**OPERATIONAL RESEARCH PROTOCOL**

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**DESTRoy TB**:

**D**iscovering **E**vidences **S**upporting the effectiveness of new **T**reatment for drug **R**esistant Tuberculosis

Protocol version: 1.0

August 2018

**Protocol Synopsis**

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| **Title** | **DESTRoy TB**: **D**iscovering **E**vidences **S**upporting the effectiveness of new **T**reatment for drug **R**esistant Tuberculosis  Open-label single-arm trial to assess the country-specific **operational feasibility** and to measure the **effectiveness** of a new treatment regimen of 40 weeks (9 months) duration in adult patients with pulmonary Rifampicin resistant (RR) and multi drug resistant (MDR) tuberculosis in adults: Prospective Observational Study |
| **Hypothesis** | The cure rate for RR-TB with the current regimen under program conditions is about 50% (WHO).  The primary analysis will be conducted using culture results from liquid (MGIT)/LJ culture. **We will evaluate the hypothesis** that the proportion of patients with a favorable efficacy outcome is 85% for the study regimen (based on an anticipated minimum benefit in efficacy of using 40 weeks treatment with Bedaquiline) |
| **Objectives** | **Primary Objectives**  This proposed operational research (OR) aims to test the country-specific **operational feasibility** and to measure the **effectiveness** of new treatment regimens of 40 weeks (9 months) duration in adult patients with RR pulmonary tuberculosis:   1. Bedaquiline (Bdq), Linezolid (Lzd), Levofloxacin (Lfx), Clofazimine (Cfz), for Fluoroquinolone Susceptible MDR/RR TB patients. 2. Bedaquiline (Bdq), Linezolid (Lzd), Delamanid (Dlm), Clofazimine (Cfz) for Fluoroquinolone Resistant MDR/RR TB patients   **Effectiveness**   * Interim treatment outcomes (at 4th and 6th months) * End of treatment outcome (Relapse rate at 6 and 12 months after the end of treatment)   **Operational feasibility**   * Proportion of enrolled patients on the study regimen (MDR-TB / RR-TB patients of the total MDR-TB/RR-TB patients detected and enrolled on drug resistant TB treatment) * Adherence of the treatment facilities to the study protocol procedures * Acceptability by the managers (national and regional), treatment centers, satellite treatment centers and patients (qualitative analysis)   **Secondary objective**   * To evaluate the safety and tolerability (frequency and severity of adverse Drug reactions (ADRs)) of a treatment regimen of 40 weeks (9 months) duration consisting of 9 Bdq-Lzd-Lfx-Cfz in patients with Fluoroquinolone Susceptible RR/MDR TB * To evaluate the safety and tolerability (frequency and severity of adverse Drug reactions (ADRs)) of a treatment regimen of 40 weeks (9 months) duration consisting of 9 Bdq-Dlm-Lfx-Cfz in patients with Fluoroquinolone Resistant RR/MDR TB * To determine the time to sputum culture conversion with this combination treatment regimen * To measure loss to follow up |
| **Study Outcomes** | **Primary Outcome Measures**   1. Favorable efficacy outcome (Cure and Treatment Completed outcomes as defined by the national policy) at the end of treatment with the study regimen   **Secondary Outcome Measures**   1. Incidence of bacteriological relapse during 60 weeks (12 months) post-treatment follow-up, after a favorable response (Cure and Treatment Completed outcomes as defined by the national policy) 2. Incidence of bacteriologic failure or clinical failure during treatment period of 40 weeks (9-months) 3. Treatment Adverse Events (TAEs) presented by incidence of:   - Grade 3 or higher adverse events of any type at any time while on combination treatment regimen (safety)  - Discontinuation of study drug(s) for any reason (tolerability)  - All-cause mortality during treatment or follow-up   1. Time to sputum culture conversion from positive to negative in the Liquid (MGIT) or LJ culture system (defined as the interval between the date of treatment initiation and the date of acquisition of the first of two consecutive negative cultures taken at least 4 weeks apart) |
| **Study Design** | Prospective Cohort Study  Intervention Model: Single Group Assignment Masking: No masking Primary Purpose: Treatment |
| **Study Population** | The study population will include the patients with evidence of resistance to at least rifampicin (by Xpert MTB/RIF test or phenotypic DST) who access participating study sites and who fulfil the inclusion and do not have exclusion criteria outlined in the respective sections below. Presumptive DR-TB will be identified according to the criteria outlined in Clinical Management Guideline of the NTP |
| **Inclusion Criteria** | All patients with diagnosed MDR-TB (or rifampicin resistance) will be invited to participate in the 40 weeks all-oral short treatment protocol if they:   1. Have pulmonary TB (smear-positive or smear-negative); Chest X-Ray results consistent with pulmonary TB (taken as part of the initial clinical assessment) 2. No previous use of second-line drugs for one month or more 3. Men or women aged 12 years and above (Are at least 15 (18) years of age at the time of enrolment) 4. Are willing to attend a treatment facility for the intensive phase of the 40-weeks regimen, and the treatment facility or a local treatment site for the continuation phase and follow-up period 5. Have signed an informed consent, including acceptance of full treatment duration of 9 months and follow-up duration of 12 months after the end of treatment 6. HIV status - HIV infected and uninfected patients are allowed in the study    * Patients already on antiretroviral treatment (ART) will be allowed in the study. The antiretroviral treatment regimen will be evaluated for any contraindications to the drugs used    * HIV infected patients at any CD4 count irrespective of antiretroviral treatment commencement and duration will be included in the study |
| **Exclusion Criteria** | Patients with any of the following criteria will not be eligible for the 40-weeks all-oral short treatment protocol:   1. Any documentation of preXDR or XDR diagnosis 2. Previous exposure to BDQ 3. Have a heart rate-corrected QT (QTc) interval of ≥450msec on ECG at screening 4. Have AST or ALT > 3 times the upper limit of normal 5. Have a creatinine clearance below 20 mL/min per 1.73 m2 body surface area 6. Have severe or intractable extra-pulmonary TB, such as tuberculous meningitis or miliary tuberculosis 7. Have extra-pulmonary TB, unless pulmonary TB is also present 8. History of allergy or known hypersensitivity to any of the trial Investigational Medicinal Products or related substances 9. Are taking any medications contraindicated with the medications in the Study treatment regimen 10. Have any condition (social or medical) which in the opinion of the investigator would make study participation unsafe 11. Are unwilling or unable to sign an informed consent 12. Are pregnant or breastfeeding 13. Are unable to attend or comply with treatment or the follow-up schedule |
| **Principal Investigator** |  |
| **Contact Information** |  |
| **Number of Sites enrolling participants** | The project will be implemented in the top 4 or 5 sites (chosen by NTP) that are reporting a high number of DR TB patients |
| **Screening Assessments** | At the initial assessment visit, all patients confirmed to have MDR or rifampicin-resistant TB (according to the current SOP) and who access care in participating study sites will be evaluated for eligibility for the study.  The following will be done:   1. *Routinely done evaluation and tests*:  * Clinical evaluation (including medical history, weight, height and vital signs) * Chest X-ray * Blood specimens will be drawn for baseline assessment of:   + liver function tests (LFTs)   + creatinine   + potassium   + blood glucose * Two sputum specimens will be collected for sputum microscopy and phenotypic culture and drug susceptibility testing (DST) to determine susceptibility to H, R, Bdq, Lfx, Lzd, Cfz  1. *Additional for this study evaluation and tests:*  * Verbal patient consent for additional testing * Pregnancy test (for pre-menopausal women) * An electrocardiogram (using an ECG machine that calculates QTc with Fridericia correction, QTcF)   One additional sputum specimen will be collected for the line probe assay (LPA) and sent to NTRL to determine whether there are mutations conferring drug resistance to fluoroquinolones |
| **Study Design** | FQ DST  RR TB diagnosed GX  DESTRoy TB Regimen (example):  BDQ, LNZ, CFZ, LFX, (+DLM)  FQ Resistant  BDQ, DLM, LNZ, CFZ  FQ Sensitive  BDQ, LNZ, LFX, CFZ  FQ unknown  BDQ, LNZ, CFZ, LFX, (+DLM)  Assessed for Eligibility |
| **Study Duration** | |  |  |  | | --- | --- | --- | | **Screening** | **Treatment** | **Follow Up** | | 14 days | 40 weeks (9 months) | 60 weeks (12 months post treatment) |   Patients will be referred to the study site for the screening process. Written informed consent (IC1) **must** be obtained from a patient before any protocol specific screening procedures are carried out. The duration of the screening period should be up to 14 days. Once found eligible, he/she will be offered participation in the study, to sign a Participation Informed Consent (IC2), and started on the study regimen.  Each participant will receive 9 months (40 weeks) of treatment. Patients will be followed for 12 months (60 weeks) after the end of treatment. |
| **Study Drugs Dose** | **40 weeks (9 months):**   |  |  |  |  | | --- | --- | --- | --- | | **Drug** | **Body weight** | | | | **30-45 Kg** | **46-70Kg** | **>70Kg** | | **Bedaquiline** | 400 mg once daily for first 14 days/200 mg thrice weekly thereafter | | | | **Clofazimine** | 100 mg | 100 mg | 100 mg | | **Levofloxacin** | 750 mg | 750 mg | 1000 mg | | **Delamanid** | 100mg twice daily | | | | **Linezolid** | 300mg daily | 600mg daily | 600mg daily | |
| **Hospitalization** | As required by the national guidelines |
| **Data**  **Management** | Clinical and demographic information will be collected from the individual participants in case report forms (CRF). The data from bacteriology, clinical pharmacology and biochemistry laboratories will be collected and entered in a database. Data will be verified for accuracy and completeness. Data access would be restricted to the PI and the study statistician. |
| **Data analysis** | Efficacy, safety and tolerability analysis will include all participants who are enrolled to the study and have received at least one dose of the study regimen. Analysis of Covariance adjusting with time to culture conversion as well as at outcome will be performed. |

**Investigators**

**Principal Investigator:**

**Co-Investigators:**

**Conflicts of Interest**

No conflict of interest reported for all participants.

**Acknowledgments**

Parts of the protocol were adapted from the following documents:

1. STREAM. The evaluation of a standardized treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis (MDR-TB). ISRCTN18148631. Version 8.0. 13 April 2018.
2. Operational research project. Feasibility, effectiveness and safety of treating MDR-TB patients in Lao PDR with a short-course treatment regimen of 9 months’ duration. Draft 4. October 2013.
3. Research Protocol. Short course regimen (9 months). Protocol for the treatment of multidrug-resistant tuberculosis (MDR-TB) in Cameroon.

**List of abbreviations**

ADR Adverse drug reaction

AE Adverse events

AIDS Acquired immune deficiency syndrome

ART Antiretroviral therapy

DOH Department of Health

DOT Directly observed therapy

DOTS Directly Observed Treatment Short Course Strategy

DR Drug-resistant

DST Drug susceptibility testing

ECG Electrocardiogram

FDA Food and Drugs Administration

HIV Human immunodeficiency virus

IUATLD (Union) International Union Against Tuberculosis and Lung Diseases

LCP Lung Center of the Philippines

LFT Liver function test

LPA Line Probe Assay

MDR Multidrug-resistant

MOP Manual of Procedures

NTP National TB Control Program

NTRL National TB Reference Laboratory

PBSP Philippine Business for Social Progress

PLHIV People living with HIV/AIDS

PMDT Programmatic Management of Drug-Resistant TB

RR Rifampicin-resistant

SLD Second-line drug

SLI Second-line injectable drug

STC Satellite treatment center

TASC Technical Assistance Support to Countries Project

TB Tuberculosis

TC Treatment center

WHO World Health Organization

Xpert Xpert® MTB/RIF assay

**Drugs abbreviations**

H, INH Isoniazid

R, RIF Rifampicin

BDQ Bedaquiline

E Ethambutol

Z Pyrazinamide

Am Amikacin

Lfx Levofloxacin

Mfx Moxifloxacin

Pto Prothionamide

Eto Ethionamide

Cs Cycloserine

Cfz Clofazimine

# INTRODUCTION

# TB and MDR-TB information in *The Country*

**Current National Guidline for RR/MDR treatment regimen**

# Problems with current MDR-TB strategy

The following problems pose challenges for successful treatment in the standard regimen:

* A high proportion of patients are lost to follow up during treatment due to the following reasons: adverse drug reactions, need to work, personal challenges, geographical barriers and the long duration of the standard regimen. The proportion of lost-to-follow-up \_\_\_\_\_\_\_
* Due to the high loss to follow up, the MDR treatment success rate has been \_\_\_\_\_\_\_\_\_\_
* The standard treatment has many ADRs, including the possibility of severe ADRs such as deafness, renal insufficiency, and psychosis
* The currently used standard regimen has high costs, both for the healthcare system and patient

The long duration of the treatment continuation phase can pose challenges to patients who live far from Treatment Sites. This introduces difficulties in monitoring and optimizing adherence to medications. The ADRs that can occur during treatment are often difficult to manage, may be irreversible or life threatening, and may require halting treatment. Patients who develop severe ADRs require referral from treatment sites to a central TB facility, which adds an additional burden in coordinating care.

# Background on the MDR-TB regimen

# In 2011, World Health Organisation (WHO) guidelines for the treatment for MDR-TB recommended an intensive phase of treatment based on at least four drugs known to be effective and given for a minimum of 20 months; this is referred to below as the WHO 2011 long regimen. Outcomes with this approach are generally poor. In the most recent WHO TB surveillance report only 50% of MDR-TB patients were successfully treated and a recent meta-analysis reported on average 62% successful outcome and a mortality of 11%. In 2010, Van Deun et al (2010)2 reported excellent long-term outcomes in a cohort of over 200 patients in Bangladesh with MDR-TB who were treated with a regimen given for only nine to 11 months. Such a regimen, if successful, represents a considerable advance over current practice. In 2010, Van Deun et al. published the results of a short-course, 9-month regimen for treating MDR-TB in Bangladesh. The treatment regimen (often referred as “Bangladesh regimen”) was based on use of Gatifloxacin (Gfx), Clofazimine (Cfz), Ethambutol (E) and Pyrazinamide (Z) for the full duration, with Prothionamide (Pto), Kanamycin (Km) and high dose Isoniazid (H) added during the 4 months of the intensive phase of treatment: *4 Km Gfx Pto Cfz H E Z / 5 Gfx Cfz E Z*

# This treatment resulted in a cure rate without relapse of 87.9% (95% CI: 82.7%-91.6%) among 206 patients never treated with second-line drugs (SLDs) before.

These results were further supported by data from two West African cohorts with 89% cure rates seen in both the Niger and Cameroon cohorts of 65 and 150 patients respectively. Both cohorts used a regimen similar to that studied in Bangladesh but of 12 months duration. Other prospective cohort studies of similar shortened regimens have also been implemented in Uzbekistan and several countries in West Africa.

In 2016, following review of the available data, the WHO MDR TB treatment guidelines were modified to recommend a 9-12 month shortened regimen under specific conditions (referred to below as the WHO 2016 short regimen). This was a conditional recommendation based on very low certainty in the evidence.

Preliminary analysis of STREAM Stage 1, made public at the Union Conference in October 2017, found that 78.8% receiving the Short regimen had a favorable outcome compared to 79.8% receiving the Long regimens, an HIV-adjusted difference of 1.0% (95% CI, -7.5%, 9.5%). Good long-term outcomes were demonstrated with both regimens, and the Short regimen had non-inferior efficacy and comparable safety to the Long regimen. The primary safety outcome of the trial, the proportions of patients who experienced a Grade 3 or greater adverse event at any time during treatment and follow-up, was also similar on the two regimens (48.2% on the Short and 45.4% on the Long regimens).

In December 2012 the US Food and Drug Administration (FDA) approved Bedaquiline as part of the treatment regimen for MDR-TB when other agents are unavailable. Stage 2 of STREAM was designed to investigate ways in which Short treatment regimen could be improved by removing the second-line injectable, which is associated with severe drug toxicity, and adding Bedaquiline. The results of the stage 2 are expected in 2021.

In June of 2018, South Africa began recommending Bedaquiline as a routine treatment for rifampin-resistant and multidrug-resistant TB (RR/MDR-TB) patients becoming the first country to implement an injection-free treatment regimen. Injectable treatments are associated with serious side effects, including irreversible hearing loss, and their efficacy against DR-TB has not been confirmed in clinical trials. In a retrospective cohort study, South African researchers found that Bedaquiline was more effective at reducing mortality among MDR/RR/XDR-TB patients than the standard regimen. By analyzing 24,014 cases from national vital statistics registries from July 2014 to March 2016, researchers found that only 12.6% of patients on Bedaquiline died compared to 24.8% of patients treated with the standard regimen. Bedaquiline is also associated with reduced risk in all-cause mortality in MDR/RR/XDR-TB.

On August 17 2018, the World Health Organization (WHO) released a Rapid Communication ahead of updated, more detailed guidelines on treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). These improved guidelines are expected to lead to major improvements in treatment and quality of life of MDR-TB patients. The rapid communication announces a priority ranking for medicines available for treatment. This is the first time that WHO has issued a public call for available data on MDR TB for gathering evidence to inform the guideline development. Bedaquiline has been recommended to be used as a core drug in the longer TB treatment regimen for RR/MDR TB patient. It should be prioritized when constructing a longer regimen. Linezolid has been also recommended to be used as a core drug in the longer TB treatment regimen for RR/MDR TB patients. Kanamycin and Capreomycin should no longer be used in treatment of RR/MDR TB. Thus, the proposed new treatment regimen includes either an oral medicine only regimen that is greater than 18 months or a 9-month regimen that contains a second line injectable (Amikacin). Neither option is optimal. There is a great need to identifying effective well tolerated, shorter and easy to use treatment regimen (s) for RR/MDR-TB.

**Summary of the rationale for research onto the all oral modified short MDR-TB treatment regimen in the Country**

The standard regimen for treatment of MDR-TB poses several problems that reduce the effectiveness of treatment and treatment success. First, the long duration of treatment, a total of at least 18 months, places significant burden on patients and health facilities. Second, the serious ADRs that may occur contribute to reduced adherence or suspension of treatment. A shorter regimen for treatment of MDR-TB could improve patients outcomes in the Philippines compared to the standard regimen through two primary mechanisms. First, a shorter duration of treatment itself can reduce loss to follow up of patients. At the same time, the short treatment regimen would directly reduce the cumulative exposure to second-line medications, which in turn may reduce the risk of certain ADRs. Reduced occurrence of adverse reactions likely would improve adherence to treatment.

# OPERATIONAL RESEARCH DESIGN

**Primary Objectives**

This proposed operational research (OR) aims to test the country-specific **operational feasibility** and to measure the **effectiveness** of new all-oral treatment regimens of 40 weeks (9 months) duration in adult patients with RR pulmonary tuberculosis:

1. Bedaquiline (Bdq), Linezolid (Lzd), Levofloxacin (Lfx), Clofazimine (Cfz), for Fluoroquinolone Susceptible MDR/RR TB patients.

2. Bedaquiline (Bdq), Linezolid (Lzd), Delamanid (Dlm), Clofazimine (Cfz) for Fluoroquinolone Resistant MDR/RR TB patients

**Effectiveness**

* Interim treatment outcomes (at 4th and 6th months)
* End of treatment outcome (Relapse rate at 6 and 12 months after the end of treatment)

**Operational feasibility**

* Proportion of enrolled patients on the study regimen (MDR-TB / RR-TB patients of the total MDR-TB/RR-TB patients detected and enrolled on drug resistant TB treatment)
* Adherence of the treatment facilities to the study protocol procedures
* Acceptability by the managers (national and regional), treatment centers, satellite treatment centers and patients (qualitative analysis)

**Secondary objective**

* To evaluate the safety and tolerability (frequency and severity of adverse Drug reactions (ADRs)) of a treatment regimen of 40 weeks (9 months) duration consisting of **9 Bdq-Lzd-Lfx-Cfz** in patients with Fluoroquinolone Susceptible RR/MDR TB
* To evaluate the safety and tolerability (frequency and severity of adverse Drug reactions (ADRs)) of a treatment regimen of 40 weeks (9 months) duration consisting of **9 Bdq-Dlm-Lfx-Cfz** in patients with Fluoroquinolone Resistant RR/MDR TB
* To determine the time to sputum culture conversion with this combination treatment regimen

To measure loss to follow up

# Timeline

The patient enrollment will be ongoing for two years. All enrolled patients will be followed after the completion of therapy for 60 weeks (12 months). Given maximum treatment duration of 40 weeks (9 months) and enrollment completion in 6 months, full data collection and analysis will be completed in 39 months.

# PATIENT POPULATION

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# Study site inclusion criteria

Participating study sites are required to meet the following criteria:

* Experience in treating MDR-TB patients adapting Short treatment regimen (STR) and/or working with new TB medications (BDQ, DLM) for at least one year
* Support from the Tuberculosis Control Program at national or regional level
* Provide a document expressing interest to participate in the study signed by a Head of the facility
* Suitable study site staff and facilities for close supervision of patients in treatment and follow up
* Study site staff willing to enroll all eligible patients into the study. This site would ideally function as a single coordinating/enrolling facility and work with satellite sites for treatment and follow-up
* Acceptable plans for close supervision of patients in treatment and follow-up (evaluation of the effectiveness and pharmacovigilance)
* Willingness to offer HIV testing to all patients who wish to participate in the study, and have all HIV clinical management services available (including provision of antiretroviral therapy, ART)
* Access to the network of well-functioning smear microscopy laboratories and laboratories performing cultures, with a system of quality assurance
* Access to drug susceptibility testing (DST) and rapid genotypic line-probe assay (LPA) for isoniazid, rifampicin, second-line injectables (SLI) and fluoroquinolones of the required quality (or ability to quickly build capacity for this testing) as well as access to GeneXpert testing
* Access to routine blood and serum testing (including complete blood counts and biochemistries)
* Capacity to monitor electrocardiogram (ECG)
* Acceptable infection control practices

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# Description of the patient population

The study population will include the patients with evidence of resistance to at least rifampicin (by Xpert MTB/RIF test or phenotypic DST) who access participating study sites and who fulfil the inclusion and do not have exclusion criteria outlined in the respective sections below. Presumptive DR-TB will be identified according to the criteria outlined in the Manual of Procedures (MOP) of the NTP.

# Patient inclusion criteria

All patients with diagnosed MDR-TB (or rifampicin resistance) will be invited to participate in the 40 weeks all-oral short treatment protocol if they:

1. Have pulmonary TB (smear-positive or smear-negative); Chest X-Ray results consistent with pulmonary TB (taken as part of the initial clinical assessment)
2. No previous use of second-line drugs for one month or more
3. Men or women aged 12 years and above (Are at least 15 (18) years of age at the time of enrolment)
4. Are willing to attend a treatment facility for the intensive phase of the 40-weeks regimen, and the treatment facility or a local treatment site for the continuation phase and follow-up period
5. Have signed an informed consent, including acceptance of full treatment duration of 9 months and follow-up duration of 12 months after the end of treatment
6. HIV status - HIV infected and uninfected patients are allowed in the study
   * Patients already on antiretroviral treatment (ART) will be allowed in the study. The antiretroviral treatment regimen will be evaluated for any contraindications to the drugs used
   * HIV infected patients at any CD4 count irrespective of antiretroviral treatment commencement and duration will be included in the study

# Patient exclusion criteria

Patients with any of the following criteria will not be eligible for the 40-weeks all-oral short treatment protocol:

1. Any documentation of preXDR or XDR diagnosis
2. Previous exposure to BDQ
3. Have a heart rate-corrected QT (QTc) interval of ≥450msec on ECG at screening
4. Have AST or ALT > 3 times the upper limit of normal
5. Have a creatinine clearance below 20 mL/min per 1.73 m2 body surface area
6. Have severe or intractable extra-pulmonary TB, such as tuberculous meningitis or miliary tuberculosis
7. Have extra-pulmonary TB, unless pulmonary TB is also present
8. History of allergy or known hypersensitivity to any of the trial Investigational Medicinal Products or related substances
9. Are taking any medications contraindicated with the medications in the Study treatment regimen
10. Have any condition (social or medical) which in the opinion of the investigator would make study participation unsafe
11. Are unwilling or unable to sign an informed consent
12. Are pregnant or breastfeeding
13. Are unable to attend or comply with treatment or the follow-up schedule

For any patient who is excluded (i.e., identified as MDR or rifampicin-resistant by the laboratory but not starting on the Study treatment regimen), a form documenting the reasons of the exclusion will be completed. Patients who are excluded from the 9-month treatment must be treated according the national MDR-TB routine practices.

**Study strategy**

At the time of treatment initiation, a sputum sample will be sent for ascertainment of fluoroquinolone sensitivity.

* If the sample shows fluoroquinolone resistance, then LFX will be stopped
* If the sample shows fluoroquinolone sensitivity, then DLM will be stopped
* If the fluoroquinolone DST is indeterminate or missing, both LFX and DLM will be continued for the duration of the treatment period
* If fluoroquinolone resistance is determined prior to the start of treatment, LFX will not be started

# Justification and documentation of exclusion of any sub-segment of the population

Patients who may be at unacceptable risk from the 40-weeks all-oral short treatment regimen will be excluded from this study, as they may more likely benefit from treatment regimens that are tailored to their needs and limitations. These include patients with difficult to treat extra-pulmonary or severe TB, extensive drug resistance, patients with known allergies or pre-existing conditions that prohibit them from taking any drug in the 40-weeks all-oral short treatment regimen, and patients who are pregnant or breastfeeding.

Because the effectiveness of the 40-weeks all-oral short treatment regimen has only been shown for MDR-TB patients who do not have resistance to fluoroquinolones, all MDR-TB strains isolated will be evaluated for fluoroquinolones resistance. The effectiveness of the 40-weeks all-oral short treatment regimen may be limited if MDR-TB strains that exhibit resistance to fluoroquinolones (especially later generation fluoroquinolones), particularly if these strains also possess resistance to pyrazinamide. Patients whose strain presents any second-line drug resistance will be referred to the Consillium for the decision on clinical management.

The Study regimen was not tested in clinical trials in pregnant women and this regimen is markedly different from regimens that make up the current norm, thus pregnant women would be excluded from this operational research study. All possible efforts must be made to avoid the possibility that women of childbearing age would become pregnant during therapy. Patients who are pregnant before treatment is initiated or become pregnant during therapy cannot be given the 40-weeks all-oral short treatment regimen and must be managed according to the national MDR-TB guidelines.

**Screening**

At the initial assessment visit, all patients confirmed to have MDR or rifampicin-resistant TB (according to the current SOP) and who access care in participating study sites will be evaluated for eligibility for the study.

The following will be done:

1. *Routinely done evaluation and tests*:

* Clinical evaluation (including medical history, weight, height and vital signs)
* Chest X-ray
* Blood specimens will be drawn for baseline assessment of:
  + liver function tests (LFTs)
  + creatinine
  + potassium
  + blood glucose
* Two sputum specimens will be collected for sputum microscopy and phenotypic culture and drug susceptibility testing (DST) to determine susceptibility to H, R, Lfx, Lnz, Cfz.

1. *Additional for this study evaluation and tests:*

* Verbal patient consent for additional testing
* Pregnancy test (for pre-menopausal women)
* An electrocardiogram (using an ECG machine that calculates QTc with Fridericia correction, QTcF)
* One additional sputum specimen will be collected for the line probe assay (LPA) and sent to NTRL to determine whether there are mutations conferring drug resistance to fluoroquinolones

# Recruitment and enrollment

# Patients who meet inclusion criteria and do not have exclusion criteria will be invited to start 40-weeks all-oral short treatment regimen. Formal consent form will be read to the patient and the patient’s signature will be obtained. The patient will be given a copy to take home and the original copy will be filed at the study site. Comprehensively, routine procedures in doing contact tracing among household members who stayed for at least 3 months with index cases shall be done.

# Any patient can refuse to participate in the 40-weeks all-oral short treatment regimen for any reason. Patients who decline participation or are not eligible will be referred for routine treatment and care with no negative consequences for the patient. Routine procedures on contact tracing among household members of index cases shall be done.

Once the eligibility of the patient is confirmed, patient is informed about the study and agrees to provide consent, the following will be done upon enrollment:

* Patient signs informed consent for the 40-weeks all-oral short treatment regimen study
* Blood specimens will be drawn for baseline assessment of:
  + Thyroid-stimulating hormone (TSH) test
  + Complete Blood Count
  + HIV antibody testing (provider initiated HIV counseling and testing, PICT)
  + Hepatitis B (HepBs Antigen) and hepatitis C (HCV antibodies) tests
* A second ECG (after the first dose of treatment)
* Visual acuity test

# Procedures for implementing and documenting informed consent

Details of the treatment regimen will be explained to the patient, risks and benefits will be discussed and an opportunity to answer all questions will be provided. This will include adverse drug reactions and action to be taken to address them (see **Appendix 1**). If patient agree, a formal consent form will be read to the patient and the patient’s signature will be obtained. The patient will be given a copy to take home and the original copy will be filed at the study site. Any patient can refuse to participate in the 9-month treatment regimen for any reason. Patients who decline participation or are not eligible will be referred for routine treatment and care with no negative consequences for the patient (see **Appendix 1**).

The informed consent from the patient will be obtained depending on the patient’s ability to read and sign. If the patient is able to read and sign, then the patient will read the information form, ask the questions he/she wants and if he/she agrees, sign the consent form. If the patient is unable to read and sign, the health worker will read the complete information form to the participant and the participant will ask the questions he/she wants. If the patient accepts verbally, the participant will put a thumb print on the consent form and the consent form will be countersigned by a witness. The patients will be provided with a copy of the informed consent and printed materials that explain the purpose of the study, procedures, and assessments and another copy will be kept at the study site where the patient is being treated. Subjects will also be provided with the telephone numbers of the investigator and qualified personnel who can assist with their questions and concerns. Informed consent will be translated by local certified translator into the four main languages spoken in the Country.

If the patient is unable to be fully informed (i.e., is unable to understand the treatment regimen or purpose of this research), then he/she will not be enrolled.

# Number of patients to treat

No statistical sampling will be done. All patients accessing participating facilities eligible for the 9-month treatment protocol who meet eligibility criteria will be invited to participate in this operational research study. The study does not have a comparator arm or randomization.

The number of the patients to be treated under this protocol was estimated based on the following assumptions. A total of \_\_ treatment facilities will start the protocol in Year 1, and an additional \_\_ facilities will start in Year 2. Based on PMDT enrolment numbers for 2016, the first \_\_ facilities enrolled a total of \_\_\_ patients with bacteriologically confirmed MDR, and the additional \_\_ facilities to be added in the second year enrolled a total of \_\_\_ patients. Data on the baseline drug resistance to second-line drugs among MDR-TB patients in the Country in two cohorts of consecutive MDR-TB patients enrolled in \_\_\_\_\_\_\_ and \_\_\_\_\_\_\_ (years of enrolment) in the Country showed that \_\_\_ % of patients had resistance to fluoroquinolones or/and second-line injectable drugs. These patients would not be eligible to receive the 40-weeks all-oral short treatment regimen based on drug resistance exclusion criteria. We expect that ~20% of patients may have other exclusion criteria or not provide informed consent. Therefore, considering that ~65% of patients accessing care at the protocol treatment facilities would be eligible and willing to enroll in the 40-weeks all-oral short treatment regimen, we estimate that in the first year ~\_\_\_ patients will be enrolled, and in the second year ~\_\_\_ patients will be enrolled. Thus, the total patient cohort during two years of enrolment is estimated to be ~\_\_\_ patients.

**TREATMENT**

# Medications and dosages

**Table 1. Dosages of second-line drugs according to weight category**

|  |  |  |  |
| --- | --- | --- | --- |
| **Drug** | **Body weight** | | |
| **30-45 Kg** | **46-70Kg** | **>70Kg** |
| **Bedaquiline** | 400 mg once daily for first 14 days/200 mg thrice weekly thereafter | | |
| **Clofazimine** | 100 mg | 100 mg | 100 mg |
| **Levofloxacin** | 750 mg | 750 mg | 1000 mg |
| **Delamanid** | 100mg twice daily | | |
| **Linezolid** | 300mg daily | 600mg daily | 600mg daily |

All drugs to be used in the study will be procured \_\_\_\_\_\_\_\_\_\_\_\_\_ (ex. through the Global Fund).

**Procedure following missed treatment**

# Days/doses missed during each phase must be made up to the total required number of doses by extending treatment by the number of days missed. The rationale for the number of doses is that for PMDT in the Country one month of treatment is computed at 28 days per month. Therefore the treatment completion is at 252 days (28 days/month x 9 months). Patients that fail to complete required number of doses within specified time will be referred to the Consilium for treatment decision.

# Treatment management and adherence

At treatment initiation, all patients will be counseled about the medications, their potential ADRs and the risks of non-adherence. Patients will then be asked to sign a contract for treatment adherence, as practiced routinely. At each visit, patients will be further counseled about the importance of taking all doses of their medications and about the risks of resistance if they fail to do so. DOT is mandatory for the full duration of treatment because:

* The patients have to swallow large amounts of pills during treatment course
* Adverse drug reactions are frequent
* The acquisition of additional drug resistance including development of extensive drug resistance (XDR) has to be avoided at all costs

All doses of all medications will be directly observed. A trained treatment partner will provide assistance and observation of each dose for each patient. Patient adherence to all doses of all medications will be recorded on the treatment card by those witnessing the patients taking their medication.

Patients will initiate treatment at a referral clinic (hospital). There will be no mandatory hospitalization period unless clinically indicated. After the patient has converted sputum smears and if the patient has no severe ADRs, the referral clinic will send the patient to a local treatment site. In order to guarantee strict professional DOT, referral to a treatment site must be organized according to one of the following procedures:

* Before referring the patient to a Treatment Site, the study staff representative should visit the patient’s home to check if the address is correct and to discuss with the household members the importance of correct treatment observance
* Treatment will be administered on a daily basis under strict supervision by staff trained in MDR-TB. At least once a week during first month of treatment and then at least monthly, every patient will be seen by a physician trained in MDR-TB. In case of complications the frequency of the medical consultations may need to be increased.
* All ADRs must be documented in detail (using the designated form), and treated appropriately. Grade 3 and above ADRs will be reported monthly to the Scientific Committee and Consillium.
* MDR-TB treatment and follow up will be free-of-charge to the patient.

MDR patients co-infected with HIV must be managed according to the national TB-HIV policy and guidelines. Particular attention must be paid to the overlapping toxicity of ART and MDR TB treatment.

If the clinician considers the patient to be failing they should contact the Scientific Committee and Consilium to discuss whether the patient’s management needs to be modified.

# Outcome definitions

The following treatment outcome definitions adapted from the current Philippines Manual of Procedures and WHO Definitions and reporting framework for tuberculosis[12](#_4bvk7pj) for the 9-month regimen are to be used to document patients’ outcomes (**Table 2**).

**Table 2. Definitions of end of treatment outcomes**

|  |  |
| --- | --- |
| **OUTCOME** | **DEFINITION** |
| Cured | |  | | --- | | A patient with bacteriologically confirmed RR-TB/ MDR-TB who has completed 9-11 months of treatment by 9-month regimen protocol without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase | |
| Treatment Completed | A patient who completes 9-11 months of treatment by 9-month regimen protocol 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 the 9-month regimen protocol of at least two anti-TB drugs because of:   * lack of sputum **smear** conversion by the end of the intensive phase\*, or * bacteriological reversion of sputum **culture**\*\* in the continuation phase after culture conversion\*\* to negative, or * evidence of additional acquired resistance to fluoroquinolones, 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 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) |
| Withdrawn | A patient is taken off the 9-month regimen for any reason other than treatment failure (for example, baseline second-line drug resistance, withdrawn patient informed consent or other reasons) and referred to the PMDT program for routine care |
| Treatment Success | The sum of *cured* and *treatment completed* |

\*For Treatment failed, lack of sputum smear conversion by the end of the intensive phase implies that the patient does not convert within the intensive phase applied to the 9-month regimen. The intensive phase is a minimum of 4 months of second-line anti-TB treatment. If the patient does not convert, a cut-off of **6 months** of treatment is applied to determine the criteria for treatment failed.

\*\* The terms “conversion” and “reversion” of culture as used here 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 a 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, culture(s) is found to be positive. For the purpose of defining Treatment failed, reversion is considered only when it occurs in the continuation phase.

Poor Outcome is defined as any death, failure, or loss to follow up while on treatment.

In addition, there are outcomes only evident during the follow up period after treatment is completed:

* Relapse: Cure or treatment completion with at least one positive culture during post-treatment follow-up, unless the strain was proven to be different from the initial isolate by molecular techniques.
* Reinfection: Recurrent disease as defined for a relapse, but with a strain exhibiting a fingerprint pattern different from the initial isolate, provided there was clinical or microscopic evidence of recurrence.
* Non-relapsing cure: treatment success without relapse or reinfection over the follow-up period. Patients may be withdrawn from the 9-month regimen based on the drug resistance pattern by the phenotypic DST from the specimen obtained at the start of treatment. These patients will be managed and have treatment outcomes of 9-month regimen assigned, as follows:

|  |  |  |
| --- | --- | --- |
| **BASELINE drug resistance results and clinical situation** | **Clinical management** | **Treatment outcome for 9-month regimen** |
| Rifampicin mono-resistance (i.e. rifampicin resistance unaccompanied by resistance to isoniazid), and no additional resistance to SLI and fluoroquinolones is detected by phenotypic DST. | The 9-month regimen will be continued. | Assess outcome according definitions for 9-month regimen |
| Drug resistance to fluoroquinolones by phenotypic DST. | The 9-month regimen will be stopped and patient will be referred to Consillium for treatment decision. | Withdrawn |
| Drug resistance to the SLI is present by phenotypic DST. DST result to only one SLI drug is available and shows resistance of isolate to SLI **or** results to two SLI drugs (aminoglycoside and capreomycin) are available and both show resistance | The 9-month regimen will be stopped and patient will be referred to Consillium for treatment decision | Withdrawn |
| The culture did not grow or was contaminated and the DST for fluoroquinolones could not be performed, but the patient response to the 9-month regimen can be assessed | Treatment with 9-month regimen will be continued | Assess outcome according definitions for 9-month regimen |

Patients whose treatment regimen had to be modified because of adverse reactions, but don’t meet the definition of “Failed” (above), will continue to be followed-up according to the study protocol, but will be evaluated as a separate category during analysis. Patients that fail to complete required number of doses within specified time will continue to be followed-up according to the protocol, but will be evaluated as a separate category during analysis.

**MONITORING AND FOLLOW UP**

# Patient monitoring during treatment

Patients who start the 9-month treatment regimen will undergo regular evaluation of clinical and para-clinical parameters. The monitoring schedule is based on the national MDR-TB guidelines, taking into consideration the shorter treatment duration, the fact that the regimen includes high-dose moxifloxacin, and the need for 12-months follow-up after stopping therapy. **Table 3** describes the schedule of clinical and laboratory examinations for patients on the 9-month treatment regimen.

**Table 3: Schedule of examinations during intensive, continuation, and follow up phases for 9-month treatment regimen**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Intensive Phase** | | | | **Continuation Phase** | | | | | **Follow-Up** | | | | | |
| **Clinical evaluation** | **Screening** | **Month 1** | **Month 2** | **Month 3** | **Month 4** | **Month 5** | **Month 6** | **Month 7** | **Month 8** | **Month 9** | **Month 10** | **Month 11** | **Month 12** | **Month 15** | **Month 18** | **Month 21** |
| Sputum smear | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Sputum culture | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Chest X-ray | X |  |  |  |  |  | X |  |  |  |  |  |  |  |  | X |
| Written informed consent | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Demographics, Medical History | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Clinical Examination | X | X**\*** | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Clinical assessment (including AEs and concomitant medication during treatment) |  | X**\*** | X | X | X | X | X | X | X | X |  |  |  |  |  |  |
| Hemoglobin/platelets count | X |  |  | X |  |  | X |  |  | X |  |  |  |  |  |  |
| White blood count | X |  |  | X |  |  | X |  |  | X |  |  |  |  |  |  |
| Serum creatinine | X |  |  | X |  |  | X |  |  | X |  |  |  |  |  |  |
| Serum potassium | X |  | X |  | X |  | X |  | X |  |  |  |  |  |  |  |
| Thyroid stimulating hormone | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Serum liver enzymes | X | X | X | X | X | X | X | X | X | X |  |  |  |  |  |  |
| ECG | X | X**\*\*** | X | X | X | X | X | X | X | X |  |  |  |  |  |  |
| Pregnancy test (female) | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| HIV test | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

**\****Patients will be examined at least once a week for the first month of treatment and thereafter monthly throughout treatment.*

**\*\****Baseline ECG should be obtained and additional ECGs conducted at week 1 and 2 after starting treatment and thereafter monthly throughout treatment. ECG should be repeated as necessary in case of clinical suspicion of heart rhythm and conduction disturbances.*

Every month throughout treatment, an early morning sputum specimen will be collected. At the end of the intensive and the continuation phase, a second specimen will be collected on the spot. Sputum smear and culture will be done monthly. DST will be done on positive culture isolates for H, Lfx, Cfz, E, Z, Pto at the baseline and on months 4 and 9.

At each visit, patients will be interviewed about ADRs and all answers will be recorded on the Patient’s Progress Report Form. If patients present with ADRs or encounter other problems requiring specific investigations between the scheduled intervals, the frequency of monitoring and supervision will be adapted, and the necessary investigations will be repeated as often as required. All observations and decisions made during monitoring and supervision will be reported and added to the individual patient records. The bacteriological examinations (sputum smear, culture, DST) and blood tests will take place at the designated laboratories as per routine practices. The initial culture isolate should be stored at -80°C in the National TB Reference Laboratory for at least 48 months from patient enrollment into the study. This will allow the distinction between relapse and re-infection in case of recurrent TB disease during 12 months after completing the 9-month regimen.

# Patient follow-up post-treatment

After successful completing of treatment, each patient will be reminded about the need for follow up visits and informed about the date of their next visit. Follow up will be done for 12 months after completing the 9-month regimen in order to detect relapse.

During the follow-up visits the following procedures will be undertaken on all patients (regardless of symptoms):

1. Clinical evaluation including evaluation for any adverse events that may have occurred after patient’s last visit and any concomitant medications s/he may has been received
2. Sputum collection for smear, Xpert, and culture. DST examination and LPA will be done if culture or Xpert-positive). If follow up sputum culture is positive, genotyping of positive follow up isolate as well as stored baseline isolate from this patient would be performed

**SAFETY MONITORING**

# Description and management of ADRs

An Adverse Drug Reaction is a response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. An ADR is characterized by the suspicion of a causal relationship between the drug and the occurrence, i.e., a reaction judged as being at least possibly related to treatment by the reporting or a reviewing health professional. Beyond the anticipated mild ADRs of medications commonly used for general TB treatment, it is possible that patients enrolled in the 9-month treatment regimen will experience moderate and severe ADRs. Some pre-existing conditions increase the risk of adverse effects, notably renal disease, liver disease, diabetes, and HIV infection.

**Table 4** lists the main *anticipated* ADRs and suggests how they should be managed. The drugs most likely to be responsible are written in bold. **Table 4** is based on the MOP and the WHO MDR-TB Guidelines.

**Table 4. Management of ADRs of first- and second-line drugs**

|  |  |  |
| --- | --- | --- |
| ADR | Drugs | Management |
| Arthralgia | Clofazimine  Bedaquiline | * Decrease dosage of suspected drug * Consider aspirin or other analgesic |
| Liver toxicity | **Bedaquiline**  Levofloxacin | * Do not give pyrazinamide if liver disease is pre-existing * Stop all hepatotoxic medication until the problem resolves * Exclude other possible causes of hepatitis * Reintroduce hepatotoxic drugs one at a time in the following order: Levofloxacin, Ethambutol, Prothionamide, Isoniazid, Pyrazinamide, while monitoring the liver function * Consider stopping the responsible drug completely |
| Cardiotoxicity | **Bedaquiline**  Clofazimine | *Treatment initiation*:   * Avoid initiating Bedaquiline or Clofazimine if QTcF > 450 msec. Could start later, if QTcF < 450 msec * If prolonged QTcF at baseline, check albumin and electrolytes and correct prior to Bedaquiline/Clofazimine initiation   *On treatment*:   * If QTcF > 450 msec but < 500 msec on at least 2 consecutive ECGs (a few minutes apart) at any time after treatment initiation with Bedaquiline/Clofazimine, continue meds and monitor ECG more closely; no need to withhold either drug unless patient is symptomatic (in which case stop all QT-prolonging drugs and admit for closer ECG monitoring and management) * If QTcF > 500 msec on at least 2 consecutive ECGs (a few minutes apart) while on treatment with Bedaquiline/Clofazimine, withhold all QT-prolonging drugs until QTcF returns to < 500 msec. Refer if patient is symptomatic or if severe electrolyte or albumin deficiency cannot be corrected   *Comments*:   * Completely reversible upon discontinuation of offending drug * Avoid other QT-prolonging drugs where possible, otherwise monitor more closely with ECGs * Many ECG machines default to calculating the corrected QT interval using the Bazett formula (QTcBaz), however most guidelines and recommendations use the Fridericia formula (QTcF) for making treatment decisions. Consider manual calculation of QTcF in cases of prolonged QTc |
| Gastro-intestinal intolerance | **Clofazimine**  **Levofloxacin**  **Bedaquiline** | * Rehydrate if necessary * Decrease dosage of suspected drug or stop the drug if the patient is in the continuation phase * Change time of drug administration * Consider antacid 2 hours before or 3 hours after TB medications * Consider anti-emetic * Stop Prothionamide for a 1 to 7 days if mild intolerance, or completely if severe intolerance * In case of acute abdomen, stop Clofazimine |
| Neuro-psychiatric symptoms | Levofloxacin | * Consider antidepressant or antipsychotic * Stop suspected drug for 1-4 weeks until the psychotic disturbances are controlled * Decrease dosage of the suspected drug except Moxifloxacin, which must not be decreased |
| Peripheral neuropathy | Levofloxacin | * Always consider and manage other causes e.g. d4T (switch), HIV (treat) * Increase pyridoxine dose: Usually 50 mg for each 250 mg of Isoniazid but may need to be higher (200 mg daily) if on other neurotoxic drugs AND * Begin exercise regimen, focus on affected regions   AS A LAST RESORT: Discontinue suspected drug and discuss substitution with an expert  Comments   * Patients with co-morbid disease e.g. diabetes, HIV and alcoholism are more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of the TB drugs * It may be possible to re-introduce drug at a later stage at a lower dose if peripheral neuropathy resolved, especially if drug is essential in regimen |
| Dermatological reaction | **Clofazimine**  Levofloxacin | * If mild to moderate: continue therapy and give symptomatic treatment * If severe: stop suspect drugs until reaction disappears * If systemic symptoms: do not reintroduce responsible drug |
| Dark colored urine | **Bedaquiline** | * Patient counseling |

All drugs in the Study regimen are currently used in the Country for treatment of MDR-TB and XDR-TB, except\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_.

# Monitoring and reporting ADRs

The occurrence of adverse events associated with medical treatment is an outcome of interest, and patients will be regularly interviewed about, and tested for, such events. ADRs will be recorded on the Patient’s Progress Report Form. All adverse events will be managed by experienced clinicians. Adverse drug reactions will be reported by their seriousness (**Table 5**) and reported on a form designed for this protocol. All adverse reactions will be systematically written in the patient files with grading of seriousness below. ADRs may emerge or persist after the cessation of treatment and need to be recorded in the follow-up phase. In addition to the reporting pathways relating to this study, all suspected ADRs need to be reported to the Country Food and Drug Administration using the “Suspected Adverse Reactions Form” as part of the spontaneous pharmacovigilance functions.

**Table 5. Grading of Adverse Events**

|  |  |  |
| --- | --- | --- |
| Grade 1 | Mild | Small or transient inconvenience that does not limit normal daily activity. No need for medical intervention or corrective treatment. |
| Grade 2 | Moderate | Partial limitation of normal daily activity. In some, but not all cases, medical intervention or corrective treatment is necessary. No need to discontinue the treatment. |
| Grade 3 | Severe | Limitation of normal daily activity. Medical intervention and corrective treatment, often requiring hospitalization, are necessary. The responsible drug may have to be stopped temporarily until the symptoms have resolved. |
| Grade 4 | Life-threatening | Severe limitation of normal daily activity. Medical intervention and corrective treatment, requiring hospitalization, are necessary. The responsible drug may need to be stopped permanently. |
| Grade 5 | Death |  |

# Relationship and causality assessment of ADRs

The principal investigator will need to grade and analyze ADRs for causal relation between the adverse event and one or several drugs and consider possible other causes of the observed ADR before concluding that they are due to a particular anti-TB drug. Determination of the category of relationship (causality categories) is shown in **Table 6**.

**Table 6. Scale for Attribution of ADRs**

|  |  |
| --- | --- |
| **Category** | **Definition** |
| Definite | Events occurring within a timely manner after administration of the drug(s); that are known sequela to the administration of the drug(s) and follow a previously documented pattern of reaction, but for which no other explanation is known. This category applies to ADRs that the PI believes are incontrovertibly related to the treatment. |
| Probable | Any event occurring in a timely manner after administration of the drug(s); that follows a known pattern of reaction to the drug(s); and for which no other explanation is known. This category applies to ADRs that, after careful medical consideration at the time they are evaluated, are believed with a high degree of certainty to be related to the drug(s). |
| Possible | Any event occurring in a timely manner after administration of the drug(s) that does not follow a known pattern of reaction and for which no other explanation is known. This category applies to ADRs that, after careful medical consideration at the time they are evaluated, are considered unlikely to be related but that cannot be ruled out with certainty. |
| Unlikely | In general, this category can be considered applicable to those ADRs that, after careful medical consideration at the time they are evaluated, are considered to be unrelated to administration of the drug(s). |
| Not related | Any ADRs for which there is evidence that an alternative etiology exists or for which no timely relationship exists to the administration of the drug(s) and the ADRs does not follow any previously documented pattern. This category applies to those ADRs that, after careful medical consideration, are clearly and incontrovertibly due to causes other than the drug(s). |
| Unclassifiable | There is insufficient information about the ADRs to allow for an assessment of causality. |

Definitions for anticipated or unanticipated ADR are provided in **Table 7**.

**Table 7. Definitions of Anticipated and Unanticipated Adverse Events**

|  |  |
| --- | --- |
| **Category** | **Definition** |
| Anticipated | AE which meets any one (or both) of the following:   1. Consistent with listing in the current study protocol narrative and/or consent form and/or pharmaceutical package insert for the study treatment(s), in terms of the nature, intensity, and frequency. 2. Based on clinical judgment by the PI/primary treating physician, the AE was expected to occur based on the study participant’s underlying medical condition and/or concomitant disorders, disease process, or non-study treatment. |
| Unanticipated | AE which meets BOTH of the following:   1. NOT consistent with listing in the current study protocol narrative and/or consent form and/or pharmaceutical package insert for the study treatment(s) in terms of the nature, intensity, and frequency.   AND   1. Based on clinical judgment by the PI/primary treating physician, the AE was NOT expected to occur based on the study participant’s underlying medical condition and/or concomitant disorder, disease process, or non-study treatment. |

# RECORDING, REPORTING AND EVALUATION

In order to strengthen evidence of the effectiveness of the Study treatment regimen, it will be necessary to collect all information on follow-up and results according to strict scientific standards.

## 

## Scientific Committee

Monitoring and evaluation of the operational research will be done by an independent body, the Scientific Committee that has national and international experts as members. It will be organized, convened and supported by the WHO. The methods and frequency of monitoring and evaluation will be agreed by the members. Remarks, suggestions, and recommendations may be exchanged through e-mail. If specific patients need to be discussed, they will only be identified by their registration number. The reports on ADRs will be received by a scientific committee monthly. Interim treatment outcomes will be assessed quarterly. The Committee may also decide to conduct monitoring visit in coordination with NTP.

## Records, registers, reports

The protocol will utilize existing documents for PMDT where available.

1. **Existing forms (records) used by the NTP:**

* Drug-resistant TB register
* DR-TB Treatment Card
* Patient’s Progress Report Form
* FDA. Suspected Adverse Reactions Form

The following forms and reports were specifically created for the Study regimen monitoring and evaluation:

1. **Monitoring forms/reports:**

* The Study regimen ADRs monitoring form.

1. **Reports:**

* Quarterly Report on Interim Treatment Outcome of DR-TB Cases Put on the Study Regimen
* Annual Report on the Treatment Outcome of DR-TB Cases Put on the Study Regimen
* Quarterly Report on Adverse Drug Reactions Occurring in the Cohort of Patients Put on the Study Regimen
* Annual Report on Adverse Drug Reactions Occurring in the Cohort of Patients Put on the Study Regimen

1. **Individual patient study case report forms (CRF)**

* Enrollment
* Non-enrollment
* Screening
* History
* Signs and symptoms
* Clinical Evaluation
* Adverse Event
* TB drug dose record
* Laboratory evaluation
* Mycobacteriology
* Treatment completion
* Treatment evaluation
* Follow up evaluation
* Follow up completion
* Severe Adverse Events (SAE)
* Notification of death

## Data collection and management

Standardized socio-demographic, clinical, and laboratory data will be collected on all patients onto both routinely used forms and registers and study specific forms. Clinical data including ADRs will be recorded onto the patient’s medical chart and the Patient’s Progress Report Form in at each visit. Laboratory data is generally documented in written reports in the patient’s medical chart as well as recorded in treatment cards. These forms will remain in the patient’s medical chart and will be abstracted from patient medical records onto specific study individual patient data collection forms at least monthly.

Individual patient data will be abstracted into the study case report forms (CRF) on at least monthly basis. Collected data will be entered into MS Access or Epi-Info database or other appropriate software. These data will be imported into SAS or similar statistical software for analysis.

## Evaluation of operational research

The aim of the operational research is to evaluate the effectiveness, safety and feasibility of the all-oral 40-weeks treatment regimen in the Country.

(1) The following indicators will be used to evaluate the **effectiveness** of the regimen:

* The interim treatment outcomes (at 4 and 6 months)
* End-of-treatment outcome
* Relapse at 6 and 12 months after the end of treatment

The cure rate for RR-TB with the current regimen under program conditions is about 50% (WHO).

The primary analysis will be conducted using culture results from liquid (MGIT)/LJ culture. **We will evaluate the hypothesis** that the proportion of patients with a favorable efficacy outcome is **85% for the Study regimen** (based on an anticipated minimum benefit in efficacy of using 40 weeks treatment with Bedaquiline).

(2) The following indicators will be used to evaluate the **safety** of the regimen:

* Frequency and severity of ADRs.

To evaluate the frequency and severity of ADRs, we will use reported data from the MDR-TB patients in the background therapy (BT) groups of the randomized clinical trials of bedaquiline (as drugs used in BT regimens would be comparable to the currently used 18-month regimen and STR) as well as published data on MDR-TB patients cohorts as well as data on QTc prolongation for Bedaquiline and Clofazimine. We will compare the frequency and severity of ADRs in the Study regimen cohort to these reported ranges.

(3) The following indicators will be used to evaluate **operational/clinical feasibility** as well as **programmatic effectiveness**:

* Proportion of enrolled on the Study regimen MDR-TB/RR-TB patients of the total MDR-TB/RR-TB patients detected and enrolled on drug-resistant TB treatment
* Adherence of the treatment facilities to the study protocol procedures
* Acceptability by the managers (national and regional), medical personnel, and patients (qualitative study, ex. Treatment Burden Questionnaire (TBQ))

## Data analysis plan

General descriptive data, including frequencies of basic demographic and clinical variables, will be calculated. The proportion of successful and poor treatment outcomes and the frequency of adverse drug reactions will be estimated in aggregate and for each study site. The analyses will also be stratified by relevant demographic and clinical variables.

Predictors of time to sputum culture conversion, successful end-of-treatment and long-term outcomes (12 months), and certain ADRs within 40-weeks regimen cohort of patients will be evaluated. Continuous variables will be summarized with standard descriptive statistics and transformed as necessary and compared using two-sample t-test between groups. The proportion with specific risk factors will be compared between groups with/without outcome of interest using the chi-square test or Fisher’s exact test as appropriate for categorical variables. Risk ratios will be calculated to determine strength and significance of associations. Multivariable regression analyses will be done to identify independent predictors of outcomes of interest. All tests will be 2-sided and a value ≤0.05 will be considered as statistically significant.

We anticipate secondary research questions will arise. Additional analyses of data collected as a part of this protocol may address these questions.

# ETHICAL CONSIDERATIONS AND APPROVAL

## Research Ethics Committee Approval

## This study will not proceed unless approved by the appropriate Ethics Review Committees

## Informed Consent

All patients will sign a consent form at enrolment.

## Patient Confidentiality

Once a patient has consented to participate in the study a unique identification number will be assigned to the patient. Patient data forms that are not kept in patient medical charts will be kept in a locked cabinet only accessible by the study investigators. After completion of patients’ enrolment and follow up in the study and completing database cleaning, the first page of the data forms that link patients’ identifying information with study identification numbers will be removed and destroyed. Study forms will be stored for 3 years after the completion of data analysis and publication, and then will be destroyed. Data entry will be done by trained personnel in a password-protected database.

# Description of risks to the operational research participants and methods to minimize risks

The potential risks for the study participants are that the 40-weeks regimen may: (1) be less effective (i.e. have increased risk of failure/death, relapse, and risk of acquired resistance), and (2) have more associated toxicities (i.e. have a higher frequency of QTcF prolongation episodes).

The assessment of interim outcomes will be part of the study so that concerns with effectiveness will be identified early and action taken to improve effectiveness. Enrollment criteria will limit inclusion to cases that have demonstrated susceptibility to fluoroquinolone; this should diminish amplification of resistance. If a patient fails to convert the sputum smear/culture, which has been shown to be reliably associated with outcome, then the patient will be documented as a treatment failure and an individualized treatment regimen in accordance with WHO guidelines will be initiated. To ensure that patients with treatment success have relapse-free cure, patients would be followed up for 12 months after completing 40-weeks regimen treatment. Twelve months follow up after treatment completing is justified by the analysis based on 64 British Medical Research Council (BMRC) trials on drug-susceptible TB, which reported that the majority of relapses (91%) occurred within 12 months after completing treatment. There is no a priori reason to think that relapse timing would be different between drug-susceptible TB and MDR-TB trials.

Most second-line drugs have associated toxicities. Isoniazid will be used in the study regimen at higher doses than are usually administered. During treatment, patients will be monitored regularly for ADRs by laboratory tests and clinical screening. This includes electrocardiographic testing (ECGs will be done for an assessment of the impact of Bedaquiline and Clofazimine on QTc interval) as indicated. Since most adverse events occur shortly after treatment with a new agent is initiated, and during the intensive phase of treatment, patients will be monitored for ADRs especially closely during that period. If any patient has a serious adverse event (defined as life-threatening ADR or one likely to cause significant or permanent impairment of bodily functioning), then treatment will be altered to minimize any further potential harm. Periodic review of the data will be conducted by the Scientific Committee to evaluate safety and take an early action to minimize ADRs.

# Description of anticipated benefits to the operational research participant

We anticipate that treatment success rate in patients who receive this regimen will not be lower than in patients who receive currently used 18-month regimen or STR. The shorter duration of treatment is expected to be easier on the patients and associated with fewer ADRs and improved treatment adherence.

# Description of the potential risks to anticipated benefit ratio

Benefits of participation of eligible patients in this evaluation outweigh the risks, because this study will use particular patient inclusion and exclusion criteria and rigorous patient monitoring and follow up, aiming to minimize anticipated risks.

## Response to new or unexpected findings

Interim analyses of treatment outcomes will be submitted to and monitored by a Scientific Committee and Consillium (NTP) quarterly. Reports on ADRs of Grade 3 or above will be submitted to and monitored by a Scientific Committee and Consillium monthly. If there is clear evidence from these or other analyses that the all-oral 40-weeks regimen is associated with worse outcomes or a significantly increased rate of adverse events of Grade 3 or above, then enrolment will be stopped. If there is any miscommunication of data to the patients, or breach in patient confidentiality, study enrolment will be halted at the site where the infraction occurred, and the ethical review committee and all study clinicians and personnel will be notified. Full disclosure will be relayed directly to the patients. Every effort will be taken to identify the root causes of the infraction, and steps will be taken to ensure that the possibility of recurrence is minimized or extinguished. Any and all corrective measures required by the ethical review boards will be undertaken.

## Notifying participants of their individual results

All patients will be made aware of the results from all tests, generally at the monthly appointments, earlier if clinically indicated.

## Notifying participants of study findings

## Prior to publication, all study personnel will be made aware of the results of data analysis. These study personnel will be responsible for relaying results to all patient participants.

# ANTICIPATED OUTCOMES

## Anticipated products resulting from the study and their use

Results from this study will be widely disseminated, and will be used in concert with other similar studies to determine if a modified short treatment regimen can be used to successfully treat MDR-TB in the Country. With DOH/NTP approval, these results will be used by WHO, USAID, and the CDC to determine if such regimens can be endorsed internationally by other countries. There will be publications from this study to document treatment success rates of the all-oral 40-weeks regimen and the occurrence of adverse events.

## Disseminating results to public

Results will be disseminated through presentations, publications and reporting of results on information websites and through patient advocacy groups.

## Ownership of data and authorship

The Country National Tuberculosis Control Program, Department of Health will have ownership of the data. A working group will be created for each analysis and report/publication. This working group will include at least one representative from each participating agency. Authorship on publications would be based on substantial contributions to conception and design of the study, acquisition of data, or analysis and interpretation of data and drafting the report, article or abstract or revising it critically for important intellectual content.

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