

# 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 Pakistan

<b>Submission date</b> 09/09/2020	<b>Recruitment status</b> No longer recruiting	<input type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
<b>Registration date</b> 08/02/2021	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 08/05/2025	<b>Condition category</b> Infections and Infestations	<input type="checkbox"/> Individual participant data <input checked="" type="checkbox"/> Record updated in last year

## Plain English summary of protocol

### Background and study aim

Multidrug-resistant tuberculosis (MDR-TB) is a form of tuberculosis (TB) infection caused by bacteria that are resistant to treatment with at least two of the most powerful first-line anti-TB drugs. 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-TB were detected and notified in 2018, of which 97% were enrolled on treatment. Patients with 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. Outcomes with this approach are generally poor, with only 56% of MDR-TB patients reported to have been successfully treated. Globally, multiple studies are being conducted to evaluate the safety and effectiveness of new shorter treatments (less than 12 months) to address the above-mentioned issue. In these new shorter treatments injectable treatments have been replaced with orally administered medicine and drugs with better safety outcomes, so patients are more likely to successfully complete the treatment. A comparison of two selected all oral shorter treatments is being proposed to find out if they are comparable in terms of successful treatment completion rate, safety and feasibility. It is expected that all-oral shorter treatments will improve treatment adherence, mainly by reducing the time duration, increased feasibility, and reduced cost of treatment.

### Who can participate?

Patients with rifampicin-resistant TB that is sensitive to fluoroquinolones

### What does the study involve?

Participants are randomly allocated to receive either the new all-oral shorter treatment (i.e. bedaquiline + linezolid) or the standard all-oral short treatment (i.e. bedaquiline). The total duration of treatment is 11 months and the duration of follow-up is 12 months after completion of treatment.

What are the possible risks and benefits of participating?

There are no direct benefits to the participants, but it is expected that all-oral shorter treatments will improve treatment adherence, mainly by reducing the costs (direct and opportunity) and the occurrence of adverse reactions. It is therefore likely that the overall health-related quality of life of patients would improve. There are no added risks involved in participating in this study. Whether the patient agrees or not to participate, he/she will have the same tests and treatment.

Where is the study run from?

The study will run from 12 main MDR-TB treating hospitals in Pakistan. Twelve Programmatic Management of Drug-resistant TB (PMDT) sites i.e. ten in Punjab, and one each in Islamabad and Muzafarabad (AJK) districts.

When is the study starting and how long is it expected to run for?

January 2020 to June 2024

Who is funding the study?

World Health Organization (Switzerland)

Who is the main contact?

Dr Muhammad Amir Khan

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## Contact information

### Type(s)

Scientific

### Contact name

Dr Muhammad Amir Khan

### Contact details

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## Additional identifiers

### EudraCT/CTIS number

Nil known

### IRAS number

### ClinicalTrials.gov number

Nil known

### Secondary identifying numbers

## Study information

### Scientific Title

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

### Acronym

ShORRT

### Study objectives

This trial will determine the effectiveness, safety, feasibility, cost-effectiveness and impact on quality of life of an all-oral shorter MDR/RR-TB regimen of 9 to 12 months duration under programmatic conditions.

### Ethics approval required

Old ethics approval format

### Ethics approval(s)

Approved 21/07/2020, National Bioethics Committee Pakistan (NBC Secretariat, PHRC, Shahrah-e-Jamhuriat, G-5/2, Islamabad, Pakistan; +92 (0)51 9224325, 9207386; nbcpakistan.org@gmail.com), ref: NBC-491, WHO ERC: 0003305

### Study design

Stepped-wedge cluster randomized trial

### Primary study design

Interventional

### Secondary study design

Stepped-wedge cluster randomized trial

### Study setting(s)

Hospital

### Study type(s)

Treatment

### Participant information sheet

Not available in web format, please use the contact details to request a participant information sheet

### Health condition(s) or problem(s) studied

Multidrug- and rifampicin-resistant tuberculosis

### Interventions

A stepped-wedge design comparing patients receiving the new all-oral shorter MDR/RR-TB regimen (i.e. bedaquiline + linezolid) and patients receiving the standard all-oral MDR/RR-TB short treatment regimen (i.e. bedaquiline) at 12 Programmatic Management of Drug-resistant TB (PMDT) sites in Pakistan.

To minimize the risk of contamination between research participants, the unit of randomization is a PMDT site. PMDT sites are randomized before recruitment of research participants into the intervention or control arm using permuted block randomization method by an independent statistician, on a 1:1 allocation ratio. SAS PROC PLAN is used to generate the randomization code.

Treatment arm: new all-oral treatment regimen:

2 months of linezolid + bedaquiline + levofloxacin\* + clofazimine + pyrazinamide + ethambutol + isoniazid (high dose) followed by 4 months of bedaquiline + levofloxacin\* + clofazimine + pyrazinamide + ethambutol + isoniazid (high dose) followed by 3 months of levofloxacin\* + clofazimine + pyrazinamide + ethambutol

Comparator arm: standard all-oral treatment regimen (currently being implemented in the country):

6 months of bedaquiline + levofloxacin\* + clofazimine + ethionamide + pyrazinamide, ethambutol + isoniazid (high dose) followed by 5 months of levofloxacin\* + clofazimine + pyrazinamide + ethambutol

\*: If levofloxacin resistance found on LPA2 (line probe assay); then substitute with moxifloxacin (if found sensitive)

The total duration of treatment is 11 months and the duration of follow-up is 12 months after completion of treatment.

## **Intervention Type**

Drug

## **Phase**

Phase II/III

## **Drug/device/biological/vaccine name(s)**

Linezolid, bedaquiline, levofloxacin, clofazimine, pyrazinamide, ethambutol, isoniazid, ethionamide, moxifloxacin

## **Primary outcome measure**

1. Treatment effectiveness: the proportion of MDR-TB patients who have a favorable treatment outcome. This is defined as 'cured' or 'treatment completed' without recurrence during 12 months after successful treatment.
2. Treatment safety: the proportion of MDR-TB patients included in the study with serious adverse events occurring during treatment and up to 12 months after the end of the treatment.

## **Secondary outcome measures**

1. The proportion of MDR-TB patients who died while on treatment, recorded using DR-TB 01 patient data collection form, during 11 months of treatment
2. The proportion of MDR-TB patients who had a treatment failure, recorded using DR-TB 01 patient data collection form, at 12 months after successful treatment
3. The proportion of MDR-TB patients who had a recurrent episode of MDR-TB, recorded using DR-TB 01 patient data collection form, at 12 months after successful treatment
4. The proportion of MDR-TB patients who are "cured without permanent disability", recorded using DR-TB 01 patient data collection form, at 12 months after successful treatment
5. The proportion of MDR-TB patients who complete at least 90% of doses (intake adherence,

- recorded using DR-TB 01 patient data collection form, during 11 months of treatment
6. The average number of adverse events of interest experienced by MDR-TB patients, recorded using DR-TB 01 patient data collection form, during 11 months of treatment
7. The proportion of MDR-TB patients experiencing each adverse event of interest, recorded using DR-TB 01 patient data collection form, during 11 months of treatment
8. The proportion of MDR-TB patients who experience serious adverse drug reactions, recorded using DR-TB 01 patient data collection form, during 11 months of treatment
9. Health-related quality of life measured using EQ-5DL at baseline, at treatment completion, 4 months of treatment intake, at treatment completion and 12 months after treatment completion
10. Feasibility assessed using mixed-method indicators at treatment completion

**Overall study start date**

10/01/2020

**Completion date**

21/06/2024

## Eligibility

**Key inclusion criteria**

The study population includes TB patients with evidence of resistance to at least rifampicin by rapid molecular drug-susceptibility testing (DST).

1.  $\geq 15$  years of age; 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)
2. Has bacteriologically or molecularly confirmed TB with evidence of resistance to at least rifampicin
3. Has no resistance to fluoroquinolones; no known previous exposure (of  $> 1$  month) or intolerance to one or more second-line drugs in the shorter MDR-TB regimen

**Participant type(s)**

Patient

**Age group**

Mixed

**Sex**

Both

**Target number of participants**

300 patients will be required in each arm (a total of 600 patients)

**Key exclusion criteria**

1. DST showing infection with a strain resistant to fluoroquinolones (or DST results not available)
2. Previous exposure to or intolerance to second-line anti-TB drugs in the intended shorter MDR-TB regimen for more than 1 month
3. Pulmonary TB that is clinically severe, or advanced (i.e. parenchymal lesions) or disseminated
4. Unable to take oral medication, or to attend or comply with treatment or follow-up schedule

5. Taking medication contraindicated with the medicines in the RR/MDRTB regimen
6. Known insufficient function of heart (QTcF >500 ms), liver (ALT/AST >5x UNL), or kidneys (creatinine >2x UNL or creatinine clearance <50 ml/min)

**Date of first enrolment**

30/07/2020

**Date of final enrolment**

30/01/2023

## Locations

**Countries of recruitment**

Pakistan

**Study participating centre****Association for Social Development**

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## Sponsor information

**Organisation**

World Health Organization

**Sponsor details**

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**Sponsor type**

Other

**Website**

[https://www.who.int/tdr/research/tb\\_hiv/shorrt/en/](https://www.who.int/tdr/research/tb_hiv/shorrt/en/)

**ROR**

<https://ror.org/01f80g185>

# Funder(s)

## Funder type

Other

## Funder Name

World Health Organization

## Alternative Name(s)

, , Всемирная организация здравоохранения, Organisation mondiale de la Santé, Organización Mundial de la Salud, WHO, , ВОЗ, OMS

## Funding Body Type

Private sector organisation

## Funding Body Subtype

International organizations

## Location

Switzerland

# Results and Publications

## Publication and dissemination plan

1. Planned publication of the study protocol
2. The researchers intend to disseminate the results of the study in high-impact peer-reviewed journals by June 2025

## Intention to publish date

30/06/2025

## Individual participant data (IPD) sharing plan

The co-investigator of the study, Ms Nida Khan, can be contacted regarding any information about the study data (nidakhan@asd.com.pk, nidakhaneco@gmail.com).

## IPD sharing plan summary

Available on request

## Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Protocol article</a>		07/05/2025	08/05/2025	Yes	No