



The Evaluation of Effectiveness and Safety of Novel Shorter Treatment Regimens for Multidrug-Resistant Tuberculosis

Operational Research Protocol Template

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(Investigators and partners may be listed here)

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Abbreviations

AE	Adverse Event
Am	Amikacin
ART	Anti-retroviral therapy
ARV	Anti-retroviral
Bdq	Bedaquiline
BMI	Body Mass Index
Cfx	Clofazimine
Cm	Capreomycin
Cs	Cycloserine
CTCAE	Common Terminology Criteria for Adverse Events
Dlm	Delamanid
DMID	Division of Microbiology and Infectious Diseases
DR-TB	Drug-resistant Tuberculosis
DST	Drug Susceptibility Testing
E	Ethambutol
ECG	Electrocardiogram
EMA	European Medicines Agency
Eto	Ethionamide
FDA	United States Food and Drug Administration
FQ	Fluoroquinolone
H	Isoniazid
HIV	Human Immunodeficiency Virus
Km	Kanamycin
Lfx	Levofloxacin
Lzd	Linezolid
MDR	Multidrug-resistance
MDR-TB	Multidrug-resistant Tuberculosis
Mfx	Moxifloxacin
MTB	Mycobacterium Tuberculosis
MWF	Monday-Wednesday-Friday
NCI	National Cancer Institute
NIAID	National Institute of Allergy and infectious Diseases
NTP	National Tuberculosis Program
Ofx	Ofloxacin
PAS	Para-Aminosalicylic Acid
Pa	Pretomanid
Pto	Prothionamide
RIF	Rifampicin
S	Streptomycin
SAE	Serious Adverse Event
TB	Tuberculosis
TSH	Thyroid Stimulating Hormone
WHO	World Health Organization
XDR	Extensive Drug Resistance
XDR-TB	Extensively Drug-resistant Tuberculosis
Z	Pyrazinamide

Instructions to countries (this section should be removed during country adaptation)

This document describes a generic protocol for the operational evaluation of novel shorter standardized treatment regimens for MDR-TB in (name of country). It provides information about procedures for enrollment, treatment and follow-up, and should be adapted to the specific regimen and patient population selected. Selected regimen design should be described in the final protocol document.

This generic protocol is itself adapted from the STREAM trial (the evaluation of a Standardised Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR-TB)¹ by members of the Global Drug-resistant Tuberculosis Initiative. Countries that are interested in piloting shorter MDR-TB regimens are encouraged to adapt this generic protocol to their local settings.

Throughout this generic protocol, there is text in italics (like this). The text in italics provide advice on how to adapt the section to local settings.

1. Summary

This section should summarize the protocol. Suggested section headers: Type of study, Study objectives, Treatment of patients/Regimen design, Outcome measurements.

2. Background

For many years MDR-TB patients have been treated with a WHO-recommended conventional MDR-TB regimen which generally has an intensive phase of treatment of 8 months and a total duration of treatment of 20 months.

In October 2016, the WHO recommended that for patients with RR-TB or MDR-TB who were not previously treated with second-line drugs and for whom resistance to fluoroquinolones and second-line injectable agents was excluded or is considered highly unlikely, a shorter MDR-TB regimen may be used instead of longer regimens (conditional recommendation, very low certainty in the evidence).² The WHO-recommended shorter regimen is composed of high-dose moxifloxacin/gatifloxacin, clofazimine, pyrazinamide and ethambutol throughout, supplemented by kanamycin, prothionamide, and high-dose isoniazid in the intensive phase. The treatment duration of the intensive phase is four months (extended to a maximum of six months until sputum smear conversion), and the duration of the continuation phase is five months. This regimen is currently completing evaluation in the Stage 1 of STREAM trial. A preliminary summary of the trial results, made public by the researchers in October 2017³, indicated almost similar outcomes of the STREAM regimen as compared to the longer regimen under trial conditions.

In addition to the shorter MDR-TB regimen recommended by the WHO, there are other shorter regimens currently being evaluated in clinical trials. Many of these regimens employ new or repurposed medicines such as bedaquiline, delamanid and linezolid, which have been shown to be

¹ Nunn AJ, Rusen ID, Van Deun A, Torrea G, Phillips PPJ, Chiang C-Y, et al. Evaluation of a standardized treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis (STREAM): study protocol for a randomized controlled trial. *Trials* 2014; 15: 353.

² WHO treatment guidelines for drug-resistant tuberculosis (October 2016 revision).
<http://apps.who.int/iris/bitstream/10665/250125/1/9789241549639-eng.pdf>

³ <https://www.theunion.org/news-centre/news/stream-clinical-trial-results-provide-vital-insight-into-nine-month-treatment-regimen-for-multidrug-resistant-tuberculosis>

effective in clinical trials. Some of the regimens forgo the use of a second-line injectable, which is associated with a high rate of adverse events and is programmatically difficult to administer. Although these regimens are currently undergoing testing in clinical trials, the programmatic use of these regimens under operational research conditions can also provide important data to the global TB community about their effectiveness and safety, while also providing more information about programmatic implementation and expanding access to their potential benefits.

3. MDR-TB in (name of country)

This section should describe the local setting in which the study is being conducted. Describe the epidemiology of TB, case finding and outcomes of treatment of TB, the prevalence of MDR-TB among new and previously treated cases, the prevalence of fluoroquinolone and second-line injectable resistance among MDR-TB cases, progress in implementation of the programmatic management of drug resistant TB (PMDT). Also describe the MDR-TB regimen currently used in the country, and the outcomes of MDR-TB patients enrolled on treatment.

4. Rationale

STREAM Stage 1 is a clinical trial comparing the WHO-recommended shorter regimen to longer regimens. Enrollment has been completed, but follow-up of the last patients will end in the middle of 2018. Preliminary results were presented at the Union Meeting in Guadalajara in October 2017, and demonstrated that the STREAM 1 regimen was similar to the 20-month regimen in terms of efficacy. 78% of the patients in the STREAM 1 regimen arm experienced a favorable outcome, compared to 81% of the patients in the longer regimen arm. However, it did not meet the non-inferiority threshold established in the trial protocol. In addition, adverse events were not significantly different in the two arms.

In addition to the STREAM trial, there are other studies being conducted to evaluate the safety and efficacy of shorter regimens less than 12 months (Table 1). Compared to the current WHO-recommended shorter regimen, all of these regimens are using new and repurposed drugs such as bedaquiline, delamanid and linezolid. Bedaquiline and delamanid appear to be well tolerated in observational studies. Linezolid has well-known toxicities consisting of peripheral neuropathy, bone marrow suppression, and optic neuritis, but it still may be better tolerated than conventional MDR-TB drugs such as prothionamide, cycloserine or the second-line injectables.

Table 1: Regimens tested in recently completed or ongoing clinical trials

Clinical trial	Regimen	Ongoing / completed	All drugs are commercially available
STREAM 1 regimen B	Cfz, E, Z, Mfx, H, Km (16 weeks); followed by Cfz, E, Z, Mfx (24 weeks)	Enrollment completed	Yes
NiX-TB	Bdq, Pa, Lzd (24-36 weeks)	Enrollment completed	No
MDR END	Dlm, Lzd, Lfx, Z (36-52 weeks)	Enrolling	Yes
STREAM 2 regimen C	Bdq, Cfz, E, Z, Lfx, H, Pto (16 weeks); followed by Bdq, Cfz, E, Z, Lfx (24 weeks)	Enrolling	Yes
STREAM 2 regimen D	Bdq, Cfz, Z, Lfx, H, Km (8 weeks); followed by Bdq, Cfz, Z, Lfx (20 weeks)	Enrolling	Yes
PRACTECAL regimen 1	Bdq, Pa, Lzd (24-36 weeks)	Enrolling	No
PRACTECAL regimen 2	Bdq, Pa, Lzd, Cfz (24-36 weeks)	Enrolling	No
PRACTECAL regimen 3	Bdq, Pa, Lzd, Mfx (24-36 weeks)	Enrolling	No

endTB regimen 1	Bdq, Lzd, Mfx, Z (39 weeks)	Enrolling	Yes
endTB regimen 2	Bdq, Cfz, Lzd, Lfx, Z (39 weeks)	Enrolling	Yes
endTB regimen 3	Bdq, Dlm, Lzd, Lfx, Z (39 weeks)	Enrolling	Yes
endTB regimen 4	Dlm, Cfz, Lzd, Lfx, Z (39 weeks)	Enrolling	Yes
endTB regimen 5	Dlm, Cfz, Mfx, Z (39 weeks)	Enrolling	Yes

N.B. The dosing and timing of the above regimens are complicated and cannot be fully described in this table. Please look at the respective trial protocol for a fuller description of the above regimens.

Longer MDR-TB regimens are associated with frequent adverse reactions. Substitution of new or repurposed drugs instead of certain conventional MDR-TB drugs could improve the overall adverse event profile and increase adherence rates. The shorter duration of treatment, the replacement of an injectable with medicine administered per os, and the use of drugs with better safety profiles, all mean that patients are more likely to complete treatment with one of these novel shorter regimens.

All three new or repurposed drugs—bedaquiline, delamanid and linezolid—have been shown in clinical trials to have anti-mycobacterial activity. Thus, substitution of conventional MDR-TB drugs with these drugs may result in effective and well tolerated regimen.

One possible risk is of a shorter regimen is a higher rate of post-treatment recurrence. One year of post-treatment follow-up is therefore recommended to detect early recurrences.

Most of the shorter regimens presented above (Table 1) include a fluoroquinolone, therefore patients with fluoroquinolone-resistance should not be enrolled in the study. However, most of these regimens do not include an injectable, meaning they would be just as effective in patients with injectable resistance. These patients may still be enrolled if the selected study regimen does not include an injectable.

(For consistent and statistically significant results, depending on number of patients planned to be enrolled, it is better to select only one or two regimens for the operational research study. Commercial availability of medicines that are needed to design several regimens in Table 1 may restrict the choice of the regimen).

5. Type of study

This is a prospective observational cohort study.

6. Study objectives

Primary objective:

- To determine the treatment outcomes of patients who are treated with novel shorter MDR-TB regimen.

Secondary objectives:

- To assess the safety of a novel shorter MDR-TB regimen through rates of adverse events.
- To determine the proportion of patients with recurrence during 12 months after successful treatment with a novel shorter MDR-TB regimen.

Additional secondary objectives that could be added, depending on the resources of the program:

- *To assess interim outcomes with sputum smear microscopy and culture conversion at 4 and 6 months.*
- *To evaluate risk factors associated with non-favorable outcomes (death, failure, loss to follow-up, relapse).*
- *To assess the accuracy of simplified outcome monitoring of a novel shorter MDR-TB regimen with smear microscopy instead of culture.*
- *To assess the outcomes in sub-groups resistant to first- or second-line drugs in the regimen.*

7. Patient selection

TB patients with evidence of resistance to rifampicin by conventional DST (culture-based) or rapid DST (Xpert MTB/RIF or LPA) will be assessed for enrollment. All patients should also be tested for second-line resistance to fluoroquinolones and injectables at a minimum, preferably with LPA.

7.1 Inclusion criteria

A patient will be eligible for treatment with a novel shorter MDR-TB treatment regimen if he/she:

1. Is willing and able to give informed consent to be enrolled in the research project and for follow-up (signed or witnessed consent if the patient is illiterate; signed or witnessed consent from a child's parent or legal guardian).
2. Has bacteriologically confirmed TB with initial laboratory result of resistance to at least rifampicin.
3. Has strong clinical and radiological evidence of active TB and is a close household contact of a patient with laboratory-confirmed MDR-TB.
4. Is willing to use effective contraception if the patient is a pre-menopausal woman.
5. Is willing to adhere to the follow-up schedule and to study procedures.

7.2 Exclusion criteria

A patient will not be eligible for treatment with a novel shorter MDR-TB treatment regimen if he/she:

1. Has DST showing infection with a strain resistant to drugs in the regimen. *(In the case of STREAM regimens C or D, resistance to some of the first-line drugs in the regimen may be allowed)*
2. Has been previously exposed to second-line anti-TB drugs in the intended shorter MDR-TB regimen for more than one month.
3. *(If some types of severe forms of extrapulmonary MDR-TB [e.g. MDR-TB empyema, Pott's disease, TB meningitis] are excluded from the shorter MDR-TB regimen, the exact types should be explained here. Extra-pulmonary MDR-TB patients who are included may also need to have other types of follow-up testing schedule besides sputum analysis.)*
4. *(If pregnant women in the first trimester are excluded from the shorter MDR-TB regimen, this should be explained here. In general, pregnant women can be included in treatment with shorter MDR-TB regimens. There are limited data about the safety in pregnancy of the new MDR-TB drugs, but there are limited data about the safety of many conventional MDR-TB drugs as well. Furthermore, some conventional MDR-TB drugs are thought to be teratogenic. If pregnant women are included, it is advisable to avoid those in the first trimester.)*
5. *(If children under a certain age are excluded from the shorter MDR-TB regimen, the age limit should be explained here. In general, children can be included in treatment with shorter MDR-TB regimens. There are more data about optimal pediatric dosing of some of the new MDR-TB drugs compared to some of the conventional MDR-TB drugs. The decision of whether to include*

children should be made after a careful examination of the scientific literature related to the specific drugs included in the shorter MDR-TB regimen.)

6. Is unable to attend or comply with treatment or follow-up schedule.
7. Is unable to take oral medication.
8. Has AST or ALT >5 times the upper limit of normal. *(If this is temporary, the patient can be enrolled once this is corrected.)*
9. Is taking any medications contraindicated with the medicines in the shorter MDR-TB regimen.
10. Has a known allergy to any of the drugs in the shorter MDR-TB regimen.
11. Is currently taking part in a clinical trial of any medicinal product.
12. Has a QTcF interval of > 500 msec.
13. Has severe renal insufficiency (an estimated creatinine clearance (CrCl) less than 30 mL/min based on the Cockcroft-Gault equation).

7.3 Informed consent

Patients who are eligible for inclusion in the study will be given information about MDR-TB and the shorter MDR-TB regimen. Patients will be provided with information in a language that is understandable to them. Consent for enrollment should be based on a Patient Information Sheet. Patients should have the opportunity to discuss the Patient Information Sheet with the medical officer/treatment supporter. The patients will be assured that their decision to participate in the study or not will not affect the quality of care they will receive. Once the patient agrees to participate in the pilot project, the patient will be asked to sign the consent form (or give a thumb print in the presence of a witness if illiterate).

All patients who are not eligible for the study, or refuse to be enrolled, or withdraw after enrollment, will be managed by a MDR-TB treatment regimen according to national guidelines.

7.4 Treatment sites and number of patients

List the specific sites where patients will be treated with the novel shorter MDR-TB regimen. These should be high-functioning, well-trained sites with the capacity to monitor for adverse events (Section 8.4). List the total number of patients to be enrolled on novel shorter MDR-TB regimens.

8. Treatment of patients

8.1 Novel shorter MDR-TB regimen and dosing

Describe the drugs included in the regimen and the duration of each drug. "Intensive phase" and "continuation phase" terminology may be used if an injectable is included, but not if the regimen includes only oral drugs, even if some have an initial loading dose.

Table 2: Dosing of medicines for adults *(remove drugs that are not included in the study regimen)*

Drug	Weight group	
	30-50 kg	More than 50 kg
Bedaquiline (100 mg tablets)	400 mg once daily for 2 weeks, then 200 mg 3 times per week afterwards	
Delamanid (50 mg tablets)	100 mg twice daily (200 mg total daily dose)	
Linezolid (600 mg tablets)	600 mg once daily*	
Levofloxacin (250 mg or 500 mg tablets)	750 mg	1000 mg
Moxifloxacin (400 mg tablets)	600 mg	800 mg
Clofazimine (100 mg gel capsules)	100 mg	100 mg

Ethambutol (400 mg tablets)	800 mg	1200 mg
Pyrazinamide (500 mg tablets)	1500 mg	2000 mg
Isoniazid, high dose (300 mg tablets)	400 mg	600 mg
Prothionamide (250 mg tablets)	500 mg	750 mg
Kanamycin (1000 mg vials)	15 mg per kilogram body weight (maximum 1 g) [†]	

* Linezolid dose is commonly reduced to 600 mg three times a week or 300 mg daily in patients with linezolid-induced peripheral neuropathy. For more information, see the *endTB clinical and programmatic guide for patient management with new TB drugs* (<http://endtb.org/resources>).

[†] Kanamycin dose may be reduced to 10 mg/kg (max dose 750 mg) or decreased in frequency to three times a week in adults over 59 years of age.

N.B. The dosing of medications included in novel shorter regimens can include loading or alternate-day periods, and more weight classes than shown above. Please look at the respective trial protocol for a fuller description of dosing of the medications in the above regimens.

Table 3: Dosing for children and adults < 30 kg (*remove drugs that are not included in the study regimen*)

Drugs	Dosing
Bedaquiline	> 12 years and > 33 kg: 400 mg daily for 14 days followed by 200 mg three times a week (same as adult dose) < 12 years or < 33 kg: correct dose is unknown, but 6 mg/kg for 2 weeks, then 3 mg/kg afterwards may be tried
Delamanid	> 35 kg: 100 mg twice daily (same as adult dose) 20-34 kg: 50 mg twice daily < 20 kg: correct dose is unknown, but 3-4 mg/kg may be tried
Linezolid	>= 12 years: 10 mg/kg once daily < 12 years: 10 mg/kg twice daily
Clofazimine	2-3 mg/kg daily or every other day for a maximum daily dose of 100 mg (gel caps cannot be split)

8.2 Inpatient and ambulatory treatment

(Describe here organization of treatment management, DOT and treatment support in practice in the country.)

Inpatient treatment is not mandatory, but patients may be hospitalized at the initiation of MDR-TB treatment for a short period of time to ensure that patients can tolerate the regimen. It may also be advisable for specific groups and for very ill people, for instance during the initiation of treatment or when adverse events occur during treatment.

Ambulatory treatment from the outset without initial hospitalization may be feasible in settings where management of MDR-TB in the community is strong. Directly Observed Therapy (DOT) should be administered throughout the whole treatment course and the shorter regimen should be administered seven days per week. Ambulatory DOT services could be either "facility-based" in which patients visit a health care facility daily for treatment, or "community-based" in which a trained treatment supporter visits the patients daily for drug administration (or vice versa) and accompanies the patient to follow-up visits and liaises with the clinical staff. Enablers and incentives (such as travel expenditure or food) during the whole treatment course are helpful and should be consistently provided whenever possible and relevant to the local context.

In the case of community-based DOT, a trained independent treatment supporter who is not directly related to the patient must be identified. The treatment supporter has the following responsibilities:

- Strictly administer DOT on a daily basis.
- Ensure that the patient attends all scheduled follow-up visits and examinations.
- Monitor adverse events closely and address adverse events in a timely manner by informing clinical staff.
- Update the patient treatment card on a daily basis.
- Initiate patient tracing if the patient fails to return for treatment as per schedule.
- Ensure that there is a sufficient buffer stock of drugs for patients who are currently on treatment.

8.3 Procedure following missed treatment

Any missed days should be made up by extending the regimen by the number of days missed but not exceed 10% of the planned study regimen duration. Treatment interruption for two consecutive months or more will be classified as "lost to follow-up", in which case the patient is no longer eligible to receive the shorter regimen. Reasons for missing treatment must be identified and addressed early.

8.4 Examinations at baseline and during treatment

This section should include a monitoring schedule of screening tests for all patients started on treatment with the shorter MDR-TB regimen. The schedule will depend on the composition of the shorter MDR-TB regimen chosen, but should be consistent with the general monitoring principles outlined in the Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-resistant Tuberculosis.⁴ Additional screening tests to identify common adverse events of new TB drugs should also be included.

- *Sputum smear, culture, and DST should be done at baseline; sputum smear and culture should then be done monthly until completion of treatment. They should also be repeated at six and 12 months after completing treatment.*
- *Body weight and height should be measured at baseline to determine body mass index, which is a predictor of outcome; weight should then be assessed monthly.*
- *Screening for diabetes is ideally done for all patients by measuring hemoglobin A1c. A fasting blood glucose is an acceptable alternative if it is not possible to measure hemoglobin A1c.*
- *Screening for HIV, hepatitis B, and hepatitis C is important, even in countries where HIV or hepatitis B/C is not endemic. Both are common co-morbidities among MDR-TB patients and can easily be diagnosed using a rapid antibody test at the point of care.*
- *HIV-positive patients should have a CD4 count and viral load before starting treatment, and regularly thereafter according to national guidelines.*
- *Serum creatinine should be measured to screen for acute kidney injury or chronic renal disease. It should be repeated monthly in patients receiving an injectable.*
- *Full blood count should be performed for all patients at the beginning of treatment, as anemia is common in MDR-TB patients and is a predictor of poor outcome. This should be repeated monthly in patients receiving linezolid.*
- *Visual acuity and Ishihara testing should be performed at the start of treatment and monthly thereafter for patients receiving linezolid.*

⁴ Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis (WHO/HTM/TB/2014.11). World Health Organization, Geneva: 2014.
http://apps.who.int/iris/bitstream/10665/130918/1/9789241548809_eng.pdf

- *Hearing tests, ideally audiometry, should be performed at baseline and monthly thereafter in patients receiving an injectable drug. If audiometry is not available, a standardized symptom screen for hearing loss should be used.*
- *Electrocardiogram (ECG) should be obtained at the start of treatment and regularly thereafter in patients who are receiving QT-prolonging drugs.*
- *Thyroid stimulating hormone (TSH) should be measured at baseline and every three months thereafter in patients receiving ethionamide or prothionamide.*
- *All female patients of child-bearing age should be evaluated for pregnancy at the start of treatment and as appropriate during treatment.*
- *A chest x-ray should be performed at baseline and as needed during treatment.*

Other examinations may be performed as necessary by the treating clinician.

8.5 Discontinuation of the study regimen

The study regimen will be discontinued in some patients. In such cases, patients will be evaluated by a clinical committee and switched to an individualized regimen, based on the WHO guidelines for regimen design. The most common situations in which the regimen may be discontinued include:

- **Resistance to drugs in the shorter MDR-TB regimen.** For patients who submit a sputum sample for culture-based second-line DST at the beginning of treatment, results may not be available until after treatment has started. If resistance to drugs in the novel shorter MDR-TB regimen is discovered after treatment is initiated, it may be necessary to modify, extend or discontinue the regimen.
- **Pregnancy during treatment.** For patients who become pregnant during treatment, it may be advisable to modify or discontinue the novel shorter MDR-TB regimen. A decision regarding continuation or discontinuation of the regimen should be made after a review by the clinical committee and discussion with the patient.
- **Intolerable severe toxicity.** One or more drugs may need to be suspended permanently due to severe toxicity. In such cases, the clinical committee should review the medical history carefully to determine how the regimen should be modified.
- **Treatment failure.** If clinical and bacteriological responses to treatment are poor, a change in the treatment regimen should be considered. DST should be repeated, whether or not the regimen is changed, in order to inform future management decisions.

8.6 Post treatment follow-up

After completion of treatment, patients will be informed of the risk of recurrent TB and advised to return for clinical assessment. Patients will also be advised to return for sputum examinations at 6 and 12 months after completion of treatment. A single sputum specimen for smear and culture will be collected at each follow-up visit.

9. Monitoring and management of adverse events

Patients should be screened monthly by a doctor trained in the diagnosis and management of adverse events (AE). An AE is an unexpected medical problem that happens during treatment with a drug or other therapy. AEs may be mild, moderate, or severe, and may be caused by something other than the drug or therapy being given.

Management of AEs should take patient safety and treatment requirements into consideration. One or more drugs may need to be suspended or the dose reduced. Replacement of offending drugs

should take the clinical condition and bacteriological status of the patient into account and a decision made after careful case review. Management of AEs commonly attributed to the use of conventional MDR-TB drugs is detailed in the *Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-resistant Tuberculosis*.⁵ and the *aDSM framework*.⁶ For management of AEs likely attributable to new or repurposed MDR-TB drugs, the *endTB clinical and programmatic guide for patient management with new TB drugs* (<http://endtb.org/resources>) is a useful resource.

The AE should be graded according to a standardized table, such as the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table"),⁷ Common Terminology Criteria for Adverse Events (CTCAE)⁸ or the MSF Severity Scale (<http://endtb.org/resources/pharmacovigilance>). All adverse events leading to the study therapy being temporarily or permanently discontinued should be carefully managed and recorded.

9.1 Safety reporting

(Note here the country specific roles and responsibilities regarding the monitoring, grading, administration, and reporting of adverse events—by whom, to whom, and when)

All serious adverse events (SAEs) should be reported immediately to the relevant national pharmacovigilance authority according to national guidelines (e.g. 72 hours). An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is life-threatening.
- Is a congenital anomaly or a birth defect.

When an AE occurs, the investigator responsible for the care of the patient must first assess whether the event is serious. If it is serious, then an SAE form must be completed and sent to the principal investigator and the relevant pharmacovigilance authority. An example of an SAE form can be found on the endTB website (<http://endtb.org/resources>).

10. Outcome measurement

Patients may be retrospectively removed from the outcome analysis in specific circumstances:

- Patients whose baseline sputum culture is determined to be negative or contaminated. Culture conversion and final treatment outcome may be difficult to assess in patients who are truly

⁵ Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis (WHO/HTM/TB/2014.11). World Health Organization, Geneva: 2014.

http://apps.who.int/iris/bitstream/10665/130918/1/9789241548809_eng.pdf

⁶ Active tuberculosis drug-safety monitoring and management (aDSM). Framework for implementation.(WHO/HTM/TB/2015.28). Geneva, World Health Organization; 2015. Available from: http://apps.who.int/iris/bitstream/10665/204465/1/WHO_HTM_TB_2015.28_eng.pdf

⁷ The Division of AIDS, National Institute of Allergy and Infectious Diseases. Table for Grading the Severity of Adult and Pediatric Adverse Events. Available at <http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx>

⁸ National Cancer Institute Division of Cancer Treatment & Diagnosis. Adverse Events/CTCAE. Available at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.

culture-negative. In general, a culture of any sputum sample obtained up to 90 days before the treatment start date may be used for the baseline culture if the patient has not received treatment during this period. The number of such patients and rationale for removal from analysis should be reported.

Outcomes are based on *Definitions and reporting framework for tuberculosis (2013 revision)* released by WHO in 2013. The outcome is assigned on the principle of "first outcome met" and is not revised during the follow up period.

- **Cured:** Treatment completed without evidence of failure AND three or more consecutive cultures taken at least 30 days apart at the end of treatment.
- **Treatment completed:** Treatment completed without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative at the end of treatment.
- **Treatment stopped due to baseline drug resistance:** Patients who receive culture-based DST results several months after starting a shorter regimen may be switched to a longer regimen if resistance to drugs in the shorter regimen is discovered. For such patients, this outcome should be reported.
- **Treatment failed:** Treatment terminated or need for permanent regimen change of ≥ 2 anti-TB drugs because of:
 - lack of conversion.
 - bacteriological reversion after conversion to negative.
 - evidence of acquired resistance to drugs in the shorter regimen.
 - adverse drug reaction.
- **Died:** A patient who dies for any reason during the course of treatment.
- **Lost to follow-up:** A patient whose treatment was interrupted for 2 consecutive months 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, or where the shorter regimen was not available.)
- **Treatment success:** The sum of cured and treatment completed.

The terms "conversion" and "reversion" of culture results are defined as follows:

- **Conversion** (to negative): culture is considered to have converted to negative when two consecutive cultures taken at least 30 days apart are found to be negative. In such case, the specimen collection date of the first negative culture is used as the date of conversion.
- **Reversion** (to positive): culture is considered to have reverted to positive when after an initial conversion, two consecutive cultures taken at least 30 days apart are found to be positive.

"Recurrent TB" is defined as having either (1) or (2) after cure or completion of treatment:

1. Two consecutive positive cultures, or
2. One positive culture with clinical signs and symptoms or radiographic deterioration (an isolated positive smear or culture without clinical or radiographic deterioration after treatment completion provides insufficient evidence to define recurrent TB).

If genotyping is available, recurrent TB may be further classified as relapse, reinfection, or undetermined as defined below:

- **Relapse:** isolates of the recurrent episode share the same genotype pattern with isolates of the first episode of MDR-TB.
- **Reinfection:** isolates of the recurrent episode and isolates of the first episode of MDR-TB have different genotype patterns.

- **Undetermined:** there is insufficient information to determine whether the recurrent episode is due to relapse or reinfection.

11. Data management and project monitoring

Patient data should be recorded on standard NTP treatment cards and documents. *(Additional data collection forms may be created for the purpose of this study).* Monitoring indicators are given in Chapter 2 and Annex 10 of the *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis*.⁹

The objectives of project monitoring are:

- To ensure that the rights of human subjects are protected and the conduct of the operational research is in compliance with the approved protocol.
- To identify constraints in the identification of MDR-TB suspects, sputum examinations, diagnosis of patients with rifampicin resistance, timely enrollment, pre-treatment assessment, initiation of treatment, management of adverse events, monitoring examinations during treatment, DOT services in the community, tracing of late patients, and assessment of outcome of treatment.
- To verify that reported data are complete, timely and accurate.

Enrollment and progress of patient treatment should be reviewed on a quarterly basis by a committee that is designated for this purpose by the NTP. *(In many countries, there is a national consilium or committee of expert clinicians that has already been created to review complicated cases of MDR-TB. This committee can monitor the progress of enrollment and also design individualized regimens for patients who need to be taken off the shorter MDR-TB regimen.)*

Study results will be shared with national health authorities, stakeholders, and the larger scientific community with the aim to influence and improve MDR-TB treatment within the country and globally.

12. Human subjects protection

The study will follow the principles of the Declaration of Helsinki. The study protocol should be submitted to and approved by a national or local ethics review committee prior to initiation of the study. No patient may be enrolled into this study until the investigator has obtained the patient's informed consent.

⁹ Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis (WHO/HTM/TB/2014.11). World Health Organization, Geneva: 2014.
http://apps.who.int/iris/bitstream/10665/130918/1/9789241548809_eng.pdf