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Non-inferiority stepped wedge cluster randomized controlled trial on all-oral shorter regimens for rifampicin resistant/ multidrug-resistant TB in Pakistan – a study protocol

Nida Khan[1*], Muhammad Ahmar Khan[1], Naila Muzaffar[1], Ahmad Ismail[1], Abdul Ghafoor[2], Jonathon R. Campbell[3,4,5], Gwenaelle Le Coroller[6], Zia Un Nisa[1], Corinne Simone Merle[7] and Muhammad Amir Khan[1]

Abstract

Introduction Pakistan has one of the largest burdens of rifampicin-resistant/ multidrug-resistant TB according to the global estimates. Novel all oral treatment regimens containing new antibiotics with reduced treatment duration are available. World Health Organization guidelines recommend the use of shorter all-oral regimens under operational research. To guide recommendations, we will compare two all-oral, short (≤ 11 months) regimens for the outcomes of efficacy, safety, cost, and health-related quality of life under programmatic conditions in Pakistan.

Methods This is a stepped wedge, cluster randomized controlled trial with economic evaluation and health related quality of life sub-studies. Modified all-oral 9-month regimen will be sequentially rolled-out compared with the standard all-oral 11-month regimen at 12 sites in Punjab, Islamabad and Azad Jammu and Kashmir region, Pakistan. A total of 400 eligible participants will be enrolled in both study arms. The primary outcome is difference in efficacy as measured by the proportion of patients with treatment success without recurrence at 12 months after the end of treatment between regimens using a non-inferiority design with a margin of 12%. The intention to treat analysis principle will be employed and a marginal mean model with Poisson generalized estimation equations, and a log-link will be used to assess the relative risk. The economic evaluation will be carried out from the healthcare providers perspective; linear mixed models will be used to estimate differences in costs between arms. Health related quality of life will be measured with the EQ-5D-3L quality of life questionnaire at four time points during the study period. The impact will be assessed by calculating the changes for each participant between time points. Ethical approval for this study has been obtained from national bioethics committee, Pakistan (Ref: No.4–87/NBC-491/20/48).

Discussion The study's findings will be disseminated to physicians, program implementers, scientific audiences, and policymakers on both a national and international level via reports, presentations, and scientific publications.

*Correspondence:
Nida Khan
nidakhan@asd.com.pk
Full list of author information is available at the end of the article

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Keywords Rifampicin-resistant/multidrug-resistant TB, Stepped wedge, Cluster randomized controlled trial, Non-inferiority, Health related quality of life, All-oral, Short regimen, Economic evaluation, Treatment efficacy, Safety

Background and rationale

The World Health Organization (WHO) END TB goals, established in 2015, envision reductions of 90% and 95% in tuberculosis (TB) incidence and deaths, respectively, by the year 2035 [1]. Yet global trajectories remain off track, and TB remains a leading cause of global mortality, and over 10 million people fall ill with TB disease each year, more than 500,000 of whom are infected with TB strains resistant to rifampicin (i.e., rifampicin-resistant TB [RR-TB]) [2]. RR-TB is characterized by resistance to only rifampicin, whereas when resistance extends to at least both rifampicin and isoniazid, TB is categorized as multidrug-resistant TB (MDR-TB) [3]; as treatment for both RR-TB and MDR-TB are typically the same, they are commonly referred to synonymously (i.e., RR/MDR-TB). Global data from 2019 identified China, India, and Pakistan as the top three countries with highest burden of RR/MDR-TB [4], with an estimated 15,000 people with RR/MDR-TB in Pakistan alone [5].

RR/MDR-TB poses a significant public health challenge, as individuals are infected with strains resistant to the two strongest anti-TB drugs and are hence left with treatment options which are usually of prolonged duration, less effective, costly, and produce a range of side effects, thus making it even more difficult to combat the disease [6]. Historically RR/MDR-TB was treated with a combination of oral and injectable drugs for a minimum of eighteen months, making it physically and psychologically burdensome for most individuals. These long treatment regimens had poor treatment outcomes with less than 60% success rate and high mortality, and loss to follow-up rates. Additionally, studies report that approximately one-third of the RR/MDR-TB patients either die or experience a recurrent disease episode when followed up within 2 to 6 years of initial diagnosis [7, 8].

Efforts have been made globally to introduce novel all oral treatment regimens containing new antibiotics such as linezolid and bedaquiline with reduced treatment duration ranging from 6 to 12 months [9] and more efficacy [10, 11]. In 2019, WHO revised its guidelines and recommended the use of shorter all-oral bedaquiline containing regimen for the treatment of RR/MDR-TB with a certain eligibility criterion. Subsequently, modified versions of all-oral shorter regimen were suggested under operational research conditions to generate evidence on effectiveness, safety, acceptability, feasibility, and cost implications through the ShORRT (Short, all-Oral Regimens for Rifampicin-Resistant Tuberculosis) research package [12].

In Pakistan, the National TB Program (NTP) established PMDT (Programmatic Management of Drug-Resistant Tuberculosis) sites in 2010 to manage the burden and spread of drug-resistant TB (DR-TB). These sites are funded by the GFTAM (Global Fund to Fight AIDS, Tuberculosis and Malaria) and WHO and are operated by the private partners who work in close collaboration with the national and provincial TB programs. The Association for Social Development (ASD) is responsible for the implementation and monitoring of the PMDT sites in Punjab province which bears 51% of the total RR/MDR-TB case load in the country. These PMDT sites offer core clinical and diagnostic services as well as DR-TB drugs free of cost. Since the initiation of PMDT sites, the NTP has been adopting novel strategies for the treatment of RR/MDR-TB [13]. Considering WHO findings and recommendations in support of RR/MDR-TB treatment shortening with regimens containing bedaquiline, the NTP issued an advisory in 2020 for all PMDT sites to start implementing an 11-month all-oral, bedaquiline-containing RR/MDR-TB regimen —substantially shorter than the previous 18-month standard of care regimen.

Since 2020, several other iterations of short RR/MDR-TB regimens emerged. Thus, to guide recommendations on use of these regimens, we adapted the ShORRT research package to compare two all-oral, short (≤ 11 months) regimens for the outcomes of non-inferiority, safety, cost, and health-related quality of life under programmatic conditions in Pakistan. This study protocol follows the SPIRIT guidelines [14].

Primary objective

To compare the efficacy of modified all-oral 9-month regimen against the standard all-oral 11-month regimen for the treatment of RR/MDR-TB.

Secondary objectives

To compare 1) the proportion of deaths and treatment failure during treatment, 2) recurrent TB episode and cure without permanent disability within one year post treatment, 3) treatment adherence, 4) proportion of patients with adverse effects and serious adverse

effects, 5) impact on health related quality of life and 6) cost implications of modified all-oral 9-month regimen against the standard all-oral 11-month regimen for the treatment of RR/MDR-TB.

Study design

A cluster randomized non-inferiority trial with stepped wedge recruitment design.

Methods

Study setting and population

This study will be conducted at 12 PMDT sites in Punjab, Islamabad and Azad Jammu and Kashmir region, Pakistan. Each PMDT site has a designated staff of eight members to provide treatment to RR/MDR-TB patients. The staff includes a physician, pharmacist, directly observed treatment facilitator/case management person, social support person, treatment coordinator, lab attendant, psychologist, and program data assistant.

Each person being treated for RR/MDR-TB, along with their treatment supporter, visits the PMDT site on monthly basis, to: a) be medically assessed; and b) receive TB medications (one-month supply) and social support (cash allowance). The inclusion and exclusion criteria for study participants is given in Table 1.

Eligible, consented individuals will be offered the standard of care regimen or intervention regimen (as per stepped-wedge design) for 11 or 9 months, respectively, and will be followed for 12 months after the successful completion of treatment. People who decline participation in the study or are not eligible will be referred for standard of care treatment with no negative consequences. The study timetable (Table 2) details the investigations and observations to conduct at each visit.

Sample size

The number of participants to be included in this study has been estimated based on surveillance data from the NTP, specifically the number of people with bacteriologically confirmed RR/MDR-TB.

The sample size was calculated using the stepped wedge cluster level power calculations in STATA (statistical software package). A sample of 400 RR/MDR-TB patients (i.e. 200 in each arm) will be required for a non-inferiority margin of 12% on the primary outcome of treatment success without recurrence at 12 months after the end of treatment while maintaining 80% power and type I error rate of 5%. The average number of RR/MDR-TB patients in the clusters will be 20 and will be included in the trial in four steps excluding baseline. Once the required sample size is completed, the national program will determine the preference between the two options for routine care (as both the options are WHO recommended).

Interventions

The regimens under investigation are 11 month and 9 month long all-oral shorter regimens. At the time of study design, the 11-month all-oral regimen was the standard of care for treating (fluoroquinolone-sensitive) DR-TB patients in Pakistan. The modified 9-month regimen was the alternate comparable all oral shorter treatment option. Both the regimens under investigation are adapted from the WHO recommended dose of drugs [15], Table 3.

Intervention care

The intervention care is the modified all-oral shorter regimen for the duration of 9 months.

2 Lzd-Bdq-Lfx -Cfz-Z-E–H(high dose)/4 Bdq- Lfx -Cfz-Z-E–H(high dose)/3 Lfx -Cfz-Z-E

Standard of care

The standard of care is the all-oral shorter regimen for the duration of 11 months.

6 Bdq- Lfx -Cfz-Eto-Z-E–H(high dose)/5 Lfx-Cfz-Z-E

Table 1 Inclusion and exclusion criteria of study participants

Inclusion criteria	Exclusion criteria
15 or more years of age	Fluoroquinolone resistance
Willingness and ability to give informed consent to be enrolled in the research study and for follow- up (signed or witnessed consent if the patient is illiterate)	Unable to take oral medication
Bacteriologically or molecularly confirmed TB with evidence of resistance to at least rifampicin	Known allergy to any of the drugs in the study regimen
	QT interval with Fredericia correction (QTcF) interval of ≥ 500 ms at the time of registration that does not correct with medical management
	Requires medications for other health conditions contraindicated with the medicines in the study regimen

Table 2 Schedule of examinations during treatment and follow-up phases of the study

	Investigation/Observation	Baseline assessment & screening	Treatment Phase (M = Month)									Post-treatment Follow-Up	
			MT 1	MT 2	MT 3	MT 4	MT 5	MT 6	MT 7	MT 8	MT 9/11	MF 6	MF 12
Clinical evaluation	Demographics, Medical History	X											
	Written informed consent	X											
	Clinical Examination	X	X	X	X	X	X	X	X	X	X	X	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	X	X	X	X	.X	X	X	X	X	X	X
Y	Sputum culture	X	X	X	X	X	X	X	X	X	X	X	X
	DST (FQ)	X											
Laboratory tests	Hemoglobin/platelets count/White blood count	X	X	X	X	X	X	X	X	X	X		
	Serum liver enzymes	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											
	Pregnancy test (female)	X											
	HIV testing	X											
Other	ECG	X	X**β**	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)		
	Chest X-ray	X											
	Disability assessment	X									X		X
	Health Related Quality of Life assessment	X				X					X		X

βBaseline ECG should be obtained and additional ECGs conducted at week 1 and 2 after starting treatment and thereafter monthly throughout treatment

Table 3 Daily drug dosage by patient weight (above 14 years old)

Drug	Weight-based daily dose	Formulation	30–35 kg	36–45 kg	46–55 kg	56–70 kg	> 70 kg	Usual upper daily dose
Bedaquiline		100 mg tab	4 tabs od first two weeks, then 2 tabs od M/W/F for 22 weeks					400 mg
Levofloxacin		250 mg tab	3	3	4	4	4	1.5 g
		500 mg tab	1.5	1.5	2	2	2	1.5 g
		750 mg tab	1	1	1.5	1.5	1.5	1.5 g
Ethionamide	15–20 mg/kg	250 mg tab	2	2	3	3	4	1 g
Clofazimine		50 mg cps or tab	2	2	2	2	2	100 mg
		100 mg cps or tab	1	1	1	1	1	100 mg
Pyrazinamide	20–30 mg/kg	400 mg tab	3	4	4	4	5	
		500 mg tab	2	3	3	3	4	
Isoniazid (high dose)	10–15 mg/kg	300 mg tab	1.5	1.5	2	2	2	
Ethambutol	15–25 mg/kg	400 mg tab	2	2	3	3	3	
Linezolid		600 mg tab	< 15 years	< 15 years	1	1	1	1.2 g

Adapted from https://iris.who.int/bitstream/handle/10665/311389/9789241550529-eng.pdf

Outcomes

Primary outcome

The primary outcome of interest is:

a) Treatment efficacy: the proportion of RR/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.

Secondary outcomes

The secondary outcomes of interest include:

a) The proportion of RR/MDR-TB patients who died while on treatment.
b) The proportion of RR/MDR-TB patients who had a treatment failure.
c) The proportion of RR/MDR-TB patients who had a recurrent episode of RR/MDR-TB during the 12-month follow-up.
d) The proportion of RR/MDR-TB patients who are "cured without permanent disability" (up to one year after the end of the treatment).
e) The proportion of RR/MDR-TB patients who complete at least 90% of doses (intake adherence indicator to be included as deem feasible in the given context).
f) The average number of adverse events of interest experienced by RR/MDR-TB patients.
g) The proportion of RR/MDR-TB patients experiencing each adverse event of interest.
h) The proportion of RR/MDR-TB patients who experience serious adverse events.

Key definitions of study outcomes are given in Table 4.

Clustering

The randomization unit or cluster in this trial is PMDT site. All patients meeting the eligibility criteria at the respective PMDT site will be randomised to the same trial arm. Taking PMDT site as unit of randomization will avoid the risk of contamination.

Randomization and blinding

The study biostatistician will create the randomization sequence using STATA14.2 statistical software. The first three sites will be designated to enter the intervention after 3 months of the standard-of-care phase, the second three after 6 months, the third group after 9 months, and the last three after 12 months (Fig. 1). For the first three months of the study, all investigators will be kept blinded about the allocation sequence, allowing all sites to begin using standard-of-care without knowing when the intervention phase will begin. Then, the biostatistician will inform which three sites will be chosen randomly to begin the first phase of the intervention.

Before moving on to the intervention phase, the three study sites will go through a transition phase for one week in which the site staff will be trained on research protocols and the administration of new treatment; along with that, logistic preparations (drug procurement, etc.) will also be done. The standard-of-care will be maintained at all other study sites, and they will be blinded to the time when the intervention will begin. The study

Table 4 Definitions of study outcomes

Outcomes	Definition
Favorable 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 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
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
Conversion (to negative)	Cultureisconsideredtohaveconvertedtonegativewhentwoconsecutiveculturestaken 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 staff notes in the treatment cards, measured over the entire treatment period
Permanent disability	A combined outcome, using the modified Medical Research Council Dyspnea scale (mMRC) based on which patients with a score above 2 are considered permanently disabled in terms of their pneumological function. A score of 2 describes that the on level ground, the person walks slower than people of same age because of breathlessness, or have to stop for breath when walking at own pace on the level In addition, all serious adverse events by system organ class that are not resolved at the end of treatment, should be summarized by treatment regimen This is a measure of a programme's ability to start treatment promptly and treat patients effectively

PMDT sites	Month 1 – 3	Month 4 – 6	Month 7 – 9	Month 10 – 12	Month 13 – 15
Group-4	Standard of care	Standard of care	Standard of care	Standard of care	Intervention
Group-3	Standard of care	Standard of care	Standard of care	Intervention	Intervention
Group-2	Standard of care	Standard of care	Intervention	Intervention	Intervention
Group-1	Standard of care	Intervention	Intervention	Intervention	Intervention

Fig. 1 Transition period from control to intervention arm

design prevents blinding of the site investigators following exposure to intervention arm. When moving from the standard of care to the intervention treatment regimen, the patients who started the standard of care treatment will continue until the end of the treatment, but the newly diagnosed RR/MDR-TB patients will be treated with the intervention treatment regimen.

Discontinuation of the study regimen

In case the study regimen must be discontinued, participants will be evaluated by a clinical committee and switched to an individualized regimen, according to the national guidelines (as per the routine practice). The most common situations in which the regimen may be discontinued are included in Table 5:

Post-treatment follow-up

After completion of treatment, participants will be informed of the risk of recurrent TB disease and advised to return for clinical assessment and sputum collection (at PMDT site) at 6 and 12 months after completion of treatment or at any time after the end of the treatment if experiencing TB clinical symptoms. In case participants are unable to visit the PMDT site, a telephonic survey encompassing clinical evaluation will be conducted.

Safety monitoring and management

Participants will be screened and managed monthly by PMDT site physicians and/or pharmacists trained in the diagnosis and management of adverse events (AE). AEs severity and seriousness will be judged based on the national guidelines for AEs recording and reporting (See Annexure 1&2 for details on AEs diagnosis and management).

Data collection and analysis

The study data will be regularly retrieved from the program electronic medical records and will be reviewed by the MDR program coordinator to look for any discrepancies or protocol deviations. The analysis will be done using the intention to treat analysis principle and non-inferiority will be declared if the lower-bound of the 95% confidence interval of the difference in treatment success without recurrence at 12 months after the end of treatment between the intervention and control group is greater than −12%. Participants with no information during the 12-month follow-up will be classified as "not assessable".

Baseline characteristics of the participants will be reported by treatments and groups of sites. Frequencies and percentages will summarize the categorical variables, whereas the quantitative variables (such as the age) will be described through mean and standard deviation (SD). The Chi-square, Fisher's exact, Mann–Whitney or Kruskal–Wallis tests will be employed to detect any imbalances in baseline characteristics across regimen treatment, with a level of significance of 5%.

For the primary outcome, a marginal mean model with Poisson generalized estimation equations (GEE) [16], and a log-link will assess the relative risk (RR), by comparing the two treatment regimens. The group of sites will be considered as a cluster effect. The period will be added in the list of predictors and will be considered as a categorical variable [17]. The models will be adjusted at least on age and gender: the selection of covariables. To correct the inflated type I error rates due to the small number of clusters, the Fay and Graubard (FG) correction will be applied to the standard errors [18]. 95% confidence intervals (CI) will be displayed. The upper limit of the CI will be compared with the non-inferiority margin of 12% (i.e. a RR equal to 1.12). Different structures of the covariance matrix will be looked at and be selected with a tool developed in R [19]. The secondary outcomes will be described by treatment regimens, with frequencies and percentages for categorical variables, and with mean and SD for continuous variable. The analysis will be executed through the R software version 2023.06.1

Health economic evaluation

The non-inferiority design of the trial warrants employing a cost-minimization analysis. We will estimate the cost of administering the two regimens from the providers perspective. All costs of providing healthcare services to participants will be considered. This includes costs of medications, costs of laboratory and monitoring tests, salary costs of healthcare personnel, costs of hospitalization, and costs of managing adverse events. We will collect costs of medications at various doses and formulations from procurement records of the NTP. Costs of laboratory and monitoring tests will be as reported from participating PMDT sites. For costs of healthcare personnel, we will use nationally representative salaries and administer time estimation questionnaires to healthcare personnel at all sites for 10 consecutive days. These questionnaires ask healthcare personnel about their time spent doing specific tasks related to RR/MDR-TB care.

Table 5 Situations to discontinue study treatment regimen

Acquired resistance to any drug in the regimen: If resistance to any drug in the regimen is acquired after treatment is initiated, it may be necessary to modify, extend or discontinue the regimen.
Severe toxicity: One or more drugs may need to be suspended permanently due to severe toxicity. In such cases, the clinical committee will 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), a change in the treatment regimen might be considered. DST will be repeated, whether the regimen is changed, to inform future management decisions.

We will use the average time spent on specific tasks and annual salaries, to arrive at a dollar value for time spent on specific activities (e.g., initial or follow-up visits). Costs of per day of hospitalization will be estimated from tertiary level facilities from the WHO-CHOICE [20]. Finally, we will estimate costs of adverse event management by micro-costing per-protocol management of different grades and types of adverse events.

We will use the above costs to arrive at costs of specific activities that occur during treatment and multiply these values by the number of occurrences of each activity during treatment based on events and activities reported in case report forms for each participant. We will then sum up all costs over the course of treatment for each participant to arrive at an overall cost per participant.

We will calculate the arithmetic mean, standard deviation, and 95% confidence interval for RR/MDR-TB treatment by arm. To estimate differences in costs between arms, we will perform multivariable analysis. This analysis will use linear mixed models, with the PMDT site as the clustering variable, and will be adjusted for treatment arm, as well as demographic and clinical characteristics. Prior to regression, costs will be log-transformed as they are very likely to be skewed and this gives them better properties for regression. Resultant model estimates will be back-transformed and are interpreted as cost ratios; we will also use the NLESTIMATE function in SAS to convert these cost ratios to absolute differences. We will perform this analysis on the modified intention to treat population. We will determine if there is a significant difference in costs by treatment arm and demographic and clinical characteristics based on the estimated 95% confidence intervals in the fully adjusted model (i.e., for cost ratios if they cross 1.0, there is no significant difference). If non-inferiority is demonstrated, we will assume that the less expensive regimen is the preferred regimen from a purely economic perspective.

Health Related Quality of Life (HRQoL)

HRQoL measures the physical and functional status and social and emotional well-being of an individual. We will conduct a sub-study to assess the HRQoL of RR/MDR-TB patients receiving the two all-oral shorter RR/MDR-TB treatment regimens. The study will be conducted on all participants recruited in the trial. This assessment will adopt a longitudinal design with data collection at four-time points i.e., at enrolment, 4 months, end of treatment, and twelve months after the end of treatment. HRQoL will be assessed through the Urdu translated version of Euro quality of life questionnaire, EQ-5D-3L [21]. This instrument will be composed by a system describing five dimensions (Mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and by a visual analogue scale (EQ-VAS).

For each time point and for each treatment regimen, the EQ-VAS will be summarized by mean and standard deviation, while the dimensions will be reported in frequencies and percentages by level (no problems, some problems, and extreme problems).

The impact of the all-oral shorter treatment regimens will be assessed by calculating the changes in the EQ-VAS for each participant between time points (between baseline and 4 months, baseline and end of treatment, baseline and end of follow-up, and end of treatment and end of follow-up). The frequencies and percentages of the trajectories of participants will be displayed based on the Paretian Classification of Health Change (PCHC). For each dimension, each participant will be classified into no change/no problems, no change/any problems, better and worse, based on the measures between time points (the same as for the EQ-VAS) [22].

Ethics approval

The research protocols were submitted for approval by National Bioethics Committee, Pakistan and ethical approval for conducting this study has been received (Ref: No.4–87/NBC-491/20/48). The protection of patient confidentiality is essential, and the study will follow the principles of the 2018 Declaration of Helsinki [23].

Discussion

The proposed trial, and associated sub studies, will be conducted at 12 PMDT sites where core diagnostic, laboratory and clinical inputs, social support, and medications are being, and will continue to be, managed through the ongoing GFTAM project support.

A stepped-wedge cluster-randomized trial design was chosen for this study due to its robustness in demonstrating the effectiveness of intervention during routine implementation. Prior studies suggest that stepped wedge design is often suitable to accommodate the logistical challenges of implementing interventions at a large scale [24]. Since the WHO guidelines suggest already established efficacy of the modified treatment regimen, it is imperative not to withhold the intervention from the study participants. This study design will take care of such ethical considerations by allowing all participants to receive the intervention eventually [25]. Each cluster will be exposed to both the control and intervention care, this will contribute to increasing the statistical power of the study by making within cluster comparisons [26]. We will follow RR/MDR TB patients for 9–11 months during treatment and for one year after the successful completion of treatment, the stepped wedge cluster trial design

will additionally support the investigation of time effect (potential changes in patient outcomes, implementation factors, or contextual influences (e.g., programmatic, seasonal, or operational variations) that may occur over the course of the trial period) by introducing intervention at different time points. The data analysis, however, will require careful considerations keeping in view the complexities produced by the study design. Moreover, it will take longer to achieve the trial outcomes [27].

The current study primarily aims to evaluate the non-inferiority of an all-oral modified shorter treatment against the all-oral standard shorter treatment for RR/MDR TB patients. Previous evaluations of the standard all-oral short treatment regimen suggest promising results, with up to 80% treatment success rate. Based on WHO recommendations this study will further contribute towards generating evidence on the non-inferiority of a 9 month long modified all-oral treatment regimen. The shorter treatment length (9 months against 11 months) is not only expected to demonstrate a similar treatment success rate but will also minimize number of visits to health facility leading to better treatment adherence, reduced cost and improved quality of life of patients [28].

The primary outcome will be declared after twelve months post successful treatment completion to understand the sustained effects of treatment. We will report data on proportion of patients who remained cured, experienced relapse or re-infection and died within one year post treatment, thus will contribute to enriching data on the impact of RR/MDR TB treatment following cure [8].

Literature suggests that second line anti-TB drugs cause adverse drugs effects in greater number of patients than the first line drugs, which warrant a more closer and regular safety monitoring during the treatment span [29]. Nevertheless, data quality and reporting has been identified as a challenge during routine program setting [30]. We anticipate that during this trial we will implement stringent protocols to ensure pharmacovigilance, rigorous reporting and timely response. This will help us to generate evidence on the safety of modified regimen as well as establish improved pharmacovigilance mechanisms within TB care in the country.

The criteria of good clinical practice shall be followed rigorously to maintain the validity and integrity of trial [31]. The Trial Steering Committee (TSC) will be responsible for the direct management and monitoring of research operations and will oversee the research personnel on the ground. The study researchers have received comprehensive training on data collection, monitoring tools, and Standard Operating Procedures (SOPs) related to the protocol, ensuring that the study is conducted with the highest level of scientific and ethical rigor.

Evidence from this research will inform programmatic implementation in Pakistan and provide crucial data to the global TB community, strengthening the evidence base necessary to inform future treatment guidance. The study's findings will be disseminated to physicians, program implementers, scientific audiences, and policymakers on both a national and international level via reports, presentations, and scientific publications. Demonstrating the benefit of integrating a shorter all-oral regimen at PMDT sites will provide strong supportive evidence to accelerate the widespread implementation of this intervention across Pakistan and in similar settings.

Trial status

At the time of the manuscript submission, the intervention has been rolled out and patients are being followed-up for the primary outcome. A delay in submission of this manuscript is due to resource limitations and long-term impact of COVID-19, which necessitated redirection of efforts to keeping the trial going rather than writing a protocol for scientific publication.

Data sharing statement

The authors plan to disseminate the findings on main study outcomes in a single paper after completing data collection, cleaning and analysis. Additional scientific publication on economic evaluation is anticipated after publishing trial results.

Disclaimer

CSM is currently a staff member of the World Health Organization; the author alone is responsible for the views expressed in this publication and they do not necessarily represent the decisions, policy or views of the WHO.

Abbreviations

WHO	World health organization
TB	Tuberculosis
MDR-TB	Multidrug resistant tuberculosis
RR-TB	Rifampicin resistant tuberculosis
PMDT	Programmatic management of drug-resistant tuberculosis
NTP	National tuberculosis program
ShORRT	Short, all-oral regimens for rifampicin-resistant tuberculosis
AE	Adverse events

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-11068-1.

Supplementary Material 1.

Authors' contributions

NK designed the study, did sample size calculations, contributed to the ethics approval of study and drafted original manuscript. MAK and AI will lead the study implementation, NM contributed in the ethics approval of the study, drafted original manuscript and will be involved in study implementation and

data analysis. AG conceptualized the study and contributed to the design, development and operationalization of intervention and other care protocols. ZN will be involved in trial data analysis. CSM conceptualized the study and contributed to writing, review and editing of the manuscript. JRC contributed to writing, review and editing of the manuscript and is leading the economic evaluation and analysis. GLC contributed to writing, review and editing of the manuscript and is leading primary statistical analysis. MAK conceptualized the study and led the team in design, development and operationalization of intervention and other care protocols. All authors reviewed the manuscript.

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Data availability
This is a study protocol manuscript, not applicable.

Declarations

Ethics approval and consent to participate
The research protocols were submitted for approval by National Bioethics Committee, Pakistan and ethical approval for conducting this study was received (Ref: No.4–87/NBC-491/20/48). Protection of patient confidentiality is essential, and the study will follow the principles of the 2018 Declaration of Helsinki.
Informed written consent will be obtained from patients or a guardian in the case of minors, as defined by local legal requirements. Those who do not consent to participate in this research will receive treatment as per national guidelines.

Consent for publication
This is a study protocol, does not require consent to publish, Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Association for Social Development, Islamabad, Pakistan. [2]National TB Control Programme, Islamabad, Pakistan. [3]Department of Medicine & Department of Global and Public Health, McGill University, Montreal, Canada. [4]McGill International TB Centre, Montreal, Canada. [5]Respiratory Epidemiology and Clinical Research Unit, Centre for Outcomes Research and Evaluation, Research Institute of the McGill University Health Centre, Montreal, Canada. [6]Competence Centre for Methodology and Statistics, Department of Medical Informatics, Luxembourg Institute of Health, Strassen, Luxembourg. [7]Special Programme for Research and Training in Tropical Diseases (TDR), World Health Organization, Geneva, Switzerland.

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