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# BMJ Open

## Randomized trial to Evaluate the Effectiveness and Safety of Varying Doses of Linezolid with Bedaquiline and Pretomanid in Adults with Pre-Extensively Drug-Resistant or Treatment Intolerant/Non-responsive Multidrug-Resistant Pulmonary Tuberculosis: Study protocol

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Manuscripts

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3 **Randomized trial to Evaluate the Effectiveness and Safety of Varying Doses of**  
4 **Linezolid with Bedaquiline and Pretomanid in Adults with Pre-Extensively Drug-**  
5 **Resistant or Treatment Intolerant/Non-responsive Multidrug-Resistant Pulmonary**  
6 **Tuberculosis: Study protocol**  
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## Abstract

**Introduction:** Drug-resistant tuberculosis (DR-TB) is a global public health problem, where patients suffer for months if undiagnosed or treated inadequately, transmitting DR-TB in the community before succumbing to the disease. Early diagnosis, prompt treatment initiation and completion play a major role in treatment success. However, longer regimens with injectable result in poor treatment adherence and outcomes. Our objective is to evaluate the effectiveness, safety, and tolerability of various doses and duration of Linezolid (Lzd) in combination with Bedaquiline (Bdq) and Pretomanid (Pa) after 26 weeks of treatment in adults with Pre-Extensively Drug-Resistant (Pre-XDR) OR Treatment Intolerant / Non-responsive multidrug-resistant (MDR<sub>TI/NR</sub>) Pulmonary Tuberculosis.

**Methods and analysis:** A multicentric, randomized pragmatic clinical trial in India will enroll participants to one of the three arms - Control arm (Arm 1): Bdq, Pa, and Lzd 600mg daily for 26 weeks OR Intervention arms (Arm 2): Bdq, Pa and Lzd 600mg for 9 weeks followed by 300mg for 17 weeks OR Arm 3: Bdq, Pa and Lzd 600mg for 13 weeks followed by 300mg for 13 weeks. The primary endpoint is the proportion of patients with favourable outcomes in terms of sustained cure and treatment completion while the secondary endpoint is unfavourable outcomes including deaths, treatment failure, and loss to follow-up. Safety and tolerability of the various Lzd combinations and TB recurrence will be recorded till 48-weeks post-treatment.

**Ethics and dissemination:** The study has been approved by the Ethics committees of participating institutes. The trial results will help in establishing evidence towards a safe and effective dose of Lzd that can be used in a fully, all-oral short course regimen for highly DR-TB patients. The results of this study will be shared with the National TB Elimination Programme of

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3 the country, and World Health Organization guidelines development group through publications,  
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5 and dissemination meetings.  
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11 **Trial Registration:** The protocol (version 3.1 dated 20 July 2021) has been registered on the  
12 Clinical Trial Registry of India as CTRI/2021/03/032189 on 22<sup>nd</sup> March 2021 and  
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14 ClinicalTrials.gov with the identifier: NCT05040126 on 10<sup>th</sup> September 2021.  
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## 23 **Article Summary**

### 24 Strength and Limitations

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29 • Pragmatic Randomized trial design will add considerable value to the study as it will  
30 consider real-life patients under field conditions in a clinical trial thus decreasing bias and  
31 minimizing unequal distribution.  
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36 • The study results and outcomes will be more generalizable and can be easily scaled up  
37 under the Country's TB elimination program.  
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41 • The trial lacks stratification based on disease severity. This may result in the possibility  
42 of more severe cases in one group of treatment. We hope randomization should be able to  
43 cover this.  
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47 • As there is no blinding in this trial, the treating physician may be biased to assign  
48 causality of all adverse events to the drug concerned.  
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52 • The heterogeneity of data may be present as it's a planned multicentric study.  
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3 **Keywords:** Linezolid Dose, Pretomanid, Randomized trial, Treatment Intolerant, Drug-  
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5 resistant TB  
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8 **Introduction:**  
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10 World Health Organization estimates that globally in 2020, 132 222 cases of multi-drug  
11 resistant (MDR)/rifampicin-resistant tuberculosis (RR-TB) and 25 681 cases of pre-extensively –  
12 drug-resistant (pre-XDR-TB) or extensively drug-resistant (XDR-TB), totaling 157,903 cases  
13 were detected, though testing for resistance to fluoroquinolones remains much lower, at just over  
14 50% worldwide in 2020.<sup>1</sup> Of these, 150 359 people with MDR/RR-TB were enrolled on  
15 treatment in 2020, lesser than the previous years. The treatment success rate of the 2018  
16 MDR/RR-TB cohort was 59%; though improved from earlier cohorts the treatment failure, loss  
17 to follow-up and death remain high.<sup>1</sup> Also, this was not uniform across the globe – for instance,  
18 the treatment success rate was below 50% in countries like India and Indonesia due to high death  
19 and loss to follow-up. Globally the treatment success rate of highly drug-resistant TB remains  
20 unacceptably low.  
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36 With the availability of newer drugs and using patient-friendly approaches, it is now  
37 possible to design newer regimens that are less toxic, safer, and of shorter duration. The WHO  
38 consolidated treatment guidelines for drug-resistant TB recommends longer and shorter  
39 treatment regimens for MDR/RR-TB treatment.<sup>2</sup> A South African study using a combination of  
40 Bedaquiline (Bdq), Pretomaid (Pa), and Linezolid (Lzd) to treat highly drug-resistant forms of  
41 TB showed a favorable outcome of 90% at the end of 6-months of treatment.<sup>3</sup> However, the high  
42 dose of linezolid used in this study led to more than 70% of patients having adverse events to  
43 Lzd often leading to either treatment interruption or dose reduction of linezolid between two to  
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3 three months of the treatment period. Though Lzd is efficacious for drug-resistant TB, adverse  
4 events and treatment discontinuation also are found to be common.<sup>4</sup>  
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8 The multicountry ZeNIX study with consistent dosing of Bdq and Pa reported a 93%  
9 success rate with linezolid 1200 mg for 6 months and 91% with linezolid 600mg for 6 months.  
10 Adverse reactions were reported in 38% of those receiving 1200mg linezolid for 6 months and  
11 24% of those receiving 600mg of linezolid for 6 months.<sup>5</sup> Though there seemed to be a modestly  
12 greater early bactericidal effect over 14 days at the highest 1200 mg daily (NC-003 study), this  
13 dose appeared to be associated with a greater incidence of neuropathic and myelosuppressive  
14 effects than the 600 mg daily dose in the ZeNIX and NixTB trials. While a full 6 months of  
15 linezolid therapy in the regimen may give greater culture conversion and avoid relapse, the  
16 mouse model found that more than 2 months of linezolid, when combined with Bdq and Pa, does  
17 not increase relapse-free cure.<sup>6</sup> The study also found that Lzd increases the sterilizing activity of  
18 the Bdq-Pa combination; no MTB could be cultured from the lungs of mice 3 months after  
19 cessation of 3 months of treatment with this combination.  
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35 Given the above evidence, both in terms of safety and toxicity of higher dose and longer  
36 duration of Lzd and the ability of Lzd to act synergistically with the combination of Bdq and Pa,  
37 the current study is planned with a primary objective to determine the effectiveness of various  
38 doses and duration of Lzd in combination with Bdq and Pa given for 26-weeks in adults with  
39 either Pre-Extensively Drug-Resistant (Pre-XDR) OR Non-responsive / Treatment Intolerant  
40 multidrug-resistant ( $MDR_{NR/TI}$ ) pulmonary TB. Secondary objectives include  
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- 49 a) to determine the safety and tolerability of various doses and duration of Linezolid  
50 with Pretomanid and Bedaquiline following 26 weeks of therapy among adults with  
51 either Pre-XDR or  $MDR_{TI/NR}$  pulmonary TB  
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3       b) to determine the baseline resistance to the newer and repurposed drugs  
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5       c) to determine the M.tb strain mutation by whole genome sequencing in participants  
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7             with treatment failure while on treatment or recurrence of TB during the follow-up  
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9             period  
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## 12 **Methods and Analysis**

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14       Study design and oversight: Modified BPaL (mBPaL) study is a multi-center, pragmatic  
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16 randomized clinical trial under field conditions. A total of 400 adult Pre-XDR or MDRTI/NR  
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18 pulmonary TB patients meeting all study eligibility criteria will be enrolled in the study after the  
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20 screening procedure. The enrolled patients will be randomized to receive any one of the 3  
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22 regimens using block randomization. The study is supported by the United States Agency for  
23  
24 International Development (USAID), under the iDEFEAT TB Project with the Union and  
25  
26 implemented by the ICMR-National Institute of Research in Tuberculosis in collaboration with  
27  
28 the National TB Elimination Programme through its tertiary care DR-TB centers and WHO  
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30 Country Office for India. This study has been approved by the institutional ethics committee of  
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32 NIRT (NIRT-IEC ID: 2021004, 12 July 2021) and the participating sites and will begin  
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34 enrollment tentatively by 20<sup>th</sup> October 2021.  
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41       Study setting: mBPaL trial will be implemented in eight sites in India. The study sites  
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43 were selected based on the 2019 census of XDR and MDR<sub>FQ</sub> TB patients attending the DR-TB  
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45 centers in the country. The study sites include DR-TB centers at Sarvodaya Charitable Trust  
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47 Hospital and Shatabdi Centenary Hospital, Mumbai; King George's Medical College and  
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49 University, Lucknow; SN Medical College, Agra; Govt. Medical College, Surat and Bhavanagar,  
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51 Gujarat, National Institute for Tuberculosis and Respiratory Diseases, New Delhi; Rajan Babu  
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Institute of Pulmonary Medicine and Tuberculosis, New Delhi and Govt. Rajaji Medical College and Hospital, Madurai, Tamilnadu.

Study patients and eligibility: Adults between 18 to 65 years of age diagnosed with Pre-XDR-TB or as MDR<sub>TI/NR</sub> accessing TB care services in selected DR TB centers of the country.

(i) Pre-XDR-TB is defined as TB that is documented by culture positive or a molecular test positive for *M. tb* in sputum specimen collected within 3 months before screening AND documented resistance to rifamycins with or without isoniazid resistance AND, additionally resistant to at least a fluoroquinolone (FQ).<sup>7</sup>

(ii) MDR-TB<sub>TI/NR</sub> is documented by culture positive or a molecular test positive for *M. tb* in sputum specimen collected within 3 months before screening AND documented resistance to rifamycins with or without isoniazid resistance AND with documented intolerance or non-response to the current treatment regimen for 6-months or more when the participant was adherent to the treatment regimen.

Table 1 provides the detailed eligibility criteria based on which patients visiting the study sites will be screened for participation in the study

**Table 1: Study Eligibility criteria**

Inclusion Criteria	Exclusion criteria
Adults aged between 18 years – 65 years	A patient who has received more than 2 weeks of Bdq or Lzd before the first dose of the mBPAL regimen OR If the result of DST for FQ or Lzd is not available and h/o more than 2 weeks consumption of drugs used in the study regimen
Pulmonary Pre-XDR-TB patients or MDR-TB <sub>TI/NR</sub> patients	
Bodyweight of $\geq 30$ kg (in light clothing)	Intolerance or risk of toxicity from medicine in the

	treatment regimens
Provide informed written consent before all study-related procedures, including HIV testing	All forms of Extrapulmonary TB (except Lymph node TB or pleural effusion associated with Pulmonary DR-TB)
Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) < 2.5 x ULN; Total bilirubin lesser than ULN	Platelet count <1,00,000 /mm <sup>3</sup> or Haemoglobin level of < 9.0 g/dl
QTc(f) less than or equal to 450 ms at baseline	<p>QTc(f) &gt; 450 at baseline &amp; normal electrolytes, ECG to be repeated after 6 hours and if both ECGs show QTc(f) &gt;450 msec, then the patient should not be challenged with cardiotoxic drugs.</p> <p>Having risk factors for Torsade de Pointes, e.g. hypokalaemia, heart failure, history of long QT syndrome among family members</p> <p>Currently having an uncontrolled cardiac arrhythmia that requires medication</p>
Female patients should not be pregnant or should be using a birth control method	Pregnant or Lactating
	HIV infected patient with a CD4+ count of ≤ 50 cells
	Grade III or IV peripheral neuropathy Major Psychiatric illness
	Very seriously ill patients (Karnofsky scores < 50 within last 30 days)

***Recruitment process:*** Potential trial participants who visit the DR-TB centers in the selected trial sites will be approached by the study staff and explained in detail about the study in their native language. Patients willing to participate in the trial will be given a patient information sheet and also the consent form that explains all study-related procedures. After getting their consent on a written consent form, patients will be screened for study participation and the eligible participants will be enrolled within the next 14 days.

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3        Study regimen and drug dosing: The study participants will be randomized in the ratio of  
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5 1:1:1 to receive one of the mentioned treatment regimens -

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8 Arm 1: 26 wks. Bdq +Pa + Lzd (600mg)

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11 Arm 2: 9 wks. Bdq +Pa + Lzd (600mg) followed by 17 wks. Bdq +Pa+ Lzd (300mg)

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14 Arm 3: 13 wks. Bdq +Pa + Lzd (600mg) followed by 13 wks. Bdq +Pa+ Lzd (300mg)

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18        Four 100 mg tablets (400 mg) of Bedaquiline will be administered by mouth once a day  
19 for 2 weeks, followed by 200 mg (two 100 mg tablets) orally thrice a week for 24 weeks.  
20 Pretomanid will be administered as (200mg) one tablet once a day for 26 weeks In Arm 2, the  
21 Lzd dose will be reduced from 600mg to 300 mg after 9 weeks and after 13 weeks in Arm 3  
22 irrespective of the smear and culture results. All dosing of Lzd is given with the ability to  
23 interrupt or reduce the dose if needed based on Grade 3 toxicity. The continuation of the regimen  
24 beyond 26 weeks and up to 39 weeks will be based on the culture results of week 16.

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28        Randomization procedures: Computer-generated list of random numbers using REDCAP  
29 software will be used for Randomization centrally. The site physician using these computer-  
30 generated randomizations will be able to randomize the study participants to any one of the three  
31 arms in the ratio of 1:1:1. Block randomization will be used to randomize participants in the trial.  
32 NIRT statistician will assign the unique study identification number after confirming all the  
33 study-related eligibility criteria. There is no blinding in the trial.

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37        Treatment Allocation: The study participants will be randomized to receive one of the 3  
38 treatment regimens in a 1:1:1 ratio using block randomization. NIRT center will be generating  
39 the Allocation codes at the time of the inclusion of patients to the study at the recruiting sites,  
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3 using a computer-generated list of random numbers. Separate randomization lists for each site  
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5 will be prepared in advance by an independent statistician and at the time of patient's admission  
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7 to the study, the site Physician will be able to randomize them at the site on RedCAP software  
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9 based on pre-defined factors.  
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13 Treatment delivery, compliance, and retention: The study participants will be  
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15 hospitalized for two weeks wherever feasible and study drugs will be administered under  
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17 supervision. Ambulatory care can also be offered if hospitalization is not feasible. After  
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19 discharge, drugs will be supplied – weekly for the first month, then fortnightly till 3<sup>rd</sup> month, and  
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21 then monthly till the end of treatment. A health care provider or a family member will be  
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23 assigned and trained to supervise the drug intake and monitor adherence to treatment. During the  
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25 treatment phase, the patient will be reviewed every week till 16 weeks of treatment, then  
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27 monthly thereafter until the end of the treatment phase (26/39 weeks). During these visits  
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29 treatment adherence will be assessed by review of treatment card, empty pill covers, on-time  
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31 drug refill, and hospital attendance. Treatment compliance will be enhanced by offering  
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33 enhancers like nutrition supplements, reimbursing nominal costs for loss of wage, or  
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35 transportation costs. Follow-up visits will be conducted for 48 weeks after treatment.  
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42 Concomitant medication while in the trial: Any medications that are consumed while in  
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44 the trial will be entered on the concomitant medications page of the case record form. Medication  
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46 entries shall be specific to the generic name, the dose, unit, frequency, and route of  
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48 administration, the start, and the stop date, and the reason for use. Drugs prohibited to be used  
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50 during the study include aspirin or ibuprofen or drugs that can cause gastrointestinal bleeding,  
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52 any antibiotics until clinically warranted, and efavirenz-based antiretroviral therapy.  
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3 Criteria for discontinuation/withdrawal of study participants: The trial regimen may be  
4 discontinued in some patients in situations such as resistance to study drugs, intolerable or severe  
5 toxicity, and treatment failure. A patient may be withdrawn from the study for non-willingness of  
6 the patient to continue for any reason, pregnancy, drug-drug interaction, non-compliance & non-  
7 availability, drug resistance, or recommendation by the Data Safety & Monitoring Board.  
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11 Study Outcome: The primary outcome of the trial is the proportion of patients with  
12 favorable treatment outcomes, defined as sustained treatment success at 12 months post  
13 successful TB treatment, being alive & free of TB. Successful TB treatment includes Cure and  
14 Treatment Completed as defined by WHO.<sup>8</sup> The secondary outcome includes the proportion of  
15 patients with unfavorable outcomes comprising of death, bacteriological or clinical failure, and  
16 loss to follow-up. We will also record the proportion of serious adverse events occurring among  
17 patients in the study during the treatment and follow-up period.  
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21 Participant timeline: Each participant involved in the trial will have a screening period of  
22 2 weeks, followed by a treatment period of 26 weeks to 39 weeks based on sputum culture result  
23 at week 16 and a post-treatment follow-up for 12 months. Figure 1 shows the entire schedule of  
24 enrolment of a patient, the interventions to be given, and assessments to be done for a participant  
25 in the trial.  
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29 Patient and public involvement: Since the scientific problem is still not proven, patients  
30 were not involved in the research question development or the design of this study. However,  
31 learning from the difficulties faced by patients on the higher dose of Lzd there is an urgent need  
32 to find the right dose of Lzd with lower toxicity, better tolerability and at the same time not  
33 compromise on the efficacy of the regimen to prevent recurrence of TB. The study proposal is  
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discussed among the members of the Institutional Scientific advisory committee, Institutional Ethics committee, Drug Controller General of India, and Community Advisory Board. Study results will be widely disseminated through meetings, conference presentations, and publication.

Sample size assumption: mBPAL trial will evaluate the effectiveness of various doses and duration of Lzd with Bdq and Pa after 26 weeks of treatment in adults with Pre-XDR, or MDR (TI/NR) pulmonary TB patients. The efficacy of Bdq with Pa and Lzd (600 mg) for 26 weeks is reported to be about 91%.<sup>5</sup> Assuming that the effectiveness of treatment arms of Bdq + Pa with either Lzd 600mg for 9 weeks followed by 300mg for 17 weeks or Lzd 600mg for 13 weeks followed by 300mg for 13 weeks would be about the same based on the recently released interim outcomes of ZeNIX trial results, we hypothesize that these treatment arms with planned reduction of Lzd would be non-inferior to Lzd 600 mg for 26 weeks arm with a non-inferiority margin of about 10% ineffectiveness. To demonstrate this, with a power of 80% and alpha error of 5% we require about 111 patients in each arm. Factoring in a loss of 20% (due to default or migration), we require 133 patients in each arm or a total of 399 patients (approx. 400) to achieve our study objective.

Data collection, management, and interim analysis: Clinical and demographic information and laboratory reports will be collected from the individual participants in the paper case report forms and entered in Redcap software at all the participating sites. Data will be verified for accuracy and completeness. Data access would be restricted to the study statisticians at NIRT and Central TB Division. Third party access to data is restricted and will be made available only on request to NIRT. Data analysis will be done using SPSS software by statisticians at NIRT. An interim analysis is planned when at least 33% (approximately 120) of

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3 the study participants complete 26 weeks of treatment and sputum smear and MGIT culture  
4 results are available.  
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9 Study outcome analysis: The primary effectiveness analysis will be conducted using  
10 culture results from MGIT culture. Modified Intent-to-treat (mITT) analysis will be carried out to  
11 evaluate the effectiveness of the newer regimens. We will evaluate the hypothesis, that the  
12 investigational regimens are non-inferior to the standard of care regimen for the treatment of Pre-  
13 XDR-TB, MDR<sub>TI/NR</sub> in terms of favorable outcome (including sustained cure and treatment  
14 completed) and unfavorable outcome (including death, treatment failure and lost to follow-up) in  
15 the field settings. Time to culture conversion and adverse events at the end of 9 weeks and 26/39  
16 weeks will be estimated using survival analysis methods. Deaths and study withdrawals within  
17 the first 7-days of treatment and those excluded at baseline due to study drug resistance will be  
18 considered as initial exclusions and will not be included in the final mITT analysis. Per protocol  
19 analysis will be done for those patients who comply with the treatment regimen to which they  
20 were assigned as the mITT method is biased towards null hypothesis in non-inferiority trials. All  
21 participants who have consumed >80% of the drugs will be included in this analysis. Safety  
22 analysis will include data from all who received at least one dose of the study regimen.  
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42 Data and Safety Monitoring Board (DSMB): The DSMB comprises a statistician, clinical  
43 trial experts, pharmacologist, and pulmonologist. They will review data from this trial on pre-  
44 specified time points as defined in the study protocol. They will review the progress of the trial,  
45 safety issues for the trial participants in the early stages focusing majorly on grade 3 or 4 adverse  
46 events, serious adverse events, and discontinuation of treatment due to adverse events. DSMB  
47 can recommend continuing or terminating/making modifications to the trial based on the  
48 findings.  
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*Study site monitoring and quality assurance:* Study monitoring committee formed by the sponsor and other stakeholders will monitor the study data quality as per trial standard operating procedures. The monitoring plan will be followed to perform field visits and audits at various stages. The CRFs, patient records, and all source documents of the study participants in this study will be made available to be reviewed by the study monitors. To discuss the study progress and the problems incurred by the sites during the conduct of the trial, regular virtual meetings with the investigators of each study site will be conducted. Any critical protocol modifications during the conduct of the research will be informed to the Institutional Ethics Committee, CTRI, and the participants involved in the trial. At any time during or after completion of the study, the Sponsor through independent non-study staff may conduct a quality assurance assessment of the site records, and the regulatory agencies may conduct a regulatory inspection.

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*Confidentiality of trial data:* All study-related CRFs, documents related to the trial will remain in the custody of the site Principal Investigator under lock and key until transferred to archives. The records identifying the patient will be kept confidential and will not be made publicly available. All electronic data will be saved securely in password-protected systems. The final data of the study will be accessible only to the statisticians in NIRT and the Central TB division. When the results of the trial are published, the patient's identity will remain confidential. The confidentiality of the patients included in this trial will be maintained during the conduct of the study period following the Indian-GCP and the relevant regulations by the laws of India.

### 50 51 **Ethics and dissemination**

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The current ICH Good Clinical Practice and the ICMR ethical guidelines for biomedical research in human participants will be followed in the current trial. This will ensure public



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3 assurance that the well-being, safety, and rights of the participants are considered, which is  
4 consistent with the principles originating from the Helsinki Declaration and will maintain the  
5 credibility of the clinical trial data. The personal data that are necessary to analyze the safety,  
6 tolerability and antibacterial activity of the investigational product will be used. Manuscripts  
7 preparation, result dissemination and publication materials are the responsibility of the Principal  
8 investigator. After the completion of the trial, the investigators anticipate publishing the study  
9 results in peer-reviewed scientific journals, presenting the findings in meetings and sharing the  
10 results widely with the program managers and policymakers.

## 11 Discussion

12 WHO has released the Global list of High Burden Countries for MDR/RR-TB for the  
13 year 2021–2025. The list contains the top 20 countries with an estimated absolute number of  
14 incident cases and the top 10 countries with a severe burden of incident rate totaling thirty  
15 countries. As compared to 2016-2020, few countries like Ethiopia have transitioned out while  
16 countries like Nepal have been added to the list.<sup>1</sup> Average success rate of conventional XDR-TB  
17 patients put on treatment (without Bdq) from 2016 to 2018 is 29%. This has increased to 48% in  
18 2018.<sup>9</sup> Managing MDR-TB and XDR-TB remains a major challenge in the elimination of TB. It  
19 is expected that DR-TB patients treated with short regimens with newer oral drugs would have a  
20 better quality of life compared to patients on standard (either short or long) DR-TB regimens due  
21 to multiple reasons. Adherence of patients improves with injectable-free treatment and facilitates  
22 the implementation of community programs. This would reduce the costs incurred for the  
23 patients on travel to health facilities for injections, loss of wages or hospitalization expenses  
24 during the intensive phase of treatment of standard regimens. Hence, it is reasonable to assume  
25 that injectable-free treatment regimens that potentially reduce the occurrence of adverse  
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3 reactions would likely improve the overall health-related quality of life of patients. Second,  
4 BDQ-containing regimens reduce the costs per treatment success by 18–20% in short course  
5 regimens and 49–50% in long course regimens. It was estimated that approximately 61,000 more  
6 patients could be treated successfully over 5 years with Bdq containing regimens.<sup>10</sup> The success  
7 rate of DR TB patients treated under the Bdq conditional access program (Bdq-Cap) is 71%.<sup>9</sup>  
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Studies in the past have compared the outcomes of a longer oral regimen containing Bdq with the shorter oral regimen. More beneficial effects were observed in the shorter all-oral Bdq-containing regimen compared to injectable-free longer regimen containing Bdq. The favorable odds ratio of 3.9 (1.7-9.1) was observed for success versus failure/recurrence, 1.6 (1.2–2.2) for success versus all unfavorable outcomes and 0.5 (0.4-0.8) for loss to follow-up, thereby supporting the use of all-oral shorter regimen.<sup>11</sup> Also studies have evaluated the safety of the newer drugs in shorter oral regimens. In the NIXTB study, Lzd toxicity such as peripheral neuropathy and myelosuppression was reported among 81% and 48% of the study population respectively. Adverse events leading to death and serious adverse events were 9% and 30% respectively in the 600 mg twice daily Lzd group and 3% and 9% in the 1200 mg once daily Lzd group.<sup>3</sup> In ZeNIX trial peripheral neuropathy was reported in 38% of those receiving 1200mg of Lzd for six months; 24% of those receiving 1200mg of Lzd for two months; 24% of those receiving 600mg of Lzd for six months and 13% of those receiving 600mg of Lzd for two months. Similarly, anemia, secondary to linezolid exposure was noticed in 22% of those receiving 1200mg of Lzd for six months; 17% of those receiving 1200mg of Lzd for two months; 2% of those receiving 600mg of Lzd for six months and 7% in those receiving 600mg of Lzd for two months.<sup>5</sup> Modified BPAL study will determine the effectiveness in the management of DR-

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3 TB patients by comparing the varying dose of Lzd with Bdq and Pa regimens. Safety assessment  
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5 in the mBPAL study is one of the major components in measuring the outcome of the regimens.  
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9 We are proposing to conduct a pragmatic clinical trial (mBPAL study) which has varying  
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11 doses of Lzd along with Bdq and Pa as planned reduction of Lzd for the treatment of Pre-XDR  
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13 and MDR<sub>TI/NR</sub> pulmonary TB patients for 26-39 weeks. Given the poor tolerability and increased  
14  
15 frequency of dose interruption in regimens containing Lzd, this trial will help us in deciding the  
16  
17 effective dosing of Lzd to be given with Bdq and Pa for a fully oral short-course regimen to treat  
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19 highly drug-resistant TB in the field setting. The main drivers of the acceptability of BPAL  
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21 regimen were the short duration of treatment, fully oral regimen without injectables, reduced pill  
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23 burden, anticipated higher treatment success, lower financial burden for patients and the  
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25 program, reduced burden on the health system, using existing diagnostic processes and lesser  
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27 burden to TB laboratories for monitoring of bacteriological treatment. This study will create a  
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29 new standard of care for Pre-XDR and MDR<sub>TI/NR</sub>-pulmonary TB patients that will not only have  
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31 better and earlier culture conversion but also reduce the proportion of patients who do not adhere  
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33 to the full course of therapy.  
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- **Authors' contributions:** CPP, CPR & RS – conceived & designed the study / CPP, BD, CPR & BR – development and writing of the study protocol / CPP, BD, CPR, BR, MP, SM & SuM – writing and editing this manuscript
  - 
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  - **Competing interests:** None

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Figure 1. Schedule of enrolment, interventions, and assessments of a participant in the trial

COMPLETED WEEKS	-2	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	16	20	26	30	38	50	62	74
Informed Consent	X																							
Inclusion/Exclusion Criteria	X																							
Demography	X																							
Medical history	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination & vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fundus examination/color vision	X										X				X					X				
12 lead ECG [B]	X			X	X	X					X		X		X	X	X	X	X	Monthly once for 6 months				
Chest X-ray	X															X		X						
Sputum smear (1EM/1 spot)*	X					X					X				X		X	X	X		X	X	X	X
Sputum culture (LJ/MGIT) and DST for 1 <sup>st</sup> and 2 <sup>nd</sup> line drugs incl. LZD	X					X					X				X		X	X	X		X	X	X	X





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2  
3 \*Patients will give 2EM and 1Spot sputum sample at baseline

4  
5 ¥ LPA performed only if sputum results are positive

6  
7 ± DST performed at baseline (with storage of the strain at -20c), 16<sup>th</sup> week in case of positive culture and if any culture is found positive during the 48 weeks  
8 after the end of the treatment (with storage of the strain of the recurrent episode for genotyping analysis)

9  
10 ∞ Sputum isolates at baseline, at time of treatment failure and relapse will be sent to NIRT for MGIT DST to Bdq, and Pretomanid and for Whole Genome  
11 Sequencing. Isolates will also be saved at the regional labs until sub-culture results are available for any further DST required for patient management

12  
13 [B] Baseline ECG should be obtained and additional ECGs conducted daily for the first two weeks after starting treatment (if hospitalized)

14  
15 ECG should be repeated as necessary in case of clinical suspicion of heart rhythm and conduction disturbances.

16  
17 ∃ Week 9 – Linezolid dose will be modified at week 9 in arm 2

18  
19 £ Week 13 - Linezolid dose will be modified at week 13 in arm 3

20  
21 # end of treatment for patients whose 12<sup>th</sup> week cultures are negative and if 16<sup>th</sup> week cultures are not available then no clinical or radiological evidence of TB

22  
23 \$ Adverse event monitoring over phone weekly from 17<sup>th</sup> week onwards till the end of treatment (except during the days of the scheduled visit)



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	17
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13, 14

## Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5,6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6

## Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7,8
Interventions	11	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	11	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10
	11	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11

1				
2	Participant	13	Time schedule of enrolment, interventions (including	11
3	timeline		any run-ins and washouts), assessments, and visits for	
4			participants. A schematic diagram is highly	
5			recommended (see Figure)	
6				
7	Sample size	14	Estimated number of participants needed to achieve	11,12
8			study objectives and how it was determined, including	
9			clinical and statistical assumptions supporting any	
10			sample size calculations	
11				
12				
13	Recruitment	15	Strategies for achieving adequate participant	8
14			enrolment to reach target sample size	
15				

### Methods: Assignment of interventions (for controlled trials)

#### Allocation:

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21	Sequenc	16	Method of generating the allocation sequence (eg,	9
22	e	a	computer-generated random numbers), and list of any	
23	generatio		factors for stratification. To reduce predictability of a	
24	n		random sequence, details of any planned restriction	
25			(eg, blocking) should be provided in a separate	
26			document that is unavailable to those who enrol	
27			participants or assign interventions	
28				
29				
30	Allocatio	16	Mechanism of implementing the allocation sequence	9-10
31	n	b	(eg, central telephone; sequentially numbered,	
32	conceal		opaque, sealed envelopes), describing any steps to	
33	ment		conceal the sequence until interventions are assigned	
34	mechani			
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38	Impleme	16	Who will generate the allocation sequence, who will	9
39	ntation	c	enrol participants, and who will assign participants to	
40			interventions	
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42	Blinding	17	Who will be blinded after assignment to interventions	NA
43	(masking)	a	(eg, trial participants, care providers, outcome	
44			assessors, data analysts), and how	
45				
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47		17	If blinded, circumstances under which unblinding is	NA
48		b	permissible, and procedure for revealing a participant's	
49			allocated intervention during the trial	
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### Methods: Data collection, management, and analysis

1				
2	Data	18	Plans for assessment and collection of outcome,	11,12,20,21,22
3	collection	a	baseline, and other trial data, including any related	
4	methods		processes to promote data quality (eg, duplicate	
5			measurements, training of assessors) and a	
6			description of study instruments (eg, questionnaires,	
7			laboratory tests) along with their reliability and validity,	
8			if known. Reference to where data collection forms can	
9			be found, if not in the protocol	
10				
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12		18	Plans to promote participant retention and complete	10
13		b	follow-up, including list of any outcome data to be	
14			collected for participants who discontinue or deviate	
15			from intervention protocols	
16				
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18	Data	19	Plans for data entry, coding, security, and storage,	12,14
19	managemen		including any related processes to promote data	
20	t		quality (eg, double data entry; range checks for data	
21			values). Reference to where details of data	
22			management procedures can be found, if not in the	
23			protocol	
24				
25				
26	Statistical	20	Statistical methods for analysing primary and	12,13
27	methods	a	secondary outcomes. Reference to where other details	
28			of the statistical analysis plan can be found, if not in	
29			the protocol	
30				
31				
32		20	Methods for any additional analyses (eg, subgroup and	12,13
33		b	adjusted analyses)	
34				
35		20	Definition of analysis population relating to protocol	12,13
36		c	non-adherence (eg, as randomised analysis), and any	
37			statistical methods to handle missing data (eg, multiple	
38			imputation)	
39				
40				
41	<b>Methods: Monitoring</b>			
42				
43	Data	21	Composition of data monitoring committee (DMC);	13,14
44	monitoring	a	summary of its role and reporting structure; statement	
45			of whether it is independent from the sponsor and	
46			competing interests; and reference to where further	
47			details about its charter can be found, if not in the	
48			protocol. Alternatively, an explanation of why a DMC is	
49			not needed	
50				
51				
52		21	Description of any interim analyses and stopping	12,13
53		b	guidelines, including who will have access to these	
54			interim results and make the final decision to terminate	
55			the trial	
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2	Harms	22	Plans for collecting, assessing, reporting, and
3			managing solicited and spontaneously reported
4			adverse events and other unintended effects of trial
5			interventions or trial conduct
6			
7	Auditing	23	Frequency and procedures for auditing trial conduct, if
8			any, and whether the process will be independent from
9			investigators and the sponsor
10			
11			
12	<b>Ethics and dissemination</b>		
13			
14	Research	24	Plans for seeking research ethics
15	ethics		committee/institutional review board (REC/IRB)
16	approval		approval
17			
18	Protocol	25	Plans for communicating important protocol
19	amendment		modifications (eg, changes to eligibility criteria,
20	s		outcomes, analyses) to relevant parties (eg,
21			investigators, REC/IRBs, trial participants, trial
22			registries, journals, regulators)
23			
24			
25	Consent or	26	Who will obtain informed consent or assent from
26	assent	a	potential trial participants or authorised surrogates,
27			and how (see Item 32)
28			
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30		26	Additional consent provisions for collection and use of
31		b	participant data and biological specimens in ancillary
32			studies, if applicable
33			
34	Confidential	27	How personal information about potential and enrolled
35	ity		participants will be collected, shared, and maintained
36			in order to protect confidentiality before, during, and
37			after the trial
38			
39			
40	Declaration	28	Financial and other competing interests for principal
41	of interests		investigators for the overall trial and each study site
42			
43	Access to	29	Statement of who will have access to the final trial
44	data		dataset, and disclosure of contractual agreements that
45			limit such access for investigators
46			
47			
48	Ancillary	30	Provisions, if any, for ancillary and post-trial care, and
49	and post-		for compensation to those who suffer harm from trial
50	trial care		participation
51			
52	Disseminati	31	Plans for investigators and sponsor to communicate
53	on policy	a	trial results to participants, healthcare professionals,
54			the public, and other relevant groups (eg, via
55			publication, reporting in results databases, or other
56			data sharing arrangements), including any publication
57			restrictions
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2		31	Authorship eligibility guidelines and any intended use
3		b	of professional writers
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5		31	Plans, if any, for granting public access to the full
6		c	protocol, participant-level dataset, and statistical code
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## Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	✓
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	20,21,22

peer review only

# BMJ Open

## Randomized trial to Evaluate the Effectiveness and Safety of Varying Doses of Linezolid with Bedaquiline and Pretomanid in Adults with Pre-Extensively Drug-Resistant or Treatment Intolerant/Non-responsive Multidrug-Resistant Pulmonary Tuberculosis: Study protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-058606.R1
Article Type:	Protocol
Date Submitted by the Author:	12-Jul-2022
Complete List of Authors:	Padmapriyadarsini, Chandrasekaran; National Institute for Research in Tuberculosis Devaleenal, Bella; ICMR-National Institute for Research in Tuberculosis Ponnuraja, C.; ICMR-National Institute for Research in Tuberculosis Ramraj, Balaji; ICMR-National Institute for Research in Tuberculosis Singla, R; National Institute of Tuberculosis and Respiratory Diseases, Parmar, Malik; 3World Health Organization, Country Office for India, New Delhi Mattoo, Sanjay; Ministry of Health & Family Welfare Mandal, Sudarsan; Ministry of Health & Family Welfare
<b>Primary Subject Heading</b>:	Respiratory medicine
Secondary Subject Heading:	Infectious diseases
Keywords:	Thoracic medicine < INTERNAL MEDICINE, RESPIRATORY MEDICINE (see Thoracic Medicine), Respiratory infections < THORACIC MEDICINE

SCHOLARONE™  
Manuscripts



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3 **Randomized trial to Evaluate the Effectiveness and Safety of Varying Doses of**  
4 **Linezolid with Bedaquiline and Pretomanid in Adults with Pre-Extensively Drug-**  
5 **Resistant or Treatment Intolerant/Non-responsive Multidrug-Resistant Pulmonary**  
6 **Tuberculosis: Study protocol**  
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17 Rupak Singla<sup>2</sup>, Malik Parmar<sup>3</sup>, Sanjay Mattoo<sup>4</sup>, Sudarsan Mandal<sup>4</sup>  
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## Abstract

**Introduction:** Drug-resistant tuberculosis (DR-TB) is a global public health problem. Patients suffer for months if undiagnosed or treated inadequately, transmitting DR-TB in the community before succumbing to the disease. Early diagnosis, prompt treatment initiation, and completion play a significant role in treatment success. However, extended regimens with injectables result in poor treatment adherence and outcomes. Our objective is to evaluate the effectiveness, safety, and tolerability of various doses and duration of Linezolid (LZD) in combination with Bedaquiline (BDQ) and Pretomanid (Pa) after 26 weeks of treatment in adults with Pre-Extensively Drug-Resistant (Pre-XDR) OR Treatment Intolerant / Non-responsive multidrug-resistant (MDR<sub>TI/NR</sub>) Pulmonary Tuberculosis.

**Methods and analysis:** A multicentric, randomized pragmatic clinical trial in India will enroll participants in one of the three arms - Control arm (Arm 1): BDQ, Pa, and LZD 600mg daily for 26 weeks OR Intervention arms (Arm 2): BDQ, Pa and LZD 600mg for nine weeks followed by 300mg for 17 weeks OR Arm 3: BDQ, Pa and LZD 600mg for 13 weeks followed by 300mg for 13 weeks. The primary endpoint is the proportion of patients with favorable outcomes as sustained cure and treatment completion. The secondary endpoint is unfavorable outcomes, including deaths, treatment failure, toxicity/adverse events, and loss of follow-up till 48 weeks post-treatment.

**Ethics and dissemination:** The study has been approved by the Ethics committees of participating institutes and the National Institute for Research in Tuberculosis. The trial results will help establish evidence towards a safe and effective dose of LZD that can be used in a fully, all-oral short course regimen for highly DR-TB patients. The results of this study will be shared

with the National TB Elimination Programme of the country and the World Health Organization guidelines development group through publications and dissemination meetings.

**Trial Registration:** The protocol (version 3.1 dated 20<sup>th</sup> July 2021) has been registered on the Clinical Trial Registry of India as CTRI/2021/03/032189 on 22<sup>nd</sup> March 2021 and ClinicalTrials.gov with the identifier: NCT05040126 on 10<sup>th</sup> September 2021.

## Article Summary

### Strength and Limitations

- Pragmatic Randomized trial design will add considerable value to the study as it will consider real-life patients under field conditions in a clinical trial, thus decreasing bias and minimizing unequal distribution.
- The Country's TB elimination program can use the results of the study to scale up the regimen as it will be more generalizable
- The trial lacks stratification based on disease severity. This may result in the possibility of more severe cases in one group of treatment. We hope randomization should be able to cover this.
- As there is no blinding in this trial, the treating physician may be biased to assign causality of all adverse events to the drug concerned.
- Data heterogeneity may be present as it's a planned multicentric study.

**Keywords:** Linezolid Dose, Pretomanid, Randomized trial, Treatment Intolerant, Drug-resistant TB

## Introduction:

World Health Organization (WHO) estimates that globally in 2020, 132222 cases of multi-drug resistant (MDR)/rifampicin-resistant tuberculosis (RR-TB) and 25681 cases of pre-extensively –drug-resistant (pre-XDR-TB) or extensively drug-resistant (XDR-TB), totaling 157903 cases were detected. However, testing for fluoroquinolone resistance remains much lower, at just over 50% worldwide in 2020.<sup>1</sup> Of these, 150359 people with MDR/RR-TB were enrolled in treatment in 2020, less than the previous years. The treatment success rate of the 2018 MDR/RR-TB cohort was 59%; though improved from earlier cohorts, the treatment failure, loss to follow-up, and death remain high.<sup>1</sup> Also, this was not uniform across the globe – the treatment success rate was below 50% in countries like India and Indonesia due to increased death and loss-to-follow-up. Globally the treatment success rate of highly drug-resistant TB (DR-TB) remains unacceptably low.

With the availability of newer drugs and patient-friendly approaches, it is now possible to design newer regimens that are less toxic, safer, and of shorter duration. The WHO consolidated treatment guidelines for DR-TB recommend longer and shorter treatment regimens for MDR/RR-TB treatment.<sup>2</sup> A South African study using a combination of Bedaquiline (BDQ), Pretomid (Pa), and Linezolid (LZD) to treat highly DR-TB showed a favorable outcome of 90% at the end of 6-months of treatment.<sup>3</sup> However, the high dose of LZD used in this study led to more than 70% of patients having adverse events to LZD, often leading to either treatment interruption or dose reduction of LZD between two to three months of treatment. Though LZD is efficacious for DR-TB, adverse events and treatment discontinuation also are found to be expected.<sup>4</sup>

The multicountry ZenIX study with consistent dosing of BDQ and Pa reported a 93% success rate with linezolid 1200 mg for six months and 91% with linezolid 600mg for six

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3 months. Among those receiving 1200mg linezolid for six months, adverse events reported was  
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5 38%, while in those receiving 600mg of linezolid for six months, it was 24%.<sup>5</sup> Though there  
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7 seemed to be a modestly greater early bactericidal effect over 14 days at the highest 1200 mg  
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9 daily (NC-003 study), this dose appeared to be associated with a greater incidence of neuropathic  
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11 and myelosuppressive effects than the 600 mg daily dose in the ZeNIX and NixTB trials. While  
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13 a full six months of linezolid therapy in the regimen may give higher culture conversion and  
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15 avoid relapse, the mouse model found that more than two months of linezolid, combined with  
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17 BDQ and Pa, does not increase relapse-free cure.<sup>6</sup> The study also found that LZD increases the  
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19 sterilizing activity of the BDQ-Pa combination; no MTB could be cultured from the lungs of  
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21 mice three months after cessation of 3 months of treatment with this combination.  
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27 Given the above evidence, both in terms of safety and toxicity of higher dose and longer  
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29 duration of LZD and the ability of LZD to act synergistically with the combination of BDQ and  
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31 Pa, the current study is planned with a primary objective to determine the effectiveness of  
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33 various doses and duration of LZD in combination with BDQ and Pa given for 26-weeks in  
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35 adults with either Pre-Extensively Drug-Resistant (Pre-XDR) OR Non-responsive / Treatment  
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37 Intolerant multidrug-resistant (MDR<sub>NR/TI</sub>) pulmonary TB. Secondary objectives include  
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41 a) to determine the safety and tolerability of various doses and duration of Linezolid  
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43 with Pretomanid and Bedaquiline following 26 weeks of therapy among adults with  
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45 either Pre-XDR or MDR<sub>TI/NR</sub> pulmonary TB  
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47 b) to determine the baseline resistance to the newer and repurposed drugs  
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49 c) to determine the M.tb strain mutation by whole genome sequencing in participants  
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51 with treatment failure while on treatment or recurrence of TB during the follow-up  
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53 period  
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## Methods and Analysis

*Study design and oversight:* Modified BPaL (mBPaL) study is a multi-center, pragmatic randomized clinical trial under field conditions. The study will enroll 400 adults, Pre-XDR or MDR<sub>TI/NR</sub> pulmonary TB patients meeting all study eligibility criteria after the screening procedure. The enrolled patients will be randomized to receive any of the three regimens using block randomization. The study is supported by the United States Agency for International Development (USAID), under the iDEFEAT TB Project with the Union, Cooperative Agreement No. 72038620CA00007, and implemented by the ICMR-National Institute of Research in Tuberculosis (NIRT) in collaboration with the National TB Elimination Programme through its tertiary care DR-TB centers and WHO Country Office for India. The institutional ethics committee of NIRT (ID:2021004, 12 July 2021), and the participating sites approved the study and began enrollment by 20<sup>th</sup> October 2021.

*Study setting:* Eight sites in India will implement the mBPaL trial. The study sites were selected based on the 2019 census of XDR and MDR<sub>FQ</sub> TB patients attending the DR-TB centers in the country and their capacity in conducting clinical trials, including trained personnel, reporting to regulators, expertise in managing DR-TB patients and severe adverse events, and previous record of conducting drug trials. The study sites include DR-TB centers at Sarvodaya Charitable Trust Hospital and Shatabdi Centenary Hospital, Mumbai; King George's Medical College and University, Lucknow; SN Medical College, Agra; Govt. Medical College, Surat and Bhavanagar, Gujarat, National Institute for Tuberculosis and Respiratory Diseases, New Delhi; Rajan Babu Institute of Pulmonary Medicine and Tuberculosis, New Delhi and Govt. Rajaji Medical College and Hospital, Madurai, Tamilnadu.

*Study patients and eligibility:* Adults between 18 to 65 years of age diagnosed with Pre-XDR-TB or MDR<sub>TI/NR</sub> accessing TB care services in selected DR TB centers of the country.

Table 1 provides the detailed eligibility criteria based on which patients visiting the study sites will be screened for participation in the study

**Table 1: Study Eligibility criteria**

Inclusion Criteria	Exclusion criteria
Adults aged between 18 years – 65 years Pulmonary Pre-XDR-TB patients or MDR-TB/NI/NR patients	A patient who has received more than two weeks of BDQ or LZD before the first dose of the mBPAL regimen OR If the result of DST for FQ or LZD is not available and h/o more than two weeks of consumption of drugs used in the study regimen
Bodyweight of $\geq 30$ kg (in light clothing)	Intolerance or risk of toxicity or allergic any of the drugs in the treatment regimens should not be enrolled in the study
Provide informed written consent before all study-related procedures, including HIV testing	All forms of Extrapulmonary TB (except Lymph node TB or pleural effusion associated with Pulmonary DR-TB)
Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) < 2.5 x ULN; Total bilirubin lesser than ULN	Platelet count < 1,00,000 /mm <sup>3</sup> or Haemoglobin level of < 9.0 g/dl
QTc(f) less than or equal to 450 ms at baseline	QTc(f) > 450 at baseline & normal electrolytes, ECG to be repeated after 6 hours, and if both ECGs show QTc(f) > 450 msec, then the patient should not be challenged with cardiotoxic drugs.  Having risk factors for Torsade de Pointes, e.g., hypokalaemia, heart failure, history of long QT syndrome among family members  Currently having an uncontrolled cardiac arrhythmia that requires medication

Female patients should not be pregnant or should be using a birth control method	Pregnant or Lactating
	HIV-infected patient with a CD4+ count of $\leq 50$ cells
	Grade III or IV peripheral neuropathy Major Psychiatric illness
	Very seriously ill patients (Karnofsky scores $< 50$ within last 30 days)

Recruitment process: Potential trial participants who visit the DR-TB centers in the selected trial sites will be approached by the study staff and explained in detail about the study in their native language. Patients willing to participate in the trial will be given a patient information sheet and a consent form explaining all study-related procedures. After obtaining written informed consent, a detailed medical, surgical, medication, and alcohol history will be collected to assess the eligibility for trial participation along with investigations as outlined in Table 2. Diagnosis of Pre-XDR TB will be made by *Mycobacterium tuberculosis* positivity in the culture of sputum specimen collected within three months AND with documented resistance to rifamycins with or without isoniazid resistance AND, additionally resistant to at least a fluoroquinolone (FQ)<sup>7</sup> while MDR-TB<sub>TI/NR</sub> was all of the above AND with documented intolerance or non-response to the current treatment regimen for 6-months or more when the participant was adherent to the treatment regimen. Eligible participants will be enrolled within the next 14 days.

Study regimen and drug dosing: The study participant will be randomized in the ratio of 1:1:1 to receive one of the mentioned treatment regimens -

Arm 1: 26 wks. BDQ +Pa + LZD (600mg)



Arm 2: 9 wks. BDQ +Pa + LZD (600mg) followed by 17 wks. BDQ +Pa+ LZD (300mg)

Arm 3: 13 wks. BDQ +Pa + LZD (600mg) followed by 13 wks. BDQ +Pa+ LZD (300mg)

**Table 2. Schedule of enrolment, interventions, and assessments of a participant in the mBPaL trial**

COMPLETED WEEKS	-2	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	16	20	26	30	38	50	62	74
Informed Consent	X																							
Inclusion/Exclusion Criteria	X																							
Demography	X																							
Medical history	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination & vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fundus examination/ colour vision	X										X				X				X					
12 lead ECG [B]	X			X	X	X					X		X		X	X	X	X	X	Monthly once for 6 months				
Chest X-ray	X															X		X						
Sputum smear (1 early morning/1 spot)*	X					X					X				X		X	X	X		X	X	X	X



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<b>HRQoL</b>	<b>X</b>																	<b>X</b>				<b>X</b>
<b>Adverse events<sup>§</sup></b>		<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>

\*Patients will give 2EM and 1Spot sputum sample at baseline

¥ LPA performed only if sputum results are positive

± DST performed at baseline (with storage of the strain at -20c), 16<sup>th</sup> week in case of positive culture and if any culture is found positive during the 48 weeks after the end of the treatment (with storage of the strain of the recurrent episode for genotyping analysis)

∞ Sputum isolates at baseline, at time of treatment failure and relapse will be sent to NIRT for MGIT DST to Bdq, and Prtomanid for Whole Genome Sequencing. Isolates will also be saved at the regional labs until sub-culture results are available for any further DST required for patient management

[B] Baseline ECG should be obtained and additional ECGs conducted daily for the first two weeks after starting treatment (if hospitalized)

ECG should be repeated as necessary in case of clinical suspicion of heart rhythm and conduction disturbances.

ə Week 9 – Linezolid dose will be modified at week 9 in arm 2

£ Week 13 - Linezolid dose will be modified at week 13 in arm 3

# end of treatment for patients whose 12<sup>th</sup>-week cultures are negative and if 16<sup>th</sup> week cultures are not available then no clinical or radiological evidence of TB

\$ Adverse event monitoring over the phone weekly from the 17<sup>th</sup> week onwards till the end of treatment (except during the days of the scheduled visit)

HRQoL – health-related Quality of Life

LJ-Lowenstein-Jensen; MGIT-Mycobacterial Growth Inhibitor Tube; DST – Drug susceptibility test;

HCV-Hepatitis C virus; HIV-Human immunodeficiency virus

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3 Four 100 mg tablets (400 mg) of Bedaquiline will be administered by mouth once a day  
4 for two weeks, followed by 200 mg (two 100 mg tablets) orally thrice a week for 24 weeks.  
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6 Pretomanid will be administered as (200mg) one tablet daily for 26 weeks. In Arm 2, the LZD  
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8 dose will be reduced from 600mg to 300 mg after nine weeks and 13 weeks in Arm 3,  
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10 irrespective of the smear and culture results. At the time of randomization, dosing of LZD and  
11  
12 other drugs is not weight-based and is pre-fixed in the protocol. LZD is given the ability to  
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14 interrupt or reduce the dose if needed based on Grade 3 toxicity. The continuation of the regimen  
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16 beyond 26 weeks and up to 39 weeks will be based on the culture results of week 16.  
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22 Randomization procedures: Computer-generated list of random numbers using REDCAP  
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24 software will be used for randomization centrally. The site physician using these computer-  
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26 generated randomizations will be able to randomize the study participants to any one of the three  
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28 arms in a ratio of 1:1:1. Block randomization will be used to randomize participants in the trial.  
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30 NIRT statistician will assign the unique study identification number after confirming all the  
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32 study-related eligibility criteria. There is no blinding in the trial.  
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37 Treatment Allocation: The study participants will be randomized to receive one of the  
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39 three treatment regimens in a 1:1:1 ratio using block randomization. A computer-generated list of  
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41 random numbers using REDCAP software will be used for randomization centrally. NIRT center  
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43 will generate the allocation codes at the time of the study. At the time of patients' admission to  
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45 the study, the site Physician will be able to randomize them at the site on RedCAP software  
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47 based on pre-defined factors.  
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51 Treatment delivery, compliance, and retention: The study participants will be  
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53 hospitalized for two weeks wherever feasible, and study drugs administered under supervision.  
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3 Ambulatory care can also be offered if hospitalization is not needed. After discharge,  
4 medications will be supplied – weekly for the first month, then fortnightly till 3<sup>rd</sup> month, and  
5 then monthly till the end of treatment. A health care provider or a family member will be  
6 assigned and trained to supervise the drug intake and monitor adherence to treatment. During the  
7 treatment phase, the patient will be reviewed every week for 16 weeks, then monthly until the  
8 end of the treatment phase (26/39 weeks). During these visits, detailed medical history will be  
9 collected; adverse drug reactions and tolerability to study drugs will be monitored. The site  
10 medical officer does the management of adverse events (AE) and the causality assessment with  
11 the grading of AEs as per DAIDS criteria.<sup>8</sup>. Treatment adherence will be assessed by reviewing  
12 treatment cards, empty pill covers, on-time drug refills, and hospital attendance. Offering  
13 enhancers like nutrition supplements, reimbursing nominal costs for loss of wage, or  
14 transportation will strengthen the treatment compliance. Post-treatment follow-up visits will be  
15 done for 48 weeks.

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34 Concomitant medication while in the trial: A detailed medical history will be collected  
35 during every study visit Any medications consumed while in the trial will be entered on the  
36 concomitant medications page of the case record form. Medication entries shall be specific to the  
37 generic name, dose, unit, frequency, route of administration, start, stop date, and reason for use.  
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Drugs prohibited to be used during the study include aspirin or ibuprofen or medicines that can  
cause gastrointestinal bleeding, any antibiotics until clinically warranted, and efavirenz-based  
antiretroviral therapy.

Criteria for discontinuation/withdrawal of study participants: The trial regimen may be  
discontinued in some patients in situations such as resistance to study drugs, intolerable or severe  
toxicity, and treatment failure. A patient may be withdrawn from the study for non-willingness of

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3 the patient to continue for any reason, pregnancy, drug-drug interaction, non-compliance & non-  
4 availability, drug resistance, or recommendation by the Data Safety & Monitoring Board.  
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9 Study Outcome: The primary outcome of the trial is the proportion of patients with  
10 favorable treatment outcomes, defined as sustained treatment success at 12 months post  
11 successful TB treatment, being alive & free of TB. Indicators of Successful TB treatment include  
12 Cure (patient who has completed 26 or 39 weeks of treatment without evidence of failure and  
13 with at least two consecutive negative sputum cultures taken at least 7-days apart) and Treatment  
14 Completed (patient who has completed 26 or 39 weeks of treatment whose outcome does not  
15 meet the definition for cure or treatment failure) as defined by WHO.<sup>9</sup> The secondary outcome  
16 includes the proportion of patients with (i) serious adverse events or adverse drug reactions,  
17 including tolerability of the study drugs during the treatment and follow-up period, and (ii)  
18 unfavorable outcomes comprising death, bacteriological or clinical failure, and loss to follow-up.  
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33 Participant timeline: Each participant involved in the trial will have a screening period of  
34 2 weeks, followed by a treatment period of 26 weeks to 39 weeks based on sputum culture result  
35 at week 16 and a post-treatment follow-up for 12 months. Table 2 shows the entire schedule of  
36 enrolment of a patient, the interventions to be given, and assessments to be done for a participant  
37 in the trial.  
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45 Patient and public involvement: Since the scientific problem is still not proven, patients  
46 were not involved in the research question development or the design of this study. However,  
47 learning from the difficulties faced by patients on the higher dose of LZD, there is an urgent need  
48 to find the correct dose of LZD with lower toxicity, better tolerability, and, at the same time, not  
49 compromise the efficacy of the regimen to prevent recurrence of TB. The study proposal is  
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discussed among the members of the Institutional Scientific advisory committee, Institutional Ethics committee, Drug Controller General of India, and Community Advisory Board. Study results will be widely disseminated through meetings, conference presentations, and publications.

Sample size assumption: mBPaL trial will evaluate the effectiveness of various doses and duration of LZD with BDQ and Pa after 26 weeks of treatment in adults with Pre-XDR or MDR (TI/NR) pulmonary TB patients. The efficacy of BDQ with Pa and LZD (600 mg) for 26 weeks is reported to be about 91%.<sup>5</sup> Assuming that the effectiveness of treatment arms of BDQ + Pa with either LZD 600mg for nine weeks followed by 300mg for 17 weeks or LZD 600mg for 13 weeks followed by 300mg for 13 weeks would be about the same based on the recently released interim outcomes of ZeNIX trial results, we hypothesize that these treatment arms with planned reduction of LZD would be non-inferior to LZD 600 mg for 26 weeks arm with a non-inferiority margin of about 10% ineffectiveness. To demonstrate this, with a power of 80% and an alpha error of 5%, we require about 111 patients in each arm. Factoring in a loss of 20% (due to default or migration), we need 133 patients in each arm or a total of 399 patients (approx. 400) to achieve our study objective.

Data collection, management, and interim analysis: Clinical and demographic information and laboratory reports will be collected from the individual participants in the paper case report forms and entered in Redcap software at all the participating sites. During the weekly and monthly visits, adverse events will be monitored by physical examination, history taking, and laboratory investigations as given in the study schedule. Solicited and unsolicited adverse events will be recorded and managed per DAIDS criteria. Data will be verified for accuracy and completeness. Data access would be restricted to the study statisticians at NIRT and Central TB

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3 Division. Third-party access to data is restricted and will be made available only on request to  
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5 NIRT. Data analysis will be done using SPSS software by statisticians at NIRT. An interim  
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7 analysis is planned when at least 33% (approximately 120) of the study participants complete 26  
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9 weeks of treatment and the results of sputum smear and MGIT culture are available.  
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12 Study outcome analysis: The primary effectiveness analysis will be conducted using  
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14 culture results from MGIT culture. Modified Intent-to-treat (mITT) analysis will be carried out to  
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16 evaluate the effectiveness of the newer regimens. We will evaluate the hypothesis that the  
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18 investigational regimens are non-inferior to the standard of care regimen for the treatment of Pre-  
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20 XDR-TB, MDR<sub>TI/NR</sub> in terms of favorable outcomes (including sustained cure and treatment  
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22 completed) and unfavorable outcomes (including death, treatment failure and lost to follow-up)  
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24 in the field settings. Time to culture conversion and adverse events at the end of 9 weeks and  
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26 26/39 weeks will be estimated using survival analysis methods. Deaths and study withdrawals  
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28 within the first 7-days of treatment and baseline study drug resistance will be considered initial  
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30 exclusions. They will not be included in the final mITT analysis. Kaplan Meier survival curves  
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32 will be constructed and time to culture conversion and adverse events will be calculated at the  
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34 end of 9 and 26/39 weeks and compared among regimens using the Log-rank test. To identify the  
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36 important covariates with culture conversion Cox regression model will be used. Count  
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38 regression models will be employed to compare the number of adverse events experienced across  
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40 treatment regimens adjusting for other covariates. The HRQOL between the regimens will be  
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42 compared using ANOVA or the nonparametric alternative. Ordinarily least square regression  
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44 will be used to compare the quality of life across regimens after adjusting for other variables. Per  
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46 protocol analysis will be done for those patients who comply with the treatment regimen they  
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48 were assigned. All participants who have consumed >80% of the drugs will be included in this  
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3 analysis. Safety analysis will include data from all who received at least one dose of the study  
4 regimen.  
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9 Data and Safety Monitoring Board (DSMB): The DSMB comprises a statistician, clinical  
10 trial experts, pharmacologist, and pulmonologist. They will be notified about the safety data after  
11 every ten patients get enrolled in the trial and complete nine weeks of treatment in each of the  
12 three arms. This review will mainly be by circulation to members. An in-person review will be  
13 conducted when at least 33% (approximately 120) of the enrolled patients have completed 26  
14 weeks of treatment and sputum smear, and MGIT culture results are available. They will review  
15 the progress of the trial and safety issues for the trial participants in the early stages focusing  
16 majorly on grade 3 or 4 adverse events and serious adverse events. DSMB may ask for ad-hoc  
17 analysis and can recommend continuing or discontinuing or making modifications in the protocol  
18 based on any of these criteria - Grade 3 or Grade 4 AE >10%; Deaths due to any cause > 15%;  
19 Non-cardiac Notifiable events >15% and QTc(F)> 500ms in more than 10% of enrolled patients.  
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34 Study site monitoring and quality assurance: Study monitoring committee formed by the sponsor  
35 and other stakeholders will monitor the study data quality per trial standard operating procedures.  
36 The monitoring plan will be followed to perform field visits and audits at various stages. The  
37 CRFs, patient records, and all source documents of the study participants in this study will be  
38 made available to be reviewed by the study monitors. Regular virtual meetings with the  
39 investigators of each study site will be conducted to discuss the study's progress. Any critical  
40 protocol modifications during the research will be informed to the Institutional Ethics  
41 Committee, CTRI, and the participants involved in the trial. At any time during or after  
42 completion of the study, the Sponsor, through independent non-study staff, may conduct a  
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3 quality assurance assessment of the site records, and the regulatory agencies may conduct a  
4 regulatory inspection.  
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8 *Confidentially of trial data:* All study-related CRFs and documents related to the trial  
9 will remain in the custody of the site Principal Investigator under lock and key until transferred  
10 to archives. The records identifying the patient will be kept confidential and will not be made  
11 publicly available. All electronic data will be saved securely in password-protected systems. The  
12 final data of the study will be accessible only to the statisticians in NIRT and the Central TB  
13 division. When trial results are published, the patient's identity will remain confidential. The  
14 confidentiality of the patients included in this trial will be maintained during the conduct of the  
15 study period following the Indian-GCP and the relevant regulations by the laws of India.  
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### 28 **Ethics and dissemination**

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30 The study has been approved by the Ethics committees of participating institutes and the  
31 ICMR-National Institute for Research in Tuberculosis. The current ICH Good Clinical Practice  
32 and the ICMR ethical guidelines for biomedical research in human participants will be followed  
33 in the current trial. This will ensure public assurance that the well-being, safety, and rights of the  
34 participants are considered, which is consistent with the principles originating from the Helsinki  
35 Declaration and will maintain the credibility of the clinical trial data. The personal data  
36 necessary to analyze the safety, tolerability, and antibacterial activity of the investigational  
37 product will be used. Manuscript preparation, result dissemination, and publication materials are  
38 the principal investigator's responsibility. After the completion of the trial, the investigators  
39 anticipate publishing the study results in peer-reviewed scientific journals, presenting the  
40 findings in meetings, and sharing the results widely with the program managers and  
41 policymakers.  
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## Discussion

WHO has released the Global list of High Burden Countries for MDR/RR-TB for 2021–2025. The list contains the top 20 countries with an estimated absolute number of incident cases and the top 10 countries with a severe burden of incident rate totaling thirty countries. Compared to 2016–2020, few countries like Ethiopia have transitioned out, while countries like Nepal have been added to the list.<sup>1</sup> Average success rate of conventional XDR-TB patients put on treatment (without BDQ) from 2016 to 2018 is 29%. This has increased to 48% in 2018.<sup>10</sup> Managing MDR-TB and XDR-TB remain a significant challenge in eliminating TB. DR-TB patients treated with short regimens with newer oral drugs are expected to have a better quality of life than patients on standard (either short or long) DR-TB regimens for multiple reasons. Patients' adherence improves with injectable-free treatment and facilitates the implementation of community programs. This would reduce the costs incurred for the patients on travel to health facilities for injections, loss of wages, or hospitalization expenses during the intensive phase of treatment of standard regimens. Hence, it is reasonable to assume that injectable-free treatment regimens that potentially reduce adverse reactions would likely improve patients' overall health-related quality of life. Second, BDQ-containing regimens reduce the costs per treatment success by 18–20% in short course regimens and 49–50% in long course regimens. Approximately 61,000 more patients are estimated to be treated successfully over five years with BDQ-containing regimens.<sup>11</sup> The success rate of DR TB patients treated under the BDQ conditional access program (BDQ-CAP) is 71%.<sup>10</sup>

Studies have compared the outcomes of an extended oral regimen containing BDQ with the shorter oral regimen. A shorter all-oral BDQ-containing regimen showed more beneficial effects than an injectable-free longer regimen containing BDQ. The favorable odds ratio of 3.9

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3 (1.7-9.1) was observed for success versus failure/recurrence, 1.6 (1.2–2.2) for success versus all  
4 unfavorable outcomes, and 0.5 (0.4-0.8) for loss to follow-up, thereby supporting the use of all-  
5 oral shorter regimen.<sup>12</sup> Also, studies have evaluated the safety of the newer drugs in shorter oral  
6 regimens. The NIXTB study reported LZD toxicity such as peripheral neuropathy and  
7 myelosuppression among 81% and 48% of the study population. Adverse events leading to death  
8 and serious adverse events were 9% and 30%, respectively, in the 600 mg twice daily LZD group  
9 and 3% and 9% in the 1200 mg once daily LZD group.<sup>3</sup> In the ZeNIX trial, peripheral  
10 neuropathy was reported in 38% of those receiving 1200mg of LZD for six months; 24% of  
11 those receiving 1200mg of LZD for two months; 24% of those receiving 600mg of LZD for six  
12 months and 13% of those receiving 600mg of LZD for two months. Similarly, anemia, secondary  
13 to linezolid exposure, was noticed in 22% of those receiving 1200mg of LZD for six months;  
14 17% of those receiving 1200mg of LZD for two months; 2% of those receiving 600mg of LZD  
15 for six months and 7% in those receiving 600mg of LZD for two months.<sup>5</sup> Modified BPaL study  
16 will determine the effectiveness in managing DR-TB patients by comparing the varying dose of  
17 LZD with BDQ and Pa regimens. Safety assessment in the mBPaL study is one of the significant  
18 components in measuring the outcome of the regimens.  
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41 We are proposing to conduct a pragmatic clinical trial (mBPaL study) with varying doses  
42 of LZD along with BDQ and Pa as a planned reduction of LZD for the treatment of Pre-XDR  
43 and MDR<sub>TI/NR</sub> pulmonary TB patients for 26-39 weeks. Given the poor tolerability and increased  
44 frequency of dose interruption in regimens containing LZD, this trial will help us decide on the  
45 effective dosing of LZD to be given with BDQ and Pa for an entirely oral short-course regimen  
46 to treat highly drug-resistant TB in the field setting. The main drivers of the acceptability of the  
47 BPaL regimen were the short duration of treatment, fully oral regimen without injectables,  
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3 reduced pill burden, anticipated higher treatment success, the lower financial burden for patients  
4 and the program, reduced load on the health system, using existing diagnostic processes and  
5 lesser burden to TB laboratories for monitoring of bacteriological treatment. This study will  
6 create a new standard of care for Pre-XDR and MDR<sub>TI/NR</sub>-pulmonary TB patients that will not  
7 only have better and earlier culture conversion but also reduce the proportion of patients who do  
8 not adhere to the entire course of therapy.  
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- 22 • **Authors' contributions:** CPP, CPR & RS – conceived & designed the study / CPP, BD,  
23 CPR & BR – development and writing of the study protocol / CPP, BD, CPR, BR, MP,  
24 SM & SuM – writing and editing this manuscript  
25  
26  
27
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34 Government. Trial Sponsors: ICMR-National Institute for Research in Tuberculosis  
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- 44 • **Competing interests:** None  
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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	17
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13, 14



## Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5,6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6

## Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7,8
Interventions	11	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	11	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10
	11	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11

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2	Participant	13	Time schedule of enrolment, interventions (including
3	timeline		any run-ins and washouts), assessments, and visits for
4			participants. A schematic diagram is highly
5			recommended (see Figure)
6			
7	Sample size	14	Estimated number of participants needed to achieve
8			study objectives and how it was determined, including
9			clinical and statistical assumptions supporting any
10			sample size calculations
11			
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13	Recruitment	15	Strategies for achieving adequate participant
14			enrolment to reach target sample size
15			

### Methods: Assignment of interventions (for controlled trials)

#### Allocation:

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21	Sequenc	16	Method of generating the allocation sequence (eg,
22	e	a	computer-generated random numbers), and list of any
23	generatio		factors for stratification. To reduce predictability of a
24	n		random sequence, details of any planned restriction
25			(eg, blocking) should be provided in a separate
26			document that is unavailable to those who enrol
27			participants or assign interventions
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30	Allocatio	16	Mechanism of implementing the allocation sequence
31	n	b	(eg, central telephone; sequentially numbered,
32	conceal		opaque, sealed envelopes), describing any steps to
33	ment		conceal the sequence until interventions are assigned
34	mechani		
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38	Impleme	16	Who will generate the allocation sequence, who will
39	ntation	c	enrol participants, and who will assign participants to
40			interventions
41			
42	Blinding	17	Who will be blinded after assignment to interventions
43	(masking)	a	(eg, trial participants, care providers, outcome
44			assessors, data analysts), and how
45			
46			
47		17	If blinded, circumstances under which unblinding is
48		b	permissible, and procedure for revealing a participant's
49			allocated intervention during the trial
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### Methods: Data collection, management, and analysis

1				
2	Data	18	Plans for assessment and collection of outcome,	11,12,20,21,22
3	collection	a	baseline, and other trial data, including any related	
4	methods		processes to promote data quality (eg, duplicate	
5			measurements, training of assessors) and a	
6			description of study instruments (eg, questionnaires,	
7			laboratory tests) along with their reliability and validity,	
8			if known. Reference to where data collection forms can	
9			be found, if not in the protocol	
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12		18	Plans to promote participant retention and complete	10
13		b	follow-up, including list of any outcome data to be	
14			collected for participants who discontinue or deviate	
15			from intervention protocols	
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18	Data	19	Plans for data entry, coding, security, and storage,	12,14
19	managemen		including any related processes to promote data	
20	t		quality (eg, double data entry; range checks for data	
21			values). Reference to where details of data	
22			management procedures can be found, if not in the	
23			protocol	
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26	Statistical	20	Statistical methods for analysing primary and	12,13
27	methods	a	secondary outcomes. Reference to where other details	
28			of the statistical analysis plan can be found, if not in	
29			the protocol	
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32		20	Methods for any additional analyses (eg, subgroup and	12,13
33		b	adjusted analyses)	
34				
35		20	Definition of analysis population relating to protocol	12,13
36		c	non-adherence (eg, as randomised analysis), and any	
37			statistical methods to handle missing data (eg, multiple	
38			imputation)	
39				
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41	<b>Methods: Monitoring</b>			
42				
43	Data	21	Composition of data monitoring committee (DMC);	13,14
44	monitoring	a	summary of its role and reporting structure; statement	
45			of whether it is independent from the sponsor and	
46			competing interests; and reference to where further	
47			details about its charter can be found, if not in the	
48			protocol. Alternatively, an explanation of why a DMC is	
49			not needed	
50				
51				
52		21	Description of any interim analyses and stopping	12,13
53		b	guidelines, including who will have access to these	
54			interim results and make the final decision to terminate	
55			the trial	
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2	Harms	22	Plans for collecting, assessing, reporting, and
3			managing solicited and spontaneously reported
4			adverse events and other unintended effects of trial
5			interventions or trial conduct
6			
7	Auditing	23	Frequency and procedures for auditing trial conduct, if
8			any, and whether the process will be independent from
9			investigators and the sponsor
10			
11			
12	<b>Ethics and dissemination</b>		
13			
14	Research	24	Plans for seeking research ethics
15	ethics		committee/institutional review board (REC/IRB)
16	approval		approval
17			
18	Protocol	25	Plans for communicating important protocol
19	amendment		modifications (eg, changes to eligibility criteria,
20	s		outcomes, analyses) to relevant parties (eg,
21			investigators, REC/IRBs, trial participants, trial
22			registries, journals, regulators)
23			
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25	Consent or	26	Who will obtain informed consent or assent from
26	assent	a	potential trial participants or authorised surrogates,
27			and how (see Item 32)
28			
29			
30		26	Additional consent provisions for collection and use of
31		b	participant data and biological specimens in ancillary
32			studies, if applicable
33			
34	Confidential	27	How personal information about potential and enrolled
35	ity		participants will be collected, shared, and maintained
36			in order to protect confidentiality before, during, and
37			after the trial
38			
39			
40	Declaration	28	Financial and other competing interests for principal
41	of interests		investigators for the overall trial and each study site
42			
43	Access to	29	Statement of who will have access to the final trial
44	data		dataset, and disclosure of contractual agreements that
45			limit such access for investigators
46			
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48	Ancillary	30	Provisions, if any, for ancillary and post-trial care, and
49	and post-		for compensation to those who suffer harm from trial
50	trial care		participation
51			
52	Disseminati	31	Plans for investigators and sponsor to communicate
53	on policy	a	trial results to participants, healthcare professionals,
54			the public, and other relevant groups (eg, via
55			publication, reporting in results databases, or other
56			data sharing arrangements), including any publication
57			restrictions
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2		31	Authorship eligibility guidelines and any intended use
3		b	of professional writers
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5		31	Plans, if any, for granting public access to the full
6		c	protocol, participant-level dataset, and statistical code
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## Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	✓
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	20,21,22

peer review only

# BMJ Open

## Randomized trial to Evaluate the Effectiveness and Safety of Varying Doses of Linezolid with Bedaquiline and Pretomanid in Adults with Pre-Extensively Drug-Resistant or Treatment Intolerant/Non-responsive Multidrug-Resistant Pulmonary Tuberculosis: Study protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-058606.R2
Article Type:	Protocol
Date Submitted by the Author:	09-Aug-2022
Complete List of Authors:	Padmapriyadarsini, Chandrasekaran; National Institute for Research in Tuberculosis Devaleenal, Bella; ICMR-National Institute for Research in Tuberculosis Ponnuraja, C.; ICMR-National Institute for Research in Tuberculosis Ramraj, Balaji; ICMR-National Institute for Research in Tuberculosis Singla, R; National Institute of Tuberculosis and Respiratory Diseases, Parmar, Malik; 3World Health Organization, Country Office for India, New Delhi Mattoo, Sanjay; Ministry of Health & Family Welfare Mandal, Sudarsan; Ministry of Health & Family Welfare
<b>Primary Subject Heading</b>:	Respiratory medicine
Secondary Subject Heading:	Infectious diseases
Keywords:	Thoracic medicine < INTERNAL MEDICINE, RESPIRATORY MEDICINE (see Thoracic Medicine), Respiratory infections < THORACIC MEDICINE

SCHOLARONE™  
Manuscripts

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3 **Randomized trial to Evaluate the Effectiveness and Safety of Varying Doses of**  
4 **Linezolid with Bedaquiline and Pretomanid in Adults with Pre-Extensively Drug-**  
5 **Resistant or Treatment Intolerant/Non-responsive Multidrug-Resistant Pulmonary**  
6 **Tuberculosis: Study protocol**  
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24 <sup>3</sup>*World Health Organization, Country Office for India, New Delhi*  
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26 <sup>4</sup>*Central TB Division, Ministry of Health & Family Welfare, New Delhi*  
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## Abstract

**Introduction:** Drug-resistant tuberculosis (DR-TB) is a global public health problem. Patients suffer for months if undiagnosed or treated inadequately, transmitting DR-TB in the community before succumbing to the disease. Early diagnosis, prompt treatment initiation, and completion play a significant role in treatment success. However, extended regimens with injectable result in poor treatment adherence and outcomes. Our objective is to evaluate the effectiveness, safety, and tolerability of various doses and duration of Linezolid (LZD) in combination with Bedaquiline (BDQ) and Pretomanid (Pa) after 26 weeks of treatment in adults with Pre-Extensively Drug-Resistant (Pre-XDR) OR Treatment Intolerant / Non-responsive multidrug-resistant (MDR<sub>TI/NR</sub>) Pulmonary Tuberculosis.

**Methods and analysis:** A multicentric, randomized pragmatic clinical trial in India will enroll participants in one of the three arms - Control arm (Arm 1): BDQ, Pa, and LZD 600mg daily for 26 weeks OR Intervention arms (Arm 2): BDQ, Pa and LZD 600mg for nine weeks followed by 300mg for 17 weeks OR Arm 3: BDQ, Pa and LZD 600mg for 13 weeks followed by 300mg for 13 weeks. The primary endpoint is the proportion of patients with favourable outcomes as sustained cure and treatment completion. The secondary endpoint is unfavourable outcomes, including deaths, treatment failure, toxicity/adverse events, and loss of follow-up till 48 weeks post-treatment.

**Ethics and dissemination:** The study has been approved by the Ethics committees of participating institutes and the National Institute for Research in Tuberculosis. The trial results will help establish evidence towards a safe and effective dose of LZD that can be used in a fully, all-oral short course regimen for highly DR-TB patients. The results of this study will be shared



with the National TB Elimination Programme of the country and the World Health Organization guidelines development group through publications and dissemination meetings.

**Trial Registration:** The protocol (version 3.1 dated 20<sup>th</sup> July 2021) has been registered on the Clinical Trial Registry of India as CTRI/2021/03/032189 on 22<sup>nd</sup> March 2021 and ClinicalTrials.gov with the identifier: NCT05040126 on 10<sup>th</sup> September 2021.

## Article Summary

### Strength and Limitations

- Pragmatic Randomized trial design will add considerable value to the study as it will consider a real-world population under field conditions in a clinical trial, thus decreasing bias and minimizing unequal distribution.
- The trial includes an active control arm (appropriate comparison arm) instead of a placebo arm and has relevant outcomes for optimal healthcare decisions at the end of the study.
- The trial lacks stratification based on disease severity. This may result in the possibility of more severe cases in one group of treatment. We hope randomization will be able to cover this.
- As there is no blinding in this trial, the treating physician may be biased to assign the causality of all adverse events to the drug concerned.
- Data heterogeneity may be present as it's a planned multicentric study.

**Keywords:** Linezolid Dose, Pretomanid, Randomized trial, Treatment Intolerant, Drug-resistant TB

## Introduction:

The World Health Organization (WHO) estimates that globally in 2020, 132222 cases of multi-drug resistant (MDR)/rifampicin-resistant tuberculosis (RR-TB) and 25681 cases of pre-extensively drug-resistant (pre-XDR-TB) or extensively drug-resistant (XDR-TB), totaling 157903 cases, were detected. However, testing for fluoroquinolone resistance remains much lower; at just over 50% worldwide in 2020.<sup>1</sup> Of these, 150359 people with MDR/RR-TB were enrolled in treatment in 2020, fewer than in the previous years. The treatment success rate of the 2018 MDR/RR-TB cohort was 59%; though improved from earlier cohorts, the treatment failure, loss to follow-up and death remain high.<sup>1</sup> Also, this was not uniform across the globe—the treatment success rate was below 50% in countries like India and Indonesia due to increased death and loss-to-follow-up. Globally, the treatment success rate of highly drug-resistant TB (DR-TB) remains unacceptably low.

With the availability of newer drugs and patient-friendly approaches, it is now possible to design newer regimens that are less toxic, safer, and of shorter duration. The WHO consolidated treatment guidelines for DR-TB recommend longer and shorter treatment regimens for MDR/RR-TB treatment.<sup>2</sup> A South African study using a combination of Bedaquiline (BDQ), Pretomanid (Pa), and Linezolid (LZD) to treat highly DR-TB showed a favorable outcome of 90% at the end of six-months of treatment.<sup>3</sup> However, the high dose of LZD used in this study led to more than 70% of patients having adverse events to LZD, often leading to either treatment interruption or dose reduction of LZD between two to three months of treatment. Though LZD is efficacious for DR-TB, adverse events and treatment discontinuation are also to be expected.<sup>4</sup>

The multicountry ZeNIX study with consistent dosing of BDQ and Pa reported a 93% success rate with linezolid 1200 mg for six months and 91% with linezolid 600mg for six months. Among those receiving 1200 mg linezolid for six months, adverse events reported were

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3 38%, while in those receiving 600 mg of linezolid for six months, it was 24%.<sup>5</sup> Though there  
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5 seemed to be a modestly greater early bactericidal effect over 14 days at the highest dose of 1200  
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7 mg/day (NC-003 study), this dose appeared to be associated with a greater incidence of  
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9 neuropathic and myelosuppressive effects than the 600 mg/day dose in the ZeNIX and NixTB  
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11 trials. While a full six months of linezolid therapy in the regimen may give higher culture  
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13 conversion and avoid relapse, the mouse model found that more than two months of linezolid,  
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15 combined with BDQ and Pa, does not increase relapse-free cure.<sup>6</sup> The study also found that LZD  
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17 increases the sterilizing activity of the BDQ-Pa combination; no MTB could be cultured from the  
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19 lungs of mice three months after cessation of three months of treatment with this combination.  
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24 Given the above evidence, both in terms of safety and toxicity of higher doses and longer  
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26 duration of LZD and the ability of LZD to act synergistically with the combination of BDQ and  
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28 Pa, the current study is planned with the primary objective of determining the effectiveness of  
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30 various doses and duration of LZD in combination with BDQ and Pa given for 26-weeks in  
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32 adults with either Pre-Extensively Drug-Resistant (Pre-XDR) OR Non-responsive / Treatment  
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34 Intolerant multidrug-resistant ( $MDR_{NR/TT}$ ) pulmonary TB. Secondary objectives include  
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38 a) to determine the safety and tolerability of various doses and duration of Linezolid  
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40 with Pretomanid and Bedaquiline following 26 weeks of therapy among adults with  
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42 either Pre-XDR or  $MDR_{TT/NR}$  pulmonary TB.  
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45 b) to determine the baseline resistance to the newer and repurposed drugs.  
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48 c) to determine the M.tb strain mutation by whole genome sequencing in participants  
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50 with treatment failure while on treatment or recurrence of TB during the follow-up  
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52 period.  
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## 54 **Methods and Analysis**

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*Study design and oversight:* Modified BPaL (mBPaL) Study is a multi-center, pragmatic randomized clinical trial under field conditions. The study will enrol 400 adults, Pre-XDR or MDR<sub>TI/NR</sub> pulmonary TB patients meeting all study eligibility criteria after the screening procedure. The enrolled patients will be randomized to receive any of the three regimens using block randomization. The study is supported by the United States Agency for International Development (USAID), under the iDEFEAT TB Project with the Union, Cooperative Agreement No. 72038620CA00007, and implemented by the ICMR-National Institute of Research in Tuberculosis (NIRT) in collaboration with the National TB Elimination Programme through its tertiary care DR-TB centers and WHO Country Office for India. The institutional ethics committee of NIRT (ID: 2021004, 12<sup>th</sup> July 2021), and the participating sites approved the study and began enrollment on 20<sup>th</sup> October 2021.

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*Study setting:* Eight sites in India will implement the mBPaL trial. The study sites were selected based on the 2019 census of XDR and MDR<sub>FQ</sub> TB patients attending the DR-TB centres in the country and their capacity for conducting clinical trials, including trained personnel, reporting to regulators, expertise in managing DR-TB patients and severe adverse events, and a previous record of conducting drug trials. The study sites include DR-TB centers at Sarvodaya Charitable Trust Hospital and Shatabdi Centenary Hospital, Mumbai; King George's Medical College and University, Lucknow; SN Medical College, Agra; Govt. Medical College, Surat and Bhavnagar, Gujarat, National Institute for Tuberculosis and Respiratory Diseases, New Delhi; Rajan Babu Institute of Pulmonary Medicine and Tuberculosis, New Delhi and Govt. Rajaji Medical College and Hospital, Madurai, Tamilnadu.

*Study patients and eligibility:* Adults between the ages of 18 to 65 years diagnosed with Pre-XDR-TB or MDR<sub>TI/NR</sub> accessing TB care services in selected DR TB centers across the country are eligible for the study.

Table 1 provides the detailed eligibility criteria based on which patients visiting the study sites will be screened for participation in the study.

**Table 1: Study Eligibility criteria**

Inclusion Criteria	Exclusion criteria
Adults aged between 18 years – 65 years	A patient who has received more than two weeks of BDQ or LZD before the first dose of the mBPAL regimen OR
Pulmonary Pre-XDR-TB patients or MDR-TBTI/NR patients	If the result of DST for FQ or LZD is not available and h/o more than two weeks of consumption of drugs used in the study regimen
Bodyweight of $\geq 30$ kg (in light clothing)	Intolerance or risk of toxicity or allergic any of the drugs in the treatment regimens should not be enrolled in the study
Provide informed written consent before all study-related procedures, including HIV testing	All forms of Extra pulmonary TB (except Lymph node TB or pleural effusion associated with Pulmonary DR-TB)
Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) $< 2.5$ x ULN; Total bilirubin lesser than ULN	Platelet count $< 1,00,000$ /mm <sup>3</sup> or Haemoglobin level of $< 9.0$ g/dl
QTc(f) less than or equal to 450 ms at baseline	QTc (f) $> 450$ msec at baseline & normal electrolytes, ECG to be repeated after 6 hours, and if both ECGs show QTc (f) $> 450$ msec, then the patient should not be challenged with cardiotoxic drugs.  Having risk factors for Torsade de Pointes, e.g., hypokalaemia, heart failure, history of long QT syndrome among family members

	Currently having an uncontrolled cardiac arrhythmia that requires medication
Female patients should not be pregnant or should be using a birth control method	Pregnant or Lactating
	HIV-infected patient with a CD4+ count of $\leq 50$ cells
	Grade III or IV peripheral neuropathy Major Psychiatric illness
	Very seriously ill patients (Karnofsky scores $< 50$ within last 30 days)

Recruitment process: Potential trial participants who visit the DR-TB centres in the selected trial sites will be approached by the study staff and explained in detail about the study in their native language. Patients willing to participate in the trial will be given a patient information sheet and a consent form explaining all study-related procedures. After obtaining written informed consent, a detailed medical, surgical, medication, and alcohol history will be collected to assess the eligibility for trial participation along with investigations as outlined in Table 2. The diagnosis of Pre-XDR TB will be made by *Mycobacterium tuberculosis* positivity in the culture of sputum specimen collected within three months AND with documented resistance to rifamycins with or without isoniazid resistance AND, additionally resistant to at least one fluoroquinolone (FQ)<sup>7</sup> while MDR-TB<sub>TI/NR</sub> was all of the above AND with documented intolerance or non-response to the current treatment regimen for six-months or more when the participant was adherent to the treatment regimen. Eligible participants will be enrolled within the next 14 days.

Study regimen and drug dosing: The study participant will be randomized in the ratio of 1:1:1 to receive one of the mentioned treatment regimens -

Arm 1: 26 wks. BDQ +Pa + LZD (600mg)

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3 Arm 2: 9 wks. BDQ +Pa + LZD (600mg) followed by 17 wks. BDQ +Pa+ LZD (300mg)  
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6 Arm 3: 13 wks. BDQ +Pa + LZD (600mg) followed by 13 wks. BDQ +Pa+ LZD (300mg)  
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For peer review only

**Table 2. Schedule of enrolment, interventions, and assessments of a participant in the mBPaL trial**

COMPLETED WEEKS	-2	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	16	20	26	30	38	50	62	74
Informed Consent	X																							
Inclusion/Exclusion Criteria	X																							
Demography	X																							
Medical history	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination & vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fundus examination/ colour vision	X										X				X				X					
12 lead ECG [B]	X			X		X		X			X		X		X	X	X	X	X	Monthly once for 6 months				
Chest X-ray	X															X			X					
Sputum smear (1 early morning/1 spot)*	X					X					X				X		X	X	X		X	X	X	X
Sputum culture (LJ/MGIT) and DST for 1 <sup>st</sup> and 2 <sup>nd</sup> line drugs incl. Linezolid	X					X					X				X		X	X	X		X	X	X	X

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\*Patients will give 2EM and 1Spot sputum sample at baseline

¥ LPA is performed only if sputum results are positive.

± DST performed at baseline (with strain stored at -20c), 16<sup>th</sup> week in case of positive culture and if any culture is found positive during the 48 weeks following the end of the treatment (with strain of the recurrent episode stored for genotyping analysis)

∞ Sputum isolates at baseline, at time of treatment failure and relapse will be sent to NIRT for MGIT DST to Bdq, and Promomanid for Whole Genome Sequencing. Isolates will also be saved at the regional labs until sub-culture results are available for any further DST required for patient management

[B] Baseline ECG should be obtained and additional ECGs conducted daily for the first two weeks after starting treatment (if hospitalized)

ECG should be repeated as necessary in case of clinical suspicion of heart rhythm and conduction disturbances.

ə Week 9 – Linezolid dose will be modified at week 9 in arm 2

£ Week 13 - Linezolid dose will be modified at week 13 in arm 3

# end of treatment for patients whose 12<sup>th</sup>-week cultures are negative and if 16<sup>th</sup> week cultures are not available then no clinical or radiological evidence of TB

\$ Adverse event monitoring over the phone weekly from the 17<sup>th</sup> week onwards till the end of treatment (except during the days of the scheduled visit)

HRQoL – health-related Quality of Life

LJ-Lowenstein-Jensen; MGIT-Mycobacterial Growth Inhibitor Tube; DST – Drug susceptibility test;

HCV-Hepatitis C virus; HIV-Human immunodeficiency virus

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3 Four 100 mg tablets (400 mg) of Bedaquiline will be administered by mouth once a day  
4 for two weeks, followed by 200 mg (two 100 mg tablets) orally thrice a week for 24 weeks.  
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6 Pretomanid will be administered as one 200mg tablet daily for 26 weeks. In Arm 2, the LZD  
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8 dose will be reduced from 600mg to 300 mg after nine weeks and 13 weeks in Arm 3,  
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10 irrespective of the smear and culture results. At the time of randomization, dosing of LZD and  
11  
12 other drugs is not weight-based and is pre-fixed in the protocol. LZD is given the ability to  
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14 interrupt or reduce the dose if needed based on Grade 3 toxicity. The continuation of the regimen  
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16 beyond 26 weeks and up to 39 weeks will be based on the culture results of week 16.  
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23 Randomization procedures: A Computer-generated list of random numbers using  
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25 REDCAP software will be used for randomization centrally. The site physician using these  
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27 computer-generated randomizations will be able to randomize the study participants to any one  
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29 of the three arms in a ratio of 1:1:1. Block randomization will be used to randomize participants  
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31 in the trial. The NIRT statistician will assign the unique study identification number after  
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33 confirming all the study-related eligibility criteria. There is no blinding in the trial.  
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38 Treatment Allocation: The study participants will be randomized to receive one of the  
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40 three treatment regimens in a 1:1:1 ratio using block randomization. A computer-generated list of  
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42 random numbers using REDCAP software will be used for randomization centrally. NIRT center  
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44 will generate the allocation codes at the time of the study. At the time of patient's admission to  
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46 the study, the site Physician will be able to randomize them at the site on RedCAP software  
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48 based on pre-defined factors.  
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52 Treatment delivery, compliance, and retention: The study participants will be  
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54 hospitalized for two weeks wherever feasible, and study drugs will be administered under  
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3 supervision. Ambulatory care can also be offered if hospitalization is not needed. After  
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5 discharge, medications will be supplied – weekly for the first month, then fortnightly till the 3<sup>rd</sup>  
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7 month, and then monthly till the end of treatment. A healthcare provider or a family member will  
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9 be assigned and trained to supervise the drug intake and monitor adherence to treatment. During  
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11 the treatment phase, the patient will be reviewed every week for 16 weeks, then monthly until the  
12  
13 end of the treatment phase (26/39 weeks). During these visits, a detailed medical history will be  
14  
15 collected; adverse drug reactions and tolerability to study drugs will be monitored. The site  
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17 medical officer does the management of adverse events (AE) and the causality assessment with  
18  
19 the grading of AEs as per DAIDS criteria.<sup>8</sup> Treatment adherence will be assessed by reviewing  
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21 treatment cards, empty pill covers, on-time drug refills, and hospital attendance. Offering  
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23 enhancers such as nutrition supplements, reimbursing nominal costs for loss of wage, or  
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25 transportation will improve the treatment compliance. Post-treatment follow-up visits will be  
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27 done for 48 weeks.  
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34 Concomitant medication while in the trial: A detailed medical history will be collected  
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36 during every study visit. Any medications consumed while in the trial will be entered on the  
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38 concomitant medications page of the case record form. Medication entries shall be specific to the  
39  
40 generic name, dose, unit, frequency, route of administration, start, stop date, and reason for use.  
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42 Drugs prohibited from being used during the study include aspirin or ibuprofen or medicines that  
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44 can cause gastrointestinal bleeding; any antibiotics until clinically warranted, and efavirenz-  
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46 based antiretroviral therapy.  
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51 Criteria for study participants discontinuation/withdrawal: The trial regimen may be  
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53 discontinued in some patients in situations such as resistance to study drugs, intolerable or severe  
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55 toxicity, or treatment failure. A patient may be withdrawn from the study if he or she is unwilling  
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3 to participate due to any reason, including pregnancy, drug-drug interaction, non-compliance &  
4 non-availability, drug resistance, or recommendation by the Data Safety & Monitoring Board.  
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9 Study Outcome: The primary outcome of the trial is the proportion of patients with  
10 favorable treatment outcomes, defined as sustained treatment success at twelve months post  
11 successful TB treatment, being alive and free of TB. Indicators of successful TB treatment  
12 include Cure (patient who has completed 26 or 39 weeks of treatment without evidence of failure  
13 and with at least two consecutive negative sputum cultures taken at least seven days apart) and  
14 Treatment Completed (patient who has completed 26 or 39 weeks of treatment whose outcome  
15 does not meet the definition of cure or treatment failure) as defined by WHO.<sup>9</sup> The secondary  
16 outcome includes the proportion of patients with (i) serious adverse events or adverse drug  
17 reactions, including tolerability of the study drugs during the treatment and follow-up period, and  
18 (ii) unfavorable outcomes, comprising death, bacteriological or clinical failure, and loss to  
19 follow-up.  
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35 Participant timeline: Each participant involved in the trial will have a screening period of  
36 2 weeks, followed by a treatment period of 26 weeks to 39 weeks based on sputum culture  
37 results at week 16, and a post-treatment follow-up of 12 months. Table 2 shows the entire  
38 schedule of enrolment of a patient, the interventions to be given, and the assessments to be done  
39 for a participant in the trial.  
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47 Patient and public involvement: Since the scientific problem is still not proven, patients  
48 were not involved in the research question development or the design of this study. However,  
49 learning from the difficulties faced by patients on the higher dose of LZD, there is an urgent need  
50 to find the correct dose of LZD with lower toxicity, better tolerability, and, at the same time, not  
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3 compromise the efficacy of the regimen to prevent recurrence of TB. The study proposal is  
4 discussed among the members of the Institutional Scientific Advisory Committee, the  
5 Institutional Ethics Committee, the Drug Controller General of India, and the Community  
6 Advisory Board. Meetings, conference presentations, and publications will be used to  
7 disseminate study findings.  
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15 Sample size assumption: mBPAL trial will evaluate the effectiveness of various doses and  
16 duration of LZD with BDQ and Pa after 26 weeks of treatment in adults with pre-XDR or MDR  
17 (TI/NR) pulmonary TB patients. The efficacy of BDQ with Pa and LZD (600 mg) for 26 weeks  
18 is reported to be about 91%.<sup>5</sup> Assuming that the effectiveness of treatment arms of BDQ + Pa  
19 with either LZD 600mg for nine weeks followed by 300mg for 17 weeks or LZD 600mg for 13  
20 weeks followed by 300mg for 13 weeks would be about the same based on the recently released  
21 interim outcomes of ZeNIX trial results, we hypothesize that these treatment arms with planned  
22 reduction of LZD would be non-inferior to the LZD 600 mg for 26 weeks arm with a non-  
23 inferiority margin of about 10% ineffectiveness. To demonstrate this, with a power of 80% and  
24 an alpha error of 5%, we require about 111 patients in each arm. Factoring in a loss of 20% (due  
25 to default or migration), we need 133 patients in each arm, or a total of 399 patients (approx.  
26 400) to achieve our study objective.  
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44 Data collection, management, and interim analysis: Clinical and demographic  
45 information and laboratory reports will be collected from the individual participants in the paper  
46 case report forms and entered in Redcap software at all the participating sites. Adverse events  
47 will be monitored during weekly and monthly visits through physical examination, history-  
48 taking, and laboratory investigations as specified in the study schedule.  
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3 Solicited and unsolicited adverse events will be recorded and managed per DAIDS  
4 criteria. The data will be verified for accuracy and completeness. Data access would be restricted  
5 to the study statisticians at NIRT and Central TB Division. Third-party access to data is restricted  
6 and will be made available only on request to NIRT. Data analysis will be done using SPSS  
7 software by statisticians at NIRT. An interim analysis is planned when at least 33%  
8 (approximately 120) of the study participants complete 26 weeks of treatment and the results of  
9 sputum smear and MGIT culture are available.

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12 *Study outcome analysis:* The primary effectiveness analysis will be conducted using the  
13 culture results from MGIT culture. A modified Intent-to-treat (mITT) analysis will be carried out  
14 to evaluate the effectiveness of the newer regimens. We will evaluate the hypothesis that the  
15 investigational regimens are non-inferior to the standard of care regimen for the treatment of Pre-  
16 XDR-TB, MDR<sub>TI/NR</sub> in terms of favorable outcomes (including sustained cure and treatment  
17 completed) and unfavorable outcomes (including death, treatment failure, and lost to follow-up)  
18 in the field settings. Time to culture conversion and adverse events at the end of 9 weeks and  
19 26/39 weeks will be estimated using survival analysis methods. Deaths and study withdrawals  
20 within the first 7-days of treatment and baseline study drug resistance will be considered initial  
21 exclusions. They will not be included in the final mITT analysis. Kaplan-Meier survival curves  
22 will be constructed, and time to culture conversion and adverse events will be calculated at the  
23 end of 9 and 26/39 weeks and compared among regimens using the Log-rank test. To identify the  
24 important covariates with culture conversion, a Cox regression model will be used. Count  
25 regression models will be employed to compare the number of adverse events experienced across  
26 treatment regimens adjusting for other covariates. The HRQOL between the regimens will be  
27 compared using ANOVA or the nonparametric alternative. Ordinarily least square regression  
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3 will be used to compare the quality of life across regimens after adjusting for other variables. Per  
4 protocol analysis will be done for those patients who comply with the treatment regimen they  
5 were assigned. All participants who have consumed >80% of the drugs will be included in this  
6 analysis. Safety analysis will include data from all who received at least one dose of the study  
7 regimen.  
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15 Data and Safety Monitoring Board (DSMB): The DSMB comprises a statistician, clinical  
16 trial experts, a pharmacologist, and a pulmonologist. They will be notified about the safety data  
17 after every ten patients are enrolled in the trial and complete nine weeks of treatment in each of  
18 the three arms. This review will mainly be by circulation to members. An in-person review will  
19 be conducted when at least 33% (approximately 120) of the enrolled patients have completed 26  
20 weeks of treatment and sputum smear, and MGIT culture results are available. They will review  
21 the progress of the trial and safety issues for the trial participants in the early stages focusing  
22 majorly on grade 3 or 4 adverse events and serious adverse events. DSMB may ask for ad-hoc  
23 analysis and can recommend continuing or discontinuing or making modifications in the protocol  
24 based on any of these criteria: Grade 3 or Grade 4 AE >10%; Deaths due to any cause > 15%;  
25 Non-cardiac Notifiable events >15% and QTc(F) > 500 ms in more than 10% of enrolled patients.  
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42 Study site monitoring and quality assurance: A study monitoring committee formed by  
43 the sponsor and other stakeholders will monitor the study data quality per trial standard operating  
44 procedures. The monitoring plan will be followed to perform field visits and audits at various  
45 stages. The CRFs, patient records, and all source documents of the study participants in this  
46 study will be made available to be reviewed by the study monitors. Regular virtual meetings with  
47 the investigators of each study site will be conducted to discuss the study's progress. Any critical  
48 protocol changes made during the research will be communicated to the Institutional Ethics  
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3 Committee, CTRI, and the trial participants. At any time during or after completion of the study,  
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5 the sponsor, through independent non-study staff, may conduct a quality assurance assessment of  
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7 the site records, and the regulatory agencies may conduct a regulatory inspection.  
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11 *Confidentially of trial data:* All study-related CRFs and documents related to the trial  
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13 will remain in the custody of the site Principal Investigator under lock and key until transferred  
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15 to archives. The records identifying the patient will be kept confidential and will not be made  
16  
17 publicly available. All electronic data will be saved securely in password-protected systems. The  
18  
19 final data from the study will be accessible only to the statisticians in NIRT and the Central TB  
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21 division. When trial results are published, the patient's identity will remain confidential. The  
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23 confidentiality of the patients included in this trial will be maintained during the conduct of the  
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25 study period following the Indian-GCP and the relevant regulations by the laws of India.  
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### 30 **Ethics and dissemination**

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32 The study has been approved by the ethics committees of participating institutes and the  
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34 ICMR-National Institute for Research in Tuberculosis. The current ICH Good Clinical Practice  
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36 and the ICMR ethical guidelines for biomedical research in human participants will be followed  
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38 in the current trial. This will ensure public assurance that the well-being, safety, and rights of the  
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40 participants are considered, which is consistent with the principles originating from the Helsinki  
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42 Declaration and will maintain the credibility of the clinical trial data. The personal data  
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44 necessary to analyze the safety, tolerability, and antibacterial activity of the investigational  
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46 product will be used. Manuscript preparation, result dissemination, and publication materials are  
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48 the principal investigator's responsibility. After the completion of the trial, the investigators  
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50 anticipate publishing the study results in peer-reviewed scientific journals, presenting the  
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3 findings in meetings, and sharing the results widely with the program managers and  
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5 policymakers.  
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## 8 **Discussion**

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10 WHO has released the Global list of High Burden Countries for MDR/RR-TB for 2021–  
11 2025. The list contains the top 20 countries with an estimated absolute number of incident cases  
12 and the top 10 countries with a severe burden of incident rate totaling thirty countries. Compared  
13 to 2016–2020, few countries like Ethiopia have transitioned out, while countries like Nepal have  
14 been added to the list.<sup>1</sup> Average success rate of conventional XDR-TB patients put on treatment  
15 (without BDQ) from 2016 to 2018 is 29%. This has increased to 48% in 2018.<sup>10</sup> Managing  
16 MDR-TB and XDR-TB remain a significant challenge in eliminating TB. DR-TB patients  
17 treated with short regimens with newer oral drugs are expected to have a better quality of life  
18 than patients on standard (either short or long) DR-TB regimens for multiple reasons. Patients'  
19 adherence improves with injectable-free treatment and facilitates the implementation of  
20 community programs. This would reduce the costs incurred for the patients on travel to health  
21 facilities for injections, loss of wages, or hospitalization expenses during the intensive phase of  
22 treatment of standard regimens. Hence, it is reasonable to assume that injectable-free treatment  
23 regimens that potentially reduce adverse reactions would likely improve patients' overall health-  
24 related quality of life. Second, BDQ-containing regimens reduce the costs per treatment success  
25 by 18–20% in short course regimens and 49–50% in long course regimens. Approximately  
26 61,000 more patients are estimated to be treated successfully over five years with BDQ-  
27 containing regimens.<sup>11</sup> The success rate of DR TB patients treated under the BDQ conditional  
28 access program (BDQ-CAP) is 71%.<sup>10</sup>  
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Studies have compared the outcomes of an extended oral regimen containing BDQ with the shorter oral regimen. A shorter all-oral BDQ-containing regimen showed more beneficial effects than an injectable-free longer regimen containing BDQ. The favorable odds ratio of 3.9 (1.7-9.1) was observed for success versus failure/recurrence, 1.6 (1.2-2.2) for success versus all unfavorable outcomes, and 0.5 (0.4-0.8) for loss to follow-up, thereby supporting the use of all-oral shorter regimen.<sup>12</sup> Also, studies have evaluated the safety of the newer drugs in shorter oral regimens. The NIXTB study reported LZD toxicity such as peripheral neuropathy and myelosuppression among 81% and 48% of the study population. Adverse events leading to death and serious adverse events were 9% and 30%, respectively, in the 600 mg twice daily LZD group and 3% and 9% in the 1200 mg once daily LZD group.<sup>3</sup> In the ZeNIX trial, peripheral neuropathy was reported in 38% of those receiving 1200mg of LZD for six months; 24% of those receiving 1200mg of LZD for two months; 24% of those receiving 600mg of LZD for six months and 13% of those receiving 600mg of LZD for two months. Similarly, anemia, secondary to linezolid exposure, was noticed in 22% of those receiving 1200mg of LZD for six months; 17% of those receiving 1200mg of LZD for two months; 2% of those receiving 600mg of LZD for six months and 7% in those receiving 600mg of LZD for two months.<sup>5</sup> The mBPAL study will determine the effectiveness in managing DR-TB patients by comparing the varying dose of LZD with BDQ and Pa regimens. Safety assessment in the mBPAL study is one of the significant components in measuring the outcome of the regimens.

We are proposing to conduct a pragmatic clinical trial (mBPAL study) with varying doses of LZD along with BDQ and Pa as a planned reduction of LZD for the treatment of Pre-XDR and MDR<sub>TI/NR</sub> pulmonary TB patients for 26-39 weeks. Given the poor tolerability and increased frequency of dose interruption in regimens containing LZD, this trial will help us decide on the

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2  
3 effective dosing of LZD to be given with BDQ and Pa for an entirely oral short-course regimen  
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5 to treat highly drug-resistant TB in the field setting. The main drivers of the acceptability of the  
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7 BPaL regimen were the short duration of treatment, fully oral regimen without injectable,  
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9 reduced pill burden, anticipated higher treatment success, the lower financial burden for patients  
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11 and the program, reduced load on the health system, using existing diagnostic processes and  
12  
13 lesser burden to TB laboratories for monitoring of bacteriological treatment. This study will  
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15 create a new standard of care for Pre-XDR and MDR<sub>TI/NR</sub>-pulmonary TB patients that will not  
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17 only have better and earlier culture conversion but also reduce the proportion of patients who do  
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19 not adhere to the entire course of therapy.  
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- 28 • **Authors' contributions**: CPP, CPR & RS – conceived & designed the study / CPP, BD,  
29  
30 CPR & BR – development and writing of the study protocol / CPP, BD, CPR, BR, MP,  
31  
32 SM & SuM – writing and editing this manuscript
- 33 • **Funding**: This Study/ Pragmatic Clinical Trial is supported by the United States Agency  
34  
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36  
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38  
39 support of the American People through the United States Agency for International  
40  
41 Development (USAID). The contents of this study document are the authors' sole  
42  
43 responsibility and do not necessarily reflect the views of USAID or the United States  
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45 Government. Trial Sponsors: ICMR-National Institute for Research in Tuberculosis  
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- 50 • **Competing interests**: None  
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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	17
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13, 14

## Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5,6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6

## Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7,8
Interventions	11	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	11	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10
	11	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11



1				
2	Participant	13	Time schedule of enrolment, interventions (including	11
3	timeline		any run-ins and washouts), assessments, and visits for	
4			participants. A schematic diagram is highly	
5			recommended (see Figure)	
6				
7	Sample size	14	Estimated number of participants needed to achieve	11,12
8			study objectives and how it was determined, including	
9			clinical and statistical assumptions supporting any	
10			sample size calculations	
11				
12				
13	Recruitment	15	Strategies for achieving adequate participant	8
14			enrolment to reach target sample size	
15				

### Methods: Assignment of interventions (for controlled trials)

#### Allocation:

20				
21	Sequenc	16	Method of generating the allocation sequence (eg,	9
22	e	a	computer-generated random numbers), and list of any	
23	generatio		factors for stratification. To reduce predictability of a	
24	n		random sequence, details of any planned restriction	
25			(eg, blocking) should be provided in a separate	
26			document that is unavailable to those who enrol	
27			participants or assign interventions	
28				
29				
30	Allocatio	16	Mechanism of implementing the allocation sequence	9-10
31	n	b	(eg, central telephone; sequentially numbered,	
32	conceal		opaque, sealed envelopes), describing any steps to	
33	ment		conceal the sequence until interventions are assigned	
34	mechani			
35	sm			
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38	Impleme	16	Who will generate the allocation sequence, who will	9
39	ntation	c	enrol participants, and who will assign participants to	
40			interventions	
41				
42	Blinding	17	Who will be blinded after assignment to interventions	NA
43	(masking)	a	(eg, trial participants, care providers, outcome	
44			assessors, data analysts), and how	
45				
46				
47		17	If blinded, circumstances under which unblinding is	NA
48		b	permissible, and procedure for revealing a participant's	
49			allocated intervention during the trial	
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### Methods: Data collection, management, and analysis

1				
2	Data	18	Plans for assessment and collection of outcome,	11,12,20,21,22
3	collection	a	baseline, and other trial data, including any related	
4	methods		processes to promote data quality (eg, duplicate	
5			measurements, training of assessors) and a	
6			description of study instruments (eg, questionnaires,	
7			laboratory tests) along with their reliability and validity,	
8			if known. Reference to where data collection forms can	
9			be found, if not in the protocol	
10				
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12		18	Plans to promote participant retention and complete	10
13		b	follow-up, including list of any outcome data to be	
14			collected for participants who discontinue or deviate	
15			from intervention protocols	
16				
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18	Data	19	Plans for data entry, coding, security, and storage,	12,14
19	managemen		including any related processes to promote data	
20	t		quality (eg, double data entry; range checks for data	
21			values). Reference to where details of data	
22			management procedures can be found, if not in the	
23			protocol	
24				
25				
26	Statistical	20	Statistical methods for analysing primary and	12,13
27	methods	a	secondary outcomes. Reference to where other details	
28			of the statistical analysis plan can be found, if not in	
29			the protocol	
30				
31				
32		20	Methods for any additional analyses (eg, subgroup and	12,13
33		b	adjusted analyses)	
34				
35		20	Definition of analysis population relating to protocol	12,13
36		c	non-adherence (eg, as randomised analysis), and any	
37			statistical methods to handle missing data (eg, multiple	
38			imputation)	
39				
40				
41	<b>Methods: Monitoring</b>			
42				
43	Data	21	Composition of data monitoring committee (DMC);	13,14
44	monitoring	a	summary of its role and reporting structure; statement	
45			of whether it is independent from the sponsor and	
46			competing interests; and reference to where further	
47			details about its charter can be found, if not in the	
48			protocol. Alternatively, an explanation of why a DMC is	
49			not needed	
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52		21	Description of any interim analyses and stopping	12,13
53		b	guidelines, including who will have access to these	
54			interim results and make the final decision to terminate	
55			the trial	
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2	Harms	22	Plans for collecting, assessing, reporting, and	13
3			managing solicited and spontaneously reported	
4			adverse events and other unintended effects of trial	
5			interventions or trial conduct	
6				
7	Auditing	23	Frequency and procedures for auditing trial conduct, if	13,14
8			any, and whether the process will be independent from	
9			investigators and the sponsor	
10				
11				
12	<b>Ethics and dissemination</b>			
13				
14	Research	24	Plans for seeking research ethics	14
15	ethics		committee/institutional review board (REC/IRB)	
16	approval		approval	
17				
18	Protocol	25	Plans for communicating important protocol	14,15
19	amendment		modifications (eg, changes to eligibility criteria,	
20	s		outcomes, analyses) to relevant parties (eg,	
21			investigators, REC/IRBs, trial participants, trial	
22			registries, journals, regulators)	
23				
24				
25	Consent or	26	Who will obtain informed consent or assent from	8
26	assent	a	potential trial participants or authorised surrogates,	
27			and how (see Item 32)	
28				
29				
30		26	Additional consent provisions for collection and use of	8
31		b	participant data and biological specimens in ancillary	
32			studies, if applicable	
33				
34	Confidential	27	How personal information about potential and enrolled	14
35	ity		participants will be collected, shared, and maintained	
36			in order to protect confidentiality before, during, and	
37			after the trial	
38				
39				
40	Declaration	28	Financial and other competing interests for principal	17
41	of interests		investigators for the overall trial and each study site	
42				
43	Access to	29	Statement of who will have access to the final trial	14
44	data		dataset, and disclosure of contractual agreements that	
45			limit such access for investigators	
46				
47				
48	Ancillary	30	Provisions, if any, for ancillary and post-trial care, and	NA
49	and post-		for compensation to those who suffer harm from trial	
50	trial care		participation	
51				
52	Disseminati	31	Plans for investigators and sponsor to communicate	14,15
53	on policy	a	trial results to participants, healthcare professionals,	
54			the public, and other relevant groups (eg, via	
55			publication, reporting in results databases, or other	
56			data sharing arrangements), including any publication	
57			restrictions	
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2 31 Authorship eligibility guidelines and any intended use NA  
3 b of professional writers  
4  
5 31 Plans, if any, for granting public access to the full NA  
6 c protocol, participant-level dataset, and statistical code  
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9 **Appendice  
s**

- 10  
11 Informed 32 Model consent form and other related documentation ✓  
12 consent given to participants and authorised surrogates  
13 materials  
14  
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16 Biological 33 Plans for collection, laboratory evaluation, and storage 20,21,22  
17 specimens of biological specimens for genetic or molecular  
18 analysis in the current trial and for future use in  
19 ancillary studies, if applicable  
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