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How do two all-oral regimens compare for rifampicin resistant/multidrug-resistant tuberculosis? A stepped wedge non inferiority cluster randomized trial in Pakistan

Nida Khan
nidakhan@asd.com.pk
Association for Social Development
Muhammad Ahmar Khan
Association for Social Development
Ahmad Ismail
Ministry of National Health Services Regulations and Coordination
Abdul Ghafoor
Ministry of National Health Services Regulations and Coordination
Naila Muzaffar
Association for Social Development
Saad Alam Khan
Association for Social Development
Abdul Wali Khan
Ministry of National Health Services Regulations and Coordination
Corinne Simone Merle
World Health Organization
Gwenaelle Le Coroller
Luxembourg Institute of Health
Jonathon R Campbell
Research Institute of the McGill University Health Centre
Afsheen Talat
Association for Social Development
Muhammad Ali
Association for Social Development
Muhammad Amir Khan
Association for Social Development

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Abstract

Background

Pakistan is among the countries with the highest burden of Rifampicin resistant/multidrug-resistant tuberculosis (RR/MR TB) globally. Based on WHO recommendations for all oral shorter regimens, we have compared two all oral regimens i.e., a standard 11-month bedaquiline-based regimen with a modified 9-month regimen with 2 months of linezolid instead of ethionamide for RR/MR TB, to assess their effectiveness, safety, and quality of life under programmatic conditions in Pakistan.

Method

A stepped-wedge, cluster-randomized, non-inferiority trial was conducted at ten drug-resistant tuberculosis sites in Punjab, Pakistan, and recruited participants from 30/07/2020 till 20/03/2022. Sites served as clusters, transitioning sequentially from standard to modified regimen as per predefined schedule. Eligible participants were adults aged 15 years or older with confirmed RR/MR TB. The primary outcome was the between-group difference in efficacy, defined as the proportion of participants achieving treatment success without recurrence at 12 months after treatment completion, using a prespecified non-inferiority margin of 12 percentage points. The analysis was done employing the intention to treat principles and a marginal Poisson model with generalized estimating equations and log-link was done to estimate the relative risk. Secondary outcomes included mortality, treatment failure, adverse events, and quality of life.

Result

A total of 438 patients were enrolled in the trial (i.e., 204 in intervention arm with modified regimen and 234 patients in control arm with standard regimen). Cure rates were similar between groups i.e., 73% modified versus 75% standard. Favourable outcome occurred in 77.5% of the modified group and 76.1% of the standard group; adjusted risk ratio was 1.03 (95% CI: 0.94–1.13) and adjusted risk difference was + 1.58 percentage points (95% CI: −5.78 - +8.95), meeting the non-inferiority criterion. No recurrence occurred in the modified group during follow-up. Serious adverse events occurred in 11.3% and 10.3% of participants in the modified and standard groups, respectively, with broadly comparable safety profiles. Quality of life improved substantially and similarly in both groups.

Conclusion

A modified nine-month all-oral regimen for RR/MR TB was non-inferior to the standard eleven-month regimen, with comparable safety and sustained improvement in quality of life, supporting it as a feasible option within routine tuberculosis programmes.

Trial registration

International Standard Randomised Controlled Trial Number registry, ISRCTN17334530. Registered 8 February 2021.

Background

Tuberculosis (TB) remains a major global public health challenge and is among the leading causes of death from a single infectious agent worldwide [1]. The emergence and spread of multidrug-resistant tuberculosis (MDR-TB), defined as resistance to at least rifampicin and isoniazid [2], has further complicated TB control efforts. The WHO *Global Tuberculosis Report 2024* estimates that approximately 400,000 individuals worldwide developed RR/MDR-TB in 2023 [3]. Treatment of MDR-TB can be considerably more complex, costly, and prolonged than treatment of drug-susceptible TB, and historically has been associated with poorer treatment outcomes.

Pakistan is among the countries with highest estimated burden of MDR-TB. According to the National Tuberculosis Control Programme (NTP), there were 16,000 new cases of MDR-TB in 2022 [4]. Since 2010, the NTP has been providing drug resistant TB preventive and therapeutic care through designated Programmatic Management of Drug-Resistant Tuberculosis (PMDT) sites. Funded by the Global Fund for AIDS, Tuberculosis, and Malaria (GFATM) and operationally managed by partners with collaboration and under guidance of the national and provincial TB control programs, these sites provide diagnostic and clinical care services for drug-resistant TB including free medicines and social support [5]. As an implementing partner in this initiative, The Association for Social Development (ASD) manages the implementation of drug-resistant TB care through PMDT sites in Punjab, the most populated province of the country.

Traditionally, the treatment of MDR/RR-TB involved regimens lasting up to 18–24 months and comprised of a minimum of 5 drugs including daily injectables (such as kanamycin or amikacin) based on the patient's specific drug susceptibility profile [6]. These regimens were often associated with poor adherence linked with prolonged treatment durations, frequent side effects, and substantial toxicity (including ototoxicity and nephrotoxicity). Consequently, there was substantial physical, psychological, and financial strain on patients and health systems, making them unsustainable in many programmatic settings [7].

The introduction of newer and repurposed drugs, particularly bedaquiline, has allowed the replacement of injectable agents and the shortening of treatment duration [8, 9, 10]. Evidence from clinical trials and observational studies [11, 12, 13, 14] has demonstrated that shorter, bedaquiline-containing regimens (of at least 6 months) can achieve treatment outcomes comparable to or better than longer conventional regimens while improving tolerability and reducing the burden of treatment for patients. Based on this evidence, the WHO recommended oral shorter therapies for MDR-TB, and the NTP, Pakistan initiated the implementation of bedaquiline containing all oral short regimen for MDR-TB with courses spanning 11 months in 2020.

Further research and clinical experiences with shorter therapy regimens led to reduction in the duration of therapy [15, 16, 17]. However, most evidence on these regimens has been generated in controlled clinical trial environments, and more data is needed on their effectiveness, safety, and acceptability when implemented under routine programmatic conditions. Implementation research is therefore essential to evaluate how such regimens perform within national TB programmes, where health system constraints, patient characteristics, and service delivery contexts may differ substantially from those in clinical trials.

Though, the treatment landscape for RR/MDR-TB has continued to evolve with the introduction of six-month BPaLM- and BPaL-based regimens [18, 19], implementation remains heterogeneous across settings. Alternative all-oral regimens continue to be used depending on patient eligibility, drug availability, programmatic capacity, and national treatment policies [20, 21, 22]. Evidence on alternative regimen generated under routine programme

conditions therefore remains important to inform regimen selection and implementation strategies within evolving DR-TB care models.

The Shorter Treatment Regimen Operational Research (ShORRT) [23] research package was developed to support rigorous evaluation of shorter MDR-TB treatment regimens in programmatic settings. To guide the process of adoption of alternative, shorter regimens for the Pakistan NTP, we adapted the ShORRT research package to conduct a stepped wedge trial. In collaboration with the NTP and with support from the Special Programme for Research and Training in Tropical Diseases (TDR), World Health Organization, the aim of our trial was to compare two all oral short (≤ 11 months) for RR/MDR-TB for effectiveness, safety, and health-related quality of life under programmatic conditions of Pakistan.

Methods

Study Design

This was a stepped-wedge, cluster-randomized, non-inferiority trial [24, 25] conducted to evaluate the efficacy and safety of two shorter all oral regimens: modified 9-month regimen compared with the standard 11-month regimen for the treatment RR/MDR-TB. The study recruited participants from 30/07/2020 till 20/03/2022, sequentially across clusters, with each cluster transitioning from the control to the intervention phase according to a predefined randomization schedule (Fig. 1). This randomized controlled trial was conducted and reported in accordance with the CONSORT statement [26]. The completed CONSORT checklist is provided as Supplementary file. (please insert Fig. 1 here)

Study Setting and Participants

The trial was conducted at 10 PMDT sites across Punjab. Each site comprised a multidisciplinary team including a physician, pharmacist, treatment facilitator, psychologist, lab attendant and programme data assistant.

Eligible participants were adults aged 15 years or older with bacteriologically or molecularly confirmed RR/MDR-TB, who were able and willing to provide informed consent and adhere to follow-up procedures. Key exclusion criteria included fluoroquinolone resistance, known allergy to study drugs, prolonged QTcF interval (≥ 500 ms), inability to tolerate oral medication, or concomitant medications contraindicated with the study regimens. The inclusion and exclusion criteria were established as per WHO guidelines.

Because the number of eligible cohorts was found to be 10 out of the initial 12, we recalculated the target sample size before starting the trial based on the stepped-wedge cluster-level power calculations [27]. Assuming a treatment success proportion of 85% with the control regimen [28], an absolute noninferiority margin of 12 percentage points (noninferiority boundary 73%), a two-sided type I error of 5%, an ICC of 0.0045, and a stepped-wedge design, the target was 400 participants (an average of 40 per cluster).

Due to the COVID-19 pandemic, recruitment was slower than anticipated and it took more time than originally planned to recruit the desired number of participants required at every stage of trial.

Randomization and Masking

The complete details of the randomization process are published in the study protocol [29]. Individual PMDT sites were labelled as clusters and all patients meeting the inclusion criteria at each PMDT site were treated as per the designated trial arm. Randomization was conducted by an independent biostatistician using STATA version 14.2. Although the original randomization plan was based on a three months interval, the COVID- 19 pandemic influenced the intervals for steps which were not equal for all stages [30], and the exact schedule is given in Fig. 1.

The time periods for all the steps of intervention initiation are given Fig. 1 and the exact names of sites for each group are provided in Table 1 in results section. All the sites provided standard of care during an initial baseline period which was followed by stepwise allocation. Allocation was concealed for the baseline period and before each transition, sites underwent a one-week preparation phase that included staff training and logistical setup. Patients already receiving the standard regimen continued their treatment, while newly diagnosed RR/MDR-TB patients at transitioning sites initiated the modified regimen. Due to the nature of the intervention, blinding of site investigators and participants was not possible after allocation.

Table 1
Baseline Characteristics

Variable (n, %)	Modified Treatment Arm (n = 204)	Standard Treatment Arm (n = 234)	p-value
Demographic Characteristics			
Age (years)			0.61
Mean (SD)	38.7 (16.6)	37.4 (14.8)	
Median (Q1, Q3)	35.5 (25.0, 53.0)	36.0 (25.0, 49.0)	
Age groups (years)			0.76
<15	0 (0.0%)	0 (0.0%)	
15–24	50 (24.5%)	55 (23.5%)	
25–44	81 (39.7%)	101 (43.2%)	
≥ 45	73 (35.8%)	78 (33.3%)	
Sex			0.82
Male	112 (54.9%)	131 (56.0%)	
Female	92 (45.1%)	103 (44.0%)	
Study site			< 0.001*
Sequence 1 (n = 3)			
Nishtar Hospital, Multan (Group 1)	61 (29.9%)	20 (8.5%)	
Jinnah Hospital, Lahore (Group 1)	18 (8.8%)	5 (2.1%)	
Syed Muhammad Hussain Government General cum TB Hospital, Samli, Murree (Group 1)	14 (6.9%)	10 (4.3%)	
Sequence 2 (n = 2)			
Mayo Hospital, Lahore (Group 2)	17 (8.3%)	13 (5.6%)	
District Headquarter Hospital, Sargodha (Group 2)	26 (12.7%)	35 (15.0%)	
Sequence 3 (n = 3)			
District Headquarter Hospital, Faisalabad (Group 3)	20 (9.8%)	31 (13.2%)	
Rawalpindi Leprosy Hospital, Rawalpindi (Group 3)	4 (2.0%)	11 (4.7%)	
Sheikh Zayed Hospital, Rahim Yar Khan (Group 3)	24 (11.8%)	17 (7.3%)	
Sequence 4 (n = 2)			
Bahawal Victoria Hospital, Bahawalpur (Group 4)	15 (7.4%)	31 (13.2%)	

* Statistically significant, [a] Less than 25% = 01 zone is involved, 25–49% = less than 03 zones involved

Variable (n, %)	Modified Treatment Arm (n = 204)	Standard Treatment Arm (n = 234)	p-value
Demographic Characteristics			
Allama Iqbal Memorial Teaching Hospital, Sialkot (Group 4)	5 (2.5%)	61 (26.1%)	
Study site group			< 0.001*
1	113 (55.4%)	66 (28.2%)	
2	47 (23.0%)	59 (25.2%)	
3	24 (11.8%)	17 (7.3%)	
4	20 (9.8%)	92 (39.3%)	
Clinical History and Examination			
Type of patient			0.69
New TB case	86 (42.2%)	98 (41.9%)	
Relapse	11 (5.4%)	11 (4.7%)	
Treatment after Loss to follow-up	1 (0.5%)	0 (0.0%)	
Treatment after failure	13 (6.4%)	10 (4.3%)	
Other previously treated patients (first line)	93 (45.6%)	115 (49.1%)	
History with TB drugs (first line)			NA
Positive history	118 (57.8%)	136 (58.1%)	
Negative history	86 (42.2%)	98 (41.9%)	
BMI in kg/m²			0.91
Mean (SD)	19.2 (3.7)	19.3 (4.1)	
Median (Q1, Q3)	18.5 (16.8, 20.4)	18.1 (16.6, 21.0)	
Existing neuropathy			0.001*
Yes	0 (0.0%)	0 (0.0%)	
No	187 (91.7%)	230 (98.3%)	
Unknown	17 (8.3%)	4 (1.7%)	
Pregnancy test			0.079
Negative	37 (18.1%)	58 (24.8%)	
Positive	0 (0.0%)	0 (0.0%)	
Unknown	55 (27.0%)	45 (19.2%)	

* Statistically significant, [a] Less than 25% = 01 zone is involved, 25–49% = less than 03 zones involved

Variable (n, %)	Modified Treatment Arm (n = 204)	Standard Treatment Arm (n = 234)	p-value
Demographic Characteristics			
Not applicable	112 (54.9%)	131 (56.0%)	
Hepatitis B			0.65
Negative	7 (3.4%)	10 (4.3%)	
Unknown	197 (96.6%)	224 (95.7%)	
Hepatitis C			0.65
Negative	7 (3.4%)	10 (4.3%)	
Unknown	197 (96.6%)	224 (95.7%)	
Haemoglobin (g/dL)			0.28
Mean (SD)	12.0 (1.9)	12.2 (1.9)	
Median (Q1, Q3)	12.0 (10.7, 13.2)	12.1 (10.9, 13.7)	
Missing	2.0 (1.0%)	6.0 (2.6%)	
Platelet (1000/ul)			0.10
Mean (SD)	389.1 (156.5)	362.4 (141.7)	
Median (Q1, Q3)	359.0 (274.0, 470.0)	336.0 (258.0, 438.0)	
Missing	2.0 (1.0%)	11.0 (4.7%)	
White blood count (1000/ul)			> 0.99
Mean (SD)	10.4 (5.3)	10.1 (3.9)	
Median (Q1, Q3)	9.6 (7.6, 11.9)	9.8 (7.8, 11.6)	
Missing	3.0 (1.5%)	7.0 (3.0%)	
ALT/SGPT (U/L)			< 0.001*
Mean (SD)	25.3 (14.4)	31.0 (18.4)	
Median (Q1, Q3)	23.0 (16.0, 30.0)	29.0 (21.0, 36.0)	
Missing	1.0 (0.5%)	5.0 (2.1%)	
Potassium (mmol/L)			0.52
Mean (SD)	4.2 (0.5)	4.2 (0.5)	
Median (Q1, Q3)	4.1 (3.9, 4.4)	4.1 (3.9, 4.4)	
Missing	18.0 (8.8%)	33.0 (14.1%)	

* Statistically significant, [a] Less than 25% = 01 zone is involved, 25–49% = less than 03 zones involved

Variable (n, %)	Modified Treatment Arm (n = 204)	Standard Treatment Arm (n = 234)	p-value
Demographic Characteristics			
Creatinine (mg/dL)			< 0.001*
Mean (SD)	0.7 (0.2)	0.8 (0.2)	
Median (Q1, Q3)	0.7 (0.6, 0.8)	0.8 (0.7, 0.9)	
Missing	5.0 (2.5%)	5.0 (2.1%)	
Glucose (mg/dL)			0.41
Mean (SD)	133.8 (90.2)	131.6 (81.5)	
Median (Q1, Q3)	97.0 (86.0, 118.1)	100.5 (89.0, 122.0)	
Missing	13.0 (6.4%)	20.0 (8.5%)	
Cavity			0.76
Yes	67 (32.8%)	73 (31.2%)	
No	137 (67.2%)	161 (68.8%)	
Unknown	0 (0.0%)	0 (0.0%)	
Extent of the disease [a]			0.83
A (< 25%)	61 (29.9%)	67 (28.6%)	
B (25%-49%)	143 (70.1%)	167 (71.4%)	
C (> 50%)	0 (0.0%)	0 (0.0%)	
Unknown	0 (0.0%)	0 (0.0%)	
Disability assessment			< 0.001*
Grade 0 - Breathless with strenuous exercise	34 (16.7%)	49 (20.9%)	
Grade 1 - Short breath	36 (17.6%)	71 (30.3%)	
Grade 2 - Walk slower	62 (30.4%)	54 (23.1%)	
Grade 3 - Stop for breath	43 (21.1%)	43 (18.4%)	
Grade 4 - Breathless	20 (9.8%)	17 (7.3%)	
Missing	9 (4.4%)	0 (0.0%)	
Bacteriological Evaluation			
Rifampicin sensitivity			NA

* Statistically significant, [a] Less than 25% = 01 zone is involved, 25–49% = less than 03 zones involved

Variable (n, %)	Modified Treatment Arm (n = 204)	Standard Treatment Arm (n = 234)	p-value
Demographic Characteristics			
Resistant	204 (100.0%)	234 (100.0%)	
Sensitive	0 (0.0%)	0 (0.0%)	
Unknown	0 (0.0%)	0 (0.0%)	
Fluoroquinolone sensitivity			0.017*
Sensitive	90 (44.1%)	131 (56.0%)	
Resistant	0 (0.0%)	0 (0.0%)	
Unknown	114 (55.9%)	103 (44.0%)	
Isoniazid sensitivity			0.14
Unknown	114 (55.9%)	109 (46.6%)	
Susceptible	23 (11.3%)	35 (15.0%)	
Resistant	67 (32.8%)	90 (38.5%)	
Sputum smear			0.001*
Negative	66 (32.4%)	45 (19.2%)	
Scanty	8 (3.9%)	17 (7.3%)	
1+	104 (51.0%)	124 (53.0%)	
2+	14 (6.9%)	38 (16.2%)	
3+	12 (5.9%)	10 (4.3%)	
Culture results			0.006*
Growth with Mtb complex	151 (74.0%)	159 (67.9%)	
No growth	43 (21.1%)	43 (18.4%)	
Contamination	10 (4.9%)	25 (10.7%)	
Missing	0 (0.0%)	7 (3.0%)	

* Statistically significant, [a] Less than 25% = 01 zone is involved, 25–49% = less than 03 zones involved

Interventions

All regimens were administered according to national guidelines and WHO dosing recommendations.

The control regimen (standard therapy) was an all-oral 11-month regimen comprising 6 months of bedaquiline, levofloxacin, clofazimine, ethionamide, pyrazinamide, ethambutol, and high-dose isoniazid, followed by 5 months of levofloxacin, clofazimine, pyrazinamide, and ethambutol (6 Bdq- Lfx -Cfz-Eto-Z-E–H(high dose)/5 Lfx-Cfz-Z-E).

The intervention regimen (modified therapy) was a modified all-oral 9-month regimen consisting of 2 months of linezolid, bedaquiline, levofloxacin, clofazimine, pyrazinamide, ethambutol, and high-dose isoniazid; 4 months of bedaquiline, levofloxacin, clofazimine, pyrazinamide, ethambutol, and high-dose isoniazid; and 3 months of levofloxacin, clofazimine, pyrazinamide, and ethambutol (2 Lzd-Bdq-Lfx -Cfz-Z-E–H(high dose)/4 Bdq- Lfx -Cfz-Z-E–H(high dose)/3 Lfx -Cfz-Z-E).

The exact dosage and dose schedule for all the drugs involved has been adapted from the WHO guidelines [31] and available in study protocol [29].

Procedures and Follow-Up

Monthly follow-up care was provided as per NTP defined guidelines and the details are provided in study protocol [29]. Briefly, care included clinical evaluation, culture and smear testing, along with laboratory testing for blood cell counts and serum liver enzymes.

Post-treatment follow-ups at 6 and 12 months were also conducted. For participants visiting the health facility, post-treatment assessment included clinical evaluation, smear testing, and sputum culture. The follow up rate for 6 months post treatment assessment (interim outcome) was very low (around 15% of the total). Therefore, a telephonic survey to ask about the clinical signs and symptoms was designed for the 12 months post treatment follow up (primary outcome), through deliberations with technical experts. Those who were found to have symptoms in telephonic survey were requested to visit the PMDT site for comprehensive evaluation. At PMDT sites, complete molecular assessment including Gene Xpert test and Microscopy assessment.

Outcomes

The primary outcome was treatment efficacy, defined as the proportion of patients achieving treatment success (cure or treatment completion) without recurrence at 12 months post-treatment completion.

Secondary outcomes included the proportion of patients who died or experienced treatment failure during therapy, experienced recurrence within one year post-treatment, cure without permanent disability (with disability defined as patients with a score above 2 on the modified Medical Research Council Dyspnea scale and/or serious adverse events not resolved by the end of treatment), treatment adherence (≥ 90% of prescribed doses), as well as adverse events.

Data Analysis

Statistical Analysis

Data was regularly exported from the programme-based Electronic Nominal Registration System (ENRS) and reviewed by the trial team for discrepancies, missing information, and protocol deviations. Clarifications were sought from the relevant PMDT site staff whenever required. All study data were maintained in a Research Electronic Data Capture (REDCap) repository.

All analyses were conducted according to the intention-to-treat principle. Baseline demographic, clinical, laboratory, and bacteriological characteristics were summarized using descriptive statistics. Continuous variables were presented as means with standard deviations (SD) or medians with interquartile ranges (IQR), as appropriate, while categorical variables were summarized as frequencies and percentages. Between-group comparisons were

performed using χ^2 tests, Fisher's exact tests, or Wilcoxon rank sum test, as appropriate. Statistical significance was considered $p < 0.05$.

The primary analysis compared the probability of a favorable outcome (success without recurrence) between treatment arms using a marginal mean model with Poisson generalized estimating equations (GEE) and a log-link function, accounting for clustering by groups of sites. Covariates included sex, year of enrollment, study site, age group, and baseline clinical and laboratory characteristics, including creatinine levels, sputum culture status, disability assessment, ALT/SGPT levels, case definition, body mass index, potassium levels, and baseline general health assessment. The Fay–Graubard correction was applied to standard errors to account for the small number of clusters. Treatment effects are presented as adjusted relative risks (RR) with 95% confidence intervals (CI).

Non-inferiority was tested against a margin of 12%. If the lower bound of the 95% confidence interval is greater than − 12%, non-inferiority is demonstrated. Multiple imputation by chained equations (MICE) was used to handle missing data, generating five imputed datasets. The data were imputed for the following baseline variables: serum ALT/SGPT, serum creatinine, disability assessment, serum potassium, and general health assessment scale. The presented risk ratio (RR) and risk difference (RD) were pooled across these five imputations. For the RR, the correlation structure for the model was selected by comparing several candidate structures, including independence, exchangeable, and autoregressive (AR1). For each imputed dataset, we fitted the model using all three structures and computed the sum of Poisson log-likelihoods based on the fitted values. The structure yielding the highest total log-likelihood was selected as the most appropriate for that imputation, which was independence.

Secondary treatment outcomes, including treatment completion, death, loss to follow-up, treatment failure, recurrence, adherence, and cure without permanent disability, were summarized descriptively and compared between treatment arms using frequencies and percentages.

Safety analyses included the assessment of adverse events (AEs) and serious adverse events (SAEs). Adverse events were classified according to severity grade and summarized by type, frequency, and severity within each treatment arm according to the NTP operationalized active TB drug-safety monitoring and management based on the WHO protocols [32]. The proportions of participants experiencing specific adverse events and serious adverse events were compared descriptively between groups. The relatedness of SAEs with the anti-tuberculosis treatment was established based on WHO TDR handbook for investigators [33].

Health-related quality of life (HRQoL) was assessed using the EuroQol Visual Analogue Scale (EQ-VAS) and the EuroQol five-dimension instrument (EQ-5D-3L). Changes in EQ-VAS scores over time were summarized using means and standard deviations, while changes across EQ-5D dimensions were assessed using the Paretian Classification of Health Change. Results are presented at baseline, during treatment, at treatment completion, and at 12 months following treatment completion.

All analyses were conducted using R software (version 2025.09.1).

Ethical Considerations

The trial was retrospectively registered in International Standard Randomised Controlled Trial Number registry on 8th February 2021 (Registration ID: ISRCTN17334530). Ethical approval was obtained from the National Bioethics Committee, Pakistan (Ref: No.4–87/NBC-491/20/48). Written informed consent was obtained from all participants or their legal guardians. The trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice.

Results

Participant flow and baseline characteristics

A total of 502 patients were screened, and 438 patients provided informed consent and were enrolled into the stepped-wedge trial (Fig. 1); of these, 234 received the standard 11-month regimen and 204 received the modified 9-month regimen (intention-to-treat population). The stepwise distribution of PMDT sites is given in Table 1. Loss to follow-up during treatment was low and comparable between arms (16/204, 7.8% in the shorter arm; 16/234, 6.8% in the standard arm).

Baseline demographic and clinical characteristics were broadly comparable between arms. The mean (SD) age was 38.7 (16.6) years in the modified STR arm and 37.4 (14.8) years in the standard STR arm; 54.9% of participants in the modified STR group and 56.0% in the standard STR group were male. The distribution of prior-treatment categories (new, relapse, previously treated, treatment after failure/LTFU) did not differ at statistically significant level between arms. There were statistically significant differences in individuals recruited on every site with Nishtar Hospital, Multan having the highest recruitment in modified STR arm while district headquarters hospital, Sialkot having highest recruitment for standard STR arm. The differences in recruitment were reflecting the site allocation of the stepped wedge design. The presence of comorbidities such as Hepatitis B and/or C was infrequent, with less than 5% of the patients in both arms having Hepatitis B & C.

Results from key baseline laboratory tests showed a statistically significant difference in results of sputum smear and culture testing in the bacteriological lab assessment. Low-grade positivity (1+) was the most predominant sputum smear finding across both comparison groups, accounting for over half of all samples (51.0% in modified treatment group vs. 53.0% in standard treatment arm), while the remaining smear gradings showed a higher proportion of negative cases in the modified treatment group (32.4% vs. 19.2%) and a higher rate of moderate (2+) positivity in the standard treatment group (16.2% vs. 6.9%). High-grade (3+) readings and scanty results remained low across both cohorts. When looking at the culture outcomes, the majority of specimens in both groups confirmed *Mycobacterium tuberculosis* complex growth, yielding slightly higher percentages in the modified treatment arm (74.0% vs. 67.9%). While both groups shared the exact same absolute number of negative cultures (43 samples each), the standard treatment group had a higher specimen contamination rate (10.7% vs. 4.9%). (Table 1) (please insert Table 1 here)

Treatment outcomes

Both treatment arms showed comparable efficacy. Cure rates were high in both groups—73.0% in the modified STR regimen and 75.0% in the standard STR regimen. Mortality, loss to follow-up, and treatment failure were low and similar across arms, with slightly fewer failures in the modified STR regimen (2.0% vs 3.4%). (Table 2)

Table 2
Arm-wise End of Treatment Outcomes

Efficacy of Treatment	Modified Treatment Arm (n = 204)	Standard Treatment Arm (n = 234)
Cured	149 (73%)	176 (75%)
Treatment completed	16 (7.8%)	14 (6.0%)
Died during treatment	18 (8.8%)	20 (8.5%)
Lost to follow-up during treatment	16 (7.8%)	16 (6.8%)
Treatment failure	4 (2.0%)	8 (3.4%)
Not evaluated	1 (0.5%)	0 (0%)

The adjusted treatment effectiveness analysis showed that favorable treatment outcomes were comparable in both arms, such as 77.5% (n = 158) in modified STR and 76.1% (n = 178) in standard STR. The adjusted risk ratio (aRR) for a favorable outcome with the modified STR regimen versus the standard STR regimen was 1.03 (95% CI 0.94–1.13). This aRR was pooled across five multiply imputed datasets and accounts for clustering and the selected covariance structure. The corresponding adjusted risk difference was + 1.6% (95% CI − 5.8% to + 8.9%), meeting non-inferiority within the predefined 12% margin. No recurrence or relapse occurred in the modified treatment group during follow-up. Lastly, post-treatment disability assessment showed that the proportion for individuals cured without permanent disability was also comparable in both groups (73.1% in modified treatment group and 72.7% in standard treatment group). (Table 3)

Table 3
Treatment Effectiveness Analysis (at 6 or 12 months)

Treatment Outcomes	**Modified Treatment Arm (n = 204)**	**Standard Treatment Arm (n = 234)**	**Adjusted RR [95% CI] [a]**
Favorable outcomes (in %)	76.14	77.72	1.58 [-5.78; 8.95]
Treatment outcomes:			1.031 [0.938 ; 1.133]
Favourable	158 (77.5%)	178 (76.1%)	
Unfavourable	39 (19.1%)	46 (19.7%)	
Not assessable	7 (3.4%)	10 (4.3%)	
Death	18 (8.8%)	20 (8.5%)	
Treatment failure	4 (2.0%)	8 (3.4%)	
Lost to follow-up	16 (7.8%)	16 (6.8%)	
Recurrent episode at 6/12 months	0 (0.0%)	2 (0.9%)	
Relapsed at 6/12 months [b]	0 (0.0%)	1 (0.4%)	
Treatment adherence at 6/12 months	202 (99.0%)	228 (97.4%)	
Cured without permanent disability	144 (73.1%)	160 (72.7%)	

[a] Adjusted on sex, year, study site, age group, on the baseline creatinine, baseline sputum, baseline disability assessment, baseline ALT/SGPT, baseline case definition, baseline BMI, baseline potassium, and baseline general health assessment (EQ-VAS). The reference is the standard treatment

[b] Infection with same strain of mycobacterium tuberculosis

Adverse events and safety

A total of 11.3% (n = 23) participants in the modified treatment arm and 10.3% (n = 24) in the standard treatment arm had at least one SAE. Among SAEs, the majority were deaths which constituted 78.3% (n = 18) and 83.3% (n = 20) SAE in modified and standard treatment arms, respectively. Among all SAEs, 21.7% (n = 5/23) were found as treatment related in the modified treatment group while none were treatment-related in standard treatment group. However, none of the SAEs required a change in the treatment regimen in both arms. For more details, please see Table 4.

Table 4
Treatment Safety Analysis

Variable (n, %)	Modified Treatment Arm (n = 204)	Standard Treatment Arm (n = 234)
Had at least one serious adverse event	23 (11.3%)	24 (10.3%)
Had at least one of the following serious adverse events		
Death	18 (78.3%)	20 (83.3%)
Life-threatening experience	5 (21.7%)	4 (16.7%)
Hospitalization/prolongation of hospitalization	0 (0.0%)	0 (0.0%)
Persistently/significantly disabling events	0 (0.0%)	0 (0.0%)
Congenital anomalies/birth defects	0 (0.0%)	0 (0.0%)
Other medically important events	0 (0.0%)	0 (0.0%)
Patients experiencing at least one treatment-related SAE	5 (21.7%)	0 (0.0%)
Patient requiring change of regimen	0 (0.0%)	0 (0.0%)
Among the prespecified AE of interest in both arms, depression (216, 49.3%) was the most common, followed by anxiety (n = 173, 39.5%) and anemia (n = 166, 37.9%). In contrast, leucopenia (n = 1, 0.2%) and optic neuritis (n = 31, 7.1%) were much less common. The average number of AEs experienced per patient were slightly higher in standard treatment arm (4.0 ± 2.5) as compared to modified arm (3.5 ± 2.2). In contrast, the mean number of different types of AE experienced per patient was comparable between the modified (2.7 ± 1.4) and the standard (2.9 ± 1.4) treatment arms. (Table 5)		

Table 5
Analysis of Adverse Events of Interest

Variable (n, %)	Modified Treatment Arm (n = 204)	Standard Treatment Arm (n = 234)	Total (n = 238)
Number of participants experienced AE of interest			
Anemia	101 (49.5%)	65 (27.8%)	166 (37.9%)
Thrombocytopenia	13 (6.4%)	11 (4.7%)	24 (5.5%)
Leukopenia	1 (0.5%)	0 (0.0%)	1 (0.2%)
Elevated liver enzymes	70 (34.3%)	95 (40.6%)	165 (37.7%)
QTcF prolongation	65 (31.9%)	95 (40.6%)	160 (36.5%)
Peripheral neuropathy	52 (25.5%)	83 (35.5%)	135 (30.8%)
Anxiety	82 (40.2%)	91 (38.9%)	173 (39.5%)
Depression	105 (51.5%)	111 (47.4%)	216 (49.3%)
Optic neuritis	10 (4.9%)	21 (9.0%)	31 (7.1%)
Grade of AE of interest			
Grade 1	384 (59.9%)	523 (65.5%)	907 (63.0%)
Grade 2	196 (30.6%)	243 (30.4%)	439 (30.5%)
Grade 3	56 (8.7%)	31 (3.9%)	87 (6.0%)
Grade 4	5 (0.8%)	2 (0.3%)	7 (0.5%)
Number of episodes of AE of interest/patient			
Mean (SD)	3.5 (2.2)	4.0 (2.5)	3.8 (2.4)
Median (Q1, Q3)	3.0 (2.0, 5.0)	3.0 (2.0, 5.0)	
Range (Min – Max)	1.0–11.0	1.0–14.0	
Number of Different Types of AE of intertest/ patient			
Mean (SD)	2.7 (1.4)	2.9 (1.4)	
Median (Q1, Q3)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	
Range (Min – Max)	1.0–7.0	1.0–7.0	

Table 6 shows that most AEs (93.5%) were grade 1 or 2 in both treatment groups, with comparable overall safety profiles. The majority were hematologic or hepatic in nature, with anemia of grade 3 (n = 47, 32.7%) observed more frequently in the modified regimen arm than in the standard regimen (n = 13, 12.4%). In contrast, severe peripheral neuropathy occurred only in the standard arm (n = 10, 11.0%), while none were reported in the modified regimen.

Table 6
Grade Wise Distribution of Adverse Events of Interest

Adverse Event (n, %)	Modified Treatment Arm (n = 204)	Standard Treatment Arm (n = 234)
Anemia		
Absent	0 (0.0%)	0 (0.0%)
Grade 1	55 (38.2%)	71 (67.6%)
Grade 2	42 (29.2%)	21 (20.0%)
Grade 3	42 (29.2%)	12 (11.4%)
Grade 4	5 (3.5%)	1 (1.0%)
Thrombocytopenia		
Absent	0 (0.0%)	0 (0.0%)
Grade 1	8 (47.1%)	10 (66.7%)
Grade 2	7 (41.2%)	5 (33.3%)
Grade 3	2 (11.8%)	0 (0.0%)
Grade 4	0 (0.0%)	0 (0.0%)
Leukopenia		
Absent	0 (0.0%)	0 (0.0%)
Grade 1	0 (0.0%)	0 (0.0%)
Grade 2	0 (0.0%)	0 (0.0%)
Grade 3	1 (100.0%)	0 (0.0%)
Grade 4	0 (0.0%)	0 (0.0%)
QTcF prolongation		
Absent	0 (0.0%)	0 (0.0%)
Grade 1	37 (39.4%)	87 (51.5%)
Grade 2	55 (58.5%)	78 (46.2%)
Grade 3	2 (2.1%)	4 (2.4%)
Grade 4	0 (0.0%)	0 (0.0%)
Elevated liver enzymes		
Absent	0 (0.0%)	0 (0.0%)
Grade 1	82 (82.0%)	110 (72.8%)
Grade 2	17 (17.0%)	36 (23.8%)
Grade 3	1 (1.0%)	4 (2.6%)
Grade 4	0 (0.0%)	1 (0.7%)

Adverse Event (n, %)	Modified Treatment Arm (n = 204)	Standard Treatment Arm (n = 234)
Anemia		
Peripheral neuropathy		
Absent	0 (0.0%)	0 (0.0%)
Grade 1	43 (71.7%)	63 (69.2%)
Grade 2	17 (28.3%)	18 (19.8%)
Grade 3	0 (0.0%)	10 (11.0%)
Grade 4	0 (0.0%)	0 (0.0%)
Anxiety		
Absent	0 (0.0%)	0 (0.0%)
Grade 1	69 (72.6%)	75 (71.4%)
Grade 2	20 (21.1%)	29 (27.6%)
Grade 3	6 (6.3%)	1 (1.0%)
Grade 4	0 (0.0%)	0 (0.0%)
Depression		
Absent	0 (0.0%)	0 (0.0%)
Grade 1	82 (69.5%)	90 (68.7%)
Grade 2	35 (29.7%)	41 (31.3%)
Grade 3	1 (0.8%)	0 (0.0%)
Grade 4	0 (0.0%)	0 (0.0%)

Grade 3 hepatotoxicity remained infrequent overall (1.0% in the modified vs 3.3% in the standard arm), and severe QTcF prolongation was rare and balanced between arms (≈ 2% each).

Psychological adverse events were common but predominantly mild to moderate in both treatment groups. Among the participants found with anxiety, majority were of grade 1–2 in modified (89/95, 93.7%) and standard regimen (104/105, 99.0%). Depression followed a similar pattern, with most cases being grade 1–2 (99.2% in modified (117/118) vs 100% in standard), and only a single grade 3 event recorded in the modified regimen arm. (please insert Table 6 here)

Health-related quality of life (HRQoL)

Health-related quality of life improved markedly over the course of treatment and follow-up in both regimen (Table 7).

Table 7
Health related Quality of Life (HRQoL) Analysis

HRQoL score	Modified Treatment Arm (n = 204)	Standard Treatment Arm (n = 234)
Baseline		
mean (SD)	41.7 (19.4)	46.7 (21.1)
median (Q1-Q3)	40.0 (30.0, 50.0)	45.0 (30.0, 60.0)
Missing	9 (4.4%)	0.0 (0.0%)
4 months		
mean (SD)	65.9 (14.6)	66.7 (14.3)
median (Q1-Q3)	70.0 (60.0, 75.0)	70.0 (60.0, 80.0)
Missing	34 (16.7%)	28.0 (12.0%)
End of treatment		
mean (SD)	88.3 (9.4)	85.7 (11.6)
median (Q1-Q3)	90.0 (80.0, 95.0)	90.0 (80.0, 90.0)
Missing	36 (17.6%)	43.0 (18.4%)
12 months after the end of treatment		
mean (SD)	92.8 (8.8)	93.4 (9.1)
median (Q1-Q3)	95.0 (90.0, 100.0)	95.0 (90.0, 100.0)
Missing	56 (27.5%)	67.0 (28.6%)
Difference between two periods in HRQoL score		
Baseline – 4 months		
mean (SD)	23.1 (17.4)	19.4 (18.7)
median (Q1-Q3)	20.0 (10.0, 35.0)	20.0 (10.0, 30.0)
Missing	43 (21.1%)	28.0 (12.0%)
Baseline - End of treatment		
mean (SD)	45.7 (20.9)	37.8 (21.5)
median (Q1-Q3)	45.0 (30.0, 62.5)	40.0 (20.0, 50.0)
Missing	45 (22.1%)	43.0 (18.4%)
Baseline – 12 months after the end of treatment		
mean (SD)	49.3 (21.3)	44.8 (23.6)
median (Q1-Q3)	50.0 (35.0, 70.0)	45.0 (30.0, 65.0)
Missing	63 (30.9%)	67.0 (28.6%)

HRQoL score	Modified Treatment Arm (n = 204)	Standard Treatment Arm (n = 234)
Baseline		
End of treatment – 12 months after the end of treatment		
mean (SD)	4.2 (10.9)	6.9 (14.7)
median (Q1-Q3)	0.0 (0.0, 10.0)	10.0 (0.0, 10.0)
Missing	56 (27.5%)	68.0 (29.1%)

At baseline, the mean EQ-VAS score was 41.7 ± 19.4 in the modified regimen and 46.7 ± 21.1 in the standard regimen (p-value = 0.014). Mean scores progressively improved over time, reaching 65.9 ± 14.6 and 66.7 ± 14.3 at 4 months, 88.3 ± 9.4 and 85.7 ± 11.6 at the end of treatment, and 92.8 ± 8.8 and 93.4 ± 9.1 at 12 months post-treatment for the modified and standard regimens, respectively. Median EQ-VAS values followed a similar pattern, increasing from 40–45 at baseline to 90–95 at end of treatment and follow-up, indicating substantial recovery in perceived health.

In change analysis, the mean improvement in EQ-VAS from baseline to end of treatment was + 45.7 ± 20.9 for the modified regimen and + 37.8 ± 21.5 for the standard regimen, with further gains noted by 12 months post-treatment.

Across EQ-5D-3L domains, similar trajectories were observed. Upward trends were evident across other domains, including mobility, self-care, usual activities, and anxiety/depression, with over 95% of participants in both groups reporting no problems by treatment completion. Lastly, > 95% of participants in both arms reported “no problems” in all domains at 12 months post-treatment (Table 8). (please insert Table 8 here)

Table 8
Analysis of Dimensions of EQ-5D-5L scores

Dimensions	Baseline – 4 months n (%)		Baseline - End of treatment n (%)		Baseline – 12 months after the treatment n (%)		End of treatment – 12 months after the treatment n (%)	
	Modified	**Standard**	**Modified**	**Standard**	**Modified**	**Standard**	**Modified**	**Standard**
Mobility								
No problem - No change	0 (0%)	5 (2.4%)	0 (0%)	3 (1.6%)	0 (0%)	4 (2.4%)	138 (93%)	155 (93%)
Any problem - No change	13 (8.1%)	18 (8.7%)	4 (2.5%)	5 (2.6%)	2 (1.4%)	3 (1.8%)	0 (0%)	1 (0.6%)
Better	147 (91%)	182 (88%)	153 (96%)	180 (94%)	139 (99%)	159 (95%)	5 (3.4%)	5 (3.0%)
Worse	1 (0.6%)	1 (0.5%)	2 (1.3%)	3 (1.6%)	0 (0%)	1 (0.6%)	5 (3.4%)	5 (3.0%)
Missing	43	28	45	43	63	67	56	68
Self-care								
No problem - No change	0 (0%)	9 (4.4%)	2 (1.3%)	7 (3.7%)	1 (0.7%)	6 (3.6%)	143 (97%)	160 (96%)
Any problem - No change	7 (4.3%)	16 (7.8%)	2 (1.3%)	2 (1.0%)	2 (1.4%)	2 (1.2%)	0 (0%)	0 (0%)
Better	152 (94%)	181 (88%)	155 (97%)	179 (94%)	138 (98%)	158 (95%)	2 (1.4%)	3 (1.8%)
Worse	2 (1.2%)	0 (0%)	0 (0%)	3 (1.6%)	0 (0%)	1 (0.6%)	3 (2.0%)	3 (1.8%)
Missing	43	28	45	43	63	67	56	68
Usual Activities								
No problem - No change	0 (0%)	5 (2.4%)	0 (0%)	3 (1.6%)	0 (0%)	4 (2.4%)	138 (93%)	156 (94%)
Any problem - No change	13 (8.1%)	26 (13%)	6 (3.8%)	2 (1.0%)	1 (0.7%)	1 (0.6%)	1 (0.7%)	1 (0.6%)
Better	146 (91%)	173 (84%)	153 (96%)	185 (97%)	140 (99%)	161 (96%)	5 (3.4%)	5 (3.0%)
Worse	2 (1.2%)	2 (1.0%)	0 (0%)	1 (0.5%)	0 (0%)	1 (0.6%)	4 (2.7%)	4 (2.4%)
Missing	43	28	45	43	63	67	56	68
Pain / Discomfort								

Dimensions	Baseline – 4 months n (%)		Baseline - End of treatment n (%)		Baseline – 12 months after the treatment n (%)		End of treatment – 12 months after the treatment n (%)	
	Modified	Standard	Modified	Standard	Modified	Standard	Modified	Standard
Mobility								
No problem - No change	0 (0%)	2 (1.0%)	1 (0.6%)	1 (0.5%)	0 (0%)	1 (0.6%)	134 (91%)	133 (80%)
Any problem - No change	16 (9.9%)	28 (14%)	5 (3.1%)	12 (6.3%)	1 (0.6%)	3 (1.8%)	0 (0%)	1 (0.6%)
Better	144 (89%)	176 (85%)	153 (96%)	178 (93%)	140 (99%)	162 (97%)	10 (6.8%)	20 (12%)
Worse	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	4 (2.7%)	12 (7.2%)
Missing	43	28	45	43	63	67	56	68
Anxiety/Depression								
No problem - No change	0 (0%)	5 (2.4%)	0 (0%)	4 (2.1%)	0 (0%)	4 (2.4%)	143 (97%)	154 (93%)
Any problem - No change	19 (12%)	33 (16%)	2 (1.3%)	6 (3.1%)	2 (1.4%)	1 (0.6%)	0 (0%)	0 (0%)
Better	142 (88%)	167 (81%)	157 (99%)	180 (94%)	139 (99%)	161 (96%)	3 (2.0%)	9 (5.4%)
Worse	0 (0%)	1 (0.5%)	0 (0%)	1 (0.5%)	0 (0%)	1 (0.6%)	2 (1.4%)	3 (1.8%)
Missing	43	28	45	43	63	67	56	68

Discussion

This trial evaluated the effectiveness, safety, and patient-reported outcomes of a modified all-oral 9-month regimen for RR/MDR-TB compared with the standard all-oral 11-month regimen across PMDT sites in Punjab. We found a modified all-oral 9-month regimen for RR/MDR-TB was non-inferior to the standard all-oral 11-month regimen for the outcome of treatment success without recurrence at 12 months after treatment completion. Post-treatment outcomes further supported this conclusion. No recurrence events were documented in the shorter regimen arm at either 6 or 12 months after treatment completion, aligning with international reports showing low relapse rates for newer, shorter DR-TB regimens. The overall pattern suggests that early bacteriological and clinical response observed during treatment translated into durable long-term outcomes, reinforcing the stability of the results. These findings indicate that shortening treatment duration did not compromise effectiveness and may offer practical advantages for patients and programs.

These findings should be interpreted within the context of a rapidly evolving DR-TB treatment landscape. Since the initiation of this trial, evidence supporting six-month BPaLM- and BPaL-based regimens has transformed treatment recommendations for eligible patients. Nevertheless, many programmes continue to implement a range of all-oral treatment options while transitioning to newer regimens [34, 35, 36]. The present study therefore provides evidence on the effectiveness, safety, and patient-centred outcomes of a shortened fluoroquinolone-based regimen under routine programme conditions, complementing rather than competing with the emerging evidence base for BPaLM-based treatment approaches.

To improve patient care during the trial, pharmacovigilance at PMDT sites was strengthened through operationalization of structured active TB drug safety monitoring and management protocols [37]. Mild to moderate adverse events were common in both regimens, which is expected in the treatment of RR/MDR-TB [38, 39], but severe events were relatively infrequent and did not differ meaningfully between arms. The modified regimen showed slightly higher proportions of severe anemia, while the standard regimen had more severe peripheral neuropathy—patterns that reflect differences in drug exposure and duration. Serious hepatotoxicity and significant QTcF prolongation were rare in both groups. Collectively, the safety profile of the modified shorter regimen compares favorably with global evidence from all-oral MDR-TB regimens [16, 40, 41], many of which report similar or higher toxicity burdens with longer courses [42]. Our findings suggest that a reduction in regimen duration does not result in increased harm and may reduce cumulative toxicity for some patients. In addition, reduction in duration of treatment, the cost incurred will also be reduced [43]. A detailed economic analysis based on the cost implications of this trial will be published elsewhere.

Patient-reported health status also improved substantially over the course of treatment, with both groups achieving near-normal HRQoL scores by the end of therapy and maintaining these improvements through 12-month follow-up. Gains were rapid and pronounced, reflecting relief from symptoms, functional limitations, and psychosocial stress at treatment initiation. Improvements in pain and discomfort were particularly striking, increasing from 1 percent to 93 percent in the shorter regimen and from 2 percent to 84 percent in the standard regimen. Similar improvements were observed in mobility, self-care, and daily functioning, with more than 95 percent of participants in both arms reporting no problems by treatment completion. These results mirror international evidence showing that shorter and simplified MDR-TB regimens are associated with substantial recovery in quality of life and patient-valued outcomes [44, 45]. Importantly, the shorter regimen demonstrated slightly greater early gains, possibly reflecting faster clinical recovery or lower treatment burden.

Taken together, the results show three consistent patterns: first, the shorter 9-month regimen was non-inferior in terms of treatment success and sustained post-treatment outcomes; second, safety and tolerability were comparable between groups, with differences aligning with expected drug-specific profiles; and third, improvements in patient-reported health were robust and sustained across both treatment arms. The coherence of bacteriological, clinical, safety, and HRQoL outcomes provide confidence in the overall conclusion that the shorter regimen performs at least as well as the standard regimen in real-world programmatic settings.

Several strengths enhance the reliability of these findings. The stepped-wedge cluster design ensured that all participating sites contributed data to both regimens while accounting for temporal and site-level differences. Follow-up extended 12 months beyond treatment completion, allowing meaningful evaluation of recurrence and long-term HRQoL. All analyses adjusted for clustering and potential confounders, and outcome verification used program standards consistent with national and international guidelines. The study was embedded in routine PMDT

practice, increasing external validity and demonstrating that the regimen can be feasibly delivered within existing systems.

Nonetheless, some limitations should be acknowledged. Missing HRQoL data, particularly at later follow-ups, may have introduced bias if participants lost to follow-up differed systematically in recovery. The rarity of recurrence events, while clinically reassuring, limited the precision of comparative estimates. As with most stepped-wedge designs, temporal effects may not be fully separable from intervention effects, although analytical adjustments were applied. The trial was designed and implemented before widespread programmatic adoption of BPaLM-based regimens and therefore does not provide a direct comparison with treatment strategies that currently represent the preferred option for many eligible patients. Finally, the trial focused on programmatic conditions in one province, and while Punjab accounts for a large portion of Pakistan's RR/MDR-TB burden, findings may not capture variations in other provinces or settings outside Pakistan.

The broader implications of this study extend beyond the comparison of two treatment durations. While six-month BPaLM-based regimens are increasingly becoming preferred options for eligible patients, implementation challenges, limited access to pretomanid in some settings, and patient-specific clinical considerations mean that alternative all-oral regimens remain relevant within national programmes. The findings contribute to the growing body of evidence supporting treatment shortening and provide programmatic data on the effectiveness, safety, and acceptability of a nine-month regimen that may inform policy decisions, implementation strategies, and treatment planning in settings undergoing transition toward newer DR-TB treatment approaches.

In conclusion, this trial demonstrates that a modified all-oral 9-month regimen for RR/MDR-TB is non-inferior to the standard 11-month regimen, comparable in safety, and associated with substantial and sustained improvements in patient-reported health. These findings provide important programmatic evidence for treatment shortening and should be interpreted alongside the growing evidence supporting BPaLM-based regimens within contemporary DR-TB care.

Abbreviations

AE
Adverse event
ALT/SGPT
Alanine aminotransferase / serum glutamic pyruvic transaminase
AR1
First-order autoregressive (correlation structure)
aRR
Adjusted risk ratio
ASD
The Association for Social Development
Bdq
Bedaquiline
BMI
Body mass index
BPaL
Bedaquiline, pretomanid, linezolid

BPaLM
Bedaquiline, pretomanid, linezolid, moxifloxacin
Cfz
Clofazimine
CI
Confidence interval
CONSORT
Consolidated Standards of Reporting Trials
COVID-19
Coronavirus disease 2019
DR-TB
Drug-resistant tuberculosis
E
Ethambutol
ENRS
Electronic Nominal Registration System
EQ-5D-3L
EuroQol five-dimension, three-level instrument
EQ-VAS
EuroQol Visual Analogue Scale
Eto
Ethionamide
GEE
Generalized estimating equations
GFATM
Global Fund to Fight AIDS, Tuberculosis and Malaria
H
Isoniazid (high dose)
HRQoL
Health-related quality of life
ICC
Intracluster (intraclass) correlation coefficient
IQR
Interquartile range
ISRCTN
International Standard Randomised Controlled Trial Number
Lfx
Levofloxacin
LTFU
Lost to follow-up
Lzd
Linezolid
MDR-TB
Multidrug-resistant tuberculosis

MICE
Multiple imputation by chained equations
ms
Milliseconds
n
Number of participants
NBC
National Bioethics Committee
NTP
National Tuberculosis Control Programme
PMDT
Programmatic Management of Drug-Resistant Tuberculosis
Q1, Q3
First quartile, third quartile
QTcF
QT interval corrected by Fridericia's formula
RD
Risk difference
REDCap
Research Electronic Data Capture
RR
Relative risk / risk ratio
RR/MDR-TB
Rifampicin-resistant/multidrug-resistant tuberculosis
SAE
Serious adverse event
SD
Standard deviation
ShORRT
Shorter Treatment Regimen Operational Research
STR
Short treatment regimen
TB
Tuberculosis
TDR
Special Programme for Research and Training in Tropical Diseases
WHO
World Health Organization
Z
Pyrazinamide

Declarations

Trial registration

International Standard Randomised Controlled Trial Number registry, ISRCTN17334530. Registered 8 February 2021.

Disclaimer

CSM is 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.

Ethics approval and consent to participate:

The study protocol was submitted to the National Bioethics Committee, Pakistan, and ethical approval was obtained (Ref: No. 4-87/NBC-491/20/48). The trial was conducted in accordance with the principles of the 2018 Declaration of Helsinki, and patient confidentiality was protected throughout. Written informed consent was obtained from all participants, or from a legal guardian in the case of minors, as defined by local legal requirements. Patients who did not consent to participate received treatment according to national guidelines.

Consent for publication:

Not applicable. This manuscript does not contain any individual person's data in any form (including individual details, images or videos).

Availability of data and materials:

The dataset is uploaded as supplementary file.

Competing Interests:

The authors declare no competing interests.

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Authors' contributions:

- NK designed the study, did sample size calculations, contributed to the ethics approval of study and drafted original manuscript
- MK and AI led the study implementation
- AG conceptualized the study and contributed to the design, development and operationalization of intervention and other care protocols
- NM contributed to the ethics approval of the study and was involved in study implementation and data analysis
- SAK contributed to drafting of manuscript and data analysis
- AWK provided programmatic oversight, inputs and troubleshooting during implementation

- CSM conceptualized the study and contributed to review and editing of the manuscript
- JRC contributed to review and editing of the manuscript and is leading the economic evaluation and analysis
- GLC led primary statistical analysis and contributed to review and editing of the manuscript
- AT and MA contributed to data management
- 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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Figures



Figure 1

Consort diagram [a]

Legend: [a] (Blue colour represents transition to modified treatment regimen

Supplementary Files

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- Dataset.xlsx
- Consortchecklistv3.docx