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ShORRT
(Short, all-Oral Regimens for Rifampicin-resistant Tuberculosis) Research Package

All-oral shorter treatment regimens for multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB): Evaluating their effectiveness, safety, feasibility, cost-effectiveness and impact on the quality of life of patients in *(name of country)*

Protocol

Version 2 February 2020

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Abbreviations and acronyms

aDSM	Active TB drug safety monitoring and management
ADR	Adverse drug reaction
AE	Adverse Event
AMR	Antimicrobial resistance
ART	Anti-retroviral therapy
ARV	Anti-retroviral
BMI	Body Mass Index
BPNS	Brief peripheral neuropathy screen
CTCAE	Common Terminology Criteria for Adverse Events
DAIDS	Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events
DMID	Division of Microbiology and Infectious Diseases
DR-TB	Drug-resistant Tuberculosis
DST	Drug Susceptibility Testing
ECG	Electrocardiogram
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
GDI	Global Drug-Resistant TB Initiative – Stop TB Partnership
GFATM	Global Fund to Fight AIDS, TB and Malaria
HCW	Health care worker
HIV	Human Immunodeficiency Virus
HRQoL	Health-related quality of life
KNCV	KNCV Tuberculosis Foundation
MIC	Minimum inhibitory concentration
MSF	Médecins Sans Frontières
MDR	Multidrug-resistance
MDR-TB	Multidrug-resistant tuberculosis
MTB	Mycobacterium tuberculosis
NTP	National Tuberculosis Program
RR-TB	Rifampicin-resistant tuberculosis
SAE	Serious Adverse Event
SOC	Standard of care
STR	Shorter treatment regimen
TB	Tuberculosis
TSH	Thyroid Stimulating Hormone
USAID	United States Agency for International Development
WHO	World Health Organization
XDR	Extensive Drug Resistance
XDR-TB	Extensively Drug-resistant Tuberculosis

Abbreviations of TB agents

Am	Amikacin
Bdq	Bedaquiline
Cs	Cycloserine
Cm	Capreomycin
Cfz	Clofazimine
Dlm	Delamanid
E	Ethambutol
Eto	Ethionamide
FQ	Fluoroquinolone
H, INH	Isoniazid
Km	Kanamycin
Lfx	Levofloxacin
Lzd	Linezolid
Mfx	Moxifloxacin
Ofx	Ofloxacin
Pa	Pretomanid
PAS	Para-Aminosalicylic Acid
Pto	Prothionamide
R, RIF	Rifampicin
S	Streptomycin
Tzd	Terizidone
Z	Pyrazinamide

About this protocol

This document describes a template protocol for the conduct of operational research studies to assess the effectiveness, safety, feasibility and cost of all-oral shorter MDR/RR-TB treatment regimens, and their impact on the quality of life of patients with MDR/RR-TB. This protocol is a living document. As new evidence on any aspect of this work becomes available, an updated version will be posted at this link: https://www.who.int/tdr/research/tb_hiv/shorrt/en/.

Part A of this document is the main template protocol which describes implementation studies investigating the effectiveness and safety of all-oral shorter MDR/RR-TB regimens**.**

Part B of this document describes protocols for recommended complementary research into the following areas:

- Health-related quality of life of MDR-TB patients (Section 2)
- Measuring stigma experienced by MDR-TB patients and health care providers (Section 3)
- Feasibility and process indicators for the implementation of all-oral shorter MDR-TB regimens (Section 4)
- Acceptability of patient support services and model of care to patients and health care providers (Section 5)
- Cost-effectiveness analysis (Section 6)

The core text of this document is in black font. Sections of this protocol in *red font and Italics* are areas that should be adapted to the local setting by the study investigators, and explanatory notes. Text in **blue colour** identifies the complementary research topics described in Part B of this document and outlined above. Investigators can integrate relevant sections of recommended complementary research into the main protocol or develop stand-alone protocols for sub-studies of interest.

The rationale for this protocol was discussed and agreed with the Global TB Programme at the World Health Organization (WHO). Development of this document was led by the Special Programme for Research and Training in Tropical Diseases (TDR) of WHO (Corinne Merle and Debora Pedrazzoli).

It was guided by a panel of experts from the following institutions:

Damien Foundation; Global Drug-Resistant TB Initiative (GDI) – Stop TB Partnership; International Union Against Tuberculosis and Lung Disease (The Union); KNCV Tuberculosis Foundation; Médecins Sans Frontières (MSF); Partners in Health; The Sentinel Project on Pediatric Drug-Resistant Tuberculosis; Global Fund to Fight AIDS TB and Malaria (GFATM); United States Agency for International Development (USAID); Karolinska Institutet; Harvard University; Liverpool School of Tropical Medicine (LSTM); London School of Hygiene and Tropical Medicine (LSHTM); McGill University; National TB Control Programme of Benin, Democratic Republic of the Congo, Lao PDR, Nigeria, Public Health Centre of the Ministry of Health of Ukraine; civil society representatives; WHO Regional Offices, Regional Green Light Committee (SEARO).

Portions of this document were adapted from the following documents made available by technical partners:

a. Global Drug-resistant TB Initiative (GDI): The evaluation of effectiveness and safety of novel shorter treatment regimen for multi-drug resistant tuberculosis. May 2018.
b. DESTRoy TB, Discovering Evidences Supporting the effectiveness of new Treatment for drug Resistant Tuberculosis. USAID; August 2018.
c. 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.
d. RISE. (R)emoved (I)njectable modified (S)hort – course regimens for (E)Xpert Multidrug Resistant Tuberculosis: Programmatic Feasibility and Clinical Effectiveness in Tanzania; National Tuberculosis and Leprosy Programme.
e. Effectiveness and safety of an injectable-free shorter regimen for Rifampicin resistant and Multidrug Resistant Tuberculosis treatment in Rusafa District, Baghdad, IRAQ. Médecins Sans Frontières; October 2018.
f. World Health Organization. Tuberculosis patient cost surveys: a handbook. Geneva, Switzerland, 2017.
g. TB stigma measurement guidance. KNCV Tuberculosis Foundation. Challenge TB 2018.

This protocol is accompanied by a data collection toolkit and a key study procedures booklet available from WHO/TDR.

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1. Protocol at a glance

The table below is a summary of the whole protocol (i.e. Part A and Part B). However, investigators may decide to consider either only part A of the protocol, or part A and selected components of part B of the protocol. Therefore, this summary should be modified accordingly.

TITLE	All-oral shorter treatment regimens for multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB): Evaluating their effectiveness, safety, feasibility, cost-effectiveness and impact on the quality of life of patients in *(name of country)*
INVESTIGATOR/STUDY LOCATION	*To be added by investigators*
STUDY RATIONALE	New all-oral shorter MDR/RR-TB treatment regimens can be used by national TB programmes under operational research conditions. This protocol aims to provide a standardised methodology for conducting such operational research so that the data generated are harmonised across different implementation settings.
STUDY OBJECTIVES	To determine the effectiveness, safety, feasibility, cost-effectiveness and impact on the quality of life of all-oral shorter MDR/RR-TB regimens of 9/12-month duration under programmatic conditions
STUDY DESIGN	Longitudinal study design with one single cohort of patients receiving the all-oral shorter MDR/RR-TB treatment regimen. Alternatively, a stepped-wedge design comparing patients receiving the all-oral shorter MDR/RR-TB regimen and patients receiving the standard MDR/RR-TB treatment regimen in use in the country.
STUDY POPULATION	The study population includes TB patients with evidence of resistance to at least rifampicin by conventional DST (culture-based) or rapid molecular DST.
Main inclusion criteria	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 or molecularly confirmed TB with evidence of resistance to at least rifampicin (or for children likely to be MDR/RR-TB based on history of close contact with a confirmed MDR/RR-TB case).
Main exclusion criteria	1. Is unable to take oral medication. 2. Must take any medications contraindicated with the medicines in the RR/MDR-TB regimen. 3. Has a known allergy to any of the drugs in the MDR/RR-TB regimen. 4. Has a QTcF interval of ≥ 500 msec at baseline that does not correct with medical management.
Total expected number of patients	Depends on the number of MDR/RR-TB patients in care at each study site in the country and the study design.
Expected number of study sites	Depends on the MDR-TB management in the country and the study design.

Shorter all-oral MDR/RR-TB treatment regimens proposed	***Note:*** *Countries should choose the most appropriate treatment regimen based on the epidemiological and programmatic conditions of the country. The treatment regimens below are proposed based on current knowledge on their safety and efficacy.* ***Further treatment regimens are listed in Annex 1.*** For FQ sensitive patients: Treatment regimen: 2 Lzd-Bdq-Lfx-Cfz-Z/4Bdq-Lfx-Cfz-Z/3 Lfx-Cfz-Z For FQ resistant patients: Treatment regimen: 6 Bdq-Pa-Lzd
COMPARATOR treatment regimen *(if appropriate)*	Standard MDR/RR-TB regimen in use in the country
EVALUATION CRITERIA	1. ***Effectiveness:*** ***Primary outcome:*** the proportion of MDR/RR-TB patients who have a favourable treatment outcome. This is defined as "cured" or "treatment completed" without recurrence during 12 months after the end of the treatment. 2. ***Safety:*** ***Primary outcome:*** the proportion of MDR/RR-TB patients who have a serious adverse event up to 6 months after the end of the treatment. 3. ***Health related Quality of Life*** 4. ***Level of stigma*** 5. ***Feasibility*** 6. ***Acceptability*** 7. ***Cost-effectiveness from a societal or health care perspective; affordability and socioeconomic impact for patients***
ASSESSMENT SCHEDULE	See timeline below
STATISTICAL CONSIDERATIONS	
Sample size	A sample size could be calculated based on desired confidence around the proportion of patients with a favourable outcome relative to an external standard (or the comparator group's performance).
Sampling/recruitment strategy	All patients who meet the eligibility criteria during a given time period will be invited to participate in this operational research study.
DURATION OF STUDY **(for each patient on the all-oral shorter MDR/RR-TB treatment regimen)**	✓ 9/12 months of treatment ✓ 12 months of follow-up after the end of the treatment
ANTICIPATED STUDY DATES	Start: TBD End: TBD

2. Overview of the timelines of the different study components (Part A and Part B)

The timelines presented in this table are for both Part A and Part B of the protocol. Investigators should adapt this table and remove the rows for those study components that are not included in their main protocol.

Please also note that the table below shows the timelines for a treatment duration of 9 months. The duration of on-treatment monitoring should be extended to 12 months, if that is the duration of the chosen treatment (or for the selected duration of treatment).

	Enrolment	Treatment Phase									Follow-up	
Study component		**M_T 1**	**M_T 2**	**M_T 3**	**M_T 4**	**M_T 5**	**M_T 6**	**M_T 7**	**M_T 8**	**M_T 9/12**	**M_F 6**	**M_F 12**
Safety												
Effectiveness [F]												
Stigma[§]												
HRQoL												
Feasibility												
Acceptability*[§]												
Cost-effectiveness: Provider												
Cost-effectiveness: Patient*												

[§] *Health care workers will also be included in this study. The first data collection time point for stigma studies is two weeks after TB diagnosis.*
[F] *The proposed follow-up is 2 visits within one year.*
** Patients will be sampled during different stages of the treatment and follow-up phases.*

PROTOCOL - PART A

Evaluating the safety and effectiveness of all-oral shorter treatment regimens for multi-drug and rifampicin-resistant tuberculosis in *(name of country)*

2.1 Schedule of examinations during treatment and follow-up phases of the study

	Investigation/Observation	Baseline assessment & Screening	Treatment Phase (M=Month)									Follow-Up	
			M_T 1	M_T 2	M_T 3	M_T 4	M_T 5	M_T 6	M_T 7	M_T 8	M_T 9/12	M_F 6	M_F 12
Clinical evaluation	Demographics, Medical History	X											
	Clinical Examination*	X	X	X	X	X	X	X	X	X	X	X€	X€
	Written informed consent	X											
	Treatment adherence		X	X	X	X	X	X	X	X	X		
	Concomitant treatment		X	X	X	X	X	X	X	X	X	X	
	Adverse events		X	X	X	X	X	X	X	X	X	X	
Bacteriology	Sputum smear	X (2)	X	X	X	X (2)	X	X	X	X	X (2)	X	X
	Sputum culture	X	X	X	X	X	X	X	X	X	X	X	X
	DST (FQ/Injectables)	X										X±	X±
Laboratory tests	Haemoglobin/platelets count / White blood count	X	X#	X#	X#	X#	X#	X#	X#	X#	X#		
	Serum creatinine (at baseline and if clinically indicated or ECG abnormalities)	X											
	Serum potassium (at baseline and if clinically indicated or ECG abnormalities)	X											
	Serum liver enzymes	X	X	X	X	X	X	X	X	X	X		
	Pregnancy test (female)	X											
	HIV and hepatitis test	Xμ											
	TSH *(Note: for patients receiving Pto/Eto)*	X			X			X					
Other	Chest X-ray$^{\xi}$	X											
	ECG	X	Xβ	X	X	X	X	X	X	X	X		
	Visual acuity & BPNS* *(Note: for patients receiving Lzd and high-dose INH/EMB)*	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)		
	Audiometry *(Note: at baseline and monthly afterwards until end of treatment with injectable agents)*	X	X	X	X	X	X	X	X	X	X		
	Disability assessment	X									X	X	X

**Patients will be examined at least once a week for the first month of treatment and thereafter monthly throughout treatment.* This task can be shifted to any health care staff trained and supported to interview and conduct basic examination to detect adverse events. For patient taking linezolid or ethambutol, peripheral neuropathy screen and visual acuity and colour-blindness screening should be performed every month until linezolid and ethambutol are stopped.

€ *Telephone contact might be envisaged if patient transportation to the TB centre is not feasible.*

± *DST performed at baseline (with storage of the strain at -20c) after reversion during treatment, and if any culture is found positive, during the 12 months' period after the end of the treatment (with storage of the strain of the recurrent episode for genotyping analysis), or after conversion.*

To be performed if the patient is taking linezolid.
μ *Hepatitis B (HepBs Ag) and hepatitis C (HCV Ab) tests.*
B *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, or other clinical signs (e.g. dehydration and electrolyte misbalance).*
F: The optional proposed follow-up is 4 visits every 3 months during one year. It may be reduced to 2 visits every 6 months during one year, if resources are limited. In this case, patients should be advised to present at health facility as soon as they experience TB symptoms.
ξ *Chest X-ray may be repeated during follow-up in case of suspicion of recurrence.*

Note: Please note that while all the information collected during screening is valuable for subgroup analysis, virtually none would indicate exclusion. It is desirable to conduct these examinations before treatment is initiated, but treatment initiation should NOT be delayed to complete these.

3. Background

3.1 Multi-drug resistant tuberculosis

M. tuberculosis (TB) kills more people globally than any other pathogen and drug-resistant tuberculosis (DRTB) accounts for one-third of antimicrobial resistance (AMR) deaths. Multi-drug resistant TB (MDR-TB) is a public health crisis and a global health security risk carrying grave consequences for those affected. Globally, 186 772 cases of MDR/RR-TB were detected and notified in 2018, of which 97% were enrolled on treatment with a second-line regimen. This accounts for only a third of the estimated 484 000 people who developed MDR/RR-TB in 2018. An estimated 214 000 people died as a result of it.

MDR-TB cannot be treated with the standard 6-month course of first-line medication which is effective in most TB patients. Patients with rifampicin-resistant or MDR-TB are treated with a different combination of drugs, which usually has an intensive phase of treatment of 8 months and a total duration of treatment of 20 months (this is referred to as the WHO 2011 long regimen). Outcomes with this approach are generally poor, with only 56% of MDR/RR-TB patients reported to have been successfully treated in the most recent WHO Global TB Report, while in 8% of MDR/RR-TB patients the treatment failed, 15% died, and 15% were lost to follow-up.

Attempts to reduce the length of conventional MDR-TB regimens and to use a combination of drugs which is tolerable have been ongoing for several years through various studies.

3.2 The 2019 WHO consolidated guidelines on DR-TB treatment

In August 2018, WHO released a Rapid Communication ahead of updated, more detailed guidelines on treatment of MDR/RR-TB, which were then published in March 2019[1]. These improved guidelines are expected to lead to major improvements in treatment outcomes (given shorter treatment duration and reduced toxicity), and quality of life of MDR-TB patients, including reduced socioeconomic impact. The new guidance announces a priority ranking for medicines available for treatment. 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 longer than 18 months or a 9-month regimen that contains a second line injectable (Amikacin). Neither option is optimal.

3.3 Operational research on the all oral shorter MDR-TB treatment regimens

Some of the regimens currently under trial do not include the use of a second-line injectable, and can potentially be programmatically easier to administer, while at the same time can improve treatment outcomes and quality of life of patients. Although these regimens are currently undergoing testing in clinical trials, should countries decide to adopt modified all oral shorter regimens, the WHO is recommending their use under operational research conditions. Evidence from this research can inform programmatic implementation in (*name of country*), and also provide important data to the global TB community to strengthen the evidence base to inform treatment guidance.

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[1] WHO consolidated guidelines on drug-resistant tuberculosis treatment, WHO, 2019
https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/

3.4 Rationale for research on the all oral shorter MDR/RR-TB treatment regimen in (name of country)

It is reasonable to assume that individuals treated for MDR-TB with all-oral shorter regimens would experience better quality of life compared to patients on a standard (either short or long) MDR-TB regimen, through two primary mechanisms. First, an injectable-free treatment itself can potentially improve treatment adherence of patients and facilitate the implementation of community-based models of care. This in turn would reduce direct costs incurred by the patients associated with travelling to the health facility for daily injections (such as transportation, food and accommodation costs), and/or the opportunity costs associated with lost productivity and income due to hospitalisation in the intensive phase of treatment.

Second, injectable-free treatment regimens that potentially reduce occurrence of adverse reactions would likely improve adherence to treatment. It is therefore likely that less QALY would be lost and overall health-related quality of life of patients would improve. These hypotheses need to be corroborated by further evidence to inform national policy. Finally, the effectiveness of shorter MDR/RR-TB treatment regimens needs to be ascertained under programmatic conditions.

3.5 TB and MDR-TB epidemiology in (name of country)

This section should describe TB and MDR-TB epidemiology in the local setting in which the study is going to be conducted. Investigators should consider to describe the following:

- *TB epidemiology;*
- *The number of bacteriologically confirmed MDR-TB cases in the country reported in the previous two years (new and previously treated cases, prevalence of fluoroquinolone and second-line injectable resistance among MDR-TB cases, other relevant findings from drug resistance surveys conducted in the country);*
- *Estimated proportion of cases diagnosed and treated compared to WHO estimates of MDR/RR-TB burden;*
- *Treatment outcomes reported in the last two cohorts of MDR-TB patients (including treatment outcomes of standardised MDR/RRTB shorter treatment regime, if in use in the country);*
- *Important comorbidities, other challenges faced by MDR/RR-TB patients in the country.*

3.6 MDR-TB treatment in (name of country)

This section should describe the following:

- *Diagnosis and DST capacity of the National Reference Laboratory;*
- *Progress in implementation of the programmatic management of drug resistant TB (PMDT);*
- *Policy and practice related to MDR-TB regimen/s currently used in the country;*
- *Model of care for MDR-TB (e.g. where MDR-TB patients are treated in the country, if they are hospitalised, community involvement);*
- *Challenges with treatment outcomes, if perceived to be poor.*

3.7 Health financing and social protection in (name of country)

This section should describe the health financing and social protection mechanisms in place in the country. You should describe if patients are covered by health insurance, receive social support in-kind, e.g. food and transport vouchers, and/or in cash, and refer to findings from any survey of costs faced by TB patients and their households.

3.8 Drug procurement in (name of country)

This section should describe the drug procurement mechanisms in place at the country level, and registration status of new and repurposed drug as per 2019 WHO guidelines on drug-resistant tuberculosis treatment.

4. Evidence on the drugs proposed in this study

4.1 New and repurposed drugs

The characteristics of new and repurposed drugs proposed in this study are described in this section in alphabetical order. Only those drugs that are part of the chosen regimens being studied should be kept in this section of the protocol.

4.1.1 Bedaquiline

Chemical composition and dosing

Bdq fumarate (bedaquiline or SIRTURO™) is a diarylquinoline anti-mycobacterial drug. It inhibits adenosine triphosphate synthesis, a novel method of action. The drug has a 5.5-month half-life. *It is* indicated for use against MDR-TB (US FDA, EMA). Because it is highly lipophilic, Bdq requires a loading dose of 400 mg daily for 14 days followed by a maintenance dosing of 200 mg thrice weekly.

Efficacy

Strong bactericidal and sterilizing activity against *M. tuberculosis* organisms have been shown in pre-clinical laboratory setting as well as in animal experiments. Data gathered from clinical trial and operational studies provided enough evidence to classify this agent in the group A during the last revision of the WHO guidelines (2019). There is reported cross-resistance of Bdq with clofazimine (Cfz) due to mutations in Rv0678, a transcriptional repressor of the genes encoding the MmpS5-MmpL5 efflux pump. Bdq shows linear pharmacokinetics and better absorption when the drug is taken with food versus when taken fasting (resulting in approximately a two-fold increase in serum drug levels)[2].

Safety and tolerability

The phase IIB trial of Bdq found higher all-cause mortality among persons who received Bdq compared with placebo —although data from other studies suggest that this finding is not being observed in observational cohorts and program conditions. Bdq is associated with QTc prolongation in anywhere from 5-20% of persons who have received the drug. Such QTc prolongation has not yet been associated with an increase in fatal arrhythmias but it does bear careful monitoring. Bdq may also be associated with elevated transaminase levels but that has been reported with multiple drugs used for the treatment of MDR-TB. For patients on Bdq, it is essential that a baseline QTc interval be assessed with regular follow up while on the drug and the continued monitoring of liver function.

In people living with HIV, ARV treatment with Efavirenz, should be considered with caution. Based on a single dose study, it appears to reduce the amount of Bdq by inducing CYP3A4.

Knowledge about the safety of Bdq in pregnancy and while breastfeeding is sparse. The FDA has therefore classified it as Category B as animal reproduction studies have failed to demonstrate a risk to the foetus and there are no adequate and well-controlled studies in pregnant women.

4.1.2 Clofazimine

Chemical composition and dosing

Clofazimine (Cfz) is a lipophilic riminophenazine initially synthesized in 1954 and licensed for treatment of leprosy in 1969. Its mechanism of action remains unclear, but existing evidence suggests

[2] Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis (https://apps.who.int/iris/bitstream/handle/10665/130918/9789241548809_eng.pdf#page=273")

production of reactive oxygen species in *Mycobacterium tuberculosis* cells. In vivo efficacy is believed to be driven by a combination of both anti-mycobacterial activity and anti-inflammatory property of clofazimine. Using a mouse model of chronic tuberculosis, Grosset et *al* demonstrated that a clofazimine-containing regimen was significantly more active in achieving culture conversion and preventing relapse compared to its clofazimine-free regimen. Studies demonstrate a prolonged lag time for absorption, high variability in bioavailability and clearance, and a terminal half-life of 70 days. The effect of treatment duration on efficacy and safety is not known.

Efficacy
The MIC of clofazimine against *M. tuberculosis* ranges from 0.06 to 2.0 µg/mL. In one study, the minimum bactericidal concentration against *M. tuberculosis* ranged from 0.12 to 0.48 µg/ml. Potent activity against hypoxic, non-replicating M. tuberculosis suggests clofazimine may have potential as a sterilizing drug. Mechanisms for resistance have not been reported. Following oral absorption, clofazimine is distributed extensively in the body and primarily into fatty tissues and the mononuclear phagocyte system. Oral administration of clofazimine 100, 300 and 400mg daily in leprosy patients resulted in average plasma levels of 0.7, 1.0 and 1.41µg/ml, respectively. In the consolidated WHO MDR-TB guidelines this drug was classified in the group B of agents for the treatment of MDR-TB.

Safety and tolerability
Patients taking clofazimine may experience dry skin, and clofazamine causes slowly reversible red-black skin discoloration in virtually all patients treated for more than a few months.

Clofazimine may also prolong the QTc interval. Such QTc prolongation has not yet been associated with an increase in fatal arrhythmias but it does bear careful monitoring. Data on breastfeeding and pregnancy are sparse (some reports of normal outcomes, and some of neonatal deaths). Clofazimine is only recommended during pregnancy when benefit outweighs risk. Infants exposed in utero or during breastfeeding may be more deeply pigmented at birth.

4.1.3 Delamanid

Chemical composition, dosing, and duration
Dlm (OPC-67683 or DeltybaTM) is a new agent derived from the nitrodihydro-imidazooxazolen class of compounds. It inhibits the synthesis of mycolic acid, which is an exclusive component of the external wall of mycobacteria. Peak plasma levels are achieved 4-5 hours after administration. The half-life of Dlm is 38 hours after drug discontinuation. Further details on dosing are given in Annex 3 and 4.

Efficacy
Dlm has also demonstrated in vitro and in vivo activity against both drug susceptible and drug resistant strains of M. Tuberculosis, and was granted conditional approval by the EMA in 2014 based on phase IIb data which demonstrated higher rates of culture conversion, faster time to culture conversion, and higher treatment success rates among person who receive less than 2 months of Dlm versus those who received 2 months or more. After the phase IIb data, WHO immediately issued guidelines recommending its use when an effective treatment regimen cannot be designed and in patients with high risk of poor outcome. These guidelines have been later updated in 2016 for the use of Dlm in the treatment of MDR-TB in children and adolescents. In the consolidated 2019 WHO guidelines on DR-TB treatment this drug was classified in the group C of agents for the treatment of MDR-TB. Dlm absorption is increased after a standard meal.

Safety and tolerability
Although early studies showed some QTc prolongation with Dlm, the phase III trial found similar rates of QTc prolongation when comparing the Dlm regimens and the placebo regimens. Dlm has an excellent safety profile and is deemed one of the least toxic agents used in the treatment of MDR-TB. Drug–drug interaction studies in healthy subjects show no clinically significant interactions when Dlm is co-administered with tenofovir, efavirenz or lopinavir/ritonavir. Knowledge about the safety of Dlm in pregnancy and while breastfeeding is sparse. Dlm has not been used extensively in children but recommended dosing for children is defined and provided in Annex 4.

4.1.4 Levofloxacin

Chemical composition and dosing
Levofloxacin (Lfx) belongs to the second-generation medicine of the fluoroquinolone class. The medicine was repurposed for treatment of MDR-TB and remains one of the pivotal medicines for MDR-TB treatment. Levofloxacin is a concentration dependent medicine and diffuses through the bacterial cell wall, acts by inhibiting DNA gyrase (bacterial topoisomerase II), an enzyme required for DNA replication, RNA transcription, and repair of bacterial DNA. Inhibition of DNA gyrase activity leads to blockage of bacterial cell growth. Single oral doses of levofloxacin 50 to 1000mg produce a mean Cmax and area under the concentration-time curve (AUC) ranging from approximately 0.6 to 9.4 mg/L and 4.7 to 108 mg.h/L, respectively, both increasing linearly in a dose-proportional fashion. Levofloxacin is widely distributed throughout the body, with a mean volume of distribution of 1.1 L/kg, and has excellent penetration into chronic cavitary TB lesions.

Kemper and colleagues (2013) demonstrated in MDR-TB patients that the free serum concentration of levofloxacin had a cavitary/serum levofloxacin concentration ratio greater than 1 in the majority of patients. The plasma elimination half-life ranges from 6 to 8 hours in individuals with normal renal function (80% of levofloxacin is eliminated as unchanged drug in the urine through glomerular filtration and tubular secretion). The effect of duration on efficacy and safety is not known.

Efficacy
Levofloxacin has strong anti-TB activity. There might be cross-resistance with other fluoroquinolones but it may not be complete. Data suggests greater activity than ciprofloxacin or ofloxacin. This drug is classified in the group A of agents for the treatment of MDR-TB in the consolidated 2019 WHO MDR-TB guidelines.

Safety and tolerability
Levofloxacin can cause QTc prolongation but less frequently than Moxifloxacin. Such QTc prolongation in fluoroquinolones has been associated with an increase in fatal arrhythmias, and it warrants careful monitoring.

Levofloxacin may potentially interfere with lamivudine clearance (increasing the levels of lamivudine), but is not contraindicated with other antiretroviral agents and no drug dosing adjustments are needed. Co-administration of levofloxacin with oral divalent cation-containing compounds (such as antacids) may impair its absorption and should be avoided. Dosage adjustments are required in patients with significant renal dysfunction.

Fluoroquinolones have been associated with arthropathy in puppy models. However, there are case reports of fluoroquinolones being used safely during pregnancy.

4.1.5 Linezolid

Chemical composition and dosing

Linezolid (Lzd) is an oxazolidinone antibiotic that inhibits bacterial protein synthesis by binding 23S ribosomal RNA, and is active in vitro against M. tuberculosis, including MDR and XDR-TB strains, at concentrations of 1 µg/mL or less in most studies. Lzd has been used in combination with other second- and third-line anti-TB drugs in multidrug regimens for the treatment of MDR and XDR-TB with variable success; however, rigorous evaluation of the safest and most effective dose, the dose response relative to TB outcomes, the singular contribution of Lzd when added to other active drugs in a regimen, and the use of Lzd together with other new anti-TB drugs is limited.

Currently it is recommended that the drug be started at a dose of 600 mg daily and given for the entire course of therapy: linezolid can either be decreased to 300 mg daily or stopped if limiting toxicity develops (more details on dosing are included in Annex 2 and 3).

Efficacy

Linezolid is an antibiotic that has been demonstrated in two randomized controlled trials (15;16) and in observational studies (17) to increase culture conversion and treatment success in DR-TB patients. It is considered to be a highly effective agent, but its use is limited by safety concerns (see below). This drug is classified in the group A of agents for the treatment of MDR-TB in the consolidated 2019 WHO MDR-TB guidelines.

Safety and tolerability

The toxicity profile of linezolid – which includes partially reversible myelosuppression, optic neuritis, neuropathy, and lactic acidosis – limits its use (18). Studies have shown that treatment limiting toxicity can occur in as many as 11% of persons who receive treatment with linezolid. Adverse events mostly occur when linezolid is given at doses of more than 600 mg a day, but they can usually be identified early with routine monitoring and are often reversible upon discontinuation of the drug or lowering of the dose. Pyridoxine (vitamin B6) could be used when linezolid is administered to minimise side effects. Knowledge about the safety of linezolid during pregnancy and breastfeeding is limited so caution is advised.

4.1.6 Moxifloxacin

Chemical composition, dosing and duration

Fluoroquinolones are potent inhibitors of DNA gyrase and topoisomerase IV and several quinolones have demonstrated activity against *M. tuberculosis*. Moxifloxacin (BAY 12-8039) is an 8-methoxyquinolone that is highly active against Gram-positive and Gram-negative bacteria and anaerobes. It has a long half-life of 11.5-15.6 hours that allows it to be given once a day. The effect of duration on efficacy and safety is not known.

Efficacy

Moxifloxacin has anti-TB activities, and achieves high levels in tissues including the lung. Moxifloxacin is available as a 400mg tablet that is rapidly absorbed and is excreted in urine and faeces. Moxifloxacin has contributed to treatment success when used off-label as part of regimens treating M/XDR-TB in humans. Later generation fluoroquinolones have been demonstrated to play an important role in the clinical management of MDR-TB and have been recommended for inclusion in the development of MDR-TB regimens. This drug is classified in the group A of agents for the treatment of MDR-TB in the consolidated 2019 WHO MDR-TB guidelines.

Safety and tolerability
In clinical trials with various indications of moxifloxacin 400mg daily, the most common adverse drug reactions (>3%) were nausea, diarrhoea, headache and dizziness. Tendinopathy/tendon rupture and QTc prolongation are some of the serious adverse drug reactions that may occur with moxifloxacin. ECG monitoring of the QT interval in patients on long-term moxifloxacin is recommended and the drug should not be used in persons with risk factors predisposing to the development of arrhythmias.

Fluoroquinolones are generally avoided during pregnancy and breastfeeding due to observation of arthropathy in puppy models. However, there are a few case reports of fluoroquinolones being used safely during pregnancy.

4.1.7 Pretomanid

Pretomanid is a nitroimidazole (same chemical class as Delamanid) and it is a prodrug that is metabolically activated by a nitroredutase, producing various metabolites that are responsible for its therapeutic action. Pretomanid inhibits cell wall biosynthesis and under anaerobic conditions, it causes respiratory poisoning of the bacterial cell through the release of reactive nitrogen species. Pretomanid was approved in August 2019 by the US FDA in combination with bedaquiline and linezolid as part of the BPaL regimen (also referred to as Nix-TB), an all-oral 6-9-month regimen for the treatment of XDR-TB or treatment-intolerant/non-responsive MDR-TB patients.

4.2 Evidence on the other drugs proposed in this study

4.2.1 Isoniazid

Chemical composition, dosing and duration
Isoniazid is a long-standing component of the standard DS-TB treatment regimen. It is a first-line TB medicine that may be an effective second-line agent in the absence of high-level isoniazid resistance.

Isoniazid is a synthetic derivative of nicotinic acid with anti-mycobacterial properties. Although its mechanism of action is still unclear, isoniazid appears to block the synthesis of mycolic acids, major components of the mycobacterial cell wall. This agent is only active against actively growing mycobacteria because, as a pro-drug, it requires activation in susceptible mycobacterial species. Isoniazid also interferes with mycobacterial metabolism of vitamin B6. Resistance occurs due to decreased bacterial wall penetration.

Safety and tolerability
Isoniazid therapy is often associated with minor, transient and asymptomatic elevations in serum aminotransferase levels but, more importantly, isoniazid is a well-known cause of acute clinically apparent liver injury which can be severe and is sometimes fatal.

Adverse reactions include hepatitis (age-related), peripheral neuropathy, and hypersensitivity reactions. Pyridoxine (vitamin B6) should be used when high-dose isoniazid is administered and in patients with diabetes, uraemia, HIV infection, seizure disorders, alcohol abuse, malnutrition or peripheral neuropathy. Additionally, pregnant and postpartum women and exclusively breastfed infants should receive vitamin B6 while taking isoniazid.

4.2.2 Ethambutol

Chemical composition, dosing and duration
Ethambutol is an antibiotic with bacteriostatic, antimicrobial and antitubercular properties. Ethambutol interferes with the biosynthesis of arabinogalactan, a major polysaccharide of the mycobacterial cell wall. This results in halting bacterial growth.

Ethambutol is a first line but adjunctive anti-tuberculosis medication which is used only in combination with other agents such as isoniazid and rifampin.

Safety and tolerability
Ethambutol therapy has been associated with minor, transient and asymptomatic elevations in serum aminotransferase levels, but is a rare cause of clinically apparent acute liver injury.

Adverse reactions include retrobulbar neuritis (dose-related, exacerbated during renal failure). It is recommended to avoid concurrent administration of ethambutol with aluminium hydroxide-containing antacids for at least 4 hours following ethambutol administration. There is no reported cross resistance. Patients should be counselled to report any changes in vision. Baseline and monthly visual acuity and colour discrimination monitoring should be performed. The use of ethambutol is safe in pregnancy, and ethambutol can be used while breastfeeding.

4.2.3 Pyrazinamide

Chemical composition, dosing and duration
Pyrazinamide is a synthetic pyrazinoic acid amide derivative with bactericidal property. Pyrazinamide is particularly active against slowly multiplying intracellular bacilli (unaffected by other drugs) by an unknown mechanism of action. Its bactericidal action is dependent upon the presence of bacterial pyrazinamidase, which removes the amide group to produce active pyrazinoic acid. Pyrazinamide is a first line anti-tuberculosis medication, but is used only in combination with other anti-tuberculosis medications such as isoniazid or rifampicin.

Safety and tolerability
Pyrazinamide is associated with transient and asymptomatic elevations in serum aminotransferase levels and is a well-known cause of clinically apparent, acute liver injury that can be severe and even fatal. Pyrazinamide may be used for drug-resistant TB when the isolate is sensitive to pyrazinamide (no known teratogenicity during pregnancy), and it can be used while breastfeeding.

5. Study objectives

5.1 Primary objective

To estimate the treatment **effectiveness** (assessed by a composite outcome ("favourable outcome", defined as "cure" or "treatment completed" without recurrence within 12 months after the end of treatment)) and **safety** (defined as the occurrence of serious adverse events) of all-oral shorter MDR/RR-TB treatment regimens under programmatic conditions in *(name of country).*

5.2 Secondary objectives

To determine the proportion of MDR-TB patients treated with an all-oral shorter MDR/RR-TB treatment regimen under programmatic conditions who:

i. **died** while on treatment
ii. had **treatment failure**
iii. had a **recurrent** episode of MDR-TB during the 12-month follow-up period
iv. **relapsed** during the 12-month follow-up period
v. were **lost to follow-up** during treatment
vi. are "**cured without permanent disability**" (up to one year after the end of the treatment)
vii. complete at least 90% of doses (*treatment adherence*)
viii. experience adverse events of special interest (see suggested list in Annex 8)

6. Study design

The rationale for the proposed study design should be adapted to the local context. While it would be preferable to have a comparison group (i.e. a cohort of patients treated with the standard regimen in use in the country), if this is not feasible, the design would include one single cohort.

6.1 One single cohort

This section describes the study design with a single cohort.

The study will adopt a longitudinal design with a single cohort of MDR/RR-TB patients receiving the all-oral shorter MDR/RR-TB regimen. Figure 1a provides an overview of the basic study design with one cohort.

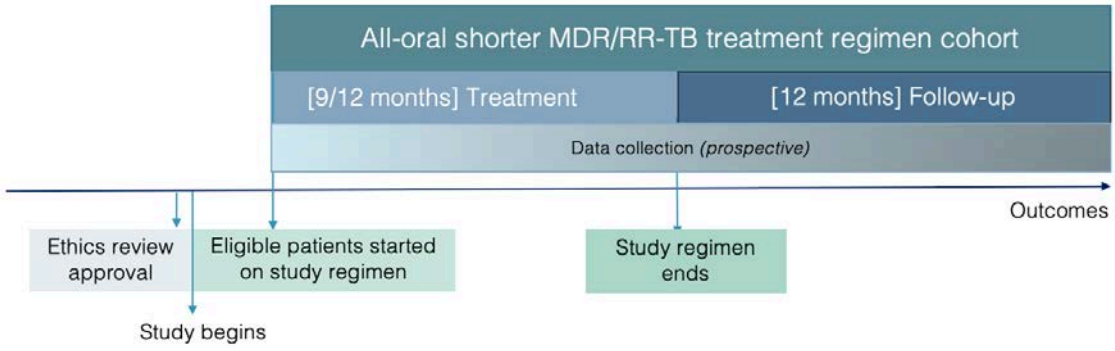

Figure 1a: Overview of the basic study design with one single cohort.

6.2 Stepped-wedge design

The following section applies if investigators choose to collect data also on patients on the standard MDR/RR-TB in use in the country in addition to patients receiving the new all-oral shorter MDR/RR-TB treatment regimen. It should be noted that this is an optional design that can provide additional information to the country and to global guidelines development.

There could be different ways to assess the effectiveness and safety of all-oral shorter MDR/RR-TB regimens compared to the standard MDR/RR-TB regimen in use in the country. Randomised controlled trials represent the gold standard for generating scientific evidence, and investigators are encouraged to conduct this type of study, if resources are available. This protocol provides a template for programmes to conduct operational research on the programmatic implementation of all-oral shorter MDR/RR-TB regimens. While a simplified methodology should be sought given the operational research nature of this study, a comparison is desirable to draw more informed conclusions on the effectiveness and safety of all-oral shorter MDR/RR-TB regimens.

Cohort studies with historical controls may be biased by improved treatment models (including patient support), and by the use of more advanced and widely used diagnostic tools (e.g. Xpert), that improve timeliness of DR-TB diagnosis compared to what was done for historical comparators, which, in turn, is likely to improve treatment outcomes.

If investigators decide to start the implementation of the new all-oral shorter regimen in some MDR-TB treatment sites while continuing the treatment regimen already in use in the country in other sites, a stepped-wedge design is proposed, which compares the all-oral shorter MDR/RR-TB regimen to the standard MDR/RR-TB treatment in use in the country (Figure 1b).

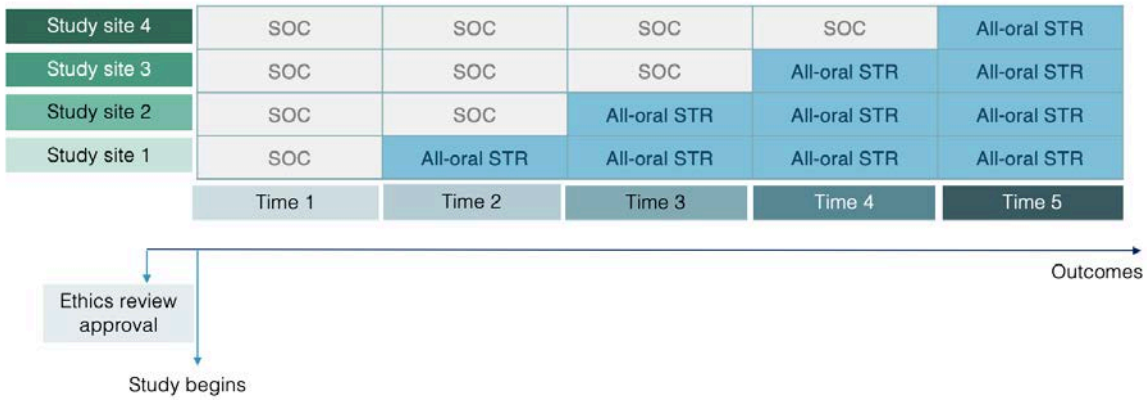

Figure 1b: Overview of the stepped-wedge design comparing the all-oral shorter MDR/RR-TB regimen to the standard MDR/RR-TB treatment in use in the country

The all-oral shorter MDR/RR-TB regimen will be sequentially rolled-out to all MDR-TB treatment sites in the country. Data on e.g. baseline characteristics, bacteriological results, and occurrence of adverse events for all patients on the MDR/RR-TB treatment (receiving either the standard MDR/RR-TB treatment regimen in use in the country, SOC, or the new all-oral shorter MDR/RR-TB treatment regimen) will be collected prospectively as soon as the study commences (Figure 1c).

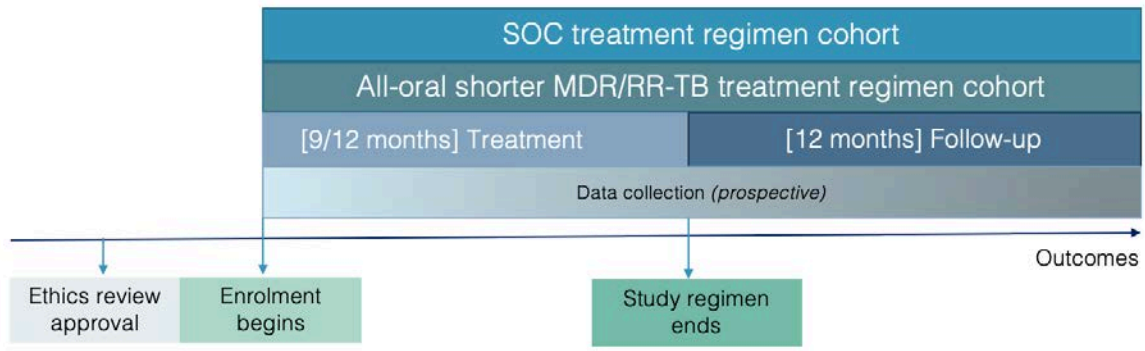

Figure 1c: Overview of data collection in the stepped-wedge study design.

7. Study population

7.1 Study population

The study population includes TB patients with evidence of resistance to at least rifampicin by conventional DST (culture-based) or rapid molecular DST, and children likely to be MDR/RR-TB based on history of close contact with a confirmed MDR/RR-TB case.

All patients should also be tested for second-line resistance to fluoroquinolones and injectables at a minimum. Testing should be done according to the practice of a country's national reference laboratory.

7.2 Inclusion criteria

A patient will be eligible for treatment with an all-oral shorter MDR/RR-TB treatment regimen, if all the following conditions are satisfied, namely he/she:

- 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);
- Has bacteriologically or molecularly confirmed TB with evidence of resistance to at least rifampicin (or for children likely to be MDR/RR-TB based on history of close contact with a confirmed MDR/RR-TB case).

7.3 Exclusion criteria

A patient will not be eligible for treatment with an all-oral shorter MDR/RR-TB treatment regimen if any of the conditions take place, namely he/she:

1. Is unable to take oral medication;
2. Must take any medications contraindicated with the medicines in the MDR/RR-TB regimen;
3. Has a known allergy to any of the drugs in the MDR/RR-TB regimen;
4. Has a QTcF interval of ≥ 500 msec; at baseline that does not correct with medical management.

Pregnant women are not excluded from the study; however, the patient information sheet should mention that safety data during pregnancy are lacking.

Investigators may consider any other exclusion criteria routinely used in the country.

7.4 Sample size

A sample size could be determined based on desired confidence around the proportion of patients with a favourable outcome relative to an external standard (or the comparator group's performance).

However, even a small number of patients included in the operational study will provide information for the countries and globally. In addition, for the country, the conduct of this operational research study will ease the translation of study research results into policy as the medical staff would have been trained on the implementation of the use of the new drugs and drug administration of the all oral shorter regimen chosen.

All patients who meet the eligibility criteria will be invited to participate in this operational research study. The number of patients to be treated under this study has been estimated based on surveillance data from the NTP, specifically the number of bacteriologically confirmed MDR-TB patients and the number of patients with resistance to fluoroquinolones. *The number of patients to be treated under this protocol should be specified here.*

Based on the above number of MDR-TB patients to be put onto the new regimen, study sites have been selected based on their recruitment capacity *(an Annex with the list of study sites should be included)*. All eligible patients fulfilling the inclusion criteria will be considered for inclusion in the study.

8. Treatment regimens under investigation

8.1 Proposed all-oral shorter MDR/RR-TB treatment regimens

In this section, investigators should indicate the treatment regimen(s) they choose to implement, or include different treatment regimen(s) of their choice.

In this study, two all-oral shorter MDR/RR-TB treatment regimens for adults and children are proposed, based on knowledge of their safety and efficacy as of 2019: one treatment regimen for patients with TB sensitive to fluoroquinolones, and one treatment regimen for patients with TB resistant to fluoroquinolones.

The treatment regimen for patient with TB sensitive to fluoroquinolones replicates the all-oral shorter MDR/RR-TB treatment regimen in use in South Africa. The treatment regimen for patients with TB resistant to fluoroquinolones is recommended to be implemented under operational research conditions in the Rapid Communication on DR-TB treatment guidelines of December 2019.

Investigators should choose the most suitable regimen based on the epidemiological and programmatic conditions of the countries. In addition, a list of all drug regimens that are currently under trial or implemented in specific settings is available in Annex 1 of this protocol in case investigators would like to consider other treatment regimens than the two proposed in this protocol.

For FQ sensitive patients:

Treatment regimen: 2 months of Linezolid + Bedaquiline + Levofloxacin + Clofazimine + Pyrazinamide, followed by 4 months of Bedaquiline + Levofloxacin + Clofazimine + Pyrazinamide, followed by 3 months of Levofloxacin + Clofazimine + Pyrazinamide

Note: In this treatment regimen, Pyrazinamide is included because it has been a traditional drug of injectable-containing regimens. If necessary, it can be replaced with cycloserine, subject to expected effectiveness and tolerance to it.

For FQ resistant patients:

Treatment regimen: 6 months of Bedaquiline + Pretomanind + Linezolid (BPaL)

Note: For paediatric patients with TB resistant to fluoroquinolones, investigators are encouraged to consult Annex 1 for suitable alternative regimens.

8.2 Dosing

Annex 2 and 3 describe the drugs included in the proposed regimens, and the duration and dosing of each drug based on the 2019 WHO Consolidated guidelines. Annex 4 presents the provisional, suggested doses of delamanid and bedaquiline for operational research (subject to revision) for paediatric patients. The provisional suggested doses of delamanid and bedaquiline are based on the IMPAACT Network trial (for bedaquiline Study P1108). Recommended dosing for the BPaL regimen in paediatric patients is not available based on current evidence.

Tables with dosing should be adapted to reflect the chosen regimen.

8.3 Access to the paediatric formulation of delamanid for paediatric patients

Annex 5 provides information on how to access the paediatric formulation of delamanid for operational research purposes. Please note that this Annex should not be included in the final version of the protocol.

8.4 Procedure following missed treatment

Any missed days will be made up by extending the regimen by the number of days missed but not exceed 10% of the planned study regimen duration. Patients with treatment interruption for two consecutive months or more will be classified as "lost to follow-up", in which case the patient will be withdrawn from the study and managed according to national guidelines*).*

In case national guidance is not provided, guidance on management of cases who are lost to follow-up should be included in the study procedures. Reasons for missing treatment must be recorded (and patients should be considered for the qualitative analysis on acceptability – see Part B, Section 4). Training should be provided to clinical staff in asking and recording reasons for missing treatment in a systematic manner.

8.5 Procedure in case of treatment failure

In case treatment failed as defined in Table 1, the status of such patients will be classified as “treatment failure” in the study records. These patients will be managed according to national guidance for the treatment of MDR/RR-TB patients.

9. Outcomes of interest measurement

9.1 Primary outcomes of interest

The following are the two main outcomes of interest of this study:

1. Treatment *effectiveness*: the proportion of MDR-TB patients who have a **favourable treatment outcome.** This is defined as “cured” or “treatment completed” without recurrence during 12 months after successful treatment (see Table 1).

2. Treatment *safety*: the proportion of MDR-TB patients included in the study with **serious adverse events** occurring during treatment and up to 6 months after the end of the treatment.

Note: Six months is the proposed follow-up time due to the half-life of bedaquiline.

9.2 Secondary outcomes of interest

Secondary outcomes of interest of this study include:

1. The proportion of MDR-TB patients who **died** while on treatment.

2. The proportion of MDR-TB patients who had a **treatment failure.**
3. The proportion of MDR-TB patients who had a **recurrent** episode of MDR-TB during the 12-month follow-up.
4. The proportion of MDR-TB patients who **relapsed** during the 12-month follow-up. *It should be noted that in order to assess this outcome, genotyping should be available to allow comparison of baseline and recurrent strains.*
5. The proportion of MDR-TB patients who are "**cured without permanent disability**" (up to one year after the end of the treatment).
6. The proportion of MDR-TB patients who complete at least 90% of doses (*treatment adherence*).
7. The average number of adverse events of interest experienced by MDR-TB patients (see list of adverse events of interest in Annex 8).
8. The proportion of MDR-TB patients experiencing each adverse event of interest (see list of adverse events of interest in Annex 8).
9. The proportion of MDR-TB patients who experience serious adverse drug reactions.

10. Key definitions

Table 1 provides the key definitions employed in the study. *These definitions are specific to this study and may slightly differ from the definitions used by programmes in routine practice (this applies specifically to the definition of "failure", by which in routine practice patients may be considered "cured" even if the treatment regimen was changed. In the study, as the efficacy of specific regimens is assessed, failure will be recorded as an outcome even if the patient is cured at the end of the successive treatment regimens).*

Table 1: Key definitions

EVENT	DEFINITION
Favourable outcome	Composite outcome corresponding to the combination of "cured" + "treatment completed" (= treatment success) without recurrence over the 12-month follow-up period. Note: this outcome can also be defined as "recurrence-free cure"
Cured	A patient with bacteriologically confirmed MDR/RR-TB who has completed 9-12 months of treatment by 9/12-month regimen protocol without evidence of failure AND at least two consecutive cultures taken at least 30 days apart are negative at the end of the treatment and at least one month earlier.
Treatment Completed	A patient who completes 9-12 months of treatment by 9/12-month regimen protocol without evidence of failure BUT without bacteriological evidence (negative culture at the end of the treatment phase and at least one month earlier).
Treatment Failed	Treatment terminated or need for permanent change of the regimen protocol of at least two anti-TB drugs because of: • lack of sputum **culture** conversion after 4 months of treatment, or • bacteriological reversion of sputum **culture** after 5 months of treatment in a patient with previous culture conversion to negative, or • evidence of additional acquired resistance to drugs in the study, or • adverse drug reactions (ADRs) (leading to the change of at least two anti-TB drugs in the regimen)
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/can't be assessed)
Withdrawn	A patient is taken off the 9/12-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.*
Recurrence	Cure or treatment completion followed by two consecutive positive cultures during post-treatment follow-up (without genotyping information on baseline and recurrent strain), or one positive culture with clinical signs and symptoms or radiographic deterioration.
Relapse	Recurrence in which isolates of the recurrent episode share the same genotype pattern with isolates of the first episode of MDR-TB.
Reinfection	Recurrence in which isolates of the recurrent episode and isolates of the first episode of MDR-TB have different genotype patterns.
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. In case patients were culture negative at baseline, a negative culture result at month 4 may be considered as "initial 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. In case of patients who are culture negative at baseline, a positive culture result at month 4 may be considered as "initial conversion".
Treatment adherence	90% of the treatment doses were taken based on information in the treatment cards, measured over the entire treatment period.
Permanent disability	A combined outcome, using the modified Medical Research Council Dyspnoea scale (mMRC) (Annex 10), based on which patients with a score above 2 are considered permanently disabled in terms of their pneumological function. In addition, all serious adverse events by system organ class that are not resolved at the end of treatment, should be summarised by treatment regimen. This is a measure of a programme's ability to start treatment promptly and treat patients effectively.
Serious Adverse Event (SAE)	Any untoward medical occurrence that may present in a TB patient during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with this treatment, which either leads to: ▪ death; ▪ a life-threatening experience; ▪ hospitalization or prolongation of hospitalization; ▪ persistent or significant disability; ▪ a congenital anomaly.

11. Investigational plan

11.1 Patient enrolment and timeline

Patient enrolment will be ongoing for at least six months to gather sufficient information to draw some conclusions (this might vary from one country to another depending of the recruitment rate). Given a maximum treatment duration of 9 to 12 months and enrolment completion in 6 months, it is expected that full data collection and primary data analysis could be completed 30 months after the start of the study. This is just an indicative study duration, and this may change depending on the recruitment rate, study design and objectives set by the investigators.

Patients who meet the inclusion criteria and give their consent will be enrolled in the study as they present at the health centre for treatment during the study period.

MDR-TB patients presenting at participating treatment sites will be referred for the screening process. Written informed consent will be obtained from the patient before any protocol specific screening procedures are carried out.

Investigators should include and adapt the section below corresponding to the study design they have chosen.

Once the patient has been found eligible, he/she will be offered participation in the study, and started on the study regimen. Each participant will receive 9-12 months of treatment, or the standard MDR/RR-TB treatment in use in the country (if a stepped-wedge design is chosen), and they all will be followed for 12 months after the end of treatment

Patients who decline participation in the study or are not eligible will be referred for routine treatment and care with no negative consequences for the patient. For all patients, routine procedures in doing contact tracing among household members will be done.

The study timetable at the beginning of this protocol (Section 2.1) details the investigations and observations to conduct at each visit.

11.2 Screening and examinations at baseline

Consent from the patient (or from guardian for children) will be sought for all patients fulfilling inclusion criteria. Clinical evaluation, bacteriological and other laboratory tests, a chest X-Ray (or two if chest X-Ray is repeated during follow-up in case of suspicion of recurrence), and a 12 lead ECG (or portable monitors single channel) will be performed. These are detailed below.

a. **Demographic characteristics** and **medical history** will be recorded.

b. **Clinical evaluation**. This will include:
   - Height and weight
   - Vital signs (blood pressure, temperature)
   - Clinical examination (particularly Brief peripheral neuropathy screen, BPNS)

c. **Bacteriological tests**, including:
   - Sputum smear (x 2)
   - Sputum culture
   - Freeze baseline culture (if possible, at least at -20°C)
   - DST (Xpert MTB/RIF, LPA, culture-based first and second line DST)

d. **Laboratory testing**, including:
   - Full blood count (Haemoglobin/platelets count / White blood count);
   - Serum creatinine
   - Biochemistry (Serum potassium)
   - Serum liver enzymes (ASAT, ALAT)
   - TSH (*if Pto/Eto included in regimen)*
   - HIV test (and CD4 count and viral load, if not recently done)
   - Hepatitis test (HBs Ag and HepC Ab)
   - Pregnancy test

e. Other exploratory tests:
   - Chest X-ray
   - ECG
   - Visual acuity and colour-blindness screen
   - Audiometry (if injectable agents are part of the treatment regimen)

Please note that additional examinations or tests that are not part of routine practice should not be carried out without informed consent from the patient.

11.3 Examinations during treatment

In this section, investigators should describe the monitoring schedule of screening tests based on the composition of the chosen all-oral shorter MDR-TB regimen.

All patients enrolled in the study will undergo regular evaluation of clinical and para-clinical parameters as described in the study timetable (Section 2.1). This monitoring schedule will vary depending of the choice of the all-oral shorter regimen chosen (e.g. more closely monitoring of Haemoglobin level for patients taking Linezolid).

The bacteriological monitoring should be the same for all patients regardless of their treatment regimen. Every month throughout treatment, an early morning sputum specimen will be collected. To ensure the availability of culture results at key moments of the treatment, a second specimen will be collected on the spot at the end of month 4 and the end of the treatment. Sputum smear and culture will be done monthly. DST and/or molecular test will be done at baseline for first and second-line drugs. In case of sputum non-conversion or reversion, DST will be performed for the same drugs plus Bedaquiline.

If the country has the capacity to store the initial culture and perform genotyping, the following text is suggested.

The initial culture isolate will be stored at -20°C (or if possible -80°C) in the National TB Reference Laboratory for at least 21 months from patient enrolment into the study. In case of recurrence during 12 months after completing the 9-month regimen, genotyping on initial and recurrent isolates will be performed to allow the distinction between relapse and re-infection. Microbiological procedures are detailed in the key study procedures kit.

At each visit, patients will be interviewed about adverse events (AE) and all answers will be recorded on the Patient's file (*ad hoc* form if patient file is not used routinely). Patients should be encouraged to seek care from study staff if adverse events occur between scheduled visits. If patients present with adverse events 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 AE observations and decisions made during monitoring and supervision will be reported and added to the individual patient records.

Please note that the above may not apply in case of e.g. emergencies. Investigators may want to specify how data would be captured in these circumstances.

11.4 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 and national guidelines. 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.
- **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 (informed by culture result of M4 or because of a culture reversion), a change in the treatment regimen might be considered. DST should be repeated, whether or not the regimen is changed, in order to inform future management decisions.

If not already in place, a clinical committee should be established to evaluate the best treatment approach for MDR-TB patients. Such committees are a consultation body, generally composed by clinicians treating MDR-TB patients, members of the national reference laboratory, the PMDT focal person in the national TB programme. They may also include experts from international organisations.

11.5 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 and sputum collection at least at 6 and 12 months after completion of treatment or at any time after the end of the treatment if experiencing TB clinical symptoms.

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 and culture. A single sputum specimen for smear and culture will be collected at each follow-up visit. DST examination (molecular and/or culture-based) and LPA will be done if culture positive. Culture isolate will be stored at -20°C for genotyping.
3. Chest X-ray in case of suspicion of TB recurrence.

Please note that community engagement from the start of the study would be essential. TB patients, their families and treatment supporters should be involved in the planning of the study, and take part in the choice of the most suited model of care in relation to the novel treatment regimen. Study results will also be shared with the local communities involved in the research, e.g. through leaflets, posters and notification at the entrance of the hospital. Patients should be asked to provide contact information for family members or friends who can help reach the patient in case the providers are

unable to reach him/her directly. Patients should be contacted by phone a week prior to their scheduled visit. In case patients miss their appointment, they should be contacted by phone to check TB clinical symptoms. In case of symptoms consistent with TB, sputum should be collected and sent to the closest TB diagnostic centre for smear and culture and further investigations if a recurrence is suspected.

12. Safety monitoring, management, reporting and recording

In this section, investigators should describe safety monitoring, management and reporting procedures.

Safety monitoring, management and reporting will be the same as the aDSM recommended by WHO[3]. The safety recording will be adapted to the needs of the study.

12.1 Safety monitoring

Patients will be screened monthly by a person trained in the diagnosis and management of adverse events (AE). An AE is an unexpected medical problem that was not present at baseline and happens (or increased in terms of intensity) during treatment period and up to 6 months after the end of the treatment (this is to take into account the half-life of bedaquiline). AEs may be mild, moderate, or severe, and may be caused by something other than the drug or therapy being given.

12.2 Safety management

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 and the aDSM framework. 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. A list of the main anticipated ADRs and suggestion on how they should be managed is provided in the accompanying Key study procedures.* All AEs will be managed until resolution, which may be after treatment completion.

12.3 Safety reporting

All serious adverse events (SAEs) will be reported immediately to the relevant national pharmacovigilance authority according to national guidelines. When an AE occurs, the investigator responsible for the care of the patient will first assess whether the event is serious or not. If it is serious, then an SAE form (or a yellow form in use in routine practice) will be completed and sent to the principal investigator and the relevant pharmacovigilance authority.

12.4 Safety recording

All SAEs and AE of interest (please see list in Annex 8) should be graded according to a standardized table, such as the Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events ("DAIDS AE Grading Table") (please see the common terminology used in Annex 9).

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[3] Active tuberculosis drug-safety monitoring and management (aDSM): Framework for implementation – WHO 2015 https://www.who.int/tb/publications/aDSM/en/

The principal investigator will grade and analyse SAEs and AEs for causal relation between the adverse event and one or several drugs and consider possible other causes of the observed AE before concluding that they are due to a particular anti-TB drug. Determination of the category of relationship (causality categories) includes "definite", "probable", "possible", "unlikely", "not related", unclassifiable". It is shown in Annex 9. Definitions for anticipated or unanticipated ADR are also provided in Annex 9.

All information related to SAEs and AEs of interest will be recorded in the study database. *This can also be used for aDSM reporting.*

Please note that the above causality assessment should be done in collaboration with the respective person or authority responsible for this activity in the country. Job aids to ease the grading and recording of SAEs and AEs of interest is available in the accompanying Key study procedures booklet.

13. Data collection and management

In this section, investigators should describe data collection and management, including the use of a paper or electronic data entry form (related paragraphs below should be deleted and adapted as appropriate). It is advisable that as much as possible, the data collection for the study be aligned with the existing data collection system already in place in the country. In case of a stepped-wedge study design, the data collection system on the all-oral shorter MDR/RR-TB treatment regimen should also be used for the comparator.

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 adverse events will be recorded onto the patient's medical record and aDSM at each visit. Laboratory data are generally documented in written reports in the patient's medical record as well as recorded in treatment cards. These forms will remain in the patient's medical record and will be considered as source documents. Data will be abstracted onto the individual patient study case report forms (CRF) at least monthly *(investigators should adapt the frequency to the study setting, taking into account the data collection system and resources available*).

An electronic data entry form (e.g. ODK) that can be used on tablet devices and laptops is provided as part of this study, and can be used for data collection. The use of an e-CRF will ease data management in a timely fashion. Data collected through the e-form will be directly exported for analysis into a statistical software (e.g. Stata or R), and monitored for completeness and accuracy in real time.

Despite the availability of this e-CRF, investigators might prefer to use paper-based forms to collect study data. They will be entered into an MS Access database (or other appropriate software such as Epi-Info). These data will then be imported into the statistical software for analysis. A data dictionary is available in the data collection toolkit.

In this section, investigators should also describe quality control and assurance mechanisms, including training of staff involved in the study.

Please see Section 15.2 for further guidance on protection of confidentiality.

14. Data analysis

14.1 Baseline characteristics of the study population

Guidance on data cleaning and analysis will be made available in the data toolkit. Data may be displayed for the overall study population, and for the patients receiving the all-oral shorter MDR/RR-TB treatment regimen and the comparator group, if relevant.

After the data have undergone cleaning, basic descriptive statistics and cross-tabulations will be produced to display the patient population, model of TB care (place of treatment, number of visits etc.), demographics (e.g. age, gender), socio-economic position, and TB treatment information (e.g. diagnostic delay).

14.2 Estimating the outcomes of interest

The effectiveness and safety outcomes of interest will be described.

Depending on the study design and study sample size, investigators may compare the outcomes between patients receiving the all-oral shorter MDR/RR-TB treatment regimen and the comparator group using chi-square test or Fisher's exact test, as appropriate.

Disaggregated outcome analysis (by e.g. socio-economic status) may be performed, as appropriate. Further details on the estimation of the proportion of the outcomes of interest will be provided in the data toolkit.

14.3 Controlling for confounders

Depending on the sample size and study design, investigators should perform multivariable analysis to control for potential confounding factors in the comparative analysis between the study groups (i.e. SOC and all-oral shorter MDR/RR-TB treatment regimens). This will include on-treatment characteristics (culture results, AEs) that could lead to regimen change or termination. Caution should be used in the interpretation of findings as confounding effect can never be fully controlled in observational studies.

15. Ethical considerations

15.1 Ethics approval

In this section, investigators should explain the local (and international, if applicable) ethics approval process and approval for the study. This may include community advisory boards and input sought from civil society and members of the affected community. Reference can be made to the approval of the master protocol by the Research Ethics Review Committee of WHO.

15.2 Protection of confidentiality and patients protection

Protection of patient confidentiality is essential, and the study will follow the principles of the 2018 Declaration of Helsinki. No patient may be enrolled into this study until the patient has provided written informed consent.

The patient file that will be used to input data into the CRF will be kept in the study site in a secure place. The data collection instrument (CRF) does not include a name and other data from which an individual can be identified. Instead a patient number will be generated based on e.g. the TB register number and the study site identification code, year of diagnosis etc. This will be used to allow linkage back to the register and medical records in case that is needed for quality control, validation of data

or a collection of treatment outcome data for study participants. Only authorised study staff will have access to the patient file. All study staff will be trained in principles of Good Clinical Practice before the study commences.

An example patient identification number is provided in the study procedures.

15.3 Informed consent

Patients who are eligible for inclusion in the study will be given information about MDR-TB and the shorter all-oral MDR-TB treatment regimen. Patients will be provided with information in a language that is understandable to them. Consent for enrolment will 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 study, the patient will be asked to sign the consent form (or give a thumb print in the presence of a witness, if illiterate). For children, consent from the guardian will be sought as well as assent of the children. The person consenting the patient will be a dedicated person (e.g. data collector) employed by the study and who will be trained to be able to explain the study (as written in the patient information sheet) and document the patient's consent (in the informed consent form). This person will not be involved in the treatment of the patient.

All patients who are not eligible for the study, or refuse to be enrolled, or withdraw after enrolment, will be managed according to national guidelines with no negative consequences for the patient.

16. Administrative considerations

16.1 Study governance

In this section, investigators should describe the governance for the conduct of the study (including NTP, Ministry of Health, academic institutions, funders, community representatives), and the steering committee which is responsible for initiating the study and monitoring its progress, disseminating the study findings and advocating for the potential translation of the findings into national policy.

16.2 Study team

In this section, investigators should describe the team involved in the conduct of the study. An organigram or a table can be included to describe the team composition and roles of each individual. At template table is provided below.

Investigator's name	Role within the study	Group/ Institution name	Country
	PI *(role description)*		
	Co-PI		
	Co-PI		

17. Data ownership and sharing

In this section, investigators should describe how findings from the study will be disseminated (e.g. through technical reports, scientific publications, presentations), fed back to the participating

communities, and shared with national health authorities, the larger scientific community and the larger affected community with the aim to influence and improve MDR-TB treatment at the country level and globally.

18. Study budget

In this section, investigators should provide an overall budget for the study and indicate the funding source. A more detailed budget should also be provided. An example of a template to establish a detailed study budget is available in the study toolkit, and it is accompanied by an explanatory note with the typical components of the budget and budget structure. Investigators may consider providing additional social support to patients enrolled in the study during post-treatment follow-up.

PROTOCOL - PART B

Evaluating the acceptability, feasibility, costs and the impact on health-related quality of life of all-oral shorter treatment regimens for multi-drug and rifampicin resistant tuberculosis patients in *(name of country)*

- Sub-study for evaluating the impact on HRQoL: **Section 2**
- Sub-study for measuring stigma: **Section 3**
- Sub-study for assessing feasibility and acceptability: **Section 4** & **Section 5**
- Sub-study for evaluating cost-effectiveness: **Section 6**

1. Foreword

While the programmatic use of all-oral shorter MDR/RR-TB treatment regimens under operational research conditions can provide important data to the global TB community about their effectiveness and safety, they can also provide information about other important outcomes, such as HRQoL and socioeconomic impact for patients and households, as well as programmatic implementation.

Quantitative, qualitative and mixed-method research approaches can be used to gain a deeper understanding of the implications that all-oral shorter regimens can have on the quality of life of MDR-TB patients (Section 2), including stigma and discrimination they may experience as a result of their condition (Section 3).

In order to have an impact, the intervention must not only be effective and safe, but must be feasible and acceptable to the local population and to the health care staff involved in its delivery. Section 4 and 5 describe qualitative operational research into feasibility and acceptability of the implementation of novel all-oral shorter regimens both to the patients and household members, and to health and social service care workers.

Complementary operational research may also include cost-effectiveness analysis, both from patient's and provider's perspective (Section 6).

The adoption of longitudinal add-on studies alongside the implementation of all-oral shorter MDR-TB regimes provides the opportunity to repeat measures and make comparisons over time, and even describe changes that extend beyond treatment completion.

During country adaptation, investigators can integrate relevant sections of the sub-studies described in Section 2-6 in their protocol.

Part B – Section 2

2. Health-related quality of life (HRQoL)

2.1 Background

This section can be integrated in the Background section of the master protocol (Section 3)

Quality of life refers to a subjective evaluation of the effects of disease and health interventions, which is embedded in a cultural, social and environmental context. Health-related quality of life (HRQoL) measures the physical and functional status, and social and emotional well-being of an individual.

Although limited, previous studies have shown that HRQoL varies among TB patients at different stages of treatment and is significantly worse than HRQoL among the general population at all stages of treatment. After completing TB treatment, HRQoL among TB patients improves significantly compared with pre-treatment baseline; however, HRQoL remains lower than in the general population in many domains, even beyond one year of completing treatment. Evidence has also shown that HRQoL among MDR-TB patients is worse compared to drug-susceptible TB.

It is reasonable to assume that individuals treated for MDR-TB with all-oral shorter regimens would experience better quality of life compared to patients on a standard (either short or long) MDR-TB regimen, through two primary mechanisms. First, an injectable-free treatment itself can potentially improve treatment adherence of patients, and facilitate the implementation of community-based models of care. This in turn would reduce direct costs incurred by the patients associated with travelling to the health facility for daily injections, and/or the opportunity costs associated with lost productivity and income due to hospitalisation in the intensive phase of treatment.

Second, injectable-free treatment regimens that potentially reduce the occurrence of adverse reactions would likely improve adherence to treatment, and lead to less HRQoL decrement. It is therefore likely that overall health-related quality of life of patients would improve.

Implementation research into HRQoL therefore provides important complementary information related to the implementation and uptake of novel MDR-TB treatment regimens.

2.2 Study objective

This section can be integrated in Section 5 of the master protocol.

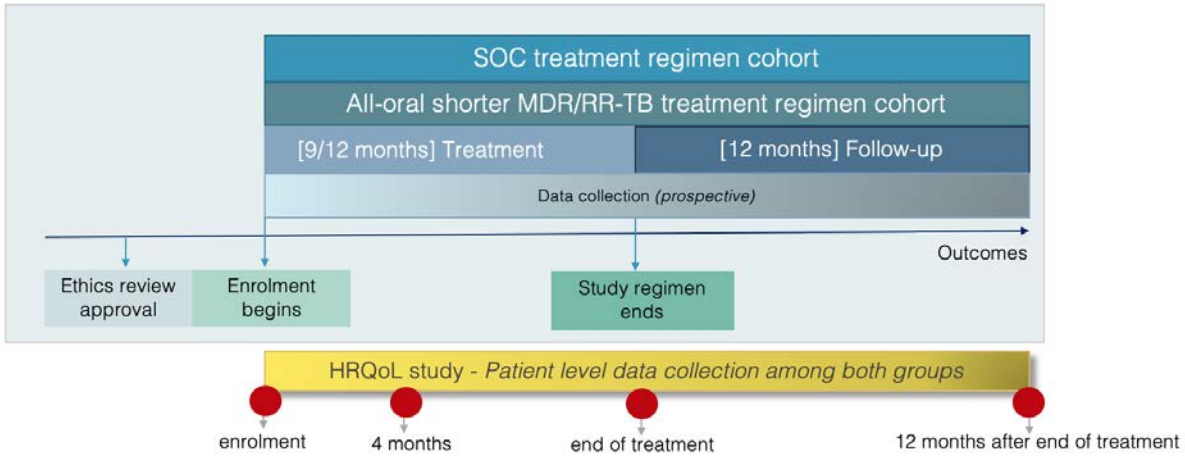
The objective of this study is to assess the HRQoL of MDR-TB patients receiving the all-oral shorter MDR/RR-TB treatment regimen *(if investigators choose a stepped-wedge design, they should specify:* compared to those on the standard MDR/RR-TB treatment regimen *in use in the country*).

2.3 Study design

This section can be integrated in Section 6 of the master protocol. If they decide to include a study on HRQoL, investigators can replace Figure 1 with Figure 3 below which includes the HRQoL into the main study design.

This study investigates HRQoL among MDR-TB patients receiving the all-oral shorter MDR/RR-TB treatment regimen (compared to those on the standard regimen *in use in the country*) (Figure 3).

Figure 3: Suggested design for the conduct of HRQoL studies



This assessment adopts a longitudinal design with data collection at enrolment, at 4 months, at end of treatment, and twelve months after end of treatment, time points that are intended to capture health-related quality of life at diagnosis, during treatment, at the end of treatment, and long-term follow-up once treatment has been completed.

This study adopts a semi-qualitative approach, employing scales to assign scores to responses from patients, and interview techniques to elicit responses.

2.4 Study population

This section can be integrated in Section 7 of the master protocol. In this section, investigators should describe the study population, including selection of participants. Investigators are encouraged to enrol as many patients as possible, depending on available resources.

The study will be conducted on patients receiving the all-oral shorter MDR/RR-TB treatment regimen. *(if a country is already using the standardised shorter MDR-TB treatment regimen, and investigators wish to collect data also on patients receiving the standard MDR/RR-TB treatment regimen in use in their country, they should specify:* "and on patients receiving the standard MDR/RR-TB treatment regimen in use in their country"*).*

2.5 Study procedures

This section can be integrated in Section 7 of the master protocol.

Simple random sampling will be used to select patients. *Please note that stratified random sampling can also be employed to select patients across a range of socio-demographic (or other) characteristics in order to maximise representativeness of the sample.*

2.6 Measurement instruments

This section can be integrated in Section 13 of the master protocol. To date, there is no validated tool to measure HRQoL among TB patients. In this protocol the EQ-5D-5L is proposed. This is a generic tool available in 130 languages. This may be subject to revision if any specific tool is developed to measure quality of life of TB patients.

2.7 Data analysis

This section can be integrated in Section 14 of the master protocol.

Demographic and baseline characteristics of the two cohorts will be summarised and compared. The distribution of categorical variables will be summarised by percentages. Quantitative variables will be summarised using the mean and standard deviation (SD), and/or the median and inter-quartile range (IQR), and the minimum and maximum values. The percentage of patients with missing data will be given, for each demographic and clinical variable.

HRQoL scores at baseline, 4 months, end of treatment, and 12 months post treatment, and percentage change in score over the treatment period will be compared using means, mean differences and t-test, with a two-sided p-value. QALYs will be calculated to be used optionally in cost-effectiveness analysis (see Section 6).

Qualitative analysis will involve the generation of themes and the use of a thematic network method. Findings will be reported using Consolidated Criteria for Reporting Qualitative Research. (*Investigators should adapt the description of the qualitative analysis they will perform based on the specific technique employed)*

Part B – Section 3

3. Measuring stigma

3.1 Background

This section can be integrated in Section 3 of the master protocol. In this section, investigators should include relevant local evidence on stigma experienced by TB patients.

TB-related stigma is an important social determinant of health which can have a considerable impact on individuals and communities, including delays in seeking health care and the ability to manage illness and complete treatment.

Persons with DR-TB may be uniquely exposed to and disadvantaged by stigma, and their experiences of stigma often differ markedly from patients with drug susceptible TB. This is due to the following reasons:

1. DR-TB treatment takes longer than DS-TB treatment, and therefore the exposure to stigma may be longer as the identity "TB patient" is less transient.
2. DR-TB treatment is typically more toxic, with more side effects. People with DR-TB are more likely to experience neuropsychiatric or perception altering side effects as a consequence of their comprehensive treatment regimens and to face catastrophic costs due to the length of their treatment, both of which can heighten their vulnerability to stigma. Hearing loss, psychological side effects, and impoverishment can reinforce the social construction of DR-TB patients being deviant, unpredictable, and dangerous.
3. DR-TB is often assumed to be caused by misbehaviour. Unlike in cases of drug-susceptible TB, in the case of DR-TB, there may be treatment adherence behaviours that may contribute to the development of acquired DR-TB. This may tempt health workers to blame individuals for their disease. DR-TB clients may be at higher risk of self-stigma if they harbour self-blame or guilt related to drug resistance caused by non-adherence.
4. DR-TB has more potential to create fear. One of the main facets of all stigma constructs is the social construction of people with TB as being dangerous to the wider community. Perceptions of TB curability is associated with lower levels of TB stigma. When a person has DR-TB, doubts about curability may fuel the notion that DR-TB patients represent a mortal risk to others. Therefore, DR-TB may have a greater 'mark' than drug-susceptible TB.

TB stigma extends beyond the denigration of people with TB/DR-TB, but can likewise harm those who may not have TB themselves (such as family members, friends, volunteer caregivers, HCWs, TB activists, and minors), but are associated with the disease through their work or relationships (so-called "secondary TB stigma"). For example, TB health care workers can experience stigmatization and discrimination due to being in close contact with TB patients (so-called "dirty work stigma"). MDR/RR-TB treatment itself may cause stigma because of visible signs such as skin pigment change due to clofazimine.

3.2 Study objective

This section can be integrated in Section 5 of the master protocol.

The objective of this study is to assess TB-related stigma among MDR/RR-TB patients receiving the all-oral shorter MDR/RR-TB treatment regimen (compared to those on the standard MDR/RR-TB regimen in use in the country, *if investigators choose to adopt a stepped-wedge design*).

3.3 Study design

This section can be integrated in Section 6 of the master protocol.

If they decide to include a study on stigma, investigators can replace Figure 1 with Figure 4 below, which includes the schematic of the study design for the conduct of stigma studies into the main study.

This study will employ a mixed-method approach. Prevalence of stigma will be measured through a quantitative approach (patient survey) employing scales. Qualitative approaches, aimed to assess knowledge, attitudes, and beliefs about TB will be used to help situate the severity of TB stigma in the wider context of patients' perceptions of quality of care

Investigators should describe which qualitative techniques the study will employ (e.g. semi-structured interviews, open-ended questioning and probing, focus groups, participatory techniques (e.g. theatre, diaries, photography, action-oriented community groups, use of visual aids, charting, ranking), and whether TB survivors will be engaged in the study process and in the planning of the research.

In the context of this study, stigma will be investigated among MDR/RR-TB patients receiving the all-oral shorter MDR/RR-TB treatment regimen (compared to those on the standard MDR/RR-TB regimen in use in the country, *if investigators choose to adopt a stepped-wedge design*) (Figure 4). Likewise, it will involve HCWs providing care to MDR/RR-TB patients *(either on the all-oral shorter MDR/RR-TB treatment regimen or standard MDR/RR-TB regimen in use in the country)*.

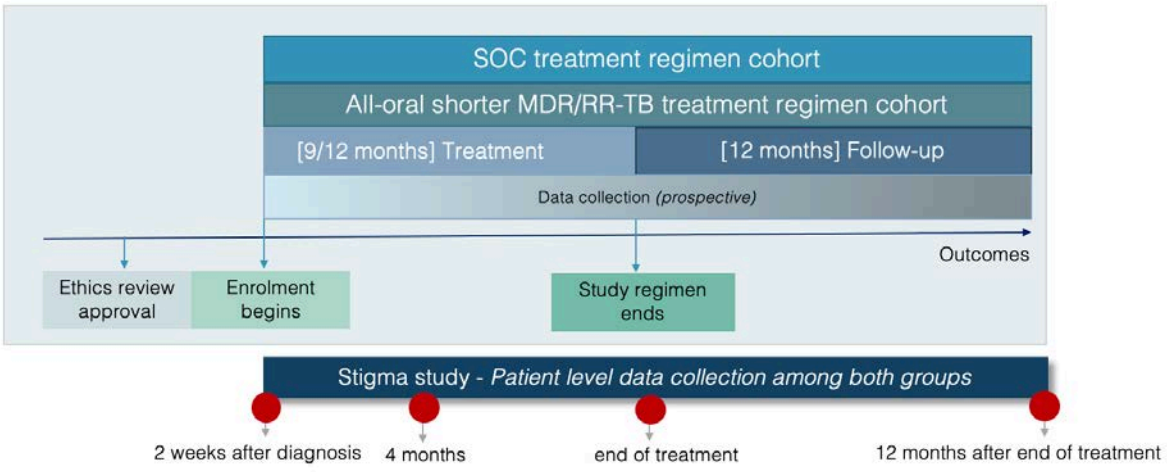


Figure 4: Suggested design for the conduct of stigma studies

3.4 Study population

This section can be integrated in Section 7 of the master protocol.

The study population will include MDR-TB patients and HCWs. Purposive samples will be used to gain perspectives and experience of MDR-TB patients and/or HCWs in qualitative studies. Simple random sampling will be used to select patients to measure the prevalence of stigma.

Investigators should perform and include sample size calculations to obtain a representative sample of MDR-TB patients to measure the prevalence of stigma (in the two study groups, if a stepped-wedge design is chosen).

This assessment adopts a longitudinal design with data collection at two weeks after TB diagnosis, at 4 months, at end of treatment, and twelve months after end of treatment, time points that are intended to capture stigma soon after diagnosis, during treatment, at the end of treatment, and long-term follow-up once treatment has been completed.

3.5 Measurement tools

This section can be integrated in Section 13 of the master protocol.

This study will employ the Cataldo Lung Cancer scale, which has been adapted to measure stigma among people with MDR-TB.

Investigators should specify which scale for TB dirty work stigma they would adapt to include DR-TB. Wouters et al. validated a tool to measure different levels of TB and HIV stigma among the healthcare workforce in South Africa, which may be relevant to countries with a high rate of TB-HIV co-infection. Other tools may be proposed.

3.6 Data analysis

This section can be integrated in Section 14 of the master protocol.

Stigma scores at 4 months, end of treatment, and 12 months post treatment, and percentage change in score over the treatment period will be compared using means, mean differences and t-test, with a two-sided p-value.

Qualitative analysis will involve the generation of themes and the use of a thematic network method. Findings will be reported using Consolidated Criteria for Reporting Qualitative Research. (*Investigators should adapt the description of the qualitative analysis they will perform based on the specific technique employed)*

Part B – Section 4

4. Feasibility and process indicators for the implementation of all-oral shorter MDR/RR-TB regimens

4.1 Background

This section can be integrated in Section 3 of the master protocol.

Feasibility refers to constraints at health system level that may impede the implementation of all-oral shorter treatment regimens for MDR-TB. In order to determine the health system requirements for implementation, adoption and uptake of all-oral shorter regimens, a feasibility assessment will be conducted alongside the roll-out of the new regimen(s).

Investigators should specify what relevant documents will be included in the desk review, and what relevant stakeholders and technical partners will be involved in the assessment.

As part of this assessment, formative work will include a document review of relevant procurement policies and interviews with purposively selected NTP/MoH and other relevant in-country stakeholders (e.g. technical partners) to inform country implementation guidance. *(Please note that it is recommended that these activities are followed-up after implementation)*

A complementary set of process indicators will also be utilized to assess feasibility of the intervention both at the health facility level and NTP level. These indicators, identified along the care continuum and the study cycle are illustrated in Figure 5, and they include:

- The total turnaround time between specimen collection and MDR-TB diagnosis.
- The number of patients with an MDR-TB diagnosis from the laboratory vs the number of MDR-TB patients in care.
- Diagnostic delays defined as the time between symptom screen and MDR-TB diagnosis.
- The number of patients with RIF resistance tested for FQ.
- Enrolment rate defined as the number of eligible patients *vs*. the number of patients enrolled on the all-oral shorter MDR/RR-TB regimen.
- Treatment delays defined as the time between eligibility assessment and treatment initiation.

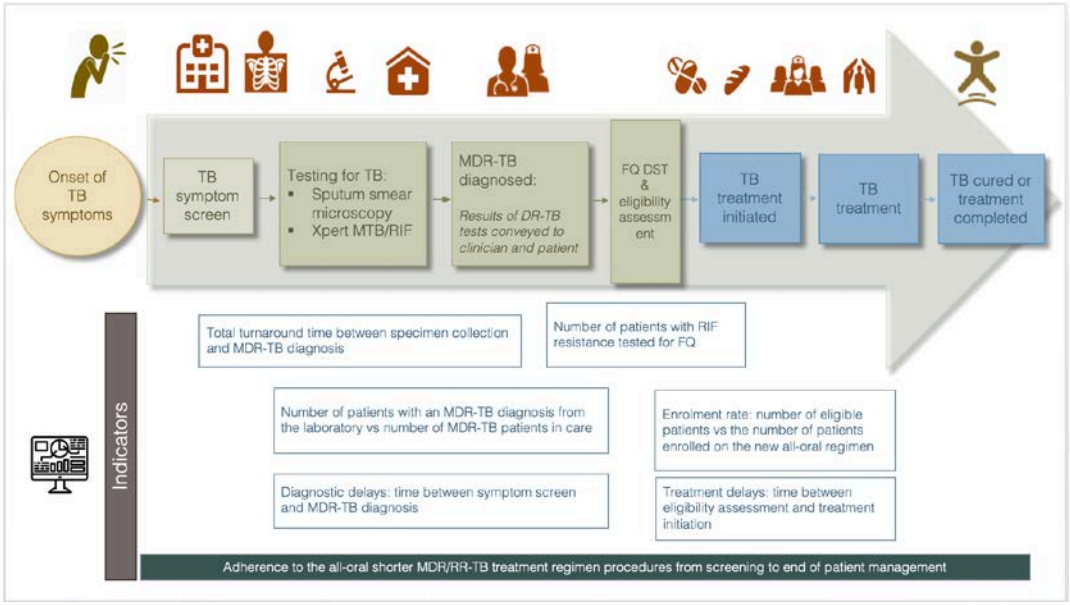


Figure 5: Feasibility indicators along the care continuum of patients receiving the all-oral shorter MDR/RR-TB regimen

Two additional indicators will be considered:

- Adherence of the HCWs to the new all-oral MDR/RR-TB treatment procedures (*fidelity*), e.g. screening procedures, administration of the correct dosage, performance of the appropriate screening and laboratory testing, both at baseline and follow-up, aDSM. A checklist will be used to aid monitoring of this indicator.
  In addition, investigators may want to document whether:
  - health care staff involved in the study implementation received training in the procedures related to the new all oral treatment;
  - monitoring of the study activities is performed as detailed in the protocol;
- Procurement of drugs: availability of drugs during the study period and the duration of the procurement cycle should also be monitored as this can inform planning uptake and scale-up in different settings.

An overall feasibility indicator will also be included to assess the number of patients who are receiving the all-oral MDR/RR-TB shorter treatment among all eligible patients, compared to the number of patients on the standard MDR/RR-TB treatment regimen in use in the country.

5. Acceptability of patient support services and model of care to patients and health care providers

5.1 Background

This section can be integrated in Section 3 of the master protocol.

Understanding patients' attitudes, concerns and perceptions to health, healthcare, and specifically TB and TB treatment, can improve healthcare access and enhance positive health outcomes. It is also important to ascertain attitudes and perceptions of health care and social service staff who are involved in patients' care as this can inform how to improve patient support services and the model of care related to the adoption of new all-oral shorter MDR/RR-TB regimens.

If investigators are also exploring different care delivery modalities as part of the implementation of novel all-oral shorter MDR/RR-TB regimens, including the adoption of different adherence technologies, they should also evaluate them as part of operational research.

5.2 Study objective

This section can be integrated in Section 5 of the master protocol.

The objective of this study is therefore to assess whether the implementation of all-oral shorter MDR/RR-TB regimens and related patient support mechanisms are acceptable to patients and suitable to their health needs, as well as to health care and social service staff, with a focus on the patient support services and model of care associated with the delivery of this intervention.

5.3 Study population

This section can be integrated in Section 7 of the master protocol.

Patients and household members, as well as health and social service care staff will purposively be sampled. Purposive sampling will also be used to identify policy-makers at the local and national level that can be included in the study.

5.4 Study design

This section can be integrated in Section 6 of the master protocol.

Investigators should specify which qualitative research technique they will employ (e.g. individual in-depth patient interviews, focus groups, workshops, or household visits.

Patients receiving the all-oral shorter MDR/RR-TB treatment regimen (and patients on the standard MDR/RR-TB treatment in use in the country, *if investigators adopt a stepped-wedge design*) will be included, and HCWs providing care to them. This assessment adopts a longitudinal design with data collection at two months after TB diagnosis, and at the end of treatment (Figure 6).

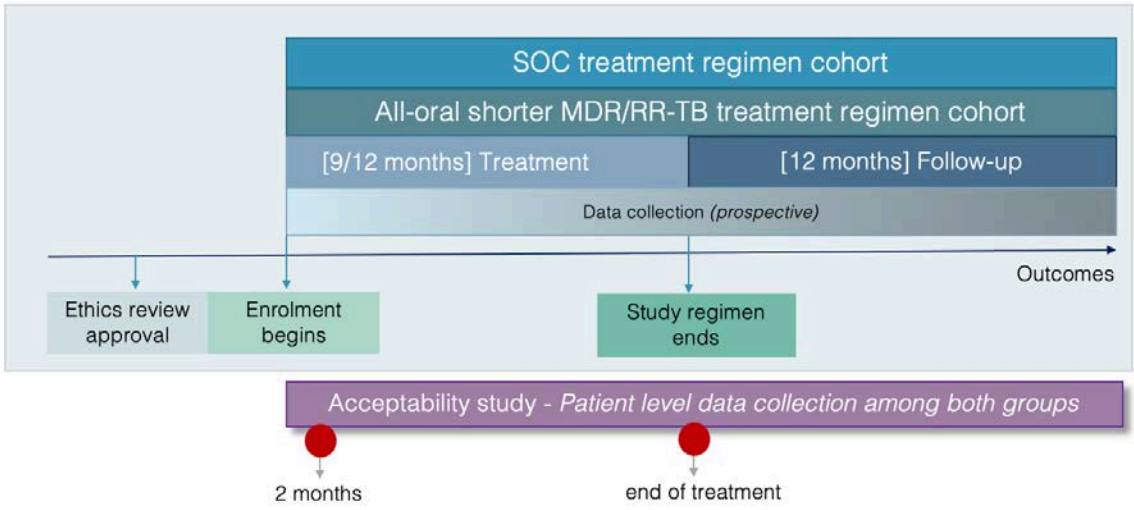


Figure 6: Suggested design for the conduct of acceptability studies

5.5 Data collection tool

This section can be integrated in Section 13 of the master protocol.

An illustrative interview topic guide is provided in the data collection toolkit. This should be adapted by the study team and piloted in-country.

Part B – Section 6

6. Cost and cost-effectiveness analysis

6.1 Background

This section can be integrated in Section 3 of the master protocol. If investigators decide to perform either provider or patient cost analysis rather than both studies, they should adapt relevant sections below.

Nationally representative surveys of costs faced by TB patients and their households are finding consistently higher costs incurred by MDR-TB patients compared to drug-sensitive TB patients, and society at large. As these higher costs are mainly due to the longer duration of treatment, more ADR, and associated number of visits to the health facilities, it is reasonable to expect that a shorter treatment regimen would reduce the number of clinic visits, thus resulting in net cost savings both to the health system and patients.

Health economic analyses can adopt a health system perspective by including only health system costs or a societal perspective by also including patient costs, both as part of the cost inputs and as an outcome in its own right. In addition, cost-effectiveness (with favourable treatment as outcome) and cost-utility analysis (with QALYs as a complementary outcome to favourable treatment) will enable the comparison between new all-oral shorter MDR/RR-TB treatment regimens and the standard regimen in use in the country, as well as with investments non-related to TB.

6.2 Study objective

This section can be integrated in Section 5 of the master protocol.

The objectives of this study are to assess the:

- Direct and indirect TB patients' costs (and their households) *(compared to patients receiving the standard MDR/RR-TB treatment regimen in use in the country, if a stepped-wedge design is chosen)*
- Cost to the health system of all-oral shorter MDR/RR-TB treatment regimens *(compared to the standard MDR/RR-TB treatment regimen in use in the country, if a stepped-wedge design is chosen).*
- Cost-effectiveness (favourable treatment as outcome) of all-oral shorter MDR/RR-TB treatment regimens compared to the standard MDR/RR-TB treatment regimen in use in the country *(if a stepped-wedge design is chosen).*
- Cost-utility (QALYs as outcome) of all-oral shorter MDR/RR-TB treatment regimens compared to the standard MDR/RR-TB treatment regimen in use in the country *(if a stepped-wedge design is chosen).*

6.3 Study design

This section can be integrated in Section 6 of the master protocol.

This analysis will adopt a longitudinal design, with data collected from patients receiving the all-oral MDR/RR-TB treatment regimen *(and compared between the two treatment regimen groups, if a stepped-wedge design is chosen)*. Data on patient and household costs will be collected at two time points, during treatment after a minimum of two weeks into treatment, and towards the end of treatment. Specific questions related to socioeconomic impact (e.g. schooling interruption, loss of employment, coping strategies) as well as to income and additional medical and non-medical costs

(e.g. for sequelae) will also be repeated at twelve months after the end of treatment. Health system costs will be collected throughout the study period (Figure 7).

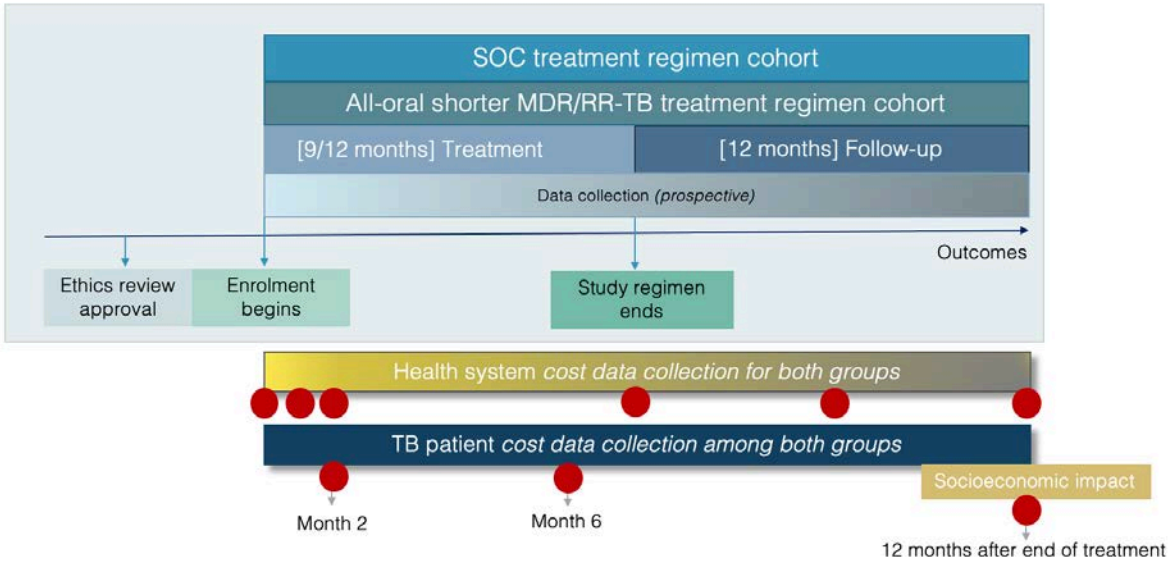


Figure 7: Suggested design for the conduct of cost-effectiveness analysis

6.4 Data collection

This section can be integrated in Section 13 of the master protocol.

Data on patient and household costs will be collected through interviews with patients, using an adapted version of the instrument developed by WHO. *A template data collection tool for country adaptation is available in the data collection toolkit. This is based on ongoing studies using a longitudinal design (although mainly for DS patients so far). Preparatory steps for this study should include mapping of health insurance and social protection mechanisms.*

The interviews will include questions on fees paid to the health system, drugs and laboratory test costs, transport, food and accommodation costs incurred as a result of the treatment process as well as time lost from economic activities due to illness or care-seeking. It will also include questions on the patient and their household's socio-economic position (e.g. assets ownership and dwelling characteristics), patient's education and occupation, receipt of welfare payments and enrolment in health insurance schemes.

Health system (provider) costs will be obtained "per protocol" through:

- An analysis of health worker time involved in prescribing, monitoring, and supervising the all-oral shorter regimen, and the standard regimen.
- Health worker salary (mid-point salary of the scale), and benefits data from the Ministry of Health based on grade of staff rather than named individuals.
- An analysis of additional, short-term technical assistance time allocated to implement the all-oral shorter regimen.
- Records of drug, consumables, lab tests for monitoring, and equipment procurements.
- Standard costs of supplies from government purchasing units or other appropriate sources.
- Study implementation financial records (overheads should be included, e.g. cleaning, inpatient stay costs, security, admin staff).

Costs will be assessed as capital costs required for establishing the study regimen and as costs for recurrent costs for sustaining it.

A random selection of ten patients will be carried out to review their charts for healthcare utilisation (number of visits, diagnostic and monitoring tests done, etc.) to validate how representative the costs calculated "per protocol" are. *An MS Excel template to collect this information is available in the data collection toolkit, ensuring all information required can be easily extracted from the EMR/charts.*

6.5 Data analysis

This section can be integrated in Section 14 of the master protocol.

Descriptive analysis of the level (median and interquartile range) and composition of costs incurred by the patients during the study period will be performed for the two time periods. Comparisons between costs for patients receiving the all-oral shorter MDR/RR-TB regimen and the standard regimen will be made using chi-square and Wilcoxon Rank Sum test, as appropriate. Metrics of affordability (e.g. proportion of patients experiencing catastrophic TB-related cost) and impoverishment (e.g. proportion of patients falling into poverty) will be computed.

Total and disaggregated provider costs for the study period will be calculated, and incremental cost-effectiveness analysis (with sensitivity analysis) will be conducted to compare the cost and impact of the all-oral shorter MDR/RR-TB regimen and standard regimen in use in the country.

Please note that the inclusion of income and other SES variables will also allow analyses of both equity in accessing treatment and equity in achieving treatment results.

Annex 1. Treatment regimens tested in selected ongoing clinical trials

Note: The use of drug regimens where Pretomanid is combined with other drugs than in the BPaL regimen warrants more rigorous research conditions than operational/implementation research implies.

Clinical trial	Regimen	Ongoing / completed	All drugs are commercially available	FQ-S/FQ-R
STREAM 1 regimen B	Cfz, E, Z, Mfx, H, Km (16 weeks); followed by Cfz, E, Z, Mfx (24 weeks)	Enrolment completed	Yes	FQ-S
NiX-TB	Bdq, Pa, Lzd (24-36 weeks)	Enrolment completed	No	XDR
MDR END	Dlm, Lzd, Lfx, Z (36-52 weeks)	Enrolling	Yes	FQ-S
STREAM 2 regimen C	Bdq, Cfz, E, Z, Lfx, H, Pto (16 weeks); followed by Bdq, Cfz, E, Z, Lfx (24 weeks)	Enrolling	Yes	FQ-S
STREAM 2 regimen D	Bdq, Cfz, Z, Lfx, H, Km (8 weeks); followed by Bdq, Cfz, Z, Lfx (20 weeks)	Enrolling	Yes	FQ-S
PRACTECAL regimen 1	Bdq, Pa, Lzd (24 weeks)	Enrolling	No	FQ-S and R
PRACTECAL regimen 2	Bdq, Pa, Lzd, Cfz (24- weeks)	Enrolling	No	FQ-S and R
PRACTECAL regimen 3	Bdq, Pa, Lzd, Mfx (24-weeks)	Enrolling	No	FQ-S and R
endTB regimen 1	Bdq, Lzd, Mfx, Z (39 weeks)	Enrolling	Yes	FQ-S and R
endTB regimen 2	Bdq, Cfz, Lzd, Lfx, Z (39 weeks)	Enrolling	Yes	FQ-S and R
endTB regimen 3	Bdq, Dlm, Lzd, Lfx, Z (39 weeks)	Enrolling	Yes	FQ-S and R
endTB regimen 4	Dlm, Cfz, Lzd, Lfx, Z (39 weeks)	Enrolling	Yes	FQ-S and R
endTB regimen 5	Dlm, Cfz, Mfx, Z (39 weeks)	Enrolling	Yes	FQ-S and R
Observational research				
STREAM adapted regimen with Linezolid	4-6 months of Linezolid + Moxifloxacin + Prothionamide + Clofazimine + Pyrazinamide + High-dose Isoniazide + Ethambutol, followed by 5 months of Moxifloxacin + Clofazimine + Pyrazinamide + Ethambutol	Enrolling	Yes	FQ-S

Annex 2. Dosing of medicines used in second-line MDR-TB regimens by weight band in patients older than 14 years

Source: 2019 WHO consolidated guidelines on drug-resistant tuberculosis treatment

Group	Medicine	Weight-based daily dose	Formulation	Weight bands for patients older than 14 years[a]					Usual upper daily dose[b]	Comments
				30–35 kg	36–45 kg	46–55 kg	56–70 kg	>70 kg		
A	Levofloxacin	-[c]	250 mg tab	3	3	4	4	4		
			500 mg tab	1.5	1.5	2	2	2	1.5 g	
			750 mg tab	1	1	1.5	1.5	1.5		
	Moxifloxacin	standard dose[c,d]	400 mg tab	1	1	1	1	1	400 mg	As used in the standardized shorter MDR-TB regimen
		high dose[c,d]	400 mg tab	1 or 1.5	1.5	1.5 or 2	2	2	800 mg	
	Bedaquiline	-[c]	100 mg tab	4 tabs od for first 2 weeks; then 2 tabs od M/W/F for 22 weeks					400 mg	
	Linezolid	-[c]	600 mg tab	(<15 y)	(<15 y)	1	1	1	1.2 g	
B	Clofazimine	-[c]	50 mg cap or tab[h]	2	2	2	2	2	100 mg	
			100 mg cap or tab[h]	1	1	1	1	1	100 mg	
	Cycloserine or terizidone	10–15 mg/kg	250 mg cap	2	2	3	3	3	1 g	
C	Ethambutol	15–25 mg/kg	400 mg tab	2	2	3	3	3	-	
	Delamanid	-[c]	50 mg tab	2 bd	2 bd	2 bd	2 bd	2 bd	200 mg	

	Pyrazinamide	20–30 mg/kg	400 mg tab 500 mg tab	3 2	4 3	4 3	4 3	5 4	-	
	Imipenem-cilastatin	-[c]	500 mg + 500 mg powder for injection, vial (10 ml)	2 vials (1 g + 1 g) bd					-	To be used with clavulanic acid
	Meropenem	-[c]	1 g powder for injection, vial (20 ml)	1 vial 3 times per day or 2 vials bd					-	To be used with clavulanic acid
	Amikacin	15–20 mg/kg	500 mg/2 ml solution for injection, ampoule[g]	2.5 ml	3 ml	3 to 4 ml	4 ml	4 ml	1 g	
	Streptomycin	12–18 mg/kg	1 g powder for injection, vial[g]	Calculate according to the dilution used					1 g	
	Ethionamide or prothionamide	15–20 mg/kg	250 mg tablet	2	2	3	3	4	1 g	Once daily dose advised but can start with 2 divided doses until tolerance improves
	p-aminosalicylic acid	8–12 g/day in 2–3 divided doses	PAS sodium salt(equivalent to 4 g PAS acid) sachet PAS acid (4 g) sachet	1 bd 1 bd	1 bd 1 bd	1 bd 1 bd	1 bd 1 bd	1 to 1.5 bd 1 to 1.5 bd	12 g	
Other medicines[f]	Isoniazid	4–6 mg/kg (standard dose)[d] 10–15 mg/kg (high dose)[d]	300 mg tab 300 mg tablet	2/3 1.5	1 1.5	1 2	1 2	1 2	-	100 mg isoniazid tablet can facilitate the administration of certain dosages Pyridoxine given with isoniazid in patients at risk (such as those with HIV, malnutrition)
	Clavulanic acid[g]	-[c]	125 mg clavulanic acid as amoxicillin/ clavulanate, 500 mg/ 125 mg tab[g]	1 bd	1 bd	1 bd	1 bd	1 bd	-	Only to be used with carbapenems
	Kanamycin	15–20 mg/kg	500 mg or 1 g powder for injection, vial (2ml);[e]	2 to 2.5 ml	2.5 to 3 ml	3 to 4 ml	4 ml	4 ml	1 g	M/W/F dosing of aminoglycosides at 25 mg/kg/day may limit

			1 g/ 4 ml solution for injection, ampoule;[e]							toxicity and inconvenience when the injectable agents are used in longer MDR-TB regimens
	Capreomycin	15–20 mg/kg	500 mg or 1 g powder for injection, vial (2 ml)[e]	2.5 ml	3ml	3 to 4 ml	4 ml	4 ml	1 g	
	Gatifloxacin	-[c]	400 mg tab	2	2	2	2	2	800 mg	Currently there is no availability of gatifloxacin on the market. Gatifloxacin is not used in persons <18 years old.
	Thioacetazone	-[c]	150 mg tab	1	1	1	1	1	-	Currently there is no availability of thioacetazone on the market. Thioacetazone is not used in persons <18 years old.

(<15 y) = follow the separate dose schedule for patients younger than 15 years of age; bd = two times a day; cap = capsule; g = gram; im = intramuscular; iv = intravenous; kg = kilogram; ml = millilitre; mg = milligram; M/W/F = Monday, Wednesday, Friday; soln = solution; susp = suspension; tab = tablet

Footnotes

a Dosages were established by the Guideline Development Group for the *WHO treatment guidelines for rifampicin- and multidrug-resistant tuberculosis, 2018 update* and the WHO Global task force on the pharmacokinetics and pharmacodynamics (PK/PD) of TB medicines and other experts. They are based on the most recent reviews and best practices in the treatment of MDR/RR-TB. For certain agents the dosages were informed by pharmacokinetic modelling results based on the principle of allometric scaling (Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol 2008;48:303–32). Due to the pharmacokinetic properties of certain medicines the doses proposed may exceed the mg/kg/day ranges shown here in order to achieve blood concentrations similar to target levels in an average adult patient. In patients <30 kg follow the schedule for <15 year olds unless otherwise indicated. If multiple dose options are given for one weight band select the lower or higher option depending on whether the patient is at the lower or higher limit of the body weight range. Dosing more closely to the target mg/kg/day should be aimed for, and is more feasible with oral or parenteral fluids and when solid forms of different dosages are available. Fractioning of tablets into halves or less should be avoided, if possible. Therapeutic drug monitoring is advised when the dose is at the upper and lower ends of the range to minimize the adverse therapeutic consequences of over- and under-exposure, respectively (especially for injectable agents, linezolid and fluoroquinolones).

b Clinicians may decide to exceed these values in particular cases to improve therapeutic effect.

c No weight-based dosing is proposed.

d Unless there is risk of toxicity, the high dose may be used if antimicrobial levels may be lowered because of pharmacokinetic interactions, malabsorption or other metabolic reasons or if the strain has low-level drug resistance.

e Weight-based daily dose is for 6 or 7 days/week administration (M/W/F scheduling may permit higher dosing). Volumes shown may differ by preparation. Streptomycin may be diluted in three different ways. For iv use, the volume may be increased.

f In the 2018 WHO treatment guidelines, these agents are either no longer recommended (kanamycin, capreomycin), only recommended as a companion agent (amoxicillin/clavulanic acid) or not included because of lack of data from the latest analysis on longer MDR-TB regimens in adults (gatifloxacin, isoniazid and thioacetazone).

g Only available in combination with amoxicillin as co-amoxyclav (e.g. 500 mg amoxicillin/125 mg clavulanic acid fixed dose combination). It is given with each dose of carbapenem, either as 125 mg bd or 125 mg 3 times daily.

h Tablets are expected to become available in the near future.

See the text of the guidelines for more details on the use of medicines.

For the BPaL regimen, the dosage of the drugs used in the NIX-TB trial was as follows: Bdq 400 mg QD for 2 weeks, followed by 200mg 3 times per week for a total of 26 weeks + Pa 200mg QD for 26 weeks + Lz 1200mg daily for 26 weeks

Annex 3. Dosing of medicines used in second-line MDR-TB regimens by weight band in patients under 15 years

Source: 2019 WHO consolidated guidelines on drug-resistant tuberculosis treatment

Group	Medicine	Weight-based daily dose[b]	Formulation	Weight bands among patients not yet 15 years old[a]							Usual upper daily dose[b]	Comments
				5–6 kg	7–9 kg	10–15 kg	16–23 kg	24–30 kg	31–34 kg	>34 kg		
A	Levofloxacin	15–20 mg/kg	100 mg dt	1	1.5	2 or 3	3 or 4	(>14 y)	(>14 y)	(>14 y)	1.5 g	
			250 mg tab	0.5	0.5	1 or 1.5	1.5 or 2	2	3	(>14 y)	1.5 g	
	Moxifloxacin	10–15 mg/kg	100 mg dt	0.8	1.5	2	3	4	(>14 y)	(>14 y)	400 mg	
			400 mg tab[c]	2 ml[c]	3 ml[c]	5 ml[c]	0.5 or 0.75	1	(>14 y)	(>14 y)	400 mg	Use 10 mg/kg in <6 months
	Bedaquiline	-	100 mg tab	-[i]	-[i]	-[i]	2 tabs od for two weeks; then 1 tab od M/W/F for 22 weeks		4 tabs od for 2 weeks; then 2 tabs od M/W/F for 22 weeks		-	Only in patients >5 years old (lower dose from 15–29 kg; higher dose from >29 kg)
	Linezolid	15 mg/kg od in <16 kg 10–12 mg/kg od in >15 kg	20 mg /ml susp	4 ml	6 ml	8 ml	11 ml	14 ml	15 ml	20 ml[d]	600 mg	
			600 mg tab[c]	0.25	0.25	0.25	0.5	0.5	0.5	0.75[d]		
B	Clofazimine	2–5 mg/kg	50 mg cap or tab[l]	1 alt days	1 alt days	1 alt days	1	2	2	(>14 y)	100 mg	Give on alternate days if dose in mg/kg/day is too high
			100 mg cap or tab[l]	M/W/F	M/W/F	1 alt days	1 alt days	1	(>14 y)	(>14 y)	100 mg	

	Cycloserine or terizidone	15–20 mg/kg	125 mg mini capsule (cycloserine)[c]	1	1	2	3	4	(>14 y)	(>14 y)	1 g	
			250 mg cap[c]	4–5 ml[c]	5–6 ml[c]	7–10 ml[c]	2	2	2	(>14 y)	1 g	
C	Ethambutol	15–25 mg/kg	100 mg dt	1	2	3	4	-	-	(>14 y)	-	
			400 mg tab[c]	3 ml[c]	4 ml[c]	6 ml[c]	1	1 or 1.5	2	(>14 y)		
	Delamanid	-	50 mg tab	-[i]	-[m, i]	-[em i]	-[m, i]	1 bd[h]	1 bd[h]	2 bd	200 mg	Only in patients >2 years old (25 mg bd in 3–5 years; 50 mg bd in 6–11 years; 100 mg bd in 12–17 years)
	Pyrazinamide	30–40 mg/kg	150 mg dt	1	2	3	4 or 5	-	-	(>14 y)	-	
			400 mg tab	0.5	0.75	1	1.5 or 2	2.5	3	(>14 y)		
			500 mg tab	0.5	0.5	0.75 or 1	1.5	2	2.5	(>14 y)		
	Imipenem-cilastatin	-	500 mg + 500 mg powder for injection, vial (10 ml)	-	-	-	-	-	-	-	-	Not used in patients <15 years (use meropenem)
	Meropenem	20–40 mg/kg iv every 8 hours	1 g powder for injection, vial (20 ml)	2 ml	4 ml	6 ml	8-9 ml	11 ml	(>14 y)	(>14 y)	-	To be used with clavulanic acid
	Amikacin	15–20 mg/kg	500 mg/2 ml solution for injection, ampoule[f]	0.4 ml	0.6 ml	0.8 - 1.0 ml	1.2 - 1.5 ml	2.0 ml	(>14 y)	(>14 y)	1 g	
	Streptomycin	20–40 mg/kg	1 g powder for injection, vial[e]	Calculate according to the dilution used					(>14 y)	(>14 y)	1 g	

	Ethionamide or prothionamide	15–20 mg/kg	125 mg dt (ethionamide)	1	1	2	3	4	4	(>14 y)	1 g	
			250 mg tab	0.5	0.5	1	2	2	2	(>14 y)	1 g	
	p-aminosalicylic acid	200–300 mg/kg in 2 divided doses	PAS acid (4 g) sachet	0.5–0.75 g bd	0.75–1 g bd	1–2 g bd	2–3 g bd	3–3.5 g bd	(>14 y)	(>14 y)	-	
			PAS sodium salt (equivalent to 4g PAS acid) sachet	0.5–0.75 g bd	0.75–1 g bd	1–2 g bd	2–3 g bd	3–3.5 g bd	(>14 y)	(>14 y)		Full dose can be given once daily if tolerated
			PAS sodium salt 60% w/w (9.2 g; equivalent to 4g PAS acid)	1.5 g bd	2–3 g bd	3–4 g bd	4 or 6 g bd	6 or 8 g bd	8–12 g bd	8–12 g bd	-	
Other medicines[f]	Isoniazid	15–20 mg/kg (high dose)	50 mg/5 ml soln	8–10 ml	15 ml	20 ml	-	-	-	-	-	300 mg isoniazid tablet can be used in patients >20 kg Pyridoxine is always given with high-dose isoniazid in children (12.5 mg od in <5 y olds and 25 mg od in >4 y olds)
			100 mg tab	1	1.5	2	3	4	4	(>14 y)		
	Clavulanic acid[g]	-	62.5 mg clavulanic acid as amoxicillin/ clavulanate, 250 mg/62.5 mg, powder for oral solution, 5 ml	2 ml bd[g]	3 ml bd[g]	5 ml bd[g]	8 ml bd[g]	10 ml bd[g]	(>14 y)	(>14 y)	-	Only to be used with carbapenems
	Kanamycin	15–20 mg/kg	500 mg or 1 g powder for injection, vial (2 ml);[e] 1g/ 4 ml solution for	0.4 ml	0.6 ml	0.8–1.0 ml	1.2–1.5 ml	2.0 ml	(>14 y)	(>14 y)	1 g	1 g vials (3 ml) also available

			injection, ampoule[e]									
	Capreomycin	15–20 mg/kg	500 mg or 1 g powder for injection, vial (2 ml)[e]	0.4 ml	0.6 ml	0.8–1.0 ml	1.2–1.5 ml	2.0 ml	(>14 y)	(>14 y)	1 g	
	Gatifloxacin	-	400 mg tab	-	-	-	-	-	-	-	-	Currently there is no availability of gatifloxacin on the market. Gatifloxacin is not used in persons <18 years old.
	Thioacetazone	-	-	-	-	-	-	-	-	-	-	Currently there is no availability of thioacetazone on the market. Thioacetazone is not used in persons <18 years old.

(<15 y) = follow the separate dose schedule for patients younger than 15 years of age; bd = two times a day; cap = capsule; g = gram; im = intramuscular; iv = intravenous; kg = kilogram; ml = millilitre; mg = milligram; M/W/F = Monday, Wednesday, Friday; soln = solution; susp = suspension; tab = tablet

Footnotes

a Dosages were established by the Guideline Development Group for the *WHO treatment guidelines for rifampicin- and multidrug-resistant tuberculosis, 2018 update* and the WHO Global task force on the pharmacokinetics and pharmacodynamics (PK/PD) of TB medicines and other experts. They are based on the most recent reviews and best practices in the treatment of MDR/RR-TB. For certain agents the dosages were informed by pharmacokinetic modelling results based on the principle of allometric scaling (Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol 2008;48:303–32). Due to the pharmacokinetic properties of certain medicines the doses proposed may exceed the mg/kg/day ranges shown here in order to achieve blood concentrations similar to target levels in an average adult patient. In patients <30 kg follow the schedule for <15 year olds unless otherwise indicated. If multiple dose options are given for one weight band select the lower or higher option depending on whether the patient is at the lower or higher limit of the body weight range. Dosing more closely to the target mg/kg/day should be aimed for, and is more feasible with oral or parenteral fluids and when solid forms of different dosages are available. Fractioning of tablets into halves or less should be avoided, if possible. Therapeutic drug monitoring is advised when the dose is at the upper and lower ends of the range to minimize the adverse therapeutic consequences of over- and under-exposure, respectively (especially for injectable agents, linezolid and fluoroquinolones).

b Clinicians may decide to exceed these values in particular cases to improve therapeutic effect.

c No weight-based dosing is proposed.

d Unless there is risk of toxicity, the high dose may be used if antimicrobial levels may be lowered because of pharmacokinetic interactions, malabsorption or other metabolic reasons or if the strain has low-level drug resistance.

e Weight-based daily dose is for 6 or 7 days/week administration (M/W/F scheduling may permit higher dosing). Volumes shown may differ by preparation. Streptomycin may be diluted in three different ways. For iv use, the volume may be increased.

f In the 2018 WHO treatment guidelines, these agents are either no longer recommended (kanamycin, capreomycin), only recommended as a companion agent (amoxicillin/clavulanic acid) or not included because of lack of data from the latest analysis on longer MDR-TB regimens in adults (gatifloxacin, isoniazid and thioacetazone).

g Only available in combination with amoxicillin as co-amoxyclav (e.g. 500 mg amoxicillin/125 mg clavulanic acid fixed dose combination). It is given with each dose of carbapenem, either as 125 mg bd or 125 mg 3 times daily.

h *If using 25mg distab, dosing should be two tabs twice daily*

i *See Annex 4 of the guidelines*

J *Tablets are expected to become available in the near future*

k *May be used in children 3–5 years of age. Giving half a 50 mg adult tablet in these children does not result in the same blood levels observed in trials using the special 25 mg paediatric tablet. Bioavailability may further be altered when the 50 mg tablet is split, crushed or dissolved'*

See the text of the guidelines for more details on the use of medicines

Annex 4. Drugs and dosing in paediatric patients

Provisional, suggested doses of delamanid and bedaquiline for operational research (subject to revision) for paediatric patients:

1) Bedaquiline

Weight range (kg)	Loading dose /day (mg) (first two weeks)	Maintenance dose mg/week (M/W/F)
3-7	100	150 (50 - 50 – 50)
>7 – 15	200	300 (100 –100 – 100)

kg = kilogram; mg = milligram; M/W/F = Monday, Wednesday, Friday

The bedaquiline "crush study" in adult volunteers* showed that bioavailability of bedaquiline 100 mg tabs suspended in water is equivalent to that for tablets swallowed whole. The suspension was well tolerated. These findings suggest that the currently available bedaquiline formulation (suspended in water) could be used to treat DR-TB in children, to bridge the gap until paediatric dispersible formulation becomes routinely available.

* Svensson et al; Br J Clin Pharmacol (2018) 84 2384–2392

2) Delamanid

Please note that the following dosing applies to the use of the 25mg dispersible tablet.

<table>
<tr><th colspan="2"><12 kg</th><th rowspan="2">>12-23 kg</th></tr>
<tr><td colspan="2">Dissolve 1 tab of 25mg in 10 mL of water*, then give:</td></tr>
<tr><td>5.5-8 kg</td><td>2 mL once daily</td><td rowspan="3">25 mg twice daily (using 25mg distab: 1 tab twice daily)</td></tr>
<tr><td>>8-10 kg</td><td>2 mL twice daily</td></tr>
<tr><td>>10-12 kg</td><td>4 mL twice daily</td></tr>
</table>

* Tablet needs to be fully dispersed before giving the aliquot, unused solution should not be conserved.

Child-friendly formulations available through the Global Drug Facility (GDF):

Pyrazinamide 150 mg *
Ethionamide 125 mg *
Levofloxacin 100 mg *
Moxifloxacin 100 mg *
Cycloserine 125mg minicapsule
Ethambutol 100 mg *
Isoniazid 100 mg *

* Dispersible tablet: to be dissolved in water and administered to the child as a solution

Annex 5. Accessing the paediatric formulation of delamanid

Please note that this annex should not be included in the final version of the protocol

An application can be made to Otsuka to access the 25 mg dispersible tablet for research purposes. This would be relevant for children weighing below 24 kg or for children weighing over 24 kg who have difficulty swallowing adult tablets.

The following steps need to be taken:

1. Contact Otsuka via email: partnership@otsuka.ch (CC Marc Destito: mdestito@otsuka-onpg.com), indicating that the country would like to apply for the use of the paediatric formulation (25 mg dispersible tablet) of delamanid
2. Attach a synopsis of the OR protocol, approved by an ethics committee. In the synopsis, the following information needs to be included:
    a. Ages of children to be enrolled
    b. Details on adverse event monitoring
    c. The location of a temperature-controlled pharmacy where the company can inspect the drug if they want to
3. After approval of the protocol, the company will send the following document*:
   Investigator Sponsored Study agreement (ISS) and details about confidentiality, data sharing, and others are captured within that agreement.
4. Teams have to undergo pharmacovigilance (PV) training and also report on all adverse events (AEs) (this is similar to what is required for access to delamanid for compassionate use)

*It is important to review these documents very carefully, to ensure that you fully agree with all aspects of the agreement and adjust as needed.
Investigators are welcome to share the proposed agreements with WHO/TDR (ShORRT@who.int) for review, prior to signing them.

Annex 6. Study sites: selection criteria

Health facilities notifying and treating MDR-TB patients within the NTP network, in line with the guidelines of the national TB programme.

In addition, study sites are required to meet the following criteria:

- Trained study site staff able to conduct close supervision of patients in treatment and follow up (especially in the initial phase of the study) for the evaluation of the effectiveness and pharmacovigilance.
- Study site staff willing to enrol 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.
- 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), psychiatric assessment, vision (acuity and colour vision) and audiometry
- Capacity to monitor electrocardiogram (ECG)

Annex 7. Inpatient and ambulatory treatment

Inpatient treatment is not mandatory, but patients may require hospitalisation at the initiation of MDR-TB treatment for clinical reasons, or 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. Investigators may keep the model of care used for the SoC, or may adapt it based on the nature of the new all-oral regimen.

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) (or VOT, video-observed therapy) 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:

- Administer DOT on a daily basis.
- Supports the patient to attend 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.

Annex 8. Adverse events of special interest

Source: World Health Organization, Active tuberculosis drug-safety monitoring and management (aDSM), 2015

All adverse events of special interest (suggested list):

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

Annex 9. Adverse Events: grading, attribution, definitions

Table 1: Grading of Adverse Events

Source: DAIDS table for grading severity of adult and paediatric adverse events – corrected version 2.1 July 2017

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	

The full DAIDS table can be found at this web link:
https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

Table 2: Scale for attribution of assessing drug relationship with AE occurrence

Source: WHO TDR Workbook for investigators, 2012
https://www.who.int/tdr/publications/documents/investigator.pdf

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 aetiology 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).
Insufficient data to assess	There is insufficient information about the ADRs to allow for an assessment of causality.

Table 3: Definitions of Anticipated and Unanticipated Adverse Events
Source: ICH E2

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 2. 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.

Annex 10. Modified Medical Research Council Dyspnea Scale

Source: Doherty DE et al. COPD: Consensus Recommendations for early diagnosis and treatment. Journal of Family Practice, Nov 2006

0	"I only get breathless with a strenuous exercise"
1	"I get short of breath when hurrying on the level or walking up a slight hill"
2	"I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level"
3	"I stop for breath after walking about 100 yards or after a few minutes on the level"
4	"I am too breathless when to leave the house" or "I am breathless when dressing"

Annex 11. Consent form

Part I: Information sheet

Title of study: All-oral shorter treatment regimens for multi-drug and rifampicin-resistant tuberculosis: Evaluating their effectiveness, safety, feasibility, cost and impact on the quality of life of patients in *(name of country)*

Co-Principal Investigators (PI): *[complete as relevant]*

Site Address: *[complete as relevant]*

Contact number: *[complete as relevant]*

Sir/Madam,
You have been invited to take part in a research study because you have been diagnosed with Drug-resistant tuberculosis (DR-TB), a serious disease with difficult treatment options. Please take some time to read the information presented here, which will explain details of this study. Please ask us any questions about any part of the study that you do not fully understand. It is very important that you are fully satisfied, that you clearly understand what this research entails and how you could be involved. Your participation is **entirely voluntary** and you **are free to decline to participate**. If you say no, this will not negatively affect you and the quality of care provided to you in any way, including health care now and in the future. If you say yes, you will also be **free to withdraw from the study at any point** without having to give reasons for your withdrawal.

Ethics approval for this study was obtained from *[complete as relevant]*, and from *[complete as relevant]*. This study will be conducted according to ethical guidelines and principles of the International Declaration of Helsinki, as well as local ethical guidelines.

What is this study all about?
Drug-resistance tuberculosis (DR-TB) is a difficult disease to treat. The treatment usually lasts 20-24 months, and includes a daily injection for 8 months which has high rates of adverse effects and not good rate of favourable outcomes. A shorter regimen (9 to 11 months), injectable-free and using new and repurposed drugs like Bedaquiline may provide improved treatment outcomes and a lower rate of adverse events.

Why have I been invited to participate?
You have been selected to participate in this study because you are an adult who has been diagnosed with drug or multi-drug resistant tuberculosis eligible to be treated with the injectable-free short course regimen.

What will happen to me if I take part?
If you accept to be part of the study, you will sign a consent form and an identification number will be assigned to you. Different information collected by the clinical team as part of the routine care will be recorded on a database, which will be analysed throughout and at the end of the study period. This information includes demographic data such as your age and gender, and clinical information on the disease, the clinical examination, the treatment and its effects, as well as laboratory results and other related exam results. All the information included in the database will not be identified with your

name, but only with the code that will be assigned to you if you agree to participate in order to preserve confidentiality. If you feel uncomfortable providing some sensitive information about you, please feel free to discuss it with the medical staff.

If you accept to take part in this study, you will be assigned to a short course regimen with only oral drugs. The regimen will take 9-12 months to complete. The treatment will be provided to you by direct observation and you will be accompanied throughout your treatment by a treatment supporter who will help you with your medication. Your tuberculosis regimen will consist *of 7 drugs provided for 4 to 6 months followed by another 5 months with 5 drugs provided [complete/adapt as relevant].*

Since there is a possibility for your disease to reappear after treatment, you will also be asked to complete *visits at 6 and 12 months after completing treatment [complete/adapt as relevant].* This will allow checking for any recurrence of the disease and appropriate clinical measures will be taken by the clinical team based on the results.

What do I have to do?
There is no difference for you regarding the clinical care you will receive. You must come to the clinic to have medical consultations and to receive the medicines according to the protocol of the treatment. Your visits to the clinic and the tests that you will do as part of this study will consist of tests that you would anyway do as part of the regular follow-up that is usually required for the follow-up of the patients affected with multi-drug resistant tuberculosis. Additional tests might be run as part of this study during your visits that will require additional sputum samples from you.

How will the data that we collect be treated?
No name will be written on the study collection forms. Also information entered into the computer in an electronic database of the study will not use your name. A number (code) will be used instead. When information is needed from your medical file, it will only be accessed by the clinical and the research team, as they will be locked and kept safely. All reports and communication related to the study (including the publication of the findings) will also not use your name. The blood and sputum collected for the routine follow-up of your disease and treatment will not be used for any other purpose. Your consent form will be kept separately and safely.

How will I benefit from taking part in this research?
This research will help us in preparing better treatment regimens and algorithms for Drug-resistant tuberculosis patients in the future and also might help you in the course of your treatment, however this is not guaranteed. It might help the wider community in *[name of country]* to have access to improved treatment regimen, but again this is not guaranteed.

What are the possible side effects of the study regimen?
All drugs can have side effects, and every patient is different. You will be checked by your doctor at every visit for possible side effects and treated accordingly. One of the reasons why you will be requested to give blood samples and perform some other tests such as an electrocardiogram (test for the heart) during your visits is to allow your treating physician to check for any possible side effect related of the treatment. You might experience gastrointestinal effects such as nausea, vomiting and gastric reflux. You might also feel muscle weakness and other neurological side effects, and might experience, among others, a skin rash, dry eyes, and sputum and urine discolouration. It is possible that the short multi-drug resistant tuberculosis regimen may also cause some problems that we are not aware of. However, you will be followed closely for any unwanted effects or any problems. Always tell your health-care provider of any side effects or problems you are experiencing.

What monitoring tests do I need while taking the short DR-TB regimen?

You will need the same monitoring test that all patients on multi-drug resistant tuberculosis treatment need; these are a first visit and a visit in 2 weeks' time followed by monthly visits. Some additional tests will be requested from you such as blood tests, vision tests, tests to check your heart (electrocardiogram) in order to follow-up on the possible unfavourable effects that the regimen might cause. You will be educated on the signs that should trigger you to see your doctor if you experience them.

Are there any risks involved in this research?
All the different procedures will be performed in the frame of the recommended medical protocol. There might be some risks related to your participation but necessary measures and close follow-up will be done by the clinical and research team accordingly. If you are currently pregnant or are planning to become pregnant during your treatment or in the six months following the end of your treatment, you should be aware that information on the safety during pregnancy of the drugs that you will be given is limited. There is no evidence that they are harmful either. Information on safety during pregnancy of the drugs used as standard of care in your country is also limited.

There is a risk that you do not benefit from this regimen as much as you would benefit from the standard regimen in use in your country, and that your treatment may fail. In that case, your regimen will be accordingly adjusted. Risk of failing treatment also exists with the standard treatment. You might also experience, as mentioned earlier, side effects some of which might be severe. A close monitoring of your side effects will be done regularly and at each visit to make sure signs are detected early and treated accordingly. We will make sure that your data will be kept confidential with no identification with your name. All paper data related to the study will be kept locked and all data entered on a computer will be protected by a password. In all cases, al study related information will be only accessible to the study team.

Can I have the right to refuse or withdraw?
You do not have to agree to take the short course regimen if you do not wish to do so. Instead, you can take the regular regimen for drug-resistant tuberculosis. Your participation is entirely voluntarily and you are free to decline to participate. If you say no, this will not affect you negatively in any way, including your treatment now or in the future. You are also free to withdraw from the study at any point, even if you do agree to take part now. The treating physician might also withdraw you from the study if they deemed it clinically necessary or better for you. In case you decide to withdraw from the study, the data that was collected related to you up to your withdrawal will still be used for analysis without the identification of your name and only for the purpose of the study, if you agree. After your withdrawal, no further analysis on any of the specimens obtained from you under the study will be carried out.

Are there any costs involved and will I be paid to take part in this study?
Investigators should decide whether any reimbursement is given to patients
You will be reimbursed the costs related to transportation you will pay for every visit to the tuberculosis medical unit in *[insert name of the clinic]* where you will present at the start of the treatment and for the further examination visits for check-up and drug collection.

If I have any other questions about the research in the future?
If you have any question, you may contact any of the following persons: *[complete as relevant]*

You will receive a copy of this information sheet and the signed consent form for your own records.

Part II: Certificate of consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it, and the questions I have asked have been answered to my satisfaction. I consent voluntarily to be a participant in this study.

Print Name of Participant _____

Signature/Thumb print of Participant _____

Date _____
day/month/year

Witness

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness _____

Signature/Thumb print of witness _____

Date _____
day/month/year

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands the purpose, procedures (i.e. interview that will last 60-90 minutes, measuring of height and weight), potential risks and benefits of the study.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily. A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent _____

Signature of Researcher /person taking the consent _____

Date _____
day/month/year

Annex 12. Informed assent form

This assent form is for children between the age of 6 and 18 and who have been selected to take part in this study and are able to read.

Part I: Information sheet

Title of study: All-oral shorter treatment regimens for multi-drug and rifampicin-resistant tuberculosis: Evaluating their effectiveness, safety, feasibility, cost and impact on the quality of life of patients in *(name of country)*

Co-Principal Investigators (PI): *[complete as relevant]*

Site Address: *[complete as relevant]*

Contact number: *[complete as relevant]*

Sir/Madam,
You have been invited to take part in a research study because you have been diagnosed with Drug-resistant tuberculosis (DR-TB), a serious disease with difficult treatment options. Please take some time to read the information presented here, which will explain details of this study. Please ask us any questions about any part of the study that you do not fully understand. It is very important that you are fully satisfied, and that you clearly understand what this research entails and how you could be involved. Your participation is **entirely voluntary** and you **are free to decline to participate**. If you say no, this will not negatively affect you and the quality of care provided to you in any way, including health care now and in the future. If you say yes, you will also be **free to withdraw from the study at any point** without having to give reasons for your withdrawal.

Ethics approval for this study was obtained from *[complete as relevant]*, and from *[complete as relevant]*. This study will be conducted according to ethical guidelines and principles of the International Declaration of Helsinki, as well as local ethical guidelines.

What is this research study all about?
Drug-resistance tuberculosis (DR-TB) is a difficult disease to treat. The treatment usually lasts 20-24 months, and includes a daily injection for 8 months which has high rates of adverse effects and not a good rate of favourable outcomes. A shorter regimen (9 to 12 months), injectable-free and using new and repurposed drugs like Bedaquiline may provide improved treatment outcomes and a lower rate of adverse events.

Why have I been invited to participate?
You have been selected to participate in this study because you have been diagnosed with drug or multi-drug resistant tuberculosis eligible to be treated with the injectable-free shorter course regimen.

What will happen to me if I take part?
If you accept to be part of the study, you will sign a consent form and an identification number will be assigned to you. Different information collected by the clinical team as part of the routine care will be recorded on a database, which will be analysed throughout and at the end of the study period. This information includes demographic data such as your age and gender, and clinical information on the

disease, the clinical examination, the treatment and its effects, as well as laboratory results and other related exam results. All the information included in the database will not be identified with your name, but only with the code that will be assigned to you (if you agree to participate) in order to preserve confidentiality. If you feel uncomfortable providing some sensitive information about you, please feel free to discuss it with the medical staff.

If you accept to take part in this study, you will be assigned to a short course regimen with only oral drugs. The regimen will take 9-12 months to complete. The treatment will be provided to you by direct observation and you will be accompanied throughout your treatment by a treatment supporter who will help you with your medication. Your tuberculosis regimen will consist *of 7 drugs provided for 4 to 6 months followed by another 5 months with 5 drugs provided [complete/adapt as relevant].*

Since there is a possibility for your disease to reappear after treatment, you will also be asked to complete *visits at 6 and 12 months after completing treatment [complete/adapt as relevant].* This will allow checking for any recurrence of the disease and appropriate clinical measures will be taken by the clinical team based on the results.

What do I have to do?
There is no difference for you regarding the clinical care you will receive. You must come to the clinic to have medical consultations and to receive the medicines according to the protocol of the treatment. Your visits to the clinic and the tests that you will do as part of this study will consist of tests that you would anyway do as part of the regular follow-up that is usually required for the follow-up of the patients affected with multi-drug resistant tuberculosis. Additional tests might be run as part of this study during your visits that will require us to ask you for additional sputum samples.

How will the data that we collect be treated?
No name will be written on the study collection forms. Also information entered into the computer in an electronic database of the study will not use your name. A number (code) will be used instead. When information is needed from your medical file, it will only be accessed by the clinical and the research team, as they will be locked and kept safely. All reports and communication related to the study (including the publication of the findings) will also not use your name. The blood and sputum collected for the routine follow-up of your disease and treatment will not be used for any other purpose. Your consent form will be kept separately and safely.

How will I benefit from taking part in this research?
This research will help us preparing better treatment regimens for Drug-resistant tuberculosis patients in the future, and might also help you during your treatment. However, this is not guaranteed. It might help the wider community in *[name of country]* to have access to improved treatment regimen.

What are the possible side effects of the study regimen?
All drugs can have side effects, and every patient is different. You will be checked by your doctor at every visit for possible side effects and treated accordingly. One of the reasons why you will be requested to give blood samples and perform some other tests such as an electrocardiogram (test for the heart) during your visits is to allow your treating physician to check for any possible side effect related of the treatment. You might experience gastrointestinal effects such as nausea, vomiting and gastric reflux. You might also feel muscle weakness and other neurological side effects, and might experience, among others, a skin rash, dry eyes, and sputum and urine discolouration. It is possible that the short multi-drug resistant tuberculosis regimen may also cause some problems that we are not aware of. However, you will be followed closely for any unwanted effects or any problems. Always tell your health-care provider of any side effects or problems you are experiencing.

What monitoring tests do I need while taking the short DR-TB regimen?
You will need the same monitoring test that all patients on multi-drug resistant tuberculosis treatment need; these are a first visit and a visit in 2 weeks' time followed by monthly visits. Some additional tests will be requested from you such as blood tests, vision tests, tests to check your heart (electrocardiogram) in order to follow-up on the possible unfavourable effects that the regimen might cause. You will be educated on the signs that should trigger you to see your doctor if you experience them.

Are there any risks involved in this research?
All the different procedures will be performed in the frame of the recommended medical protocol. There might be some risks related to your participation but necessary measures and close follow-up will be done by the clinical and research team accordingly. There is a risk that you do not benefit from this regimen as much as you would benefit from the standard regimen and that your treatment fails. In that case, your regimen will be accordingly adjusted. Risk of failing treatment also exists with the standard treatment. You might also experience, as mentioned earlier, side effects some of which might be severe. A close monitoring of your side effects will be done regularly and at each visit to make sure signs are detected early and treated accordingly.

We will make sure that your data will be kept confidential with no identification with your name. All paper data related to the study will be kept locked, and all data entered on a computer will be protected by a password. All information related to the study will be only accessible to the study team.

Can I have the right to refuse or withdraw?
You do not have to agree to take the short course regimen if you do not wish to do so. Instead, you can take the regular regimen for drug-resistant tuberculosis. Your participation is entirely voluntarily and you are free to decline to participate. If you say no, this will not affect you negatively in any way, including your treatment now or in the future. You are also free to withdraw from the study at any point, even if you do agree to take part now. The treating physician might also withdraw you from the study if they deem it clinically necessary or better for you. In case you decide to withdraw from the study, the data that was collected related to you up to your withdrawal will still be used for analysis without the identification of your name and only for the purposes of the study, if you agree. After your withdrawal, no further analysis on any of the specimen obtained from you under the study will be carried out.

Are there any costs involved and will I be paid to take part in this study?
Investigators should decide whether any reimbursement is given to patients
You will be reimbursed the costs related to transportation for every visit to the tuberculosis medical unit in *[insert name of the clinic]* where you will present at the start of the treatment and for the further examination visits for check-up and drug collection.

If I have any other questions about the research in the future?
If you have any questions, you may contact any of the following persons: *[complete as relevant]*

You will receive a copy of this information sheet and the signed consent form for your own records.

Part II: Certificate of assent

I have read this information (or the information has been read to me). I have had my questions answered and I know that I can ask questions later.

I agree to take part in the research.

Only if child assents:

Print name of child: _____

Signature of child: _____

Date: _____
day/month/year

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and, to the best of my ability, made sure that the participant understands the purpose, procedures, potential risks and benefits of the study.

I confirm that the participant was given the opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this assent form has been provided to the participant.

Print Name of Researcher/person taking the assent _____

Signature of Researcher /person taking the assent _____

Date _____
day/month/year

Copy provided to the participant _____ (initialled by researcher)

Parent/Guardian has signed an informed consent ___Yes ___No _____(initialled by researcher)

Annex 13. Parental/guardian consent form

Part I: Information sheet

Title of study: All-oral shorter treatment regimens for multi-drug and rifampicin-resistant tuberculosis: Evaluating their effectiveness, safety, feasibility, cost and impact on the quality of life of patients in *(name of country)*

Co-Principal Investigators (PI): *[complete as relevant]*

Site Address: *[complete as relevant]*

Contact number: *[complete as relevant]*

Sir/Madam,
Your child has been invited to take part in this research study because he/she has been diagnosed with Drug-resistant tuberculosis (DR-TB), a serious disease with difficult treatment options. Please take some time to read the information presented here, which will explain the details of this study. Please ask us any questions about any part of the study that you do not fully understand. It is very important that you are fully satisfied, that you clearly understand what this research entails and how you and your child could be involved. Your participation is **entirely voluntary** and you **are free to decline to participate**. If you say no, this will not negatively affect your child and the quality of care provided to him/her in any way, now or in the future. If you say yes, you will also be **free to withdraw your child from the study at any point** without having to give reasons for this.

Ethics approval for this study was obtained from *[complete as relevant]*, and from *[complete as relevant]*. This study will be conducted according to ethical guidelines and principles of the International Declaration of Helsinki, as well as local ethical guidelines.

What is this research study all about?
Drug-resistance tuberculosis (DR-TB) is a difficult disease to treat. The treatment usually lasts 20-24 months, and includes a daily injection for 8 months with high rates of adverse effects and not a good rate of favourable outcomes. A shorter regimen (9 to 12 months), injectable-free and using new and repurposed drugs like Bedaquiline may provide improved treatment outcomes and a lower rate of adverse events.

Why has my child been invited to participate?
Your child has been selected to participate in this study because he/she has been diagnosed with drug or multi-drug resistant tuberculosis and he/she is eligible to be treated with the injectable-free short course regimen.

What will happen to my child if he/she take part in this study?
If you accept that your child is part of this study, you will sign a consent form and an identification number will be assigned to your child. Different information collected by the clinical team as part of routine care will be recorded in a database, which will be analysed throughout and at the end of the study period. This information includes demographic data such as the age and gender of your child, and clinical information on the disease, the clinical examination, the treatment and its effects, as well as laboratory results and other related exam results. All the information included in the database will

not be identified with your child's name, but only with the code that will be assigned to him/her if you agree that he/she participates in order to preserve confidentiality. If you feel uncomfortable providing some sensitive information about your child, please feel free to discuss it with the medical staff.

If you accept that your child takes part in this study, he/she will be assigned to a short course regimen with only oral drugs. The regimen will take 9-12 months to complete. The treatment will be provided to your child by direct observation and he/she will be accompanied throughout your treatment by a treatment supporter who will help your child with the medication. Your child's tuberculosis regimen will consist *of 7 drugs provided for 4 to 6 months followed by another 5 months with 5 drugs provided [complete/adapt as relevant].*

Since there is a possibility for the disease to reappear after treatment, your child will also be asked to come to the health facility for *visits at 6 and 12 months after completing treatment [complete/adapt as relevant].* This will allow checking for any recurrence of the disease and appropriate clinical measures will be taken by the clinical team based on the results.

What does my child have to do?
There is no difference for your child in terms of the clinical care he/she will receive. Your child must come to the clinic to have medical consultations and to receive the medicines according to the protocol of the treatment. Visits to the clinic and the tests that your child will do as part of this study will consist of tests that are part of the regular follow-up required for patients affected with multi-drug resistant tuberculosis. Additional tests might be run as part of this study during these visits that will require additional samples from your child.

How will the data that we collect be treated?
No name will be written on the study collection forms. Also information entered into an electronic database of the study will not include the name of your child. A number (code) will be used instead. When information is needed from your child's medical file, it will only be accessed by the clinical and the research team, as they will be locked and kept safely. All reports and communication related to the study (including the publication of the findings) will also not use the name of your child. The blood and sputum collected for the routine follow-up of the disease and treatment will not be used for any other purpose. This consent form will be kept separately and safely.

How will my child benefit from taking part in this research?
This research will help us in preparing better treatment regimens for drug-resistant tuberculosis patients in the future, and it might also help your child during the course of his/her treatment, although this is not guaranteed. It might help the wider community in *[name of country]* to have access to improved treatment regimens.

What are the possible side effects of the study regimen?
All drugs can have side effects, and every patient is different. Your child will be checked by the doctor at every visit for possible side effects and treated accordingly. One of the reasons why your child will be requested to give blood samples and perform some other tests such as an electrocardiogram (test for the heart) during his/her visits is to allow the treating physician to check for any possible side effect related of the treatment. Your child might experience gastrointestinal effects such as nausea, vomiting and gastric reflux. He/she might also feel muscle weakness and other neurological side effects, and might experience, among others, skin rash, dry eyes, and sputum and urine discolouration. It is possible that the short multi-drug resistant tuberculosis regimen may also cause some problems that we are not aware of. However, your child will be followed closely for any unwanted effects or any problems. You should always tell your health-care provider about any side effects or problems your child is experiencing.

What monitoring tests does my child need while taking the short DR-TB regimen?
Your child will need the same monitoring test that all patients on multi-drug resistant tuberculosis treatment need; these are a first visit and a visit in 2 weeks' time followed by monthly visits. Some additional tests will be requested from your child such as blood tests, vision tests, tests to check his/her heart (electrocardiogram) in order to monitor possible unfavourable effects that the regimen might cause. You will be educated on the signs that should trigger you to see the doctor if your child experiences them.

Are there any risks involved in this research?
All the different procedures will be performed according to the recommended medical protocol. There might be some risks related to your child's participation but necessary measures and close follow-up will be done by the clinical and research team accordingly.

You should be aware that information on the safety of the drugs that your child will be given is limited in children. There is no evidence that they are harmful either. Information on safety for children of the drugs used as standard of care in your country is also limited.

There is a risk that your child does not benefit from this regimen as much as he/she would benefit from the conventional standard long one, and that his/her treatment fails. In that case, your child's regimen will be modified accordingly. Risk of failing treatment also exists with the standard treatment. Your child might also experience, as mentioned earlier, side effects, some of which might be severe. A close monitoring of the side effects your child might experience will be done regularly and at each visit to make sure signs are detected early and treated accordingly. We will make sure that information about your child data is kept confidential with no identification with his/her name. All paper data related to the study will be kept locked and all data entered on a computer will be protected by a password. All information related to the study will only be accessible to the study team.

Can I have the right to refuse or withdraw my child's participation in this study?
You do not have to agree to your child taking the short course regimen if you do not wish to do so. Instead, your child can take the regular Drug-resistant tuberculosis regimen. Your child's participation is entirely voluntarily. If you say no, this will not affect your child in a negative way. You are also free to withdraw your child from the study at any point, even if you do agree to his/her participation now. The treating physician might also withdraw your child from the study if and when they deem it clinically necessary. In case you decide to withdraw your child from the study, the data that was collected up to withdrawal will still be used for analysis without your child's name and only for the purpose of the study. After your child's withdrawal, no further analysis on any of the specimen obtained from your child will be carried out.

Are there any costs involved and will my child be paid to take part in this study?
Investigators should decide whether any reimbursement is given to patients
You will be reimbursed the costs related to taking your child to the health centre in *[insert name of the clinic]* at the start of the treatment and for further check-up visits and drug collection.

If I have any other questions about the research in the future?
If you have any questions, you may contact any of the following persons: *[complete as relevant]*

You will receive a copy of this information sheet and the signed consent form for your own records.

Part II: Certificate of consent

I have been asked to give consent for my daughter/son to participate in this research study. I will complete one interview on his/her behalf. I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions I have asked have been answered to my satisfaction. I consent voluntarily for my child to participate as participant in this study and to answer questions on his/her behalf.

Print Name of Parent/Guardian _____

Signature/Thumb print of Parent/Guardian _____

Date _____
day/month/year

Witness
I have witnessed the accurate reading of the consent form to parent of the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness _____

Signature/ Thumb print of witness _____

Date _____
day/month/year

Statement by the researcher/person taking consent

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands the purpose, procedures, potential risks and benefits of the study.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent _____

Signature of Researcher /person taking the consent _____

Date _____
day/month/year