ARTICLE DETAILS

TITLE (PROVISIONAL) | 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

AUTHORS | Padmapriyadarsini, Chandrasekaran; Devaleenal, Bella; Ponnuraja, C.; Ramraj, Balaji; Singla, R; Parmar, Malik; Matteo, Sanjay; Mandal, Sudarsan

VERSION 1 – REVIEW

REVIEWER | Li, Huai-chen
Shandong Provincial Hospital

The authors declare that the peer review was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

REVIEW RETURNED | 26-Dec-2021

GENERAL COMMENTS | MDR/XDR-TB causes significant morbidity and to date no one has demonstrated efficacy of a single anti-tuberculosis drug in this population. Combination anti-TB shave shown benefit in animal models and are often discussed as promising. However, the few treatment studies conducted in this field have not demonstrated efficacy. After I read the abstract, I had hoped this exploration would change this record.

In this manuscript, researchers planned an interesting prospective cohort study comparing the effectiveness of various doses and duration of Lzd in combination with Bdq and Pa. The study designs and possible results from this study may be important for the management of MDR/XDR-TB.

Points for attention in revision are:

Q1. The detailed exclusion criteria should demonstrate how to deal with patients who are allergic to a single drug (Lzd, Bdq or Pa). Whether these patients can be enrolled or not?

Q2. The study should specify the effectiveness of treatment outcomes. Such as primary and secondary efficacy indicators relevant to the design. Also, safety evaluation.

Q3. Please explain the different dosage of Lzd, Bdq or Pa used (600mg or 300mg). Was it weight based?

Q4. The authors are in a position to comment on safety and tolerability of the combination therapy. This information should be added.

Q5. The authors should clarify diagnostic detection methods and their standardability of MDR/XDR-TB.

Q6. The research design also has the following limitation:
The single-arm study did not have a control group, so treating physicians may be biased to assign causality to all adverse events to related drugs. Due to the long treatment course of MDR/XDR-TB, it may not be able to complete the consolidation treatment for most patients. So the final results cannot be collected temporarily.

**REVIEWER**  
Hossain, Shahed  
icddr,b, Centre for Equity and Health Systems

**REVIEW RETURNED**  
28-Dec-2021

**GENERAL COMMENTS**

Title: 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

This is a well written protocol and merits publication. Despite many difficulties to undertake a pragmatic trial, it seems to be an appropriate design to evaluate the effectiveness of modified Bedaquiline / Pretomanid / Linezolid (mBPaL) which is necessary and important for the elimination targets of TB in India and the global point of view.

I have only a few comments:
1. Does tolerability include toxicity and other side effects (page 5, objective a)? How toxicity is defined and at what point of adverse events the study will be call off?
2. Will the medical history include the followings: taking of other drugs e.g., steroids; recent episodes of Covid 19, diabetes and associated lung conditions, liver function status?
3. How adverse events log be maintained and at what frequently? Will it be looking for either solicited and unsolicited adverse Events (AE) or only unsolicited AEs?
4. Supervision: Hospitalization versus ambulatory Rx (page 6). Who will bear the cost of hospitalization during treatment and during any AEs? What about other cost?
5. There might be heterogeneity among the 8 sites. A little description of the sites would be useful (Feasibility and research capability).
6. Sample size estimation: Intra cluster differentiation among 8 sites (page 12) considered?
7. How frequently the DSMB will be organized?
8. Future cost effectiveness study should be considered.

Hopefully, addressing these issues will enrich the protocol and make it more doable practically.

**REVIEWER**  
Kloprogge, Frank  
University College London, Institute for Global Health

**REVIEW RETURNED**  
27-May-2022

**GENERAL COMMENTS**

Thank you for the invitation to review the protocol manuscript. I am happy to read this study is on the way, given the various questions around linezolid dosing.

Abstract: This is reads confusing as it reads as if second outcome is the counterpart of the primary outcome. Analogy, flipping coin; primary outcome is heads, secondary outcome is tails. Maybe specify that secondary outcome is deaths, loss to follow-up,
Reviewer: 1

1. The detailed exclusion criteria should demonstrate how to deal with patients who are allergic to a single drug (Lzd, Bdq, or Pa). Whether these patients can be enrolled or not?
   
   **Response:** Patients allergic to study drugs should not be enrolled in the study; this has now been mentioned in Table 1 of the Methods and Analysis section.

2. The study should specify the effectiveness of treatment outcomes, such as primary and secondary efficacy indicators relevant to the design—also safety evaluation.
   
   **Response:** Primary and Secondary efficacy indicators have been better explained in the Methods and Analysis section of the Study Outcomes section.

3. Please explain the different dosages of Lzd, Bdq, or Pa used. Was it weight-based?
   
   **Response:** The dosing of the drugs in the study was not weight-based. Dosing of BDQ, Pa, and LZD (600mg) at randomization was pre-determined as per the manufacturers. This is included in the subsection study regimen and dosing under section Methods and Analysis. In comparison, LZD 300mg is half the recommended dose and was chosen for the practicality of administration (breaking the available drug into two halves). Also, other global studies have suggested reducing the dose to 300mg in case of toxicity.

4. The authors are in a position to comment on the safety and tolerability of the combination therapy. This information should be added.
   
   **Response:** This information has now been added in the Study Outcomes section, as they form a part of the secondary outcomes of the study.
5. The authors should clarify diagnostic detection methods and their standardability of MDR/XDR-TB.

Response: The diagnostic detection method for this study was sputum positivity for acid-fast bacilli, which has been better explained in the Recruitment Process section under the Materials And Analysis section.

6. The single-arm study did not have a control group, so treating physicians may be biased to assign causality to all adverse events to related drugs.

Response: We agree with the Reviewer that this trial does not have a control group without the drugs in the intervention's arms. However, by the time the study was initiated, WHO had recommended using the mBPaL regimen for Pre-XDR TB patients. Hence the BPaL regimen with 600mg LZD for 6-months will be considered the standard of care, and the other two regimens (with 300mg LZD) will be compared against the first regimen (600mg daily)

Reviewer 2

1. Does tolerability include toxicity and other side effects? How toxicity is defined, and at what point of adverse events the will be call off?

Response: Yes, tolerability includes toxicity and other side effects. Toxicity or adverse events will be graded and managed based on DAIDS criteria, which have been referenced in the manuscript. The Data Safety Monitoring Board will be notified about the grade 3 or above adverse events after every ten patients enrolled and completing week 9 in each of the three arms. The DSMB will inform about the continuation or stopping of the study based on any of these criteria - Grade 3 or Grade 4 AE >10%; Deaths due to any cause > 15%; Non-cardiac Notifiable events >15% and QTc(F) > 500ms in more than 10% of enrolled patients. These have now been added to the manuscript.

2. Will the medical history include the following: taking other drugs like steroids, recent episodes of COVID-19, diabetes and associated lung conditions, and liver function status?
Response: Any concomitant medication taken during the trial will be appropriately documented (mentioned in the subsection “Concomitant medications while in the trial” under the Methodology and Analysis section). Detailed medical, surgical, medication, and alcohol history will be collected to assess the eligibility for trial participation (“Recruitment process” subsection). A detailed medical history will be collected during the study visit. This has been added to the manuscript (“Concomitant Medications while in the trial” subsection).

3. How are adverse events log to be maintained and at what frequency? Will it be looking for either solicited and unsolicited adverse events or only unsolicited adverse events?

Response: 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. This has been added to the “Data collection, management and Interim analysis” section.

4. Supervision: Hospitalization versus ambulatory treatment. Who will bear the cost of hospitalization during treatment and during any AEs? What about other costs?

Response: Hospitalization costs during treatment and any AE will be borne by the study protocol/sponsors. The study protocol/sponsor will pay other patient-related costs like study-related visits to the hospital, travel costs, loss of wages on the day the participant attends the hospital, etc., which will be borne by the study protocol/sponsor.

5. There might be heterogeneity among the eight sites. A little description of the sites would be useful (feasibility and research capability)

Response: This has now been added to the manuscript in the “Study settings” subsection under the Methods and Analysis heading.

6. Sample Size estimation: Intra cluster differentiation among eight sites considered?

Response: With regard to the variables measured on sociodemographic, clinical, and treatment outcome, the previous multi-centric studies conducted by NIRT, (like High Dose
Rifampin for TB OR Repurposing Metformin for TB treatment OR treatment of pre-XDR or XDR TB treatment, have not demonstrated considerable variations. Therefore, we assumed that patient characteristics are distributed similarly across the study centers. Due to this, we did not include design effect in our current study’s sample size calculation. According to Emilie Vierron et al. (2009), a stratified multicenter individually randomized trial's design effect is less than 1, and the power increases as the ICC increases.

[Reference: Vierron E, Giraudeau B. Design effect in multicenter studies: gain or loss of power? BMC Med Res Methodol. 2009 Jun 18;9:39. doi: 10.1186/1471-2288-9-39. PMID: 19538744; PMCID: PMC2715424]

7. How frequently the DSMB will be organized?

Response: The DSMB will be notified about the safety data after every ten patients get enrolled and complete week 9 in each of the three arms. This review will mainly be by circulation to members. An in-person review will be conducted when at least 33% (approximately 120) of the enrolled patients have completed 26 weeks of treatment and sputum smear, and MGIT culture results are available. This is now added to the manuscript.

8. Future cost-effectiveness study should be considered

Response: We thank the Reviewer for this suggestion. We will do a cost-effectiveness analysis of this trial.

Reviewer 3:

1. Abstract: Specify that secondary outcome is deaths, loss to follow-up, toxicity, etc.

Response: We thank the Reviewer for this, which has now been added to the manuscript.

2. Study outcome analysis: Information on statistical test missing, please elaborate.

Response: As per the study protocol the primary effectiveness analysis will be conducted with MGIT culture results. Modified Intent-to-treat analysis will be carried out to evaluate the effectiveness of the newer regimens. Deaths and study withdrawals within the first 7-days of
treatment and baseline study drug resistance will be considered as initial exclusions and will not be included in the final mITT analysis. Kaplan Meier survival curves will be constructed and time to culture conversion and adverse events will be calculated at the end of 9 and 26/39 weeks and compared among regimens using Log-rank test. To identify the important covariates in relation to culture conversion Cox-regression model will be used. Count regression models will be employed to compare the number of adverse events experienced across treatment regimens adjusting for other covariates. The HRQOL between the regimens will be compared using ANOVA or the nonparametric alternative. Ordinarily least square regression will be used to compare the quality of life across regimens after adjusting for other variables. Per protocol analysis will be done for those patients who comply with the treatment regimen to which they were assigned. All participants who have consumed >80% of the drugs will be included in this analysis. Safety analysis will include data from all who received at least one dose of the study regimen. This has now been explained in the “Study outcome analysis” subsection.

VERSION 2 – REVIEW

| REVIEWER                  | Hossain, Shahed icddr,b, Centre for Equity and Health Systems |
|---------------------------|------------------------------------------------------------|
| REVIEW RETURNED           | 28-Jul-2022                                                 |
| GENERAL COMMENTS          | Thanks for updating and revising this important protocol. I think all the earlier concerns from all the reviewers are addressed. |

| REVIEWER                  | Kloprogge, Frank University College London, Institute for Global Health |
|---------------------------|---------------------------------------------------------------------|
| REVIEW RETURNED           | 28-Jul-2022                                                          |
| GENERAL COMMENTS          | Thank you for the additional work, I am happy with the changes made. |