D1*

Pyrazinamide				
30-40 mg/kg				
Kg	400 mg tablet		500 mg tablet	
1.0-2.9	*Not recommended*			
3.0-4.9	0.25	Tab	0.25	Tab
5.0-5.9	0.50	Tab	0.25	Tab
6.0-9.9	0.50	Tab	0.5	Tab
10.0-11.9	1	Tab	0.5	Tab
12.0-14.9	1	Tab	1	Tab
15.0-18.9	1.5	Tabs	1	Tab
19.9-20.9	1.5	Tabs	1.5	Tabs
21.0-25.9	2	Tabs	1.5	Tabs
26.0-26.9	2	Tabs	2	Tabs
27.0-29.9	2.5	Tabs	2	Tabs

Ethambutol		
15-25 mg/kg		
Kg	100 mg tablet	
1.0-2.9	*Not recommended*	
3.0-7.9	1	Tab
8.0-12.9	2	Tab
13.0-15.9	3	Tab
16.0-26.9	4	Tab
27.0-29.9	5	Tabs

Isoniazid *			
7-15 mg/kg for patients less than 30 kg: maximum daily dose 300mg			
Kg	50 mg per 5ml oral solution	100 mg tablet	300mg tablet
5	5 ml	0.5 tab	-
6	6 ml	1.0 tab	-
7	7 ml	1.0 tab	-
8	8 ml	1.0 tab	-
9	9 ml	1.0 tab	-
10	10 ml	1.5 tab	-
11	11 ml	1.5 tab	-
12	12 ml	1.5 tab	-
13	13 ml	2.0 tab	-
14	14 ml	2.0 tab	-
15	15 ml	2.0 tab	-
16-20	-	2.0 tab	-
21-29.9	-	-	1.0 tab

* The “regular” dose is shown, not high-dose H, which is rarely used in children.

D2

Bedaquiline [9]	
Age 11 to 14 years	300mg daily for 2 weeks, then 200mg 3 times a week

Delamanid		
Kg		
<20	Not *recommended*	
20-34	50 mg	Twice daily
>35	100 mg	Twice daily

*D3***PAS**				
200-300 mg /kg				
PASER granules (4g sachet)				
Kg	Daily		Twice daily	
1.0-2.9	*Not recommended*			
3.0-3.9	500	mg	250	mg
4.0-5.9	1000	Mg	500	Mg
6.0-8.9	1500	Mg	750	Mg
9.0-12.9	2000	Mg	1000	Mg
13.0-15.9	2500	Mg	1250	Mg
16.0-20.9	3000	Mg	1500	Mg
21.0-24.9	4000	Mg	2000	Mg
25.0-28.9	5000	Mg	2500	Mg
29.0-29.9	6000	mg	3000	mg

Drug	**Daily dose**	**Maximum daily dose**
Amoxicillin – clavulanate	80mg/kg in two divided doses based on the amoxicillin component	4000mg amoxicillin and 500mg clavulanate
Meropenem	20-40mg/kg IV every 8 hours	6000mg

[9] Currently there is no WHO recommended dose for bedaquiline in children. Hence the dosage suggested above is based on current clinical experience from Belarus.

Annex G. Contraindications and precautions for medicines used for treatment of DR-TB[10] [4]

Contraindications and precautions	
Fluoroquinolones	
Levofloxacin	**Contraindication:** Intolerance to quinolones **Precaution:** Prolonged QT interval or if taken with co-medication that prolong QT interval and in patients predisposed to seizures **Use in renal disease**: Dosage adjustment is recommended if creatinine clearance is <50 ml/min. **Use in hepatic disease:** Presumed to be safe in severe liver disease. **Pregnancy/breastfeeding**: Safety class C. Fluoroquinolones are not recommended during breastfeeding due to the potential for arthropathy.
Moxifloxacin	**Contraindication:** Intolerance to quinolones, prolonged QT interval **Use in renal disease:** Presumed to be safe **Use in hepatic disease**: Rarely associated with hepatotoxicity; use with caution **Pregnancy/breastfeeding**: Safety class C. Fluoroquinolones are not recommended during breastfeeding due to the potential for arthropathy.
Gatifloxacin	**Contraindication:** Intolerance to quinolones **Precaution:** Diabetes. Gatifloxacin can worsen diabetes and glycemic control. Prolonged QT interval or if taken with co-medication that prolong QT interval **Use in renal disease**: Doses of gatifloxacin should be reduced in patients with renal impairment. **Use in hepatic disease**: Presumed to be safe **Pregnancy/breastfeeding:** Safety class C. Fluoroquinolones are not recommended during breastfeeding due to the potential for arthropathy.
Second-line injectable drugs	
Amikacin	**Contraindication:** Intolerance to aminoglycosides **Precaution:** Vestibular or auditory impairment **Use in renal disease:** Use with caution

[10] www.medscape.com

	Use in hepatic disease: Presumed to be safe **Use in pregnancy/breastfeeding**: Generally avoided during pregnancy due to congenital deafness seen with streptomycin and kanamycin. Can be used while breastfeeding.
Capreomycin	**Contraindication:** Intolerance to aminoglycosides **Precaution:** Vestibular or auditory impairment **Use in renal disease**: Use with caution **Use in hepatic disease**: Presumed to be safe **Use in pregnancy/breastfeeding**: Generally avoided during pregnancy due to congenital deafness seen with streptomycin and kanamycin. There are case reports of its safe use in pregnancy (unaffected newborns). Can be used while breastfeeding.
Kanamycin	**Contraindication:** Intolerance to aminoglycosides **Precaution:** Vestibular or auditory impairment and patients with intestinal obstructions **Use in renal disease:** Use with caution **Use in hepatic disease:** Presumed to be safe **Use in pregnancy/breastfeeding**: Generally avoided in pregnancy due to documented congenital deafness. Can be used while breastfeeding.
Ethionamide /Prothionamide	**Contraindication:** Intolerance to ethionamide/protionamide **Use in renal disease:** Presumed to be safe **Use in hepatic disease:** Use with caution in liver disease **Use in pregnancy/breastfeeding:** Generally avoided during pregnancy due to reports of teratogenicity; little data about use during breastfeeding – an estimated 20% of the infant therapeutic dose will be passed on to the baby in the breast milk (dose the infant with vitamin B6 if breastfed).
Cycloserine/ terizidone	**Contraindication**: Intolerance to cycloserine/terizidone **Precaution**: Seizure disorder, psychotic disease or alcohol abuse **Use in renal disease:** Cycloserine is cleared by the kidney and requires dose adjustment for renal failure **Use in hepatic disease**: Presumed to be safe **Use in pregnancy/breastfeeding:** Not well studied, but no teratogenicity documented. Use if there are not better choices. Can be used while breastfeeding (dose the infant with vitamin B6 if breastfed).
Linezolid	**Contraindication:** Intolerance to linezolid and symptoms of neuropathy

	Precaution: Patients with pheochromocytoma, concurrent apraclonidine, brimonidine, uncontrolled hypertension, thyrotoxicosis, carcinoid syndrome, diabetes mellitus, or seizure disorders **Use in renal disease:** No dose adjustments recommended **Use in hepatic disease**: Presumed to be safe **Use in pregnancy/breastfeeding:** Not recommended during pregnancy or breastfeeding due to limited data.
Clofazimine	**Contraindication**: Intolerance to clofazimine **Use in renal disease:** No dose adjustment required **Use in hepatic disease**: Use caution and/or adjust the dose for severe hepatic insufficiency **Use in pregnancy/breastfeeding**: Not recommended due to limited data (some reports of normal outcomes, some reports of neonatal deaths). Avoided with breastfeeding due to pigmentation of the infant.
Pyrazinamide	**Contraindication:** Intolerance to pyrazinamide and severe gout **Use in renal disease**: Cleared by the kidneys; dose 3 times a week after dialysis. **Use in hepatic disease:** Use with caution; pyrazinamide is associated with hepatotoxicity in about 1% of patients. It can be quite severe and worsen treatment progress. **Use during pregnancy/breastfeeding**: In the United States, pyrazinamide is avoided during pregnancy for drug-susceptible disease due to lack of data regarding teratogenicity, but should be used for drug-resistant TB when the isolate is sensitive to pyrazinamide (no known teratogenicity). Can be used while breastfeeding.
Ethambutol	**Contraindication:** Intolerance to ethambutol and in case of optic neuritis **Use in renal disease**: Use with caution – cleared by the kidneys; dose adjustment required for renal failure. Increased risk of toxicity with renal failure. If needed for use in the regimen, consider therapeutic drug monitoring. **Use in hepatic disease:** Safe in liver disease **Use in pregnancy/breastfeeding:** Safe in pregnancy; can be used while breastfeeding.
Isoniazid	**Contraindication:** Intolerance to isoniazid. **Precaution:** With alcohol, illicit injectable drug use, predisposition to neuropathy and malnourishment **Use in renal disease:** No dose adjustment for renal failure, but pyridoxine supplementation should be used **Use in hepatic disease**: May exacerbate liver failure. Use with caution. **Use in pregnancy/breastfeeding**: Safe during pregnancy; safe during breastfeeding (both baby and mother should receive pyridoxine supplementation).

Bedaquiline	**Contraindication:** Intolerance to bedaquiline, clinically significant ventricular arrhythmia, clinically significant ventricular arrhythmia, a QTcF interval of >500 ms (confirmed by repeat ECG) and severe liver disease. **Precaution:** • Use with other QT prolonging drugs (see drug interactions) • A history of torsade de pointes • A history of congenital long QT syndrome • A history of hypothyroidism and bradyarrhythmias • A history of uncompensated heart failure • Serum calcium, magnesium or potassium levels below the lower limits of normal. **Use in renal disease:** No dosage adjustment is required in patients with mild to moderate renal impairment **Use in hepatic disease**: No dosage adjustment is required in patients with mild to moderate hepatic impairment. Dosing and toxicity not well established in severe hepatic impairment, use with caution and only when the benefits outweigh the risks **Use in pregnancy/breastfeeding**: Not recommended during pregnancy or breastfeeding due to limited data. Reproduction studies performed in rats and rabbits have revealed no evidence of harm to the fetus.
Delamanid	**Contraindication:** Intolerance to Delamanid, patients with a QT interval >500ms or cardiac ventricular arrhythmias **Precaution**: Patients with risk factors like taking medicinal products that are known to prolong the QTc interval **Use in renal disease**: No data known **Use in hepatic disease:** Use with caution in mild to severe hepatic impairment. **Pregnancy/breastfeeding**: Use of the drug in children and in pregnant and breastfeeding women is not currently advised due to a lack of evidence on safety, efficacy and proper dosing in these groups