South African National Essential Medicine List
Primary Healthcare Medication Review Process
Component:

MEDICINE REVIEW

Guideline question: In adults diagnosed with RR-TB, should a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600mg) and a fluoroquinolone be used rather than 9-month or longer (18-month) regimen?

Adolopment of the WHO consolidated guidelines on tuberculosis: Drug-resistant tuberculosis treatment 2022

1. Executive Summary

Date: 30 March 2023

Medicine (INN): bedaquiline, pretomanid, linezolid, moxifloxacin

Medicine (ATC): J04AK05; J01XX08, J04AK08, J01MA14

Indication (ICD10 code): A15.0-3/A15.7-8/A16.0-2/A16.7-8/B20.0 + (U50.00-01)

Patient population: Adults with rifampicin resistant tuberculosis (RR-TB)

Prevalence of condition:

- In a cross-sectional study of identified tuberculosis cases in South Africa between 2012 and 2014, prevalence of multidrug resistant tuberculosis (MDR-TB) was 2.8% (95% CI 2.0, 3.6) and of extensively drug resistant tuberculosis (XDR-TB) was 4.9% (95% CI 1.0, 8.8). (Ismail et al. 2018)(1) https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(18)30222-6/fulltext#supplementaryMaterial
- In 2021, there were approximately 21 000 incident cases of RR-TB in South Africa, as reported by WHO. (WHO Global Tuberculosis Report, 2022)(2) https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022/tb-disease-burden/2-3-drug-resistant-tb

Level of Care: Primary healthcare

Prescriber Level: Medical officer in consultation with a dedicated specialist center.

Motivator/reviewer name(s): Adolopment review team: Jessica Taylor (JT), Natasha Gloeck (NG), Sumayya Ebrahim (SE), Funeka Bango (FB), Norbert Ndjeka (NN), Gary Maartens (GM), Michael McCaul (MM) (methodologist), Jeremy Nel (JN), Tamara Kredo (TK) (methodologist), Karen Cohen (KC), Zahiera Adam (ZA).

Declarations of interest: The review team have no interests to declare in the establishment of this evidence summary. KC, TK, MM, FB, NG, and SE are members of the South African GRADE Network.

Funding and acknowledgments:

NG, TK, MM, SE, FB are partly supported by the Research, Evidence and Development Initiative (READ-It) project. READ-It (project number 300342-104) is funded by UK aid from the UK government; however, the views expressed do not necessarily reflect the UK government's official policies. ZA is a consultant for Right to Care.

We would like to thank and acknowledge the following people:

- Trudy Leong, who supported FB with planning the economic analyses and presenting the results.
- Greg Fox, the reviewer of the WHO systematic review, for sharing the results.
- Fuad Mirzayev and Samuel Schumacher from WHO's TB Programme, for their engagement and willingness to share the WHO guideline information prior to publication.
- Beverly Stringer, Karen Lowton, Katherine Fielding, Martina Cusinato and the TB-PRACTECAL-PRO team for presenting the results of the qualitative component of the trial conducted in South Africa.

PTC affiliation: n/a

Key findings

- The South African TB programme is seeking to find the most efficacious, safe, acceptable, and cost-effective regimens to treat people with RR-TB. Therefore, we aimed to review whether a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600mg) and a fluoroquinolone be used rather than 9-month or longer (18-month) regimen in adults with RR-TB?

- Current South African standard of care regimens for the treatment of RR-TB include the following:
  - A short-course treatment regimen for less extensive RR-TB disease, without fluoroquinolone resistance. This regimen consists of two months of linezolid (600mg daily), four to six months of high-dose isoniazid, six to nine months of bedaquiline and nine months of levofloxacin, pyrazinamide, ethambutol and clofazimine.
  - An 18-month long-course treatment regimen for RR-TB without additional fluoroquinolone resistance, but with extensive pulmonary or disseminated disease. This regimen consists of six months of bedaquiline and linezolid (600mg daily), and 18 months of clofazimine, terizidone and levofloxacin.
  - An 18-month long-course treatment regimen for RR-TB with additional fluoroquinolone resistance. This regimen consists of six months of bedaquiline and delamanid, and 18 months of clofazimine, terizidone and linezolid (600mg daily).

- In 2022, the WHO published an update of consolidated guidelines on drug-resistant tuberculosis treatment, in which they recommended the use of a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600mg) and moxifloxacin (BPaLM) rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients. *(Conditional, very low certainty of evidence).*

- Additional remarks published alongside the above recommendation included:
  - "Results of drug susceptibility testing for fluoroquinolone resistance were recommended to guide the decision on whether moxifloxacin should be retained or dropped from the regimen."
  - "In cases of documented resistance to fluoroquinolones, it was recommended that BPaL without moxifloxacin should be initiated or continued."
  - "This recommendation applies only to the following populations: people with MDR/RR-TB or with MDR/RR-TB and resistance to fluoroquinolones (pre-XDR TB); people with confirmed pulmonary TB and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular and disseminated (miliary) TB; adults and adolescents aged 14 years and older; all people regardless of HIV status; patients with less than 1-month previous exposure to bedaquiline, linezolid, pretomanid or delamanid. When exposure is greater than 1 month, these patients may still receive these regimens if resistance to the specific medicines with such exposure has been ruled out."
  - "This recommendation does not apply to pregnant and breastfeeding women owing to limited evidence on the safety of pretomanid. "
  - "The recommended dose of linezolid is 600mg once daily, both for the BPaLM and the BPaL regimen."

- To efficiently use available resources and to avoid duplication we conducted an adaptation of these guidelines using the GRADE 'adolopment' methodology.
  - The guideline was appraised in duplicate using the AGREE II instrument and found to be of sufficient quality for adolopment with an overall assessment score of 83%.

- The systematic review that underpinned the WHO guideline was appraised in duplicate using the AMSTAR II critical appraisal tool and found to be of "critically low quality" as several aspects of reporting a systematic review were not available or were unclear. Despite the critically low quality we considered the WHO review and underlying evidence synthesis to be the most up to date (i.e., not missing important evidence), relevant (i.e., directly addressing our target PICOs) and GRADE evidence-to-decision aligned evidence available, and sufficient for guideline adaptation.

- We considered the evidence and judgements published in the WHO guideline evidence to decision framework with respect to effectiveness criteria (benefit, harms and balance of effects), economic criteria (resources and cost-effectiveness), and qualitative criteria (values, equity, feasibility and acceptability). Aligned with the purpose of adaptation to consider local context, we collected evidence of resources and economic consequences and data on acceptability from the perspective of patients from a trial specifically conducted in South Africa.

- The BPAL regimen (with linezolid dosed at 600mg daily for 26 weeks) compared to a WHO long course regimen may result in improved treatment success rates in pre-XDR TB RR 1.34, 95% CI 1.20 to 1.40, NNT 4, n = 872, very low certainty evidence) and MDR TB (RR 1.32, 95% CI 1.19 to 1.39, NNT 4, n = 893,very low certainty evidence), and lower levels of treatment failure, recurrence, death and loss to follow up (very low certainty evidence). Additionally, participants from the ZeNix trial receiving the BPaL (n = 43) regimen may have higher levels of treatment success (RR 1.52, 95% CI 1.38 to 1.55, NNT 3, very low certainty evidence) when compared to a cohort receiving the current South African short course regimen (n = 4 216), as well as reduced rates of death and loss to follow up. However, the risk grade 3 – 5 adverse events associated with BPaL in these comparisons was increased 3 to 4-fold and were judged to be moderate (very low certainty evidence).

- The BPaLM regimen (with linezolid dosed at 600mg daily for 16 weeks, then reduced to 300mg for 8 weeks) compared to local standard of care regimens in a study population with predominantly MDR-TB from the randomised control trial, TB-PRACTECAL, may result in improved treatment success rates (aRR 1.73, 95% CI 1.31 to 2.27, NNT 3, n = 128, very low certainty evidence), lower rates of treatment failure and recurrence (aRR 0.26, 95% CI 0.1 to 0.71, NNT 6, n = 128, very low certainty evidence), lower levels of grade 3 to 5 adverse events (aRR 0.41, 95% CI 0.04 to 0.61, NNT 3, n = 213, very low certainty evidence), and lower levels of loss to follow up (RR 0.16, 95% CI 0.12 to 0.52, NNT 6, n = 128, very low certainty evidence).

- As a result of the associated reduction in pill burden and treatment duration, both BPaL and BPaLM regimens were judged to probably be acceptable, feasible and to increase health equity.

- BPaL and BPaLM are both likely to have lower resource requirements and cost than the current South African long regimens, with similar costs when compared to the current South African short course regimen.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative. **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				x	

Recommendation: The PHC/Adult hospital ERC suggests the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600mg) and a fluoroquinolone rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients. (Conditional recommendation, very low certainty of evidence)

Although WHO recommend moxifloxacin for inclusion in their updated regimen (BPaLM), the PHC/Adult hospital level committee suggest that levofloxacin to be used as fluoroquinolone of choice.

Rationale: The recommended regimen is shorter in duration, less complex and may be cost-saving, particularly for those patients requiring treatment with current South African long regimens. Additionally, the recommended regimen was judged to probably be feasible and acceptable and to improve equity. However, the committee noted the very low quality of evidence on which WHO recommendations are based. In view of the paucity of evidence, the committee felt that the implementation of operational research and enhanced pharmacovigilance to detect safety signals is essential.

Level of Evidence: Very low quality evidence
Review indicator: New high quality evidence

NEMLC RECOMMENDATION (30 March 2023):
The committee supports the ERC's adapted recommendation as follows:
We suggest the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600mg) and a fluoroquinolone rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients. (Conditional recommendation, very low certainty of evidence) Levofloxacin to be used instead of moxifloxacin as fluoroquinolone of choice for inclusion in the revised regimen.

Monitoring and evaluation considerations
Operational research and enhanced pharmacovigilance essential.

Research priorities
Shortened regimens for paediatric and pregnant populations

2. Name of author(s)/motivators/Author affiliation and conflict of interest details

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3. Introduction/ Background

In 2021, approximately 450 000 people developed rifampicin resistant tuberculosis (RR-TB), and 191 000 deaths due to RR-TB were recorded globally.(2) A further 20% of these RR-TB cases were estimated to have additional fluoroquinolone resistance. In South Africa, at least 21 000 incident cases of RR-TB occurred during the year 2021. (2)

RR-TB is associated with poor treatment outcomes as a result of prolonged (9 - 18 months) treatment regimens that are difficult to adhere to, and consist of less effective and more toxic drugs.(3) Historically,

aminoglycosides in particular, were associated with both treatment limiting nephrotoxicity and ototoxicity, leaving patients who had successfully completed RR-TB treatment with significant morbidity. The introduction of novel and repurposed drugs to achieve injectable-free regimens heralded a new era in RR-TB treatment, with some improvement in treatment outcomes. For example, a 2018 cohort of South African patients with RR-TB and additional fluoroquinolone resistance, recorded 73% of treatment outcomes as favorable when using bedaquiline containing regimens. ((3)

Since 2019, three all-oral treatment regimens have been made available in South Africa for the management of RR-TB in adults with pulmonary tuberculosis (TB)(4):

1. The shorter RR-TB regimen (SCR) is available for patients with RR-TB without additional fluoroquinolone resistance and less severe pulmonary disease. This 9-month treatment regimen consists of two months of linezolid, four to six months of high-dose isoniazid, six to nine months of bedaquiline and nine months of levofloxacin, pyrazinamide, ethambutol and clofazimine.
2. The longer RR-TB regimen (LCR-1) is available for patients with RR-TB without additional fluoroquinolone resistance but with extensive pulmonary disease. This 18-month treatment regimen consists of six months of bedaquiline and linezolid, and 18 months of clofazimine, terizidone and levofloxacin.
3. The fluroquinolone-resistant RR-TB regimen (LCR-2) is available for patients with RR-TB and additional fluoroquinolone resistance. This 18-month treatment regimen consists of six months of bedaquiline and delamanid, and 18 months of clofazimine, terizidone and linezolid.

Despite the national implementation of all-oral treatment regimens, free of the toxicities associated with aminoglycosides, these regimens are not without their own concerns. (5) These regimens remain long and are complicated for both patients to adhere to and healthcare workers to implement and are associated with a significant pill burden. Furthermore, the oral drugs included in these regimens are still associated with the potential for significant toxicity, some of which may be related to treatment duration. (6)

In 2022, the World Health Organization (WHO) recommended the use of a six month treatment regimen composed of bedaquiline, pretomanid, linezolid (600mg) and moxifloxacin (BPaLM), rather than the nine month or longer regimens, for the treatment of pulmonary TB and all forms of extrapulmonary TB, except for TB involving the central nervous system, osteoarticular TB, and disseminated (miliary) TB.(7) Desirable characteristics of this regimen include the use of fewer drugs with a reduced pill burden and a shorter treatment duration.(8) To efficiently use available resources and to avoid duplication we conducted an adaptation of these guidelines using the GRADE 'adolopment' methodology. (7, 9)

3. Purpose/Objective and PICO prioritization

To determine if, in adults diagnosed with RR-TB, a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600mg) and a fluoroquinolone is non-inferior to and/or safer than current standard-of-care regimens (9-month or 18-months).

Table 1. PICO eligibility criteria:

Population	Adults with RR-TB
Intervention	1. BPaL (bedaquiline, pretomanid, linezolid) 2. BPaLM (bedaquiline, pretomanid, linezolid, moxifloxacin)
Comparator	1. South African RR-TB short course regimen (SCR) 2. South African RR-TB long course regimen (LCR-1) 3. South African RR-TB with additional fluoroquinolone resistance long course regimen (LCR-2)
Outcome	1. Efficacy 1.1 Mortality 1.2 Treatment failure 1.3 Treatment success 1.4 Loss to follow-up 1.5 Time to sputum culture conversion 2. Safety 2.1 Adverse events 2.2 Treatment interruption/substitution due to adverse events

Three specific PICO questions were prioritized by the review team:

a) Is BPaL (intervention 1) non-inferior to, and/or safer than the South African standard of care (comparator 3) in the treatment of adults with or without fluoroquinolone-resistant tuberculosis?
b) Is BPaLM (intervention 2) non-inferior to, and/or safer than the South African standard of care (comparator 1 and 2) in the treatment of adults with rifampicin-resistant tuberculosis without additional fluoroquinolone resistance?
c) Is BPaL (intervention 1) non-inferior to, and/or safer than BPaLM (intervention 2) in the treatment of rifampicin-resistant tuberculosis without additional fluoroquinolone resistance?

4. Methods:

We conducted a guideline adaptation process using the GRADE adolopment methodology (9) which aims to use existing high-quality, timely and relevant clinical practice guidelines (CPGs) and evidence synthesis (i.e., systematic reviews) to answer prioritised guideline questions. We drew on supporting resources in evidence synthesis and rapid guideline development to further guide methods and processes.(10-12) The adolopment approach to guideline production combines guideline adoption, adaptation, and, as needed, *de novo* development of recommendations, by assessing the underlying relevance, timeliness and directness of synthesised evidence from a source guideline and translating this to the GRADE Evidence-to-Decision (EtD) table. In summary, steps include i) selection of the guideline topic, ii) PICO prioritisation and outcome ranking, iii) identification of appropriate source guidelines, iv) matching source guidelines and recommendations, v) assessment of the underlying evidence according to the EtD criteria and vi) populating the EtD framework and developing a recommendation.

The matched source guideline was appraised using the AGREE II Tool (13) with guideline appraisal by two authors independently for credibility. The underlying evidence synthesis was appraised using the AMSTAR II (14) tool for systematic reviews. We reviewed and extracted the underlying evidence per PICO for the effectiveness EtD criteria (benefit, harms and balance of effects), economic criteria (resources and cost-effectiveness) and qualitative criteria (values, equity, feasibility and acceptability) from the WHO guideline and assessed this for sufficiency. We aimed to supplement this with local contextual evidence (e.g. resources, acceptability, equity).

a. Identification of appropriate sources guideline

The WHO consolidated guidelines on tuberculosis: Drug-resistant tuberculosis treatment 2022 was identified as the most appropriate source guideline for adolopment.

b. Matching source guideline recommendations to each prioritized PICO and determining if a direct matching recommendation exists.

The specific PICO questions prioritized by the review team were matched to recommendations and sub-PICOs with corresponding evidence-to-decision frameworks (EtDs) from the WHO consolidated guidelines on tuberculosis: Drug-resistant tuberculosis treatment. All matched recommendations and sub-PICOs from the WHO consolidated guidelines were considered sufficiently direct. Table 2 outlines the matching process and directness of each matching recommendation and sub-PICO. Directness refers to the concept that the recommendations are appropriate to the context of the health care setting of interest by addressing population, intervention and prioritised outcomes of interest.

WHO sub-PICO questions 7.1, 7.2, 8.2, 8.3 and 8.5 were not linked to EtDs within the published guideline. These EtDs were requested from the guideline but unfortunately were not available, although additional data analysis was provided. Additional data analysis from original study authors was also requested.

Table 2.

Review target PICO questions	Matching WHO consolidated guideline recommendation	WHO Sub-PICO Number	WHO Target PICO or Sub-PICO	WHO Sub-PICO Recommendation	Directness
Is BPaLM (intervention 2) non-inferior to, and/or safer than the South African standard of care (comparator 1 and 2) in the treatment of adults with rifampicin-resistant tuberculosis without additional fluoroquinolone resistance?	WHO suggests the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600mg) and moxifloxacin (BPaLM) rather than 9-monht or longer (18-month) regimens in MDR/RR-TB patients. (Conditional recommendation, very low certainty of evidence)	5.2	Should BPaL vs. WHO_long be used for pulmonary MDR/RR-TB? BPAL compared to WHO_Long in pulmonary MDR/RR TB	Conditional for the intervention. The use of the 6-month treatment regimen, composed of bedaquiline, pretomanid and linezolid (BPaL), rather than longer (18-month) regimens is suggested in patients with MDR/ RR-TB and without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month.	Considered sufficiently direct by review team. Although intervention is BPaL not BPaLM, comparator and population is appropriate.
		5.3	Should BPaL vs. SA_new be used for pulmonary MDR/RR-TB? BPAL compared to SA_new in MDR/RR TB	Conditional for the intervention. The use of the 6-month treatment regimen, composed of bedaquiline, pretomanid and linezolid (BPaL), rather than the 9-month regimen (with linezolid) is suggested in patients with MDR/RR-TB without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month.	Considered sufficiently direct by review team. Although intervention is BPaL and not BPaLM, comparator and population is appropriate.
		6.1	Should BPaLM vs local SoC (TB-PRACTECAL comparator) be used for pulmonary MDR/RR-TB or pre-XDR-TB? BPaLM compared to TB-PRACTECAL comparator in pulmonary MDR/RRTB and pre-XDR TB	Conditional for the intervention. The use of the 6-month treatment regimen, composed of bedaquiline, pretomanid and linezolid (BPaL), rather than 9-month or longer (18-month) regimens is suggested in patients MDR/RR-TB patients with or without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month.	Considered sufficiently direct. Appropriate intervention and comparator consists of regimens that are South African standard of care. However, population includes both MDR/RR-TB and pre-XDR-TB.
		6.6	"Should BPaL (linezolid 600mg/300mg) vs. local SoC regimens (TB-PRACTECAL comparator) be used for pulmonary MDR/RR-TB and pre-XDR-TB? BPaL (linezolid 600mg/300mg) compared to TB PACTECAL comparator in pulmonary MDR/RR-TB and pre-XDR-TB	Conditional for the intervention. The use of the 6-month treatment regimen, composed of bedaquiline, pretomanid and linezolid (BPaL), rather than 9-month or longer (18-month) regimens is suggested in patients MDR/RR-TB patients with or without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month.	Considered sufficiently direct. Although intervention considered is BPaL not BPaLM, the comparator includes regimens that are South African standard of care. However, population includes both MDR/RR-TB and pre-XDR-TB.
		8.2	Should 6-month regimen using bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) be used in patients with pulmonary MDR/RR-TB and without fluoroquinolone resistance? TB PRACTECAL BPaLM vs WHO long-IPD 2021 in pulmonary MDR/RR TB	Not found	Considered sufficiently direct.
		8.3	Should 6-month regimen using bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) be used in patients with pulmonary MDR/RR-TB and without fluoroquinolone resistance? TB PRACTECAL BPALM vs SA_new in pulmonary MDR/RR-TB	Not found	Considered sufficiently direct.
Is BPaL (intervention 1) non-inferior to,	WHO suggests the use of the 6-month treatment regimen	4.1	Should a 6-month regimen using bedaquiline, pretomanid, linezolid vs. longer regimens be used for pulmonary pre-XDR-TB?	Conditional for the intervention. The use of the 6-month treatment regimen, composed of bedaquiline, pretomanid and linezolid (BPaL), rather than longer	Considered sufficiently direct.

and/or safer than the South African standard of care (comparator 3) in the treatment of adults with fluoroquinolone-resistant tuberculosis?	composed of bedaquiline, pretomanid, linezolid (600mg) and moxifloxacin (BPaLM) rather than 9-monht or longer (18-month) regimens in MDR/RR-TB patients. (Conditional recommendation, very low certainty of evidence)		BPAL compared to WHO_Long in pulmonary pre-XDR TB	(18-month) regimen is suggested in patients with MDR/RR-TB and resistance to fluoroquinolones (pre-XDR-TB), who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month.	
		7.1	Should a 6-month regimen using bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) be used in patients with pulmonary pre-XDR-TB? TB PRACTECAL BPaLM vs WHO long-IPD 2021	Not found	Considered sufficiently direct by the review team. Although the intervention is BPaLM not BPaL, the comparators consists of regimens that are South African standard of care.
Is BPaL (intervention 1) non-inferior to, and/or safer than BPaLM (intervention 2) in the treatment of rifampicin-resistant tuberculosis without additional fluoroquinolone resistance?	WHO suggests the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600mg) and moxifloxacin (BPaLM) rather than 9-monht or longer (18-month) regimens in MDR/RR-TB patients. (Conditional recommendation, very low certainty of evidence)	6.2	Should BPaLM vs BPaL (LD 600mg/300mg) be used for pulmonary MDR/RR-TB and pre-XDR-TB? BPaLM compared to BPAL (linezolid 600/300mg)	Conditional for the intervention. The use of the 6-month treatment regimen, composed of bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM), rather than BPaL is suggested in MDR/RR-TB patients with or without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month.	Considered sufficiently direct by the review team, despite population including those with MDR/RR-TB and pre-XDR-TB.
		7.2	Should 6-month regimen using bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) be used in patients with pulmonary pre-XDR-TB? TB PRACTECAL BPaLM vs BPaL (excluding 1200mg regimen) from PRACTECAL, ZENIX studies (4 cohorts) in pulmonary pre-XDR TB	Not found	Considered sufficiently direct by the review team despite the population consisting of those with pre-XDR-TB.
		8.5	Should 6-month regimen using bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) be used in patients with pulmonary MDR/RR-TB and without fluoroquinolone resistance? TB PRACTECAL BPaLM vs BPaL (excluding 1200mg regimen) from PRACTECAL, ZENIX and NIX Studies (6 cohorts) in pulmonary MDR/RR-TB.	Not found	Considered sufficiently direct

c. Assess underlying evidence per recommendation.

i. Availability of an effectiveness systematic review underlying the recommendations

The evidence underpinning the recommendations in the WHO guideline was based on evidence synthesis of the datasets from the TB-PRACTECAL trial, the NIX trial, the ZENIX trial, the South African TB Program 2019 cohort, the South African TB Program 2017 cohort and 2021 WHO individual patient data (multiple cohorts following a public call for data from the WHO).(15-17) The evidence-to-decision (EtD) frameworks based on this data were available in the guideline. Those not available were sourced from the background review authors as highlighted previously.

ii. Evidence quality:

Guideline AGREE-II appraisal.

The 2022 'WHO consolidated guidelines on tuberculosis: Drug-resistant tuberculosis treatment' was appraised by JT and NG using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument.(13) We found the guideline to be of sufficient quality, with an overall assessment score of 83% (recommended with modifications). Individual overall domain scores can be reviewed in table 2. The individual scores and judgement comments of both appraisers can be found in appendix 1.

Table 2. AGREE-II Appraisal

Guideline	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	Overall Assessment
WHO consolidated guidelines on tuberculosis: Drug-resistant tuberculosis treatment, 2022	86%	78%	63%	89%	65%	67%	83%

Domain 1: Scope and purpose
Domain 2: Stakeholder involvement
Domain 3: Rigor of development
Domain 4: Clarity of presentation
Domain 5: Applicability
Domain 6: Editorial independence
OA: overall assessment

Guideline AMSTAR II appraisal

The systematic review that underpinned the WHO guideline was appraised by SE and NG using the AMSTAR II critical appraisal tool.(14) Both reviewers rated this review as "**Critically low quality**" – there was no or minimal information around search strategy, study selection, data extraction, excluded studies with reasons, methods for assessing risk of bias in individual studies, sources of included study funding and meta-analysis methods. The individual AMSTAR II appraisal for both appraisers can be found in appendix 2.

Despite the critically low quality of the underpinning systematic review, the authors considered the WHO review and underlying evidence synthesis to be the most up to date (i.e. not missing important evidence), relevant (i.e. directly addressing our target PICOs) and GRADE EtD aligned evidence available, and sufficient for guideline adaptation.

iii. Qualitative evidence and sufficiency

A summary of the available qualitative evidence was presented at the ERC meeting (16 March 2023) by Beverly Stringer and team from TB-PRACTECAL-PRO, a qualitative sub study of TB-PRACTECAL that captured patient-reported experiences and quality of life outcomes. The results of this study were used to update the evidence presented by WHO and presented to the ERC.

iv. Economic evidence and sufficiency

Two studies were found to have assessed the cost effectiveness of the BPaL regimen as the intervention. Both these studies were assessed and included in the decision framework by the WHO. The studies were multinational analyses which included patients from South Africa in their study populations. The study population in the paper by Gomez et al. 2021 was patients with XDR-TB, MDR-TB failure and treatment-intolerant patients and compared BPaL to the 18-month XDR regimen.(18) Treatment outcomes for study were from the Nix and ZeNix trials. The second study which was also trial based (TB-PRACTECAL) by Sweeney et al. 2022 assessed the cost effectiveness of BPaL with or without moxifloxacin (BPaLM) or clofazimine (BPaLC).(19) Although this study focused on patients with RR-TB, the regimen used as a comparison was a mix of the long and short regimens. A summary of the economic evidence is included in table 3.We did not find a study that focused on patients with RR-TB which assessed the cost effectiveness of the BPaL regimen compared to the short oral regimen, which is one of the current standard of care regimens in South Africa.

A normative cost analysis of direct costs associated with BPaL and BPaLM regimens was conducted by the review team and included for consideration by the ERC.

Table 3. Summary of Economic Evidence

Study ID	Study Title	Participants	EE Methods	Study Perspective	Intervention	Comparison	Model	Input parameters	Outcome measure	Results	Unit costs for BPaL (M/C)	Cost for standard of care regimen (short oral regimen)
Gomez, et al. 2021.	Cost-effectiveness of bedaquiline, pretomanid and linezolid for treatment of extensively drug-resistant tuberculosis in South Africa, Georgia and the Philippines	Patients with XDR-TB, MDR-TB failure and treatment intolerant patients.	Cost-utility analysis	Provider's perspective	BPaL	Std of care (SA: 18 month regimen: 6 months of linezolid, bedaquiline, delamanid, clofazimine, terizidone, pyrazinamide, high-dose isoniazid (or ethionamide) and 12 months of linezolid, clofazimine, terizidone, pyrazinamide, high-dose isoniazid (or ethionamide)	Markov model	Demographics Treatment outcomes (Nix and ZeNix trials) Costs (drugs, visits, tests) Disability weights	1. DALYs averted 2. The potential maximum price at which the BPaL regimen could become cost neutral.	Study showed that BPaL for the treatment of XDR-TB compared to the 18 month regimen has the potential to be cost saving.	Presented per month in 2018 US$: $296,4 (drugs) $65,3 (delivery)	
Sweeney et al. 2022.	Cost-effectiveness of short, oral treatment regimens for rifampicin resistant tuberculosis	Patients with RR-TB, also potentially including resistance to isoniazid and/or fluoroquinolones	Cost-utility analysis	Provider's perspective	BPaL with and without moxifloxacin (BPaLM) or clofazimine (BPaLC)	Current mix of long and short standard of care (SOC) regimens to treat RR-TB	Markov model	Demographics Treatment outcomes (TB-PRACTECAL trial) Costs (drugs, visits, tests) Disability weights	DALYs averted	The cost savings associated with a move from the current SOC mix to BPaL for all MDR/RR-TB patients range was $1,173 per person in South Africa	Costs presented in 2019 US$ Total costs per person for South Africa: BPaL: $3,344, BPaLM: $3,520, and BPaLC: $3,470	Current SOC regimen mix (74% short, 26% long): $4,517

d. Evidence to Decision Framework

We populated one consolidated EtD framework per prioritised PICO as below. Overlapping evidence per EtD criteria from the WHO sub-PICOs were merged as necessary per target prioritised PICO.

We incorporated additional data analysis relevant to WHO sub-PICO 7.1 and 7.2, that was made available in the absence of individual EtDs in the guideline document. This data is listed as additional considerations in the EtDs labelled "b" and "c" respectively.

Subgroup analyses obtained from the authors of TB-PRACTECAL were included under additional considerations in the Etd labelled "b" due to the lack of a populated EtD for WHO sub-PICO 8.3, which was deemed to be of critical importance by the review team.

For each EtD criteria/domain the original WHO EtD evidence, judgement and if applicable additional considerations are presented alongside the PHC/Adult hospital level committee's judgements, local or updated evidence and additional considerations.

A summary of judgements per prioritised PICO is presented below:

a) Is BPaL (intervention 1) non-inferior to, and/or safer than the South African standard of care (comparator 3) in the treatment of adults with or without fluoroquinolone-resistant tuberculosis?

Should a 6-month regimen using bedaquiline , pretomanid, linezolid (600mg/300mg) vs. current South African standard-of-care regimes be used for pulmonary MDR/RR or pre-XDR TB? (Combined WHO sub-PICOs 4.1, 5.2, 5.3 and 6.6)

Problem: Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ No ○ Probably no ○ Probably yes **x Yes** ○ Varies ○ Don't know	**Research evidence** The COVID-19 pandemic has reversed years of progress in providing essential TB services and reducing TB disease burden. The most obvious impact is a large global drop in the number of people newly diagnosed with TB and reported. This fell from 7.1 million in 2019 to 5.8 million in 2020, an 18% decline back to the level of 2012 and far short of the approximately 10 million people who developed TB in 2020. Reduced access to TB diagnosis and treatment has resulted in an increase in TB deaths. Best estimates for 2020 are 1.3 million TB deaths among HIV-negative people (up from 1.2 million in 2019) and an additional 214 000 among HIV-positive people (up from 209 000 in 2019), with the combined total back to the level of 2017. Other impacts include reductions between 2019 and 2020 in the number of people provided with treatment for drug-resistant TB (-15%, from 177 100 to 150 359, about 1 in 3 of those in need).	Drug-resistant TB is a global challenge and access to treatment often problematic, with regimens typically being long, toxic, and expensive. More efficacious and shorter treatment regimens for DR-TB are necessary to optimize and improve treatment outcomes while minimizing adverse events and preventing acquisition of additional drug resistance.

	Globally in 2020, 71% (2.1/3.0 million) of people diagnosed with bacteriologically confirmed pulmonary TB were tested for rifampicin resistance, up from 61% (2.2/3.6 million) in 2019 and 50% (1.7/3.4 million) in 2018. Among these, 132 222 cases of MDR/RR-TB and 25 681 cases of pre-XDR-TB or XDR-TB were detected, for a combined total of 157 903. This was a large fall (of 22%) from the total of 201 997 people detected with drug-resistant TB in 2019, consistent with similarly large reductions in the total number of people newly diagnosed with TB (18%) and the total number of people diagnosed with bacteriologically confirmed pulmonary TB (17%) observed between 2019 and 2020. Worldwide, 150 359 people with MDR/RR-TB were enrolled on treatment in 2020, down 15% from the total of 177 100 in 2019. This level of enrolment was equivalent to about one in three of the people who develop MDR/RR-TB each year. More positively, there have been improvements in treatment success rates. Globally in 2018 (the latest patient cohort for which data are available), the treatment success rate for MDR/RR-TB was 59%, reflecting steady improvements in recent years from 50% in 2012. (Global TB Report 2021)	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○ No ○ Probably no ○ Probably yes **x Yes** ○ Varies ○ Don't know	In addition to the research evidence considered by the WHO GDG , the ERC considered the burden of disease in the locally relevant population. A cross-sectional study of identified tuberculosis cases, conducted in South Africa between 2012 and 2014, reported the prevalence of RR-TB as 4.6%, MDR-TB as 2.8% (95% CI 2.0, 3.6) and the prevalence of XDR-TB as 4.9% (95% CI 1.0, 8.8). (Ismail et al. 2018). More recently for the year 2021, the WHO reported an estimated 21 000 incident cases of RR-TB in South Africa. (WHO Global Tuberculosis Report, 2022) The ERC judged the problem to be a priority.	
Desirable effects: How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○Trivial ○ Small ○ Moderate **x Large** ○ Varies ○ Don't know	***BPaL compared to WHO_Long in pulmonary pre-XDR TB (WHO sub- PICO 4.1)*** **Research evidence** The BPaL 600–26 arm of the ZeNix trial, where linezolid 600 mg daily was used for 26 weeks, and population included patients with MDR/RR-TB with quinolone resistance was compared to a cohort of MDR/RR-TB patients with fluoroquinolone resistance from 2021 IPD, receiving longer regimens for treatment of MDR/RR-TB designed in line with 2020 WHO guidelines. Participants with pulmonary pre-XDR-TB (MDR/RR-TB with fluoroquinolone resistance) receiving BPaL 600–26 (n=33) compared to participants receiving longer regimens for MDR/RR-TB (n=839) experienced higher levels of treatment success (100% vs 75%), i.e. a 34% relative increase (RR=1.34, 95%CI 1.20 to 1.40); lower levels of failure and recurrence (0.0% vs 6.6%), i.e. a 7% absolute reduction (RD=-0.07, 95%CI -0.08 to -0.04); lower levels of deaths (0.0% vs 9.9%), i.e. a 10% absolute reduction (RD=-0.10, 95%CI -0.12 to -0.01); lower levels of loss to follow-up (0.0% vs 9.1%), i.e. a 9% absolute reduction (RD=-0.09, 95%CI -0.11 to -0.01); higher levels of adverse events (15% vs 4.4%), i.e. a 3.4-fold increase (RR=3.44, 95%CI 1.44 to 8.17); and lower levels of amplification of drug-resistance (0.0% vs 7.4%), i.e. a 7% absolute reduction (RD=-0.07, 95%CI -0.09 to -0.03). BPaL 600–26 may improve treatment success, failure and recurrence, death, loss to follow-up and amplification of drug-resistance while leading to more adverse events but the evidence is very uncertain.	**Additional Considerations applicable to all sub-PICO's** Beyond the outcomes captured directly as research evidence in the presented statistical analyses, the WHO 'Target Regimen Profile for rifampicin-resistant tuberculosis' (WHO, 2016) identified certain regimen characteristics as having desirable anticipated effects. These include a shorter treatment duration, reduced pill burden and number of component drugs and manageable DDIs. Decrease in the treatment duration is therefore an important desirable effect. **Additional considerations applicable to sub-PICO 4.1 only** The panel noted moderate to large improvements for most of the critical

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with WHO_long	Risk difference with BPaL
Treatment success	872 (15 observational studies)	⨁◯◯◯ Very low[abcdef]	**RR 1.34** (1.20 to 1.40)	Study population 745 per 1 000	**253 more per 1 000** (149 more to 298 more)

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with WHO_long	Risk difference with BPaL
Failure and recurrence	872 (15 observational studies)	⨁◯◯◯ Very low[abcdef]	**RD -0.07** (-0.08 to -0.04)	Study population 66 per 1 000	**70 fewer per 1 000** (71 fewer to 68 fewer)
Death	937 (15 observational studies)	⨁◯◯◯ Very low[abcdef]	**RD -0.10** (-0.12 to -0.01)	Study population 99 per 1 000	**109 fewer per 1 000** (111 fewer to 100 fewer)
Lost to follow up	872 (15 observational studies)	⨁◯◯◯ Very low[abcdef]	**RD -0.09** (-0.11 to -0.01)	Study population 91 per 1 000	**99 fewer per 1 000** (101 fewer to 91 fewer)
Amplification of drug resistance	872 (15 observational studies)	⨁◯◯◯ Very low[abcdef]	**RD -0.07** (-0.09 to -0.03)	Study population 74 per 1 000	**79 fewer per 1 000** (81 fewer to 76 fewer)

BPaL compared to WHO_Long in pulmonary MDR/RR TB (WHO sub-PICO 5.2)

Research evidence

The BPaL 600-26 arm of the ZeNix trial, where linezolid 600 mg daily was used for 26 weeks, and population included patients with MDR/RR-TB with or without quinolone resistance was compared to cohort of MDR/RR-TB patients (without quinolone resistance) from 2021 IPD, treated with longer regimens for MDR/RR-TB constructed in line with 2020 WHO guidelines.

Participants with MDR/RR-TB (with or without quinolone resistance) receiving BPaL 600-26 regimen (n=43) compared to participants with MDR/RR-TB (without quinolone resistance) receiving WHO recommended longer regimens (n=850) experienced higher levels of treatment success (100% vs 74%), i.e. a 32% relative increase (RR=1.32, 95%CI 1.19 to 1.39); lower levels of failure and recurrence (2% vs 3%), i.e. a 29% relative reduction (RR=0.71, 95%CI 0.12 to 3.8); lower levels of death (0% vs 11%), i.e. 11% absolute reduction (RD= -0.11, 95%CI -0.12 to -0.030; lower levels of loss to follow-up (0% vs 12%), i.e. 12% absolute reduction (RD= -0.12, 95%CI -0.14 to -0.04); higher levels of grade 3 to 5 adverse events (14% vs 5%), i.e. a 4 fold relative increase (aRR=3.99, 95%CI 1.67 to 9.57); and lower levels of amplified resistance (0% vs 2%), i.e. 2% absolute decrease (RD= - 0.02, 95%CI -0.04 to 0.06). The evidence is very uncertain about the effect of BPaL 600-26 regimen on all outcomes.

outcomes. Additionally, the panel noted that with the intervention regimen, treatment duration is reduced by 12 – 18 months, i.e. $^1/_3$ to $^1/_2$ of duration of comparator regimen (6-9 months vs 18-24 months); and that pill burden of the intervention is significantly lower, by 5-6 times (on average from 3'400 to 530)

Considering this research evidence and the additional considerations, the GDG judged that BPaL with Linezolid 600–26 may have large desirable effects and noted the very low certainty of the evidence.

Additional considerations applicable to sub-PICO 5.2 only

Treatment duration reduced by 12-18 months, i.e. to 1/3 to ½ of duration of comparator regimen (6-9 months vs 18-24 months).
Pill burden: significant decrease 5-6 times (on average from 3'400 to 530).

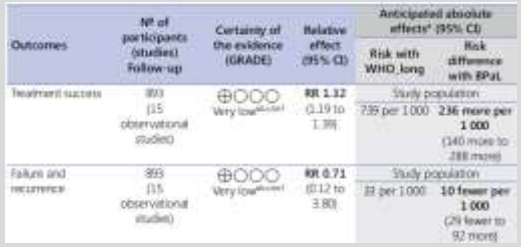
Considering this research evidence and the additional considerations, the GDG panel judged that BPaL 600– 26 regimen may have large desirable effects and noted the very low certainty of the evidence.

Additional considerations applicable to sub-PICO 5.3 only

Treatment duration reduced by 0-6 months (6-9 months vs 9 – 12 months)

Considering this research evidence and the additional considerations, the GDG panel judged that the BPaL 600– 26 regimen may have large desirable effects and noted the very low certainty of the evidence.

Additional considerations applicable to sub-PICO 6.6 only



Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with WHO_long	Risk difference with BPaL
Treatment success	893 (15 observational studies)	⨁◯◯◯ Very low[abcde,f]	RR 1.32 (1.19 to 1.39)	Study population 739 per 1 000	236 more per 1 000 (146 more to 288 more)
Failure and recurrence	893 (15 observational studies)	⨁◯◯◯ Very low[abcde,f]	RR 0.71 (0.12 to 3.80)	Study population 33 per 1 000	10 fewer per 1 000 (29 fewer to 92 more)

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with WHO_long	Risk difference with BPaL
Death	893 (15 observational studies)	⨁◯◯◯ Very low[abcde,f]	RD -0.11 (-0.13 to -0.03)	Study population 111 per 1 000	110 fewer per 1 000 (130 fewer to 30 fewer)
Lost to follow up	893 (15 observational studies)	⨁◯◯◯ Very low[abcde,f]	RD -0.12 (-0.14 to -0.04)	Study population 118 per 1 000	120 fewer per 1 000 (140 fewer to 40 fewer)
Amplification of drug resistance	893 (15 observational studies)	⨁◯◯◯ Very low[abcde,f]	RD -0.02 (-0.04 to 0.06)	Study population 24 per 1 000	20 fewer per 1 000 (40 fewer to 60 more)

BPaL compared to SA_new in MDR/RR TB (WHO sub-PICO 5.3)

Research evidence

The BPal 600-26 arm of the ZeNix trial, where linezolid 600 mg daily was used for 26 weeks, and population included patients with MDR/RR-TB with or without quinolone resistance was compared to cohort of MDR/RR-TB patients (without quinolone resistance) treated in South Africa with 9-month regimen with linezolid for two months.

Participants with MDR/RR-TB (with or without quinolone resistance) receiving BPaL with linezolid 600-26 (n=43) compared to participants with MDR/RR-TB (without quinolone resistance) receiving 9-month regimen with linezolid (n=4 216) experienced higher levels of treatment success (100% vs 66%) i.e. 52% relative increase (RR= 1.52, 95%CI 1.38 to 1.55), lower levels of failure and recurrence (0% vs 1%), i.e.1% absolute reduction (RD= -0.01, 95%CI -0.02 to 0.07); lower levels of death (0% vs 18%), i.e. 18% absolute reduction (RD= -0.18, 95%CI -0.19 to-0.1); lower levels of loss to follow up (0% vs 15%), i.e. 15% absolute reduction (RD= -0.15, 95%Ci -0.16 to -0.07); higher levels of grade 3 to 5 adverse events (14% vs 5%), i.e. a 3 fold increase (aRR=2.92, 95%CI 1.38 to 6.18); and lower levels of amplified resistance (0% vs 1%), i.e. 1% absolute reduction (RD= -0.01, 95%CI -0.01 to 0.08). The evidence is very uncertain about the effect of BPaL 600-26 regimen on all outcomes.

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with SA_new	Risk difference with BPaL
Treatment success	4 259 (2 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e]	RR 1.52 (1.38 to 1.55)	Study population 659 per 1 000	343 more per 1 000 (250 more to 363 more)

The panel also considered the duration and pill burden with the intervention and comparator regimens. The duration of the intervention regimen is 24 weeks (5.5 months) so treatment duration is reduced compared to the control arm by between 3–18 months. The exact magnitude of reduction in time on treatment depends on the specific comparator regimen, which includes shorter (9–12 months) and longer (18–24 months) regimens. The pill burden of the intervention regimen is lower than that for the comparator regimens. The exact magnitude of reduction in pill burden depends on the specific comparator regimen.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with SA_new	Risk difference with BPaL
Failure and recurrence	425 9 (2 observational studies)	⨁◯◯◯ Very low[absolute]	RD -0.01 (-0.02 to 0.07)	Study population	
				12 per 1 000	**10 fewer per 1 000** (20 fewer to 70 more)
Death	425 9 (2 observational studies)	⨁◯◯◯ Very low[absolute]	RD -0.18 (-0.19 to -0.10)	Study population	
				180 per 1 000	**180 fewer per 1 000** (190 fewer to 100 fewer)
Lost to follow up	425 9 (2 observational studies)	⨁◯◯◯ Very low[absolute]	RD -0.15 (-0.16 to -0.07)	Study population	
				149 per 1 000	**150 fewer per 1 000** (160 fewer to 70 fewer)
Amplification of drug resistance	425 9 (2 observational studies)	⨁◯◯◯ Very low[absolute]	RD -0.01 (-0.01 to 0.08)	Study population	
				6 per 1 000	**10 fewer per 1 000** (10 fewer to 80 more)

BPaL compared to TB-PRACTECAL comparator in pulmonary MDR/RR-TB and pre-XDR TB (WHO sub-PICO 6.6)

Research evidence

The BPaL (B-Pa-Linezolid600->300) regimen arm of the TB-PRACTECAL trial with population including patients with MDR/RR-TB with or without quinolone resistance (MDR/RR-TB or pre-XDR-TB) was compared to comparator arm of the TB-PRACTECAL trial comprised of MDR/RR-TB or pre-XDR-TB patients treated with multiple local SoC regimens (including: 9–12-month injectable containing regimen; 18–24-month long WHO regimen (pre-2019); 9–12 month all oral regimen; 18–20 month all oral regimen).

Participants with MDR/RR-TB (with or without quinolone resistance) receiving BPaL (n=60) compared to participants receiving WHO recommended standard of care regimens used in TB-PRACTECAL trial (n=66) experienced higher levels of treatment success (77% vs 52%), i.e. a 47% relative increase (RR=1.47, 95%CI 1.09 to 1.99); lower levels of failure and recurrence (13% vs 26%), i.e. a 48% relative reduction (RR=0.52, 95%CI 0.22 to 1.18); lower levels of deaths (0.0% vs 3.0%), i.e. a 3% absolute reduction (RD=-0.03, 95%CI -0.10 to 0.03); lower levels of loss to follow-up (10% vs 20%), i.e. a 40% relative reduction (RR=0.60, 95%CI 0.24 to 1.56); lower levels of adverse events (20% vs 51%), i.e. a 62% relative reduction (RR=0.38, 95%CI 0.24 to 0.60); and higher levels of amplification of drug-resistance (2.9% vs 1.9%), i.e. a 59% relative increase (RR=1.59, 95%CI 0.32 to 7.84).

BPaL may improve treatment success, failure and recurrence, death, loss to follow-up and adverse events while leading to more amplification of drug-resistance but the evidence is very uncertain.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with TB-PRACTECAL comparator	Risk difference with BPaL (Lzd 600mg/300mg)
Treatment success	126 (1 RCT)	⨁◯◯◯ Very low[abcdefg]	**RR 1.47** (1.09 to 1.99)	Study population 515 per 1 000	**242 more per 1 000** (46 more to 510 more)
Failure and recurrence	126 (1 RCT)	⨁◯◯◯ Very low[abcdefg]	**RR 0.52** (0.22 to 1.18)	Study population 258 per 1 000	**124 fewer per 1 000** (201 fewer to 46 more)
Lost to follow up	126 (1 RCT)	⨁◯◯◯ Very low[abcdefgh]	**RR 0.60** (0.24 to 1.56)	Study population 197 per 1 000	**79 fewer per 1 000** (150 fewer to 110 more)
Adverse events	210 (1 RCT)	⨁◯◯◯ Very low[abcdefg]	**RR 0.38** (0.24 to 0.60)	Study population 509 per 1 000	**316 fewer per 1 000** (387 fewer to 204 fewer)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with TB-PRACTECAL comparator	Risk difference with BPaL (Lzd 600mg/300mg)
Death	126 (1 RCT)	⨁◯◯◯ Very low[abcdefg]	**RD -0.03** (-0.10 to 0.03)	Study population 30 per 1 000	**30 fewer per 1 000** (100 fewer to 30 more)

Considering this research evidence and the additional considerations, the GDG judged that BPaL may have large desirable effects and noted the very low certainty of the evidence.

- **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**

○Trivial ○ Small ○ Moderate **x Large** ○ Varies ○ Don't know	The ERC considered all research relevant to efficacy presented by the WHO GDG in sub-PICO 4.1, 5.2, 5.3 and 6.6. No additional research was presented by the review team. Considering that all comparisons of BPaL to various comparator regimens demonstrated statistically significant increases in successful treatment outcomes and reduced mortality, and a trend towards reduced treatment failure or recurrence, combined with a shorter treatment duration and reduced pill burden that may favour adherence, the ERC judged the desirable effects of the intervention to be large.	Additional considerations and limitations highlighted by the ERC relevant to the comparisons in this EtD include: • That sub-PICO's 4.1, 5.2 and 5.3 are indirect comparisons of trial data to programmatic data. Clinical outcomes in clinical trials tend to be better.

Undesirable effects: How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

- **WHO Guideline panel**

○Trivial
○ Small
x Moderate
○ Large
○ Varies
○ Don't know

BPaL compared to WHO_Long in pulmonary preXDR TB (WHO sub-PICO 4.1)

Research Evidence

The BPaL 600–26 arm of the ZeNix trial, where linezolid 600 mg daily was used for 26 weeks, and population included patients with MDR/RR-TB with quinolone resistance was compared to a cohort of MDR/RR-TB patients with fluoroquinolone resistance from 2021 IPD, receiving longer regimens for treatment of MDR/RR-TB designed in line with 202 WHO guidelines.

Participants with pulmonary pre-XDR-TB (MDR/RR-TB with fluoroquinolone resistance) receiving BPaL 600–26 (n=33) compared to participants receiving longer regimens for MDR/RR-TB (n=839) experienced higher levels of treatment success (100% vs 75%), i.e. a 34% relative increase (RR=1.34, 95%CI 1.20 to 1.40); lower levels of failure and recurrence (0.0% vs 6.6%), i.e. a 7% absolute reduction (RD=-0.07, 95%CI -0.08 to -0.04); lower levels of deaths (0.0% vs 9.9%), i.e. a 10% absolute reduction (RD=-0.10, 95%CI -0.12 to -0.01); lower levels of loss to follow-up (0.0% vs 9.1%), i.e. a 9% absolute reduction (RD=-0.09, 95%CI -0.11 to -0.01); higher levels of adverse events (15% vs 4.4%), i.e. a 3.4-fold increase (RR=3.44, 95%CI 1.44 to 8.17); and lower levels of amplification of drug-resistance (0.0% vs 7.4%), i.e. a 7% absolute reduction (RD=-0.07, 95%CI -0.09 to -0.03).

BPaL 600–26 may improve treatment success, failure and recurrence, death, loss to follow-up and amplification of drug-resistance while leading to more adverse events but the evidence is very uncertain.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with WHO_long	Risk difference with BPaL
Adverse events	872 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]	**RR 3.44** (1.44 to 8.17)	Study population	
				44 per 1 000	**108 more per 1 000** (19 more to 316 more)

BPaL compared to WHO_Long in pulmonary MDR/RR TB (WHO sub-PICO 5.2)

Research Evidence

The BPaL 600-26 arm of the ZeNix trial, where linezolid 600 mg daily was used for 26 weeks, and population included patients with MDR/RR-TB with or without quinolone resistance was compared to cohort of MDR/RR-TB patients (without quinolone resistance) from 2021 IPD, treated with longer regimens for MDR/RR-TB constructed in line with 2020 WHO guidelines.

Participants with MDR/RR-TB (with or without quinolone resistance) receiving BPaL 600-26 regimen (n=43) compared to participants with MDR/RR-TB (without quinolone resistance) receiving WHO recommended longer regimens (n=850) experienced higher levels of treatment success (100% vs 74%), i.e. a 32% relative increase (RR=1.32, 95%CI 1.19 to 1.39); lower levels of failure and recurrence (2% vs 3%), i.e. a 29% relative reduction (RR=0.71, 95%CI0.12 to 3.8); lower levels of death (0% vs 11%), i.e. 11% absolute reduction (RD= -0.11, 95%CI -0.12 to -0.030; lower levels of loss to follow-up (0% vs 12%), i.e. 12% absolute reduction (RD= -0.12, 95%CI -0.14 to -0.04); higher levels of grade 3 to 5 adverse events (14% vs 5%), i.e. a 4 fold relative increase (aRR=3.99, 95%CI 1.67 to 9.57); and lower levels of amplified resistance (0% vs 2%), i.e. 2% absolute decrease (RD= - 0.02, 95%CI -0.04 to 0.06).
The evidence is very uncertain about the effect of BPaL 600-26 regimen on all outcomes

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with WHO_long	Risk difference with BPaL
Adverse events	893 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]	**RR 3.99** (1.67 to 9.57)	Study population	
				47 per 1 000	**141 more per 1 000** (32 more to 403 more)

Additional considerations and judgments related to all comparisons:

Pretomanid safety

Rodent Toxicology Studies – evidence of direct testicular toxicity
Monkey Toxicology Studies – no evidence of direct testicular toxicity; abnormal sperm findings considered to be secondary to declining physical condition
Hormone Data from Clinical Studies – no changes in FSH, LH, Inhibin B consistent with testicular toxicity
Paternity Survey – 44 children fathered by 38 men (12%) who participated in pretomanid studies of 4 -6 months treatment duration
Semen Study – ongoing study measuring semen in men undergoing pretomanid treatment.

The panel was reassured by the presentation of preclinical and clinical data relevant to testicular toxicity of Pretomanid, judging that clinically relevant effects appeared to be unlikely.

BPaL compared to SA_new in MDR/RR TB (WHO sub-PICO 5.3)

Research Evidence

The BPal 600-26 arm of the ZeNix trial, where linezolid 600 mg daily was used for 26 weeks, and population included patients with MDR/RR-TB with or without quinolone resistance was compared to cohort of MDR/RR-TB patients (without quinolone resistance) treated in South Africa with 9-month regimen with linezolid for two months.

Participants with MDR/RR-TB (with or without quinolone resistance) receiving BPaL with Linezolid 600-26 (n=43) compared to participants with MDR/RR-TB (without quinolone resistance) receiving 9-month regimen with linezolid (n=4 216) experienced higher levels of treatment success (100% vs 66%) i.e. 52% relative increase (RR= 1.52, 95%CI 1.38 to 1.55), lower levels of failure and recurrence (0% vs 1%), i.e.1% absolute reduction (RD= -0.01, 95%CI -0.02 to 0.07); lower levels of death (0% vs 18%), i.e. 18% absolute reduction (RD= -0.18, 95%CI -0.19 to-0.1); lower levels of loss to follow up (0% vs 15%), i.e. 15% absolute reduction (RD= -0.15, 95%CI -0.16 to -0.07); higher levels of grade 3 to 5 adverse events (14% vs 5%), i.e. a 3 fold increase (aRR=2.92, 95%CI 1.38 to 6.18); and lower levels of amplified resistance (0% vs 1%), i.e. 1% absolute reduction (RD= -0.01, 95%CI -0.01 to 0.08).
The evidence is very uncertain about the effect of BPaL 600-26 regimen on all outcomes.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with SA_new	Risk difference with BPaL
Adverse events	4 259 (2 observational studies)	⨁◯◯◯ Very low[abcde]	**RR 2.92** (1.38 to 6.18)	Study population	
				49 per 1 000	**95 more per 1 000** (19 more to 256 more)

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The panel discussed the importance of adverse events in the treatment of RR/MDR-TB and noted the significantly higher number of adverse events observed with BPaL. It was acknowledged that recording of AEs as part of the ZeNix trial is much more detailed than for data sets arising from routine care (i.e. data for the longer regimens).

Considering the increased number of adverse events with BPaL, the GDG judged that BPaL may have moderate undesirable effects and noted the very low certainty of the evidence.

BPaL compared to TB-PRACTECAL comparator in pulmonary MDR/RR-TB and pre-XDR TB (WHO sub-PICO 6.6)

Research Evidence

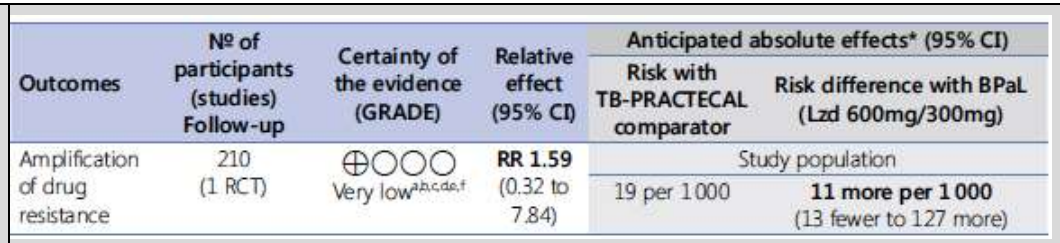
The BPaL (B-Pa-Linezolid600->300) regimen arm of the TB-PRACTECAL trial with population including patients with MDR/RR-TB with or without quinolone resistance (MDR/RR-TB or pre-XDR-TB) was compared to comparator arm of the TB-PRACTECAL trial comprised of MDR/RR-TB or pre-XDR-TB patients treated with multiple local SoC regimens (including: 9–12-month injectable containing regimen; 18–24-month long WHO regimen (pre-2019); 9–12 month all oral regimen; 18–20 month all oral regimen).

Participants with MDR/RR-TB (with or without quinolone resistance) receiving BPaL (n=60) compared to participants receiving WHO recommended standard of care regimens used in TB-PRACTECAL trial (n=66) experienced higher levels of treatment success (77% vs 52%), i.e. a 47% relative increase (RR=1.47, 95%CI 1.09 to 1.99); lower levels of failure and recurrence (13% vs 26%), i.e. a 48% relative reduction (RR=0.52, 95%CI 0.22 to 1.18); lower levels of deaths (0.0% vs 3.0%), i.e. a 3% absolute reduction (RD=-0.03, 95%CI -0.10 to 0.03); lower levels of loss to follow-up (10% vs 20%), i.e. a 40% relative reduction (RR=0.60, 95%CI 0.24 to 1.56); lower levels of adverse events (20% vs 51%), i.e. a 62% relative reduction (RR=0.38, 95%CI 0.24 to 0.60); and higher levels of amplification of drug-resistance (2.9% vs 1.9%), i.e. a 59% relative increase (RR=1.59, 95%CI 0.32 to 7.84).

(Judgement for WHO sub-PICO 6.6)

X Trivial
○ Small

BPaL may improve treatment success, failure and recurrence, death, loss to follow-up and adverse events while leading to more amplification of drug-resistance but the evidence is very uncertain.

○ Moderate ○ Large ○ Varies ○ Don't know	 Considering this research evidence and the additional considerations, the GDG judged that BPaL may have trivial undesirable effects and noted the very low certainty of the evidence.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○Trivial ○ Small **x Moderate** ○ Large ○ Varies ○ Don't know	The ERC considered the research evidence presented by the WHO GDG, with no additional evidence presented. Based on the more doubled increase in relative risk of adverse events in 3 of 4 comparisons (sub-PICO 4.1, 5.2 and 5.3), but which may have arisen from differences in reporting between clinical trial and programmatic data, as well as the fact that there were trivial differences between TB PRACTECAL, the ERC recommended a summary judgment that the undesirable effects of the intervention (BPaL) are moderate. The ERC highlighted the few studies contributing to data for this domain, the high degree of uncertainty and the indirect comparisons.	Additional considerations and limitations highlighted by the ERC relevant to the comparisons in this EtD include: • That sub-PICO's 4.1, 5.2 and 5.3 are indirect comparisons of trial data to programmatic data. Programmatic data may underreport of adverse events. • That in sub-PICO 6.6, the BPaL arm of TB-PRACTECAL used reduced Linezolid dosing from 16 weeks, and thus adverse events reported for this arm may not reflect adverse events associated with a regimen of 26 weeks of Linezolid 600mg daily dosing.
Certainty of evidence: What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
X Very low ○ Low ○ Moderate ○ High ○ No included studies	***BPaL compared to WHO_Long in pulmonary pre-XDR TB (WHO sub-PICO 4.1)*** **Research Evidence** Certainty was rated *very low* for all outcomes. Risk of bias was very serious, due to likely unmeasured confounding, small event numbers in the BPaL 600–26 group that precluded adjustment for differences in baseline covariates (measured confounding) and likely measurement bias due to underestimates of death and relapse following treatment in the WHO IPD 2021. Inconsistency was serious due to differences in the outcomes between cohorts in the WHO	**Additional considerations applicable to WHO sub-PICO 4.1, 5.2 and 5.3** This is an indirect comparison of patients treated within a clinical trial to data from patients treated under routine programmatic conditions so selection

IPD 2021 (downgraded one level). We did not downgrade for indirectness. Imprecision was very serious, due to the small sample size in the intervention group (n=33) (downgraded two levels).

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)
Treatment success	872 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]
Failure and recurrence	872 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]
Death	937 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]
Lost to follow up	872 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]
Adverse events	872 (15 observational studies)	⨁◯◯◯ Very low[a,c,d,e,f,g]
Amplification of drug resistance	872 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]

a. Lack of allocation concealment in the intervention arm. In the ZENIX study, participants, trial investigators and staff (including laboratory staff) were blinded to the dose and scheduled duration of linezolid. Participants were unblinded to the use of bedaquiline and pretomanid. However, this comparison is between one arm of ZENIX and an individual participant data meta-analysis of 14 datasets – i.e. a non-randomised comparison. Therefore, we have not downgraded due to the partial blinding of ZENIX

b. Confounding bias. Baseline imbalances were observed in the age, gender, HIV status, prior TB and prior drug-resistant TB history, smear status and culture positivity at baseline between the two groups. In most comparisons we were unable to adjust for measured confounding as the small number of events in the intervention group did not allow this (<5 individuals with a positive or negative outcome). Confounding bias is therefore likely. This imbalance in measured covariates suggests unmeasured confounding is also likely.

c. Potential misclassification bias: As the WHO IPD data were collected under programmatic conditions, there is considerable potential to underestimate relapse, as details pertaining to the follow-up period is often missing. Misclassification of death during the follow-up period is also possible as there is no death registry to link to the cohort data for deaths that occurred after treatment completion.

d. Considerable variability was observed in the effect estimates between cohorts in the comparator group. The overall effect in the comparator is strongly influenced by a small number of larger cohorts, which have varying effect estimates.

e. The ZENIX study was a clinical trial conducted in the Russian Federation, Republic of Moldova and South Africa. The procedures within the trial in these settings are not necessarily comparable with those used in other programmatic settings in which MDR-TB commonly occurs (e.g. countries in Southeast Asia). The decision as to whether to downgrade for indirectness is a difficult one. Given that the study was conducted in three countries, the intervention and outcomes are more likely to reflect practice in a range of other settings. Hence, we have chosen not to downgrade the certainty due to indirectness

f. The small number of individuals included in both the intervention group (n=43) results in a very serious risk of imprecision. Therefore, the certainty has been downgraded by two levels.

criteria, support during treatment and other interventions are likely to differ.

Treatment outcomes are typically better under trial conditions while AEs are typically underreported under programmatic conditions.

The GDG acknowledged that the indirect comparison and the propensity adjustment is leaving us with very low certainty.

Additional considerations applicable to WHO sub-PICO 6.6

As noted in the CoE assessment, it is important to highlight that:

- the population included in the trial that gave rise to the data is a mix of MDR/RR and pre-XDR/XDR TB patients (82–92% RR/MDR, depending on study arm)
- treatment outcomes for the comparator regimen differ for these populations and that 24% of patients were treated with regimens no longer recommended by WHO, e.g. containing injectable drugs and not containing Bdq

g. Confounding bias. Baseline imbalances were observed in the age, gender, HIV status, prior TB and prior drug-resistant TB history, smear status and culture positivity at baseline between the two groups. While we were able to adjust for these baseline covariates for the outcome of adverse events, this imbalance in measured covariates suggests unmeasured confounding is also likely.

BPaL compared to WHO_Long in pulmonary MDR/RR TB (WHO sub-PICO 5.2)

Research Evidence

Adjustment for baseline covariates was not possible for any of the outcomes, except adverse events, owing to the small number of events occurring in one or more groups. Certainty was rated *very low* for all outcomes. Risk of bias was very serious, with confounding bias evident in the imbalance between baseline covariates between groups (adjustment not possible). Downgraded two levels for risk of bias. Indirectness was not serious. Inconsistency was serious, with variation in the outcomes between the WHO IPD 2021 cohorts. Imprecision was very serious, with small numbers in the intervention group (n=43), leading to a downgrading by two levels.

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)
Treatment success	893 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]
Failure and recurrence	893 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]
Death	893 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]
Lost to follow up	893 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]
Adverse events	893 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]
Amplification of drug resistance	893 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]

a. Lack of allocation concealment in the intervention arm. In the ZENIX study, participants, trial investigators and staff (including laboratory staff) were blinded to the dose and scheduled duration of linezolid. Participants were unblinded to the use of bedaquiline and pretomanid. However, this comparison

	is between one arm of ZENIX and the WHO long (WHO IPD 2021) cohort – a non-randomised comparison. Therefore, we have not downgraded due to the partial blinding of ZENIX. b. Confounding bias. Baseline imbalances were observed in the gender, HIV status, prior TB history, past DR-TB treatment status, smear status, culture status and fluoroquinolone-resistance status between the two groups (although by including FQ-R TB it is likely to result in worse outcomes for the intervention group due to unmeasured confounding factors linked to FQ-R). We were able to adjust for the aforementioned measured confounders for the outcomes of success, failure/recurrence, loss to follow-up and grade 3 and above adverse events. However, the small number of events precluded adjustment for these factors for death or amplified resistance. The substantial imbalance in measured covariates suggests unmeasured confounding is also likely. c. Potential misclassification bias: As the WHO IPD 2021 (WHO long) cohort data were collected under programmatic conditions, there is considerable potential to underestimate recurrence, as details pertaining to the follow-up period were often missing. Misclassification of death during the follow-up period was also possible, with no linked death registry data available in the comparator cohort. d. Considerable variability was observed in the effect estimates between cohorts in the comparator group. The overall effect in the comparator is strongly influenced by a small number of larger cohorts, which have varying effect estimates. e. The ZENIX study was a clinical trial conducted in the Russian Federation, Republic of Moldova and South Africa. The procedures within the trial in these settings are not necessarily comparable with those used in other programmatic settings in which MDR-TB commonly occurs (e.g. countries in Southeast Asia). The decision as to whether to downgrade for indirectness is a difficult one. Given that the study was conducted in three countries, the intervention and outcomes are more likely to reflect practice in a range of other settings. There was serious indirectness because the intervention was in a clinical trial, while the comparator was a programmatic dataset. Therefore, we have downgraded for indirectness. f. The small number of individuals included in both the intervention group (n=43) results in a very serious risk of imprecision. Therefore, the certainty has been downgraded by two levels. ***BPaL compared to SA_new in MDR/RR TB (WHO sub-PICO 5.3)*** **Research Evidence** Adjustment for baseline covariates was not possible for any of the outcomes owing to the small number of events in one or more groups. Certainty was rated *very low*. Risk of bias was very serious, with confounding bias evident in the imbalance between baseline covariates between groups (adjustment not possible). Downgraded two levels for risk of bias. Indirectness was rated as not serious. Imprecision was very serious, with small numbers in the intervention group (n=43), leading to a downgrading by two levels	

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)
Treatment success	4 259 (2 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e]
Failure and recurrence	4 259 (2 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e]
Death	4 259 (2 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e]
Lost to follow up	4 259 (2 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e]
Adverse events	4 259 (2 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e]
Amplification of drug resistance	4 259 (2 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e]

a. Confounding bias. Baseline imbalances were observed in the gender, HIV status, prior TB treatment, smear status, culture positivity and fluoroquinolone resistance status between the two groups. In all comparisons we were unable to adjust for measured confounding as the small number of events in the intervention group did not allow this (<5 individuals with a positive or negative outcome). Confounding bias is due to measured confounding therefore serious. The substantial imbalance in measured covariates suggests unmeasured confounding is also likely.
b. Lack of allocation concealment in the intervention arm. In the ZENIX study, participants, trial investigators and staff (including laboratory staff) were blinded to the dose and scheduled duration of linezolid. Participants were unblinded to the use of bedaquiline and pretomanid. However, this comparison is between one arm of ZENIX and the WHO short (SA 2017) cohort – a non-randomised comparison. Therefore, we have not downgraded due to the partial blinding of ZENIX.
c. Potential misclassification bias: As the SA 2019 cohort data were collected under programmatic conditions, there is considerable potential to underestimate relapse, as details pertaining to the follow-up period is often missing. Misclassification of death during the follow-up period is also possible, although deaths reported in the South African death registry were linked to the participant follow-up data (using a national identification number).
d. The ZENIX study (intervention arm) was a clinical trial conducted in the Russian Federation, Republic of Moldova and South Africa. The procedures within the trial in these settings are not necessarily comparable with those used in other programmatic settings in which MDR-TB commonly occurs. The decision as to whether to downgrade for indirectness is a difficult one. Given that the study was conducted in three countries, the intervention and outcomes are more likely to reflect practice in a range of other settings. Given the important difference between a trial and programmatic setting, we have downgraded for indirectness.
e. The small number of individuals included in both the intervention group (n=43) results in a very serious risk of imprecision. Therefore, the certainty has been downgraded by two levels.

BPaL compared to TB-PRACTECAL comparator in pulmonary MDR/RR-TB and pre-XDR TB (WHO sub-PICO 6.6)

Research Evidence

Certainty was rated *very low*. Risk of bias was serious or very serious, for different outcomes. There was a lack of blinding, early termination of the trial for benefit, measured confounding and likely unmeasured confounding and small event numbers precluding adjustment for some comparisons. These

concerns resulted in downgrading by one or two levels depending upon outcome. We did not downgrade for inconsistency. We downgraded for indirectness due to differences in the population, definitions of outcomes and the comparator regimen. Imprecision was serious or very serious according to outcomes, with a small number of events for some outcomes.

The overall certainty is generally based on the lowest certainty for the agreed critical outcomes

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)
Treatment success	126 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]
Failure and recurrence	126 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]
Death	126 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]
Lost to follow up	126 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,h]
Adverse events	210 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]
Amplification of drug resistance	210 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f]

a. An imbalance in measured covariates (prior TB, prior DR-TB) likely arises from the small number of participants in each group. While the adjusted analyses will account for measured confounding, unmeasured confounding is also likely.
b. Small numbers of events in some outcomes precludes adjustment in some comparisons.
c. A lack of blinding of patients, caregivers and those adjudicating outcomes may introduce bias in the conduct of the trial. Higher loss to follow-up was noted in the comparator group, which is an outcome that may be influenced by patient or clinician knowledge of the regimen.
d. The trial was stopped early for benefit, with few events (<200). This can introduce bias. Formal stopping rules do not reduce bias (GRADE Handbook, 2013).
e. Multiple comparator regimens were used, varying across site. This may explain some of the substantial inconsistency in the point estimates for treatment outcomes seen between countries (Belarus, South Africa and Uzbekistan). The decision whether to downgrade is a difficult decision. We did not downgrade for inconsistency as the issue of comparators was addressed under indirectness.
f. A single trial. Serious indirectness (i) Populations: Differences in population of a trial and population to which guidelines will apply. (ii) Comparator: Some comparator regimens are sub-optimal, not according with the WHO standard of care (at the time or presently) and vary by country. Downgraded one level.
g. The number of participants in both intervention and comparator groups was small (n=60 and n=66). Very few events in the outcomes of interest, causing very serious imprecision. We downgraded two levels for imprecision for some outcomes, and one level for others.
h. A lack of blinding is important for loss to follow-up, and adverse event reporting where participant and clinician knowledge of the regimen may influence behaviours relating to treatment follow-up.

- **PHC/ADULT HOSPITAL LEVEL COMMITTEE**

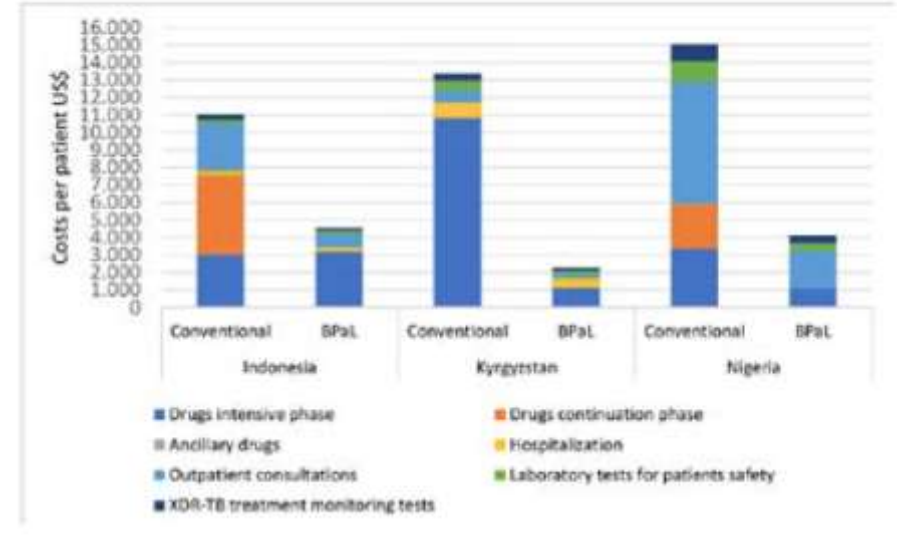
X Very low ○ Low ○ Moderate ○ High ○ No included studies	The ERC considered all information and research presented by the WHO GDG and agreed that the certainty of evidence is very low.	
Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Important uncertainty or variability ○ Possibly important uncertainty or variability **x Probably no important uncertainty or variability** ○ No important uncertainty or variability ○ No known undesirable outcomes	***BPaL compared to WHO_Long in pulmonary preXDR TB (WHO sub-PICO 4.1)*** ***BPaL compared to WHO_Long in pulmonary MDR/RR TB (WHO sub-PICO 5.2)*** ***BPaL compared to SA_new in MDR/RR TB (WHO sub-PICO 5.3)*** ***BPaL compared to TB-PRACTECAL comparator in pulmonary MDR/RR-TB and pre-XDR TB (WHO sub-PICO 6.6)*** **Research Evidence** No evidence research searched for. Higher treatment efficacy, shorter duration of treatment, lower pill burden and less adverse events are usually valued by patients. The panel judged that there was probably no important uncertainty or variability in how much people value the main outcomes.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○ Important uncertainty or variability ○ Possibly important uncertainty or variability **x Probably no important uncertainty or variability** ○ No important uncertainty or variability ○ No known undesirable outcomes	No additional research was presented by the review team. The ERC agreed with the WHO GDG that there is probably no important uncertainty or variability in how much people value the main outcomes.	
Balance of effects: Does the balance between desirable and undesirable effects favour the intervention or the comparison?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline panel**		
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison **x Probably favours the intervention** ○ Favours the intervention ○ Varies ○ Don't know	***BPaL compared to WHO_Long in pulmonary preXDR TB (WHO sub-PICO 4.1)*** ***BPaL compared to WHO_Long in pulmonary MDR/RR TB (WHO sub-PICO 5.2)*** **Research Evidence** Nil additional ***BPaL compared to SA_new in MDR/RR TB (WHO sub-PICO 5.3)*** **Research Evidence** Nil additional ***BPaL compared to TB-PRACTECAL comparator in pulmonary MDR/RR-TB and pre-XDR TB (WHO sub-PICO 6.6)*** **Research Evidence** Nil additional The GDG judged the benefits of BPaL to be large and the undesirable effects to be trivial compared to WHO recommended standard of care regimens. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaL regimen.	**Additional considerations relevant to sub-PICO's 4.1 and 5.2 only** The panel highlighted (as noted in the CoE assessment) that we are comparing data from patients treated within a clinical trial to data from patients treated under routine programmatic conditions so selection criteria, support during treatment etc. are likely to differ. E.g. treatment outcomes are typically better under trial conditions while AEs are typically underreported under programmatic conditions. The GDG judged the benefits of BPaL with Linezolid 600-26 to be large and the undesirable effects to be moderate compared to WHO recommended longer regimens. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favors BPaL with Linezolid 600-26. **Additional considerations relevant to sub-PICO 5.3 only** This is an indirect comparison of patients treated within a clinical trial to data from patients treated under routine programmatic conditions so selection criteria, support during treatment and other interventions are likely to differ. Treatment outcomes are typically better under trial conditions while AEs are typically underreported under programmatic conditions. The GDG acknowledged that the indirect comparison and the propensity adjustment is leaving us with very low certainty. The GDG judged the benefits of BPaL with linezolid 600-26 to be large and the undesirable effects to be moderate

		compared to receiving 9-month regimen with linezolid. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaL with linezolid 600-26. **Additional considerations relevant to sub-PICO 6.6 only** As noted in the CoE assessment, it is important to highlight that: • the population included in the trial that gave rise to the data is a mix of MDR/RR and pre-XDR/XDR TB patients (82–92% RR/MDR, depending on study arm) • treatment outcomes for the comparator regimen differ for these populations and that 24% of patients were treated with regimens no longer recommended by WHO, e.g., containing injectable drugs and not containing Bdq As a result, the balance of effects may be different in settings/populations with different FQ-resistance prevalence and if only currently recommended regimens are used.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison **x Probably favours the intervention** ○ Favours the intervention ○ Varies ○ Don't know	The ERC considered all evidence presented by the WHO GDG and no additional research was presented. Considering the ERC judgements of large desirable effects, including reduction in treatment duration and pill burden, and moderate undesirable effects, with very low certainty evidence, the balance of effect s was judged to probably favour the intervention.	

Resources required: How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings **x Large savings** ○ Varies ○ Don't know	***BPaL compared to WHO_Long in pulmonary pre-XDR TB (WHO sub-PICO 4.1)*** ***BPaL compared to WHO_Long in pulmonary MDR/RR TB (WHO sub-PICO 5.2)*** **Research Evidence** **Summary of findings from three publications on the cost of BPaL compared to WHO_long** (further detail on each study below) • From these three publications, the total cost (drugs+delivery) of **WHO_long appear to be between ~1.5x to 6x higher than for BPaL** when looking at comparative estimates within country • Note that studies are not 100% addressing the comparison of interest: Mulder and Gomez papers based on Linezolid dose of 1 200 (so cost of Linezolid in these publications is higher than intervention of interest here) and Sweeney is based on 600–300 for 24 weeks and a mixed RR/MDR/pre-XDR population **Mulder et al, 2022: Cost and budget impact analysis** [noting co-authors from TB Alliance and KNCV] **Methods** • Per-patient treatment cost of BPaL regimen was compared head-to-head with the conventional XDR-TB treatment regimen (i.e. WHO_long) in Indonesia, Kyrgyzstan and Nigeria based on cost estimates primarily assessed using microcosting method and expected frequency of each TB service • The 5-year budget impact of gradual introduction of BPaL against the status quo was assessed using a Markov model that represented patient's treatment management and outcome pathways **Findings** • The cost per patient completing treatment with BPaL was US$ 7142 in Indonesia, US$ 4782 in Kyrgyzstan and US$ 7152 in Nigeria – 57%, 78% and 68% lower than the conventional regimens in the respective countries. • A gradual adoption of the BPaL regimen over 5 years would result in a 5-year average national TB service budget reduction of 17% (US$ 12 880) in XDR-TB treatment related expenditure in Indonesia, 15% (US$ 700 247) in Kyrgyzstan and 32% (US$ 1 543 047) in Nigeria • BPaL regimen can be highly cost-saving compared with the conventional regimens to treat patients with XDR-TB in high drug-resistant TB burden settings.	**Additional considerations relevant to sub-PICO 4.1 and 5.2 only** Regimen cost at GDF prices: ~800 $ BPaL (600–26), ~1 300$ longer regimen. The panel judged that the costs for BPaL among patients with pulmonary pre-XDR-TB and among patients with pulmonary MDR/RR-TB are lower because costs of drugs are lower and cost of delivery are also lower due to the shorter duration of treatment and lower complexity **Additional considerations relevant to sub-PICO 5.3 only** Comparative costing analyses from Mulder and Gomez papers not applicable here since they are comparing to WHO_long (and, less importantly, are based on Linezolid dose of 1 200) **Additional considerations relevant to sub-PICO 6.6 only** The panel judged that the costs for BPaL are lower because costs of drugs are lower and cost of delivery are also lower due to the shorter duration of treatment and lower complexity. The GDG judged that the reduction in costs varies between moderate and large.

Figure: The drug and treatment management costs (in US$) per XDR-TB patient 100% adhering to the conventional regimens and BPaL by country. BPaL, bedaquiline, pretomanid and linezolid; XDR-TB, extensively drug-resistant tuberculosis



Gomez et al, 2021: Cost & cost-effectiveness [noting co-authors from TB Alliance]

Methods

- CEA using Markov model of BPaL (Nix regimen) in South Africa, Philippines and Georgia
- Primary and secondary outcome measures
  - (1) Incremental cost per disability-adjusted life years averted by using BPaL against standard of care at the Global Drug Facility list price;
  - (2) The potential maximum price at which the BPaL regimen could become cost neutral

Findings

- BPaL for XDR-TB is likely to be cost saving in all study settings
- when BPaL is introduced to a wider population, including MDR-TB treatment failure and treatment intolerant, we observe increased savings and clinical benefits
- Cost savings from the introduction of the BPaL regimen are higher in settings with a more expensive current standard of care
- consequently, the threshold price at which BPaL becomes cost neutral is higher in less expensive settings: US$ 3 650 and US$ 3 800 for Georgia and the Philippines, respectively, and US$ 500 for South Africa for our base case of only patients with XDR-TB, after factoring in incremental cost of ART

(sub-PICO 5.3 judgement)
○ Large costs
○ Moderate costs
○ Negligible costs and savings
x Moderate savings
○ Large savings
○ Varies
○ Don't know

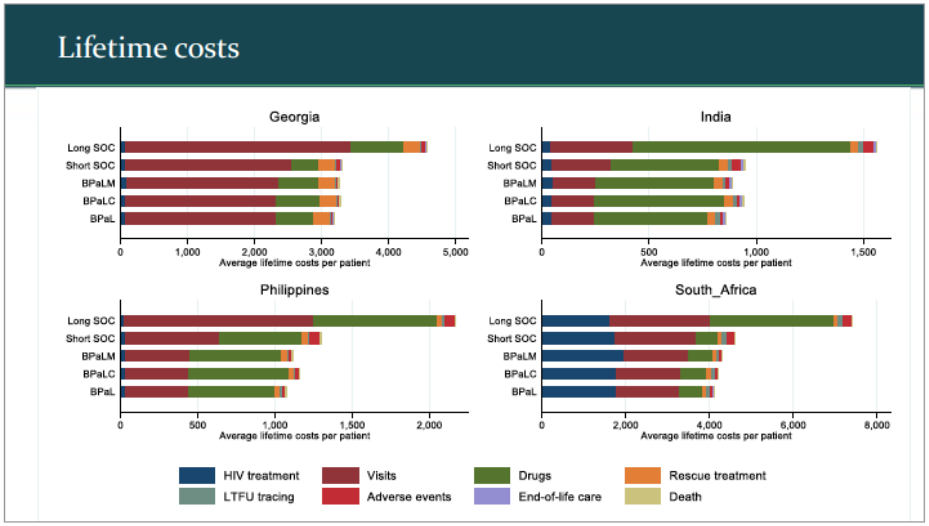
Table 2 Input cost estimates for cost-effectiveness analyses (US$2018 per month)

	South Africa	Georgia	The Philippines	Reference
Standard of care (intensive phase)	558.9 (drugs) 64.9 (delivery)	424.6 (drugs) 25.0 (delivery)	424.6 (drugs) 30.1 (delivery)	35 51–55
Standard of care (continuation phase)	208.9 (drugs) 30.1 (delivery)	74.58 (drugs) 14.0 (delivery)	74.58 (drugs) 13.7 (delivery)	35 51–55
BPaL	296.4 (drugs) 65.3 (delivery)	214.0 (drugs) 31.0 (delivery)	214.0 (drugs) 38.3 (delivery)	35 51–55
Palliative care*	428.1	330.9	328.0	56
Antiretroviral treatment	249.2	–	–	57

*Average of 10% hospice inpatient unit; 40% community care and 50% no care.
BPaL, bedaquiline, pretomanid and linezolid.

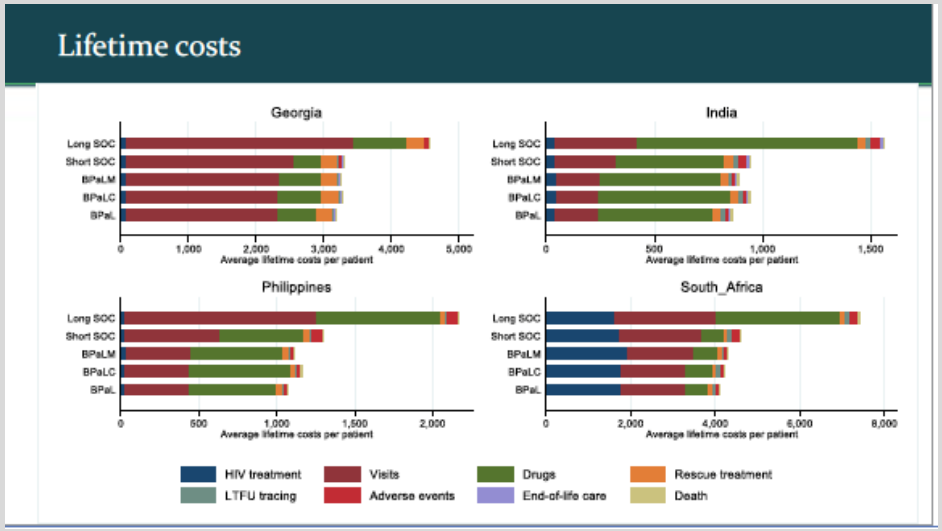
BPaL compared to SA_new in MDR/RR TB (WHO sub-PICO 5.3)
Research Evidence

Sedona Sweeney's presentation on CEA of PRACTECAL regimens from pre-GDG webinar



Sedona Sweeney's presentation on cost & CEA of PRACTECAL regimens from pre-GDG webinar

- From the data presented, the total cost (drugs + delivery) of BPaL appear to be between 4% - 18% lower than for WHO_short when looking at comparative estimates within country
- In most settings, BPaL is cost-saving; these cost savings are mostly due to reduced time in care and therefore reductions in numbers of outpatient visits, inpatient bed-days, and lab tests

(sub-PICO6.6 judgement) ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings **x Varies** ○ Don't know	• The study presented by Sweeney is not addressing the PICO of interest directly as it is based on a mixed RR/MDR/pre-XDR population (and thus mixed comparator) and on BPaL 600-300 for 24 weeks, instead of BPaL 600-26 and using WHO_short rather than SA_new (i.e. Eto instead of Linezolid as the comparator. ***BPaL compared to TB-PRACTECAL comparator in pulmonary MDR/RR-TB and pre-XDR TB (WHO sub-PICO 6.6)*** **Research Evidence** Sedona Sweeney's presentation on cost & CEA of PRACTECAL regimens from pre-GDG webinar • From the data presented, the total cost (drugs+delivery) of WHO_short appear to be between 4%-18% higher than for BPaL and between ~1.5x to 6x higher for WHO_long when looking at comparative estimates within country • In most settings, BPaL is cost-saving; these cost savings are mostly due to reduced time in care and therefore reductions in numbers of outpatient visits, inpatient bed-days, and lab tests • Note that the study presented by Sweeeney is not 100% addressing the PICO of interest (as it is based on 600-300 for 24 weeks, instead of 600-26) 	

Results by country: conservative approach

Country and regimen	Total costs per person	Total DALYs	Incremental Costs per person
Philippines			
SOC long	$2,127	6.2	
SOC short	$1,286	5.1	-$841
BPaL	$1,050	5.1	-$236
BPaLC	$1,146	5.0	$96
BPaLM	$1,099	4.4	-$47
South Africa			
SOC long	$6,896	6.9	
SOC short	$4,120	6.3	-$2,776
BPaL	$3,554	6.3	-$566
BPaLC	$3,687	6.2	$132
BPaLM	$3,739	5.7	$52
India			
SOC long	$1,531	6.8	
SOC short	$923	6.1	-$608
BPaL	$838	6.1	-$84
BPaLC	$923	6.0	$85
BPaLM	$872	5.5	-$51
Georgia			
SOC long	$4,499	4.7	
SOC short	$3,290	4.1	-$1,209
BPaL	$3,164	4.1	-$125
BPaLC	$3,264	4.0	$100
BPaLM	$3,246	3.3	-$19

- **PHC/ADULT HOSPITAL LEVEL COMMITTEE**

BPaL vs. long course regimens for MDR and pre-XDR TB (sub-PICO 4.1, 5.2, 6.6)

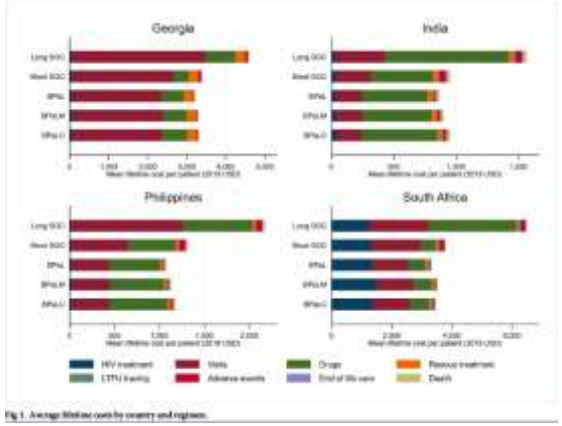
○ Large costs
○ Moderate costs
○ Negligible costs and savings
○ Moderate savings
x Large savings
○ Varies
○ Don't know

Additional information presented by the review team included updated evidence from the Sweeney et al. publication (published since the WHO GDG meeting, and on which WHO GDG judgement is based) , and the normative cost analysis of direct costs conducted by the review team.

Updated version of Sedona Sweeney's presentation with official publication:

BPaL vs. SA_new_short (sub-PICO 5.3)

○ Large costs
○ Moderate costs
× Negligible costs and savings
○ Moderate savings
○ Large savings
○ Varies
○ Don't know



The cost savings associated with a move from the current SOC mix to BPaL for all MDR/RR-TB patients range was $1,173 per person in South Africa. (Costs presented in 2019 US$; Total costs per person for South Africa: BPaL: $3,344, BPaLM: $3,520, and BPaLC: $3,470.
Current SOC regimen mix (74% short, 26% long): $4,517)

Table 2. Base case results.

			Comparison with current SOC mix	
Country and regimen	**Total costs per person**	**Total DALYs per person**	**Incremental Costs Per Person**	**Incremental DALYs Averted Per Person**
Philippines				
Current SOC regimen mix (99% short, 1% long)	$1,329	5.4		
BPaL	$1,078	5.4	-$251	0.0
BPaLC	$1,174	5.3	-$155	0.1
BPaLM	$1,124	4.6	-$204	0.8
South Africa				
Current SOC regimen mix (74% short, 26% long)	$4,517	6.8		
BPaL	$3,344	6.6	-$1,173	0.2
BPaLC	$3,470	6.5	-$1,047	0.3
BPaLM	$3,520	6.0	-$997	0.8

Normative cost analysis conducted by review team. For more information consult Appendix 3.

Appendix 3.xlsx

Normative cost analysis based on specific direct costs						Sensitivity analysis excl. clinic visit costs
Regimen	Drug costs (ZAR)	Bacteriological tests (Costs in ZAR)	Other lab tests (Costs in ZAR)	Clinic visit costs (ZAR)	Total costs per patient treated incl. clinic visit costs (ZAR)	Total costs per patient treated excl. clinic visit costs (ZAR)
Short oral course (Min)	11 437,70	1 058,58	472,42	2 680,79	15 649,49	12 968,70
Short oral course (Max)	13 650,99	1 058,58	472,42	2 680,79	17 862,78	15 181,99
BPaL (Lsd_Adjusted dose)	11 710,64	705,72	2 158,89	2 632,56	17 207,81	14 575,25
BPaLM (Lsd_Adjusted dose)	12 307,88	705,72	2 158,89	2 632,56	17 805,05	15 172,49
BPaLM (Lsd_Standard)	11 787,08	705,72	2 158,89	2 632,56	17 284,25	14 651,69
Long course 1 (Basic)	27 159,16	2 117,16	783,55	4 407,60	34 467,47	30 059,87
Long course 2	49 601,58	2 117,16	2 028,07	6 581,40	60 328,21	53 746,81

Note:
Where weight calibrated dosing is recommended, drug costs have been applied at the maximum weight band/adult dose
1 US$ equivalent to R18.30
Drug calculations all based on a 28 day cycle per month
Diagnostic Xpert, microscopy, culture and DST not included in costs for bacteriological tests
Clinic visits classified according to nature of clinical visits and based on secondary data representing a fully decentralised model.

The ERC noted that drug costs, and treatment monitoring costs are significantly affected by treatment duration. Based on the research presented by the WHO GDG and the normative costs analysis conducted for the locally relevant context, the ERC felt that BPaL regimen was associated with large savings when compared to the long course regimens for MDR and pre-XDR TB, and negligible costs when compared to the current South African short course regimen.

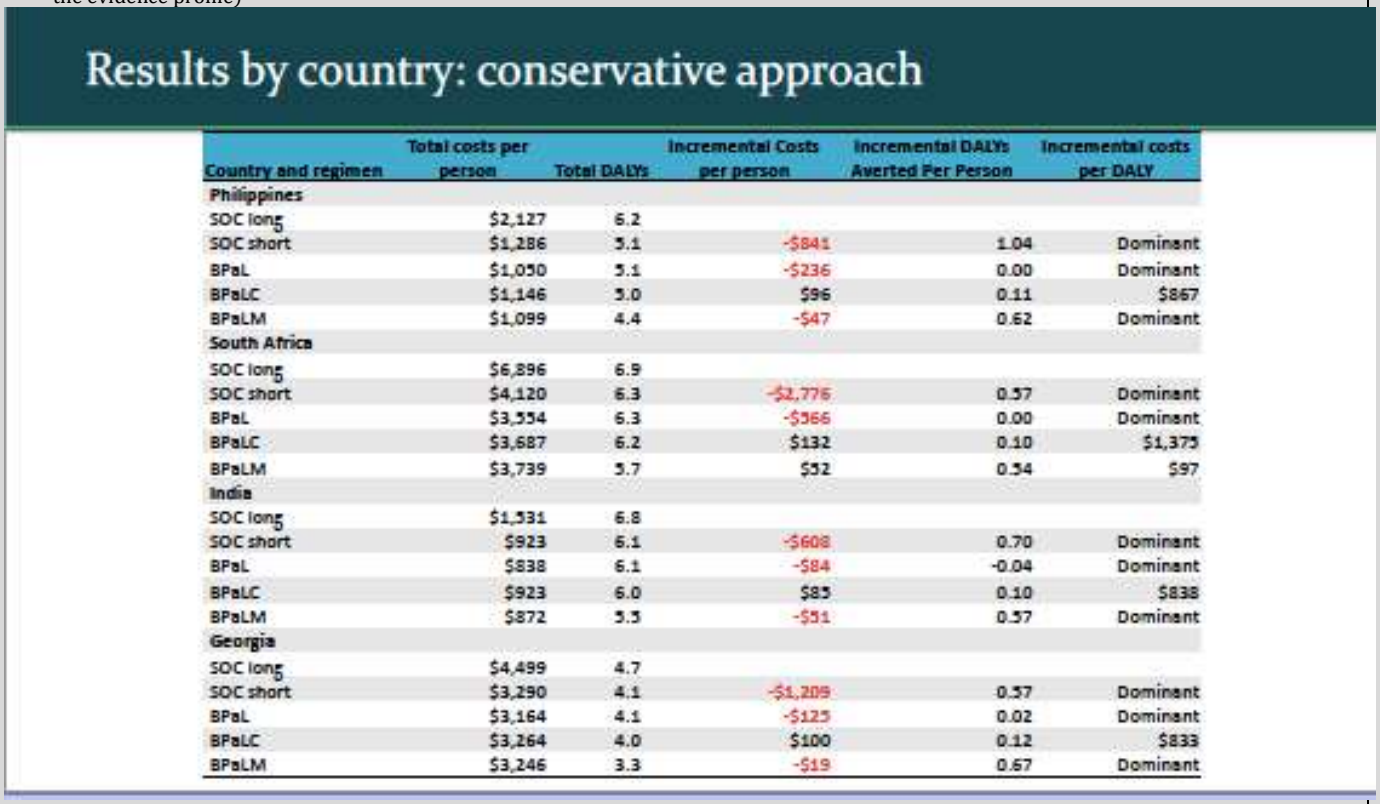
Certainty of evidence of resource requirements: What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline panel**		
x Very low ○ Low ○ Moderate ○ High ○ No included studies	***BPaL compared to WHO_Long in pulmonary preXDR TB (WHO sub-PICO 4.1)*** ***BPaL compared to WHO_Long in pulmonary MDR/RR TB (WHO sub-PICO 5.2)*** ***BPaL compared to TB-PRACTECAL comparator in pulmonary MDR/RR-TB and pre-XDR TB (WHO sub-PICO 6.6)*** **Research Evidence** No research evidence searched for. ***BPaL compared to SA_new in MDR/RR TB (WHO sub-PICO 5.3)*** **Research Evidence** The panel reviewed available data presented by the TB-PRACTECAL team from trial embedded study on cost effectiveness presented during one of the preparatory pre-GDG webinars by Sedona Sweeney and colleagues.	

	The panel judged the certainty of evidence of required resources to be very low since the study presented by Sweeney is not addressing the PICO of interest directly as it is based on a mixed RR/MDR/pre-XDR population (and thus mixed comparator), on BPaL 600–300 for 24 weeks, instead of BPaL 600–26 and on the 9-month regimen using Ethionamide instead of Linezolid.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Very low ○ Low **x Moderate** ○ High ○ No included studies	The ERC considered the evidence of resources required to be moderate as the normative cost analysis of direct costs was performed for the locally relevant context increasing the certainty.	
Cost effectiveness: Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison **x Probably favours the intervention** ○ Favours the intervention ○ Varies ○ No included studies	***BPaL compared to WHO_Long in pulmonary preXDR TB (WHO sub-PICO 4.1)*** ***BPaL compared to WHO_Long in pulmonary MDR/RR TB (WHO sub-PICO 5.2)*** **Research Evidence** **Gomez et al, 2021: Cost & cost-effectiveness** [noting co-authors from TB Alliance] • some indirectness as analyses were based on efficacy estimates from Nix study and a different comparator cohort but overall estimates of effect were similar **Methods** • CEA using Markov model of BPaL (Nix regimen) in South Africa, Philippines and Georgia • Primary and secondary outcome measures - (1) Incremental cost per disability-adjusted life years averted by using BPaL against standard of care at the Global Drug Facility list price; - (2) The potential maximum price at which the BPaL regimen could become cost neutral **Findings** • BPaL for XDR-TB is likely to be cost saving in all study settings • when BPaL is introduced to a wider population, including MDR-TB treatment failure and treatment intolerant, we observe increased savings and clinical benefits • Cost savings from the introduction of the BPaL regimen are higher in settings with a more expensive current standard of care • consequently, the threshold price at which BPaL becomes cost neutral is higher in less expensive settings: US$ 3 650 and US$ 3 800 for Georgia and the Philippines, respectively, and US$ 500 for South Africa for our base case of only patients with XDR-TB, after factoring in incremental cost of ART Given their prior judgements (balance of effects probably favours the intervention; intervention leads to large savings), the panel judged that the cost-effectiveness of the intervention probably favours the intervention. ***BPaL compared to TB-PRACTECAL comparator in pulmonary MDR/RR-TB and pre-XDR TB (WHO sub-PICO 6.6)*** **Research Evidence**	.

Sedona Sweeney's presentation on cost & CEA of PRACTECAL regimens from pre-GDG webinar

- From the data presented: "strong evidence that BPaL would be cost-effective" in the setting studied (costs reduced and DALYs averted)
- Note that estimates of effectiveness (from which DALYs averted were derived) are different from those presented in the evidence profile for this PICO (CEA assumes smaller benefits of BPaL over comparator and thus estimates for DALYs averted would be conservative vis a vis data from the evidence profile)



Results by country: conservative approach

Country and regimen	Total costs per person	Total DALYs	Incremental Costs per person	Incremental DALYs Averted Per Person	Incremental costs per DALY
Philippines					
SOC long	$2,127	6.2			
SOC short	$1,286	5.1	-$841	1.04	Dominant
BPaL	$1,050	5.1	-$236	0.00	Dominant
BPaLC	$1,146	5.0	$96	0.11	$867
BPaLM	$1,099	4.4	-$47	0.62	Dominant
South Africa					
SOC long	$6,896	6.9			
SOC short	$4,120	6.3	-$2,776	0.57	Dominant
BPaL	$3,554	6.3	-$566	0.00	Dominant
BPaLC	$3,687	6.2	$132	0.10	$1,375
BPaLM	$3,739	5.7	$52	0.54	$97
India					
SOC long	$1,531	6.8			
SOC short	$923	6.1	-$608	0.70	Dominant
BPaL	$838	6.1	-$84	-0.04	Dominant
BPaLC	$923	6.0	$85	0.10	$838
BPaLM	$872	5.5	-$51	0.57	Dominant
Georgia					
SOC long	$4,499	4.7			
SOC short	$3,290	4.1	-$1,209	0.57	Dominant
BPaL	$3,164	4.1	-$125	0.02	Dominant
BPaLC	$3,264	4.0	$100	0.12	$833
BPaLM	$3,246	3.3	-$19	0.67	Dominant

Given their prior judgements (balance of effects probably favours the intervention; intervention leads to moderate to large savings), the panel judged that the cost-effectiveness of the intervention probably favours the intervention.

(sub-PICO 5.3 judgement)

○ Favours the comparison
○ Probably favours the comparison
○ Does not favour either the intervention or the

BPaL compared to SA_new in MDR/RR TB (WHO sub-PICO 5.3)

Research Evidence

Sedona Sweeney's presentation on cost & CEA of PRACTECAL regimens from pre-GDG webinar

- From the data presented: "strong evidence that BPaL would be cost-effective" in the setting studied (costs reduced and DALYs averted)

comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies **x No included studies**	• The study presented by Sweeney is not addressing the PICO of interest directly as it is based on a mixed RR/MDR/pre-XDR population (and thus mixed comparator) and on BPaL 600–300 for 24 weeks, instead of BPaL 600–26 and using WHO_short rather than SA_new (i.e. Eto instead of Linezolid) as the comparator • Estimates of effectiveness (from which DALYs averted were derived) are different from those presented in the evidence profile for this PICO (CEA assumes smaller benefits of BPaL over comparator and thus estimates for DALYs averted would be conservative vis a vis data from the evidence profile) Comparative costing analyses from Gomez papers not applicable here since they are comparing to long WHO regimen (+ are based on Linezolid dose of 1 200 and efficacy estimates from Nix study). For sub-PICO 5.3 no studies of cost-effectiveness were included.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison **x Probably favours the intervention** ○ Favours the intervention ○ Varies ○ No included studies	The ERC considered all research evidence included in the WHO GDG judgement. No new cost-effectiveness studies were presented or considered. Based on the normative cost analysis of direct costs for South Africa performed by the review team, showing costs savings when the intervention is compared to current South African long course, the intervention would favour cost-effectiveness. However, evidence for cost-effectiveness for the intervention when compared to the current South African short course is based on the evidence from the study by Sweeney et al. that indirectly compared BPaL to South African standard of care regimens (a mix of 75% short course and 25% long course) and showed cost savings and reduced DALYs associated with the intervention. The ERC judged that overall, cost-effectiveness probably favours the intervention.	
Equity: What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Reduced ○ Probably reduced ○ Probably no impact **x Probably increased** ○ Increased ○ Varies ○ Don't know	***BPaL compared to WHO_Long in pulmonary preXDR TB (WHO sub-PICO 4.1)*** ***BPaL compared to WHO_Long in pulmonary MDR/RR TB (WHO sub-PICO 5.2)*** ***BPaL compared to SA_new in MDR/RR TB (WHO sub-PICO 5.3)*** ***BPaL compared to TB-PRACTECAL comparator in pulmonary MDR/RR-TB and pre-XDR TB (WHO sub-PICO 6.6)*** **Research Evidence** No research evidence searched for. The panel judged that use of the BPaL regimen would probably increase equity.	The panel considered the treatment duration and the ability to decentralize treatment (to enable access for remote, underserviced settings and disadvantaged populations) to affect equity. Despite not being able to identify relevant research evidence, the panel used their collective experience to judge that there would likely be advantages associated with the use of the BPaL regimen due to its reduced complexity and shorter duration.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		

○ Reduced ○ Probably reduced ○ Probably no impact **x Probably increased** ○ Increased ○ Varies ○ Don't know	The ERC considered no additional research. The ERC agreed with the WHO GDG judgment that the intervention would probably increase health equity.	
Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		

○ No
○ Probably no
x Probably yes
○ Yes
○ Varies
○ Don't know
	BPaL compared to WHO_Long in pulmonary preXDR TB (WHO sub-PICO 4.1)
	BPaL compared to WHO_Long in pulmonary MDR/RR TB (WHO sub-PICO 5.2)
	
	Research Evidence
	
	van de Berg et al, 2021 (based on 2019 KNCV report, funded by TB Alliance) on the provider perspective
	Methods
	• Mixed-methods study among a cross-section of health care workers, programmatic and laboratory stakeholders between May 2018 and May 2019 in Indonesia, Kyrgyzstan, and Nigeria
	  • 188 stakeholders participated in this study: 63 from Kyrgyzstan, 51 from Indonesia, and 74 from Nigeria; majority were health care workers (110), other stakeholders interviewed were Laboratory stakeholders and Programmatic Stakeholders
	• semi-structured interviews and focus group discussions to assess perceptions on acceptability and feasibility of implementing BPaL
	  • acceptability: anticipated benefits and challenges regarding DR TB management with the BPaL regimen by the stakeholders; recorded 3-point Likert scale (acceptable; neutral; unacceptable)
	
	Findings
	• Acceptability: overall high and rated as acceptable by >80% across domains
	• Stakeholders
	  • appreciated that BPaL would reduce workload and financial burden on the health care system
	  • expressed concerns regarding BPaL safety (monitoring), long-term efficacy, and national regulatory requirements
	  • stressed the importance of addressing current health systems constraints as well, especially in treatment and safety monitoring systems
	
	Beverly Stringer's presentation on PROs from pre-GDG webinar (qualitative study) on the patient perspective
	  • Positive impact of shorter treatment on employment status welcomed
	
	BPaL compared to SA_new in MDR/RR TB (WHO sub-PICO 5.3)
	Research Evidence
	
	No research evidence searched for.
	
	Beverly Stringer's presentation on PROs from pre-GDG webinar (qualitative study) on the patient perspective: Positive impact of shorter treatment on employment status welcomed.
		Additional considerations relevant to sub-PICO 4.4 and 5.2 only
		
		For sub-PICO 5.2 findings from the study by van de Berg et al, 2021 (based on 2019 KNCV report, funded by TB Alliance) on the provider perspective are listed under other considerations (instead of under research evidence) as acceptability was assessed for the pre-XDR population.
		
		For sub-PICO 5.3 analyses from van de Berg paper are not applicable here since in their study they asked about acceptability of using BPaL for pre-XDR patients and when compared to the long WHO regimen
		
		The panel considered patients and health care providers as key stakeholders. The panel considered the following aspects as critical with regards to acceptability: regimen duration and drug safety monitoring needs (both relating to necessary travel, loss of income and general disruption of the life of patients; workload for the health care system), needs for drug susceptibility testing. The panel judged that the BPaL regimen would probably be acceptable.
		
		Additional considerations relevant to sub-PICO 5. 3 only

	BPaL compared to TB-PRACTECAL comparator in pulmonary MDR/RR-TB and pre-XDR TB (WHO sub-PICO 6.6) **Research Evidence** **Beverly Stringer's presentation on PROs from pre-GDG webinar (qualitative study) on the patient perspective** Positive impact of shorter treatment on employment status welcomed.	The panel considered patients and health care providers as key stakeholders. The panel considered the following aspects as critical with regards to acceptability: regimen duration and drug safety monitoring needs (both relating to necessary travel, loss of income and general disruption of the life of patients; workload for the health care system), needs for drug susceptibility testing. The panel judged that the BPaL regimen would probably be acceptable. **Additional considerations relevant to sub-PICO 6.6 only** **van de Berg et al, 2021 (based on 2019 KNCV report, funded by TB Alliance) on the provider perspective** • Noting that analyses from van de Berg paper are only partially applicable here since in their study they asked about acceptability of using BPaL for pre-XDR patients and when compared to the long WHO regimen • **Findings** Acceptability: overall high and rated as acceptable by >80% across domains The panel considered patients and health care providers as key stakeholders. The panel considered the following aspects as critical with regards to acceptability: regimen duration and drug safety monitoring needs (both relating to necessary travel, loss of income and general disruption of the life of patients; workload for the health care system), needs for drug susceptibility testing. The panel judged that the BPaL regimen would probably be acceptable
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		

○ No ○ Probably no **x Probably yes** ○ Yes ○ Varies ○ Don't know	**Additional Research Evidence presented by TB-PRACTECAL-PRO team:** All trial participants respiratory-specific QOL scores improved with treatment, irrespective of the regimen they received. However, faster improvement in the investigational arms as compared to SoC was noted by both the individual and their friends/family with a positive effect on treatment support. It was noted that a participant in the intervention arm experiences a 15% reduction (95% CI 12 to 18%) in the mean SGRQ symptom score per month versus an average of 5% (95% CI 0 – 9%) reduction experienced by a participant in the SoC arm. It was highlighted that South African participants were slightly underrepresented in the trial (32 South Africans of 137 participants) and that no analysis of QoL outcomes across countries was performed. For interviewees, in the qualitative study, supportive care experienced was as important as satisfaction and tolerability of the novel drug regimen. The ERC judged that the intervention is probably acceptable to key stakeholders.	

Feasibility: Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline Panel**		
○ No ○ Probably no **x Probably yes** ○ Yes ○ Varies ○ Don't know	***BPaL compared to WHO_Long in pulmonary preXDR TB (WHO sub-PICO 4.1)*** ***BPaL compared to TB-PRACTECAL comparator in pulmonary MDR/RR-TB and pre-XDR TB (WHO sub-PICO 6.6)*** **Research Evidence** **van de Berg et al, 2021 (based on 2019 KNCV report, funded by TB Alliance) on the provider perspective** **Methods** • Mixed-methods study among a cross-section of health care workers, programmatic and laboratory stakeholders between May 2018 and May 2019 in Indonesia, Kyrgyzstan, and Nigeria • 188 stakeholders participated in this study: 63 from Kyrgyzstan, 51 from Indonesia, and 74 from Nigeria; majority were health care workers (110) • semi-structured interviews and focus group discussions to assess perceptions on acceptability and feasibility of implementing BPaL • feasibility: stakeholders' expectations regarding the practical requirements for implementing the BPaL regimen within the context of their health system; recorded as overall likelihood of implementing BPaL (likely; neutral; unlikely) **Findings** • **Feasibility: 88% (146/166) of the stakeholders would likely implement BPaL** once available • Stakeholders - appreciated that BPaL would reduce workload and financial burden on the health care system - expressed concerns regarding BPaL safety (monitoring), long-term efficacy, and national regulatory requirements - stressed the importance of addressing current health systems constraints as well, especially in treatment and safety monitoring systems	**Additional considerations applicable to sub-PICO 4.1 and 6.6 only** Noting that analyses from van de Berg paper are only partially applicable to sub-PICO 6.6 since in their study they asked about feasibility of using BPaL for pre-XDR patients and when compared to the long WHO regimen The panel considered the following aspects to affect feasibility (i.e. to be potential barriers to implementation): requirements for drug safety monitoring and requirements for drug susceptibility testing. The panel noted limited availability of drugs in the BPaL regimen for use in DST as a potential barriers to implementation and also noted that data on the critical concentration of Pretomanid for use in DST is limited. However, given the reduced duration, complexity and associated workload, the panel judged that implementation is probably feasible
(sub-PICO 5.2 and 5.3 judgement) ○ No ○ Probably no ○ Probably yes **x Yes**	***BPaL compared to WHO_Long in pulmonary MDR/RR TB (WHO sub-PICO 5.2)*** ***BPaL compared to SA_new in MDR/RR TB (WHO sub-PICO 5.3)*** **Research Evidence**	**Additional considerations applicable to sub-PICO 5.2 and 5.3 only** The panel considered the following aspects to affect feasibility (i.e. to be

○ Varies ○ Don't know	Nil	potential barriers to implementation): requirements for drug safety monitoring and requirements for drug susceptibility testing. The panel noted limited availability of drugs in the BPaL regimen for use in DST as a potential barrier to implementation and also noted that data on the critical concentration of Pretomanid for use in DST is limited. However, given the reduced duration, complexity and associated workload, the panel judged that implementation is feasible. Listing findings from the study by **van de Berg et al, 2021** (based on 2019 KNCV report, funded by TB Alliance) on the **provider** perspective here under other considerations (instead of under research evidence) as feasibility was assessed for the pre-XDR population. **Methods** • Mixed-methods study among a cross-section of health care workers, programmatic and laboratory stakeholders between May 2018 and May 2019 in Indonesia, Kyrgyzstan, and Nigeria - 188 stakeholders participated in this study: 63 from Kyrgyzstan, 51 from Indonesia, and 74 from Nigeria; majority were health care workers (110) • semi-structured interviews and focus group discussions to assess perceptions on acceptability and feasibility of implementing BPaL - feasibility: stakeholders' expectations regarding the practical requirements for implementing the BPaL regimen within the context of their health

		system; recorded as overall likelihood of implementing BPaL (likely; neutral; unlikely) **Findings** • **Feasibility: 88% (146/166) of the stakeholders would likely implement BPaL** once available • Stakeholders - appreciated that BPaL would reduce workload and financial burden on the health care system - expressed concerns regarding BPaL safety (monitoring), long-term efficacy, and national regulatory requirements - stressed the importance of addressing current health systems constraints as well, especially in treatment and safety monitoring systems Analyses from van de Berg paper not applicable for sub-PICO 5.3 since in their study they asked about feasibility of introducing BPaL for pre-XDR patients and when compared to the long WHO regimen.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ No ○ Probably no **x Probably yes** ○ Yes ○ Varies ○ Don't know	All research presented by the WHO GDG was considered by the ERC. The ERC also considered the impact of Pretomanid stock availability on feasibility of implementation of the regimen, and was reassured by the NDoH TB programme that stock and funding for drug costs is available, and that no supply issues are expected. The ERC also considered the need for enhanced pharmacovigilance to accompany implementation of the intervention. The ERC heard from the NDOH TB programme that feasibility could be impacted if the level of prescriber be restricted to medical officer only, as clinical nurse practitioners and clinical associates are important human resources for decentralized care. The ERC judged that the intervention is probably feasible to implement.	

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	23 March 2023	JT, NG, SE, FB, NN, GM, MM, JN, TK, KC	Initial ERC discussion took place on 16th March 2023, with ongoing discussion and updated ERC decision at an extraordinary meeting of the ERC on 23 March 2023, where a conditional recommendation for the use of the BPaL in the treatment of drug resistant TB with or without fluoroquinolone resistance was suggested. The recommendation is conditional based on the very low quality of evidence underlying the WHO recommendation.

b) Is BPaLM (intervention 2) non-inferior to, and/or safer than the South African standard of care (comparator 1 and 2) in the treatment of adults with rifampicin-resistant tuberculosis without additional fluoroquinolone resistance?

Should BPaLM vs. local SoC regimens (TB-PRACTECAL comparator) be used for pulmonary MDR/RR-TB or pre-XDR-TB? (WHO Sub-PICO 6.1)

(Note: Where judgements differed, both WHO and PHC/Adult Hospital Level's assessments have been described)

Problem: Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ No ○ Probably no ○ Probably yes x **Yes** ○ Varies ○ Don't know	**Research evidence** The COVID-19 pandemic has reversed years of progress in providing essential TB services and reducing TB disease burden. The most obvious impact is a large global drop in the number of people newly diagnosed with TB and reported. This fell from 7.1 million in 2019 to 5.8 million in 2020, an 18% decline back to the level of 2012 and far short of the approximately 10 million people who developed TB in 2020. Reduced access to TB diagnosis and treatment has resulted in an increase in TB deaths. Best estimates for 2020 are 1.3 million TB deaths among HIV-negative people (up from 1.2 million in 2019) and an additional 214 000 among HIV-positive people (up from 209 000 in 2019), with the combined total back to the level of 2017. Other impacts include reductions between 2019 and 2020 in the number of people provided with treatment for drug-resistant TB (-15%, from 177 100 to 150 359, about 1 in 3 of those in need). Globally in 2020, 71% (2.1/3.0 million) of people diagnosed with bacteriologically confirmed pulmonary TB were tested for rifampicin resistance, up from 61% (2.2/3.6 million) in 2019 and 50% (1.7/3.4 million) in 2018. Among these, 132 222 cases of MDR/RR-TB and 25 681 cases of pre-XDR-TB or XDR-TB were detected, for a combined total of 157 903. This was a large fall (of 22%) from the total of 201 997 people detected with drug-resistant TB in 2019, consistent with similarly large reductions in the total number of people newly diagnosed with TB (18%) and the total number of people diagnosed with bacteriologically confirmed pulmonary TB (17%) observed between 2019 and 2020. Worldwide, 150 359 people with MDR/RR-TB were enrolled on treatment in 2020, down 15% from the total of 177 100 in 2019. This level of enrolment was equivalent to about one in three of the people who develop MDR/RR-TB each year. More positively, there have been improvements in treatment success rates. Globally in 2018 (the latest patient cohort for which data are available), the treatment success rate for MDR/RR-TB was 59%, reflecting steady improvements in recent years from 50% in 2012. (Global TB Report 2021) More efficacious and shorter treatment regimens for DR-TB are necessary to optimize and improve treatment outcomes while minimizing adverse events and preventing acquisition of additional drug resistance.	Drug-resistant TB is a global challenge and access to treatment often problematic, with regimens typically being long, toxic, and expensive. More efficacious and shorter treatment regimens for DR-TB are necessary to optimize and improve treatment outcomes while minimizing adverse events and preventing acquisition of additional drug resistance.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		

○ No ○ Probably no ○ Probably yes **x Yes** ○ Varies ○ Don't know	In addition to the research evidence considered by the WHO GDG , the ERC considered the burden of disease in the locally relevant population. A cross-sectional study of identified tuberculosis cases, conducted in South Africa between 2012 and 2014, reported the prevalence of RR-TB as 4.6%, MDR-TB as 2.8% (95% CI 2.0, 3.6) and the prevalence of XDR-TB as 4.9% (95% CI 1.0, 8.8). (Ismail et al. 2018). More recently for the year 2021, the WHO reported an estimated 21 000 incident cases of RR-TB in South Africa. (WHO Global Tuberculosis Report, 2022) The ERC judged the problem to be a priority.	

Desirable effects: How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○Trivial ○ Small ○ Moderate **x Large** ○ Varies ○ Don't know	**Research evidence** The BPaLM regimen arm of the TB-PRACTECAL trial with population including patients with MDR/RR-TB with or without quinolone resistance (MDR/RR-TB or pre-XDR-TB) was compared to comparator arm of the TB-PRACTECAL trial comprised of MDR/RR-TB or pre-XDR-TB patients treated with multiple local SoC regimens (including: 9–12-month injectable containing regimen; 18–24-month long WHO regimen (pre-2019); 9–12 month all oral regimen; 18–20 month all oral regimen). Participants with MDR/RR-TB (with or without quinolone resistance) receiving BPaLM regimen (n=62) compared to participants receiving WHO recommended standard of care regimens used in TB-PRACTECAL trial (n=66) experienced higher levels of treatment success (89% vs 52%), i.e. 73% relative increase (aRR=1.73, 95%CI 1.31 to 2.27); lower levels of failure and recurrence (8% vs 26%) i.e. 74% relative reduction (aRR=0.26, 95%CI 0.1 to 0.71); lower levels of death (0% vs 3%), i.e. 3% absolute reduction (RD= -0.03, 95%CI -0.1 to 0.03); lower levels of loss to follow-up (3% vs 20%), i.e. 84% of relative reduction (RR=0.16, 95%CI 0.12 to 0.52); lower levels of grade 3 to 5 adverse events (21% vs 51%), i.e. 59% relative reduction (aRR=0.41, 95%CI 0.04 to 0.61) and lower levels of amplified resistance (0% vs 2%), i.e. 2% absolute reduction (RD= -0.02, 95%CI -0.07 to 0.02). BPaLM may improve treatment success, failure and recurrence, death, loss to follow-up, amplification of drug-resistance and adverse events but the evidence is very uncertain. Considering this research evidence and the additional considerations, the GDG judged that BPaLM may have large desirable effects and noted the very low certainty of the evidence.	The panel also considered the duration and pill burden with the intervention and comparator regimens. The duration of the intervention regimen is 24 weeks (5.5 months) so treatment duration is reduced compared to the control arm by between 3–18 months. The exact magnitude of reduction in time on treatment depends on the specific comparator regimen, which includes shorter (9–12 months) and longer (18–24 months) regimens. The pill burden of the intervention regimen is lower than that for the comparator regimens. The exact magnitude of reduction in pill burden depends on the specific comparator regimen. Beyond the outcomes captured directly as research evidence in the presented statistical analyses, the WHO 'Target Regimen Profile for rifampicin-resistant tuberculosis' (WHO, 2016) identified certain regimen characteristics as having desirable anticipated effects. These include a shorter treatment duration, reduced pill burden and number of component drugs and manageable DDIs. Decrease in the treatment duration was therefore identified as an additional important desirable effect.

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with TB-PRACTECAL comparator	Risk difference with BPaLM
Treatment success	128 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]	**RR 1.73** (1.31 to 2.27)	Study population 515 per 1 000	**376 more per 1 000** (160 more to 654 more)
Failure and recurrence	128 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]	**RR 0.26** (0.10 to 0.71)	Study population 258 per 1 000	**191 fewer per 1 000** (232 fewer to 75 fewer)
Lost to follow up	128 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]	**RR 0.16** (0.04 to 0.61)	Study population 197 per 1 000	**165 fewer per 1 000** (189 fewer to 77 fewer)
Adverse events	213 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]	**RR 0.41** (0.26 to 0.63)	Study population 509 per 1 000	**300 fewer per 1 000** (377 fewer to 188 fewer)

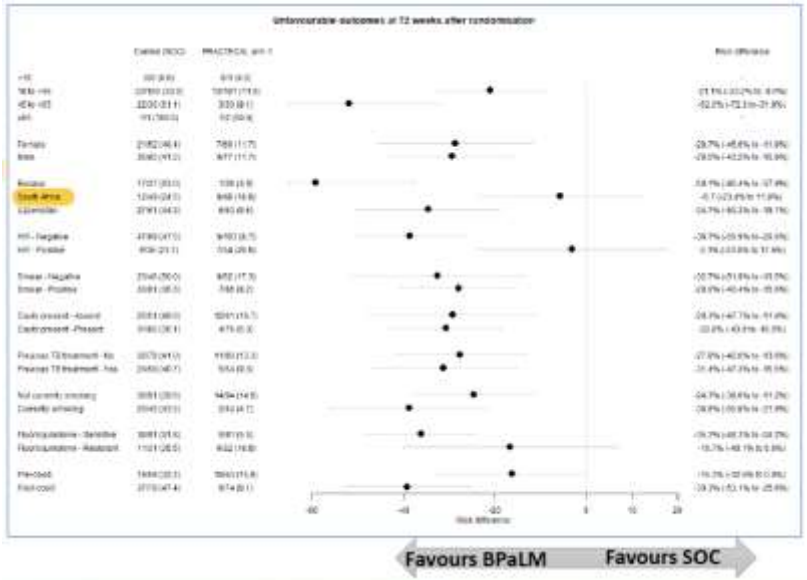
Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with TB-PRACTECAL comparator	Risk difference with BPaLM
Amplification of drug resistance	213 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]	**RD -0.02** (-0.07 to 0.02)	Study population 19 per 1 000	**19 fewer per 1 000** (20 fewer to 18 fewer)
Death	128 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]	**RD -0.03** (-0.10 to 0.03)	Study population 30 per 1 000	**31 fewer per 1 000** (33 fewer to 29 fewer)

- **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**

○Trivial
○ Small
○ Moderate
x Large

Additional evidence presented to the ERC by the review team included sub-group analysis of the South African sites from TB-PRACTECAL and the data relating to WHO sub-PICO 7.7 requested from Gregory Fox.

From TB-PRACTECAL presentation sent by Catherine Berry:

○ Varies ○ Don't know	In the subgroup analysis of efficacy by country, South African participants receiving BPaLM had more favourable outcomes as compared to participants receiving South African standard of care regimens (81.25% vs 75.5%; risk difference of 5.7 (95% CI -10.6% to 22%), although this result was not statistically significant.  **From WHO presentation of sub-PICO 7.1 (BPaLM (fluoroquinolone -resistant) vs WHO_long (fluoroquinolone-resistant) – IPD 2021) sent by Gregory Fox:** Based upon the point estimates with wide confidence intervals crossing no effect, BPaLM was associated with higher treatment success (adjusted RR 1.1; 95% CI 0.84, 1.45) (Certainty of evidence very low for all outcomes)	

PICO 7 Comparison 7.1	BPaLM (FQ-r) vs WHO long (FQ-r) (revised LTF, failure/recurren
Intervention	BPaLM (FQ-r) TB-PRACTECAL
Comparator	WHO long (FQ-r) - IPD 2021 (multiple cohorts, all-oral regimens c
Time of follow-up	18 months post treatment initiation

	Regimens		Outcome measures					Propensity score model
	BPaLM	WHO long	Unadj. RR	(95% CI)	Adj. RR (or RD)	(95% CI)	p-value	Covariates included in m
	n (%)	n (%)						
Total	11	839						
Outcomes								
Treatment success	9 (82%)	625 (74%)	1.1	(0.7, 1.28)	1.11	(0.84, 1.45)	0.4732	Age, sex, HIV status, ART treat AFB smear, previous DRTB
Failure & recurrence	2 (18%)	55 (7%)	2.77	(0.77, 7.63)			0.1647	
Death	0 (0%)	83 (10%)	-0.10	(-0.12, 0.16, RD)			0.613	
Loss to follow-up	0 (0%)	76 (9%)	-0.09	(-0.11, 0.17, RD)			0.612	
Grade 3 or more AE	5/18 (28%)	37 (4%)	6.3	(2.81, 14.14)	5.78	(2.39, 14.01)	0.0001	
Amplified resistance	0/18 (0%)	62 (7%)	-0.07	(-0.09, 0.1)RD			1	

The ERC, noting the improvement in treatment success and reduction in loss to follow up for all trial data in TB-PRACTECAL, as well as the shortened regimen with reduced pill burden, judged the desirable effects to be large. This judgement considers that the sub-group analysis and analysis of sub-PICO 7.1 consists of too few participants to show any definitive benefit in the FLQ resistant population only or when compared to South African standard or care regimens specifically.

Undesirable effects: How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

• **WHO Guideline panel**		
X Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Research Evidence** The BPaLM regimen arm of the TB-PRACTECAL trial with population including patients with MDR/RR-TB with or without quinolone resistance (MDR/RR-TB or pre-XDR-TB) was compared to comparator arm of the TB-PRACTECAL trial comprised of MDR/RR-TB or pre-XDR-TB patients treated with multiple local SoC regimens (including: 9–12-month injectable containing regimen; 18–24-month long WHO regimen (pre-2019); 9–12 month all oral regimen; 18–20 month all oral regimen). Participants with MDR/RR-TB (with or without quinolone resistance) receiving BPaLM regimen (n=62) compared to participants receiving WHO recommended standard of care regimens used in TB-PRACTECAL trial (n=66) experienced higher levels of treatment success (89% vs 52%), i.e. 73% relative increase (aRR=1.73, 95%CI 1.31 to 2.27); lower levels of failure and recurrence (8% vs 26%) i.e. 74% relative reduction (aRR=0.26, 95%CI 0.1 to 0.71); lower levels of death (0% vs 3%), i.e. 3% absolute reduction (RD= 0.03, 95%CI 0.1 to 0.03); lower levels of loss to follow-up (3% vs 20%), i.e. 84% of relative reduction (RR=0.16, 95%CI 0.12 to 0.52); lower levels of grade 3 to 5 adverse events (21% vs 51%), i.e. 59% relative reduction (aRR=0.41, 95%CI 0.04 to 0.61) and lower levels of amplified resistance (0% vs 2%), i.e. 2% absolute reduction (RD= 0.02, 95%CI 0.07 to 0.02). BPaLM may improve treatment success, failure and recurrence, death, loss to follow-up, amplification of drug-resistance and adverse events but the evidence is very uncertain. There were no undesirable effects among the specified outcomes Pretomanid safety Rodent Toxicology Studies – evidence of direct testicular toxicity Monkey Toxicology Studies – no evidence of direct testicular toxicity; abnormal sperm findings considered to be secondary to declining physical condition Hormone Data from Clinical Studies – no changes in FSH, LH, Inhibin B consistent with testicular toxicity Paternity Survey – 44 children fathered by 38 men (12%) who participated in pretomanid studies of 4 -6 months treatment duration Semen Study – ongoing study measuring semen in men undergoing pretomanid treatment.	**Additional considerations** Considering this research evidence and the additional considerations, the GDG judged that BPaLM may have trivial undesirable effects and noted the very low certainty of the evidence.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
x Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**From TB-PRACTECAL presentation sent by Catherine Berry:** Subgroup analysis of safety by country: Less SAE or Grade ≥ 3 were reported for in South African participants receiving BPaLM than those receiving South African standard of care regimes (16.1% vs 49.1%; RD -33.0%; 95% CI -50.9 to -15.1%)	The ERC noted that only one RCT with a very small sample size contributed to the data relating to efficacy and safety of BPaLM. However, this should be considered in light of the fact that current and previous standard of care regimens for the treatment of drug resistant TB were based on even less evidence . The ERC noted that the limitations of the available evidence and the resulting Imprecision do not prohibit a recommendation.

Country		SOC	BPaLM	BPaLC	BPaL
BY	n	29	28	21	21
	Grade ≥3 or SAE	9	4	6	5
	%	31.0%	14.3%	28.6%	23.8%
	Risk difference	0	-16.7%	-2.5%	-26.0%
	lower		-39.7%	-28.1%	-39.0%
	upper		6.2%	23.2%	-13.0%
UZ	n	69	67	57	55
	Grade ≥3 or SAE	37	21	19	13
	%	53.6%	31.3%	33.3%	23.6%
	Risk difference	0	-22.3%	-20.3%	-19.5%
	lower		-39.8%	-37.3%	-39.9%
	upper		-4.8%	-3.3%	0.9%
SA	n	53	56	48	46
	Grade ≥3 or SAE	26	9	13	11
	%	49.1%	16.1%	27.1%	23.9%
	Risk difference	0	-33.0%	-16.0%	-22.0%
	lower		-50.9%	-37.9%	-40.4%
	upper		-15.1%	5.8%	0.9%

From WHO presentation of sub-PICO 7.1 (BPaLM (fluoroquinolone -resistant) vs WHO_long (fluoroquinolone-resistant) – IPD 2021) sent by Gregory Fox:
Based upon the point estimates with wide confidence intervals crossing no effect, BPaLM was associated with higher rates of failure/recurrence (unadjusted RR 2.77, 95% CI 0.77, 7.63), lower mortality (RD – 0.10; 95% CI -0.12, 0.16), less loss to follow-up (RD -0.09; 95% CI -0.11, 0.17). BPaLM was associated with more Grade ≥ 3 adverse events (adjusted RR 5.78; 95% CI 2.39, 14.01). (Certainty of evidence very low for all outcomes)

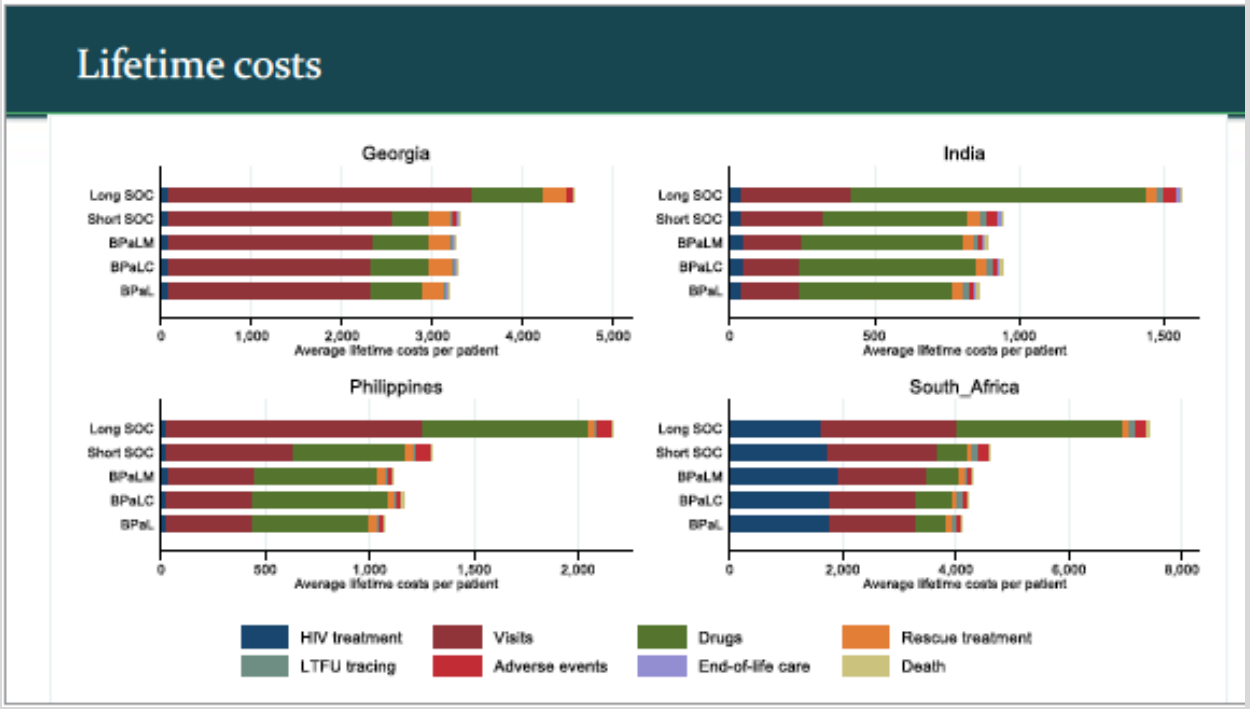
PICO 7 Comparison 7.1	BPaLM (FQ-r) vs WHO_long (FQ-r) (revised LTF, failure/recurrence)							
Intervention	BPaLM (FQ-r) TB-PRACTECAL							
Comparator	WHO long (FQ-r) - IPD 2021 (multiple cohorts, all-oral regimens containing Bdq)							
Time of follow-up	18 months post treatment initiation							
	Regimens		Outcome measures					Propensity score model
	BPaLM	WHO long	Unadj. RR	(95% CI)	Adj. RR (or RD)	(95% CI)	p-value	Covariates included in model
	n (%)	n (%)						
Total	11	839						
Outcomes								
Treatment success	9 (82%)	625 (74%)	1.1	(0.7, 1.28)	1.11	(0.84, 1.45)	0.4732	Age, sex, HIV status, ART treatment (for those with HIV), AFB smear, previous DRTB treatment, site of disease
Failure & recurrence	2 (18%)	55 (7%)	2.77	(0.77, 7.63)			0.1647	Adjustment not possible
Death	0 (0%)	83 (10%)	-0.10	(-0.12, 0.16, RD)			0.613	Adjustment not possible
Loss to follow-up	0 (0%)	76 (9%)	-0.09	(-0.11, 0.17, RD)			0.612	Adjustment not possible
Grade 3 or more AE	5/18 (28%)	37 (4%)	6.3	(2.81, 14.14)	5.78	(2.39, 14.01)	0.0001	
Amplified resistance	0/18 (0%)	62 (7%)	-0.07	(-0.09, 0.1)RD			1	Adjustment not possible

Overall, BPaLM was associated with less AEs than the SoC arms, and when stratified by country for South African SoC regimens specifically. Therefore, the ERC judgement found that the anticipated undesirable effects of the intervention are trivial.

Certainty of evidence: What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
x Very low ○ Low ○ Moderate ○ High ○ No included studies	**Research Evidence** The certainty of evidence was rated very low. The risk of bias was judged to be serious or very serious, depending on outcome. There was a lack of blinding, early termination of the trial for benefit, measured confounding and likely unmeasured confounding and small event numbers precluding adjustment for some comparisons. These concerns resulted in downgrading by one or two levels depending upon outcome. We did not downgrade for inconsistency. We downgraded for indirectness due to differences in population and the comparator regimen by one level. Imprecision was serious or very serious according to outcomes, with a small number of events for some outcomes resulting downgrading by one to two levels according to outcomes.  a. An imbalance in measured covariates (gender, prior DR-TB, smear status) likely arises from the small number of participants in each group. While the adjusted analyses will account for measured confounding, unmeasured confounding is also likely. b. Small numbers of events in some outcomes precludes adjustment in some comparisons. c. A lack of blinding of patients, caregivers and those adjudicating outcomes may introduce bias in the conduct of the trial. Higher loss to follow-up was noted in the comparator group, which is an outcome that may be influenced by patient or clinician knowledge of the regimen. d. The trial was stopped early for benefit, with few events (<200). This can introduce bias. Formal stopping rules do not reduce bias (GRADE Handbook, 2013). e. Multiple comparator regimens were used, varying across site. This may explain some of the substantial inconsistency in the point estimates for treatment outcomes seen between countries (Belarus, South Africa and Uzbekistan). The decision whether to downgrade is difficult. We did not downgrade for inconsistency as the issue of comparators was addressed under indirectness. f. A single trial. Serious indirectness (i) Populations: Differences in population of a trial and population to which guidelines will apply. (ii) Comparator: Some comparator regimens are sub-optimal, not according with the WHO standard of care (at the time or presently) and vary by country. Downgraded one level. g. The number of participants in both intervention and comparator groups was small (n=60 and n=66). Very few events in the outcomes of interest, causing very serious imprecision. We downgraded two levels for imprecision for some outcomes, and one level for others.	As noted in the CoE assessment, it is important to highlight that: • the population included in the trial that gave rise to the data is a mix of MDR/RR and pre-XDR/XDR TB patients (82–92% RR/MDR, depending on study arm) • treatment outcomes for the comparator regimen differ for these populations, and that • 24% of patients were treated with regimens no longer recommended by WHO, e.g., containing injectable drugs and not containing Bdq
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		

x Very low ○ Low ○ Moderate ○ High ○ No included studies	No additional research evidence was provided. The ERC agreed with the judgment that the certainty of evidence is very low.	
Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Important uncertainty or variability ○ Possibly important uncertainty or variability **x Probably no important uncertainty or variability** ○ No important uncertainty or variability ○ No known undesirable outcomes	**Research Evidence** No evidence research searched for. Higher treatment efficacy, shorter duration of treatment, lower pill burden and less adverse events are usually valued by patients. The panel judged that there was probably no important uncertainty or variability in how much people value the main outcomes.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○ Important uncertainty or variability ○ Possibly important uncertainty or variability **x Probably no important uncertainty or variability** ○ No important uncertainty or variability ○ No known undesirable outcomes	No additional research was searched for by the review team. The ERC agreed with the WHO GDG judgement that there is probably no important uncertainty or variability in how much people value the main outcomes.	
Balance of effects: Does the balance between desirable and undesirable effects favour the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		

○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison **x Probably favours the intervention** ○ Favours the intervention ○ Varies ○ Don't know	**Research Evidence** Nil The GDG judged the benefits of BPaLM to be large and the undesirable effects to be trivial compared to WHO recommended standard of care regimens. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaLM regimen	As noted in the CoE assessment, it is important to highlight that: • the population included in the trial that gave rise to the data is a mix of MDR/RR and pre-XDR/XDR TB patients (82–92% RR/MDR, depending on study arm) • treatment outcomes for the comparator regimen differ for these populations, and that • 24% of patients were treated with regimens no longer recommended by WHO, e.g., containing injectable drugs and not containing Bdq As a result, the balance of effects may be different in settings/populations with different FQ-resistance prevalence and if only currently recommended regimens are used.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison **x Probably favours the intervention** ○ Favours the intervention ○ Varies ○ Don't know	The ERC considered that even if the benefits of BPaLM in comparison to South African SoC specifically are smaller than in the comparison of BPaLM to SoC arm in TB-PRACTECAL, the shortened duration of treatment and less complex treatment regimen that may favour adherence probably favours the intervention.	
Resources required: How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		

○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings **x Varies** ○ Don't know	**Research Evidence** Sedona Sweeney's presentation on cost & CEA of PRACTECAL regimens from pre-GDG webinar From the data presented, the total cost (drugs and delivery) of WHO_short appear to be between 1%-15% higher than for BPaLM and between ~1.4x to 1.9x higher for WHO_long when looking at comparative estimates within country. In most settings, BPaLM is cost-saving; these cost savings are mostly due to reduced time in care and therefore reductions in numbers of outpatient visits, inpatient bed-days, and lab tests.  	The panel judged that the costs for BPaLM are lower because costs of drugs are lower, and cost of delivery are also lower due to the shorter duration of treatment and lower complexity. The GDG judged that the reduction in costs varies between moderate and large.

Results by country: conservative approach

Country and regimen	Total costs per person	Total DALYs	Incremental Costs per person
Philippines			
SOC long	$2,127	6.2	
SOC short	$1,286	5.1	-$841
BPaL	$1,050	5.1	-$236
BPaLC	$1,146	5.0	$96
BPaLM	$1,099	4.4	-$47
South Africa			
SOC long	$6,896	6.9	
SOC short	$4,120	6.3	-$2,776
BPaL	$3,554	6.3	-$566
BPaLC	$3,687	6.2	$132
BPaLM	$3,739	5.7	$52
India			
SOC long	$1,531	6.8	
SOC short	$923	6.1	-$608
BPaL	$838	6.1	-$84
BPaLC	$923	6.0	$85
BPaLM	$872	5.5	-$51
Georgia			
SOC long	$4,499	4.7	
SOC short	$3,290	4.1	-$1,209
BPaL	$3,164	4.1	-$125
BPaLC	$3,264	4.0	$100
BPaLM	$3,246	3.3	-$19

- **PHC/ADULT HOSPITAL LEVEL COMMITTEE**

BPaLM vs long regimens for MDR and Pre-XDR TB

Suggested ERC Judgment:

○ Large costs
○ Moderate costs
○ Negligible costs and savings
○ Moderate savings
x Large savings
○ Varies
○ Don't know

BPaLM vs SA_New SCR

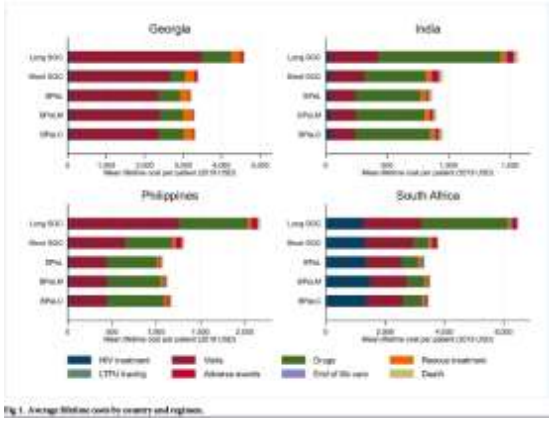
Resources required

Suggested ERC Judgment:

○ Large costs
○ Moderate costs
x Negligible costs and savings
○ Moderate savings
○ Large savings
○ Varies
○ Don't know

Additional information presented by the review team included updated evidence from the Sweeney et al. publication (published since the WHO GDG meeting, and on which WHO GDG judgement is based), and the normative cost analysis of direct costs conducted by the review team.

Updated version of Sedona Sweeney's presentation with official publication:



The cost savings associated with a move from the current SOC mix to BPaL for all MDR/RR-TB patients range was $1,173 per person in South Africa.
Costs presented in 2019 US$;
Total costs per person for South Africa: BPaL: $3,344, BPaLM: $3,520, and BPaLC: $3,470.
Current SOC regimen mix (74% short, 26% long): $4,517

Table 2. Base case results.

			Comparison with current SOC mix	
Country and regimen	**Total costs per person**	**Total DALYs per person**	**Incremental Costs Per Person**	**Incremental DALYs Averted Per Person**
Philippines				
Current SOC regimen mix (99% short, 1% long)	$1,329	5.4		
BPaL	$1,078	5.4	-$251	0.0
BPaLC	$1,174	5.3	-$155	0.1
BPaLM	$1,124	4.6	-$204	0.8
South Africa				
Current SOC regimen mix (74% short, 26% long)	$4,517	6.8		
BPaL	$3,344	6.6	-$1,173	0.2
BPaLC	$3,470	6.5	-$1,047	0.3
BPaLM	$3,520	6.0	-$997	0.8

Normative cost analysis conducted by review team. For more information consult Appendix 3.

Appendix 3.xlsx

Normative cost analysis based on specific direct costs						Sensitivity analysis excl.clinic visit costs
Regimen	Drug costs (ZAR)	Bacteriological tests (Costs in ZAR)	Other lab tests (Costs in ZAR)	Clinic visit costs (ZAR)	Total costs per patient treated incl. clinic visit costs (ZAR)	Total costs per patient treated excl. clinic visit costs (ZAR)
Short oral course (Min)	11 437,70	1 058,58	472,42	2 680,79	15 649,49	12 968,70
Short oral course (Max)	13 650,99	1 058,58	472,42	2 680,79	17 862,78	15 181,99
BPaL (Lzd_Adjusted dose)	11 710,64	705,72	2 158,89	2 632,56	17 207,81	14 575,25
BPaLM (Lzd_Adjusted dose)	12 307,88	705,72	2 158,89	2 632,56	17 805,05	15 172,49
BPaLM (Lzd_Standard)	11 787,08	705,72	2 158,89	2 632,56	17 284,25	14 651,69
Long course 1 (Basic)	27 159,16	2 117,16	783,55	4 407,60	34 467,47	30 059,87
Long course 2	49 601,58	2 117,16	2 028,07	6 581,40	60 328,21	53 746,81

Note:
Where weight calibrated dosing is recommended, drug costs have been applied at the maximum weight band/adult dose
1 US$ equivalent to R18.30
Drug calculations all based on a 28 day cycle per month
Diagnostic Xpert, microscopy, culture and DST not included in costs for bacteriological tests
Clinic visits classified according to nature of clinical visits and based on secondary data representing a fully decentralised model.

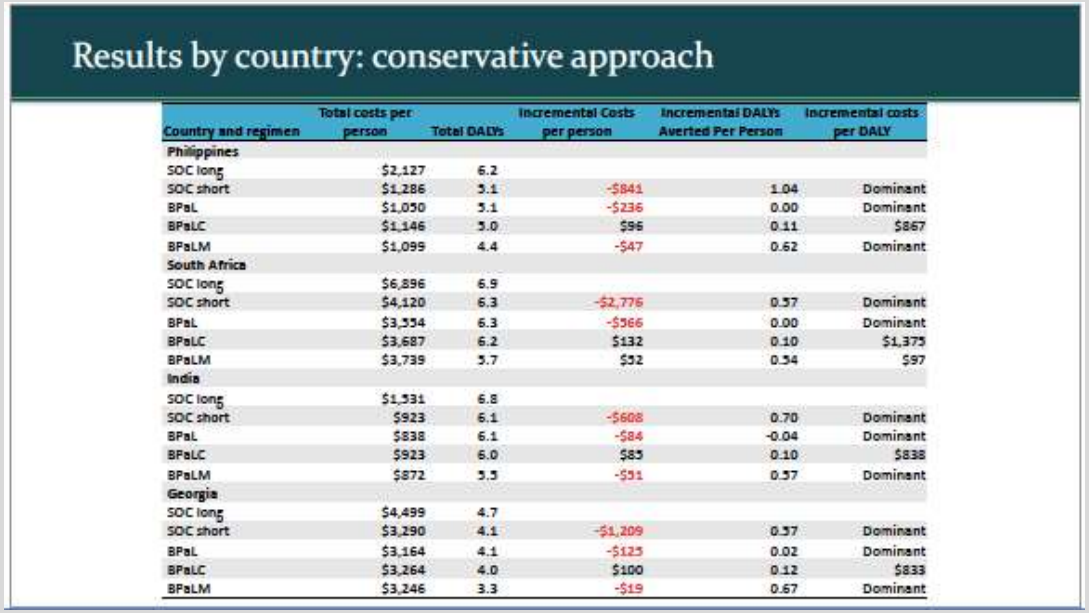
Marginally increased drug costs associated with BPaLM regimen as compared to current South African short course regimen despite the reduced duration of treatment. Increased costs of treatment monitoring laboratory tests (such as monthly full blood and differential counts as recommend by WHO) driving the increased direct costs associated with BPaLM, which is not entirely offset by the reduced number of bacteriological treatment monitoring tests associated with the shorter duration of treatment.

Based on the normative cost analysis performed by the review team, the ERC judged that BPaLM when compared to the current South African short course regimen would be associated with negligible costs and/or savings. BPaLM when compared to the current South African long courses (for MDR and fluoroquinolone resistances) would be associated with large savings.

Certainty of evidence of resource requirements: What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline panel**		
x Very low ○ Low ○ Moderate ○ High ○ No included studies	**Research Evidence** Nil	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Very low ○ Low x Moderate ○ High ○ No included studies	The ERC considered the certainty of evidence of resource requirements to be moderate considering the normative cost analysis performed by the review team is locally relevant.	

Cost effectiveness: Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline panel**		
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison **x Probably favours the intervention** ○ Favours the intervention ○ Varies ○ No included studies	**Research Evidence** **Sedona Sweeney's presentation on cost & CEA of PRACTECAL regimens from pre-GDG webinar** From the data presented: «strong evidence that BPaLM would be cost-effective» in the setting studied (costs reduced and DALYs averted) Note that estimates of effectiveness (from which DALYs averted were derived) are different from those presented in the evidence profile for this PICO  Results by country: conservative approach Given their prior judgements (balance of effects probably favours the intervention; intervention leads to moderate to large savings), the panel judged that the cost-effectiveness of the intervention probably favours the intervention	.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the	No additional research evidence was considered by the ERC. Based on the data and studies considered by WHO GDG, the ERC agreed that cost-effectiveness of the intervention probably favours the intervention.	

Country and regimen	Total costs per person	Total DALYs	Incremental Costs per person	Incremental DALYs Averted Per Person	Incremental costs per DALY
Philippines					
SOC long	$2,127	6.2			
SOC short	$1,286	5.1	-$841	1.04	Dominant
BPaL	$1,050	5.1	-$236	0.00	Dominant
BPaLC	$1,146	5.0	$96	0.11	$867
BPaLM	$1,099	4.4	-$47	0.62	Dominant
South Africa					
SOC long	$6,896	6.9			
SOC short	$4,120	6.3	-$2,776	0.57	Dominant
BPaL	$3,554	6.3	-$566	0.00	Dominant
BPaLC	$3,687	6.2	$132	0.10	$1,375
BPaLM	$3,739	5.7	$52	0.54	$97
India					
SOC long	$1,531	6.8			
SOC short	$923	6.1	-$608	0.70	Dominant
BPaL	$838	6.1	-$84	-0.04	Dominant
BPaLC	$923	6.0	$85	0.10	$838
BPaLM	$872	5.5	-$51	0.57	Dominant
Georgia					
SOC long	$4,499	4.7			
SOC short	$3,290	4.1	-$1,209	0.57	Dominant
BPaL	$3,164	4.1	-$125	0.02	Dominant
BPaLC	$3,264	4.0	$100	0.12	$833
BPaLM	$3,246	3.3	-$19	0.67	Dominant

comparison **x Probably favours the intervention** ○ Favours the intervention ○ Varies ○ No included studies		
Equity: What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Reduced ○ Probably reduced ○ Probably no impact **x Probably increased** ○ Increased ○ Varies ○ Don't know	**Research Evidence** No research evidence searched for. Despite not being able to identify relevant research evidence, the panel used their collective experience to judge that there would likely be advantages associated with the use of the BPaLM regimen due to its reduced complexity and shorter duration. The panel judged that use of the BPaLM regimen would probably increase equity.	The panel considered the treatment duration and the ability to decentralize treatment (to enable access for remote, underserviced settings and disadvantaged populations) to affect equity.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Reduced ○ Probably reduced ○ Probably no impact **x Probably increased** ○ Increased ○ Varies ○ Don't know	No additional research evidence was considered by the ERC. The ERC was in agreement with the WHO GDG that due to the reduced complexity and shorter duration of the treatment regimen with resultant ability to decentralize care, the use of BPaLM would probably increase equity.	
Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ No ○ Probably no **x Probably yes** ○ Yes ○ Varies ○ Don't know	**Research Evidence** **Beverly Stringer's presentation on PROs from pre-GDG webinar (qualitative study) on the patient perspective** Positive impact of shorter treatment on employment status welcomed.	**van de Berg et al, 2021 (based on 2019 KNCV report, funded by TB Alliance) on the provider perspective:** • Noting that analyses from van de Berg paper are only partially applicable here since in their study they asked about acceptability of using

	The panel considered patients and health care providers as key stakeholders. The panel considered the following aspects as critical with regards to acceptability: regimen duration and drug safety monitoring needs (both relating to necessary travel, loss of income and general disruption of the life of patients; workload for the health care system), needs for drug susceptibility testing. The panel judged that the BPaLM regimen would probably be acceptable.	• BPaL for pre-XDR patients and when compared to the long WHO regimen. • **Findings:** Acceptability: overall high and rated as acceptable by >80% across domains
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ No ○ Probably no **x Probably yes** ○ Yes ○ Varies ○ Don't know	**Additional Research Evidence presented to the ERC by TB-PRACTECAL-PRO team:** All trial participants respiratory-specific QOL scores improved with treatment, irrespective of the regimen they received (intervention or SoC). However, faster improvement in the investigational arm as compared to SoC was noted. It was noted that a participant in the intervention arm experiences a 15% reduction (95% CI 12 to 18%) in the mean SGRQ symptom score per month versus an average of 5% (95% CI 0 – 9%) reduction experienced by a participant in the SoC arm. (Note: lower SGRQ symptom score associated with greater quality of life). The qualitative data showed that the improvement in QOL was noted by both the individual and their friends/family, with a resultant positive effect on treatment support. It was highlighted that South African participants were slightly underrepresented in the trial (32 South Africans of 137 participants) and that no subgroup analysis of QOL outcomes across countries or by site was performed. For participants interviewed in this qualitative study, the supportive care experienced was as important as the tolerability of the novel drug regimen. The ERC concluded that based on the research considered by the WHO GDG and additional information form the TB-PRACTECAL-PRO team the intervention is probably acceptable to stakeholders.	
Feasibility: Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO GUIDELINES, 2020**		
○ No ○ Probably no **x Probably yes** ○ Yes ○ Varies ○ Don't know	**Research Evidence** Nil additional The panel considered the following aspects to affect feasibility (i.e. to be potential barriers to implementation): requirements for drug safety monitoring and requirements for drug susceptibility testing. The panel noted limited availability of drugs in the BPaLM regimen for use in DST as a potential barrier to implementation and also noted that data on the critical concentration of Pretomanid for use in DST is limited. However, given the reduced duration, complexity and associated workload, the panel judged that implementation is probably feasible.	**van de Berg et al, 2021 (based on 2019 KNCV report, funded by TB Alliance) on the provider perspective:** Noting that analyses from van de Berg paper are only partially applicable here since in their study they asked about feasibility of using BPaL for pre-XDR patients and when compared to the long WHO regimen.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ No ○ Probably no **x Probably yes** ○ Yes	Additional barriers to implementation that may affect feasibility considered by the ERC included that need for an enhanced programmatic pharmacovigilance plan. The ERC considered feedback from the NDOH TB programme that planning for enhanced pharmacovigilance and data collection is underway. The ERC also considered concern around stock availability of pretomanid and consulted the NDOH TB programme. The ERC heard that currently, stock availability is not a potential barrier to implementation as pretomanid has been ordered and funding has been made available for further procurement.	

○ Varies ○ Don't know	With regard to the impact of drug resistance testing on the feasibility of implementation, the ERC heard that resistance testing for Bdq and Linezolid is already available, and provisions for resistance testing for pretomanid are being made. The ERC heard from the NDOH TB programme that feasibility could be impacted if the level of prescriber be restricted to medical officer only, as clinical nurse practitioners and clinical associates are important human resources for decentralized care. After consideration of these potential barriers to implementation, the ERC judged that BPaLM is probably feasible to implement.	

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	23 March 2023	JT, NG, SE, FB, NN, GM, MM, JN, TK, KC	Initial ERC discussion took place on 16th March 2023, with ongoing discussion and updated ERC decision at an extraordinary meeting of the ERC on 23 March 2023, where a conditional recommendation for the use of the BPaLM in the treatment of drug resistant TB with or without fluoroquinolone resistance was suggested. The recommendation is conditional based on the very low quality of evidence underlying the WHO recommendation.

c) Is BPaL (intervention 1) non-inferior to, and/or safer than BPaLM (intervention 2) in the treatment of rifampicin-resistant tuberculosis without additional fluoroquinolone resistance?

Should BPaLM vs. BPaL (Linezolid 600mg/300mg) be used for pulmonary MDR/RR-TB and pre-XDR-TB? (sub-PICO 6.2)

(Note: Where judgements differed, both WHO and PHC/Adult Hospital Level's assessments have been described)

Problem: Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ No ○ Probably no ○ Probably yes **x Yes** ○ Varies ○ Don't know	**Research evidence** The COVID-19 pandemic has reversed years of progress in providing essential TB services and reducing TB disease burden. The most obvious impact is a large global drop in the number of people newly diagnosed with TB and reported. This fell from 7.1 million in 2019 to 5.8 million in 2020, an 18% decline back to the level of 2012 and far short of the approximately 10 million people who developed TB in 2020. Reduced access to TB diagnosis and treatment has resulted in an increase in TB deaths. Best estimates for 2020 are 1.3 million TB deaths among HIV-negative people (up from 1.2 million in 2019) and an additional 214 000 among HIV-positive people (up from 209 000 in 2019), with the combined total back to the level of 2017. Other impacts include reductions between 2019 and 2020 in the number of people provided with treatment for drug-resistant TB (-15%, from 177 100 to 150 359, about 1 in 3 of those in need). Globally in 2020, 71% (2.1/3.0 million) of people diagnosed with bacteriologically confirmed pulmonary TB were tested for rifampicin resistance, up from 61% (2.2/3.6 million) in 2019 and 50% (1.7/3.4 million) in 2018. Among these, 132 222 cases of MDR/RR-TB and 25 681 cases of pre-XDR-TB or XDR-TB were detected, for a combined total of 157 903. This was a large fall (of 22%) from the total of 201 997 people detected with drug-resistant TB in 2019, consistent with similarly large reductions in the total number of people newly diagnosed with TB (18%) and the total number of people diagnosed with bacteriologically confirmed pulmonary TB (17%) observed between 2019 and 2020. Worldwide, 150 359 people with MDR/RR-TB were enrolled on treatment in 2020, down 15% from the total of 177 100 in 2019. This level of enrolment was equivalent to about one in three of the people who develop MDR/RR-TB each year.	

	More positively, there have been improvements in treatment success rates. Globally in 2018 (the latest patient cohort for which data are available), the treatment success rate for MDR/RR-TB was 59%, reflecting steady improvements in recent years from 50% in 2012. (Global TB Report 2021)	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○ No ○ Probably no ○ Probably yes **x Yes** ○ Varies ○ Don't know	In addition to the research evidence considered by the WHO GDG , the ERC considered the burden of disease in the locally relevant population. A cross-sectional study of identified tuberculosis cases, conducted in South Africa between 2012 and 2014, reported the prevalence of RR-TB as 4.6%, MDR-TB as 2.8% (95% CI 2.0, 3.6) and the prevalence of XDR-TB as 4.9% (95% CI 1.0, 8.8). (Ismail et al. 2018). More recently for the year 2021, the WHO reported an estimated 21 000 incident cases of RR-TB in South Africa. (WHO Global Tuberculosis Report, 2022) The ERC judged the problem to be a priority.	
Desirable effects: How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○Trivial ○ Small **x Moderate** ○ Large ○ Varies ○ Don't know	**Research evidence** The BPaLM regimen arm of the TB-PRACTECAL trial with population including patients with MDR/ RR-TB with or without quinolone resistance (MDR/RR-TB or pre-XDR-TB) was compared to BPaL arm of the TB-PRACTECAL trial comprised of MDR/RR-TB or pre-XDR-TB patients. Participants with MDR/RR-TB (with or without quinolone resistance) receiving BPaLM regimen (n=62) compared to participants receiving BPaL in TB-PRACTECAL trial (n=60) experienced higher levels of treatment success (89% vs 77%), i.e. 15% relative increase (aRR=1.15, 95%CI 0.95 to 1.38); lower levels of failure and recurrence (8.1% vs 13%), i.e. 47% relative reduction (aRR= 0.53, 95%CI 0.17 to 1.63); lower levels of loss to follow-up (3.2% vs 10%), i.e. 68% relative reduction (RR=0.32, 95%CI 0.08 to 1.34); no difference in death (0% vs 0%), i.e. 0% absolute difference (RD= 0.00, 95%CI –0.06 to 0.06); higher levels of grade 3 to 5 adverse events (21% vs 20%), i.e. 7% relative increase (aRR=1.07, 95%CI 0.62 to 1.88) and lower levels of amplified resistance (0% vs 3%), i.e. 3% absolute reduction (RD= –0.03, 95%CI –0.08 to 0.01). The evidence is very uncertain about the effect of the BPaLM regimen with linezolid on all outcomes.	

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with BPaL (Lzd 600mg/300mg)	Risk difference with BPaLM
Treatment success	122 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]	**RR 1.15** (0.95 to 1.38)	Study population	
				767 per 1 000	**115 more per 1 000** (38 fewer to 291 more)
Failure and recurrence	122 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]	**RR 0.53** (0.17 to 1.63)	Study population	
				133 per 1 000	**63 fewer per 1 000** (111 fewer to 84 more)
Lost to follow up	122 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]	**RR 0.32** (0.08 to 1.34)	Study population	
				100 per 1 000	**68 fewer per 1 000** (92 fewer to 34 more)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with BPaL (Lzd 600mg/300mg)	Risk difference with BPaLM
Death	122 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,g]	**RD 0.00** (-0.06 to 0.06)	Study population	
				0 per 1 000	**0 fewer per 1 000** (60 fewer to 60 more)
Amplification of drug resistance	207 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]	**RD -0.03** (-0.08 to 0.01)	Study population	
				29 per 1 000	**30 fewer per 1 000** (80 fewer to 10 more)

	Considering this research evidence and the additional considerations, the GDG judged that BPaLM may have moderate desirable effects and noted the very low certainty of the evidence.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○Trivial ○ Small ○ Moderate ○ Large ○ Varies **x Don't know**	Based on the wide confidence intervals, crossing no effect for the comparison of BPaLM vs BPaL from TB-PRACTECAL, the ERC judged that it is not known how substantial the desirable effects of the intervention are.	
Undesirable effects: How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○Trivial **x Small** ○ Moderate ○ Large ○ Varies ○ Don't know	**Research Evidence** The BPaLM regimen arm of the TB-PRACTECAL trial with population including patients with MDR/ RR-TB with or without quinolone resistance (MDR/RR-TB or pre-XDR-TB) was compared to BPaL arm of the TB-PRACTECAL trial comprised of MDR/RR-TB or pre-XDR-TB patients. Participants with MDR/RR-TB (with or without quinolone resistance) receiving BPaLM regimen (n=62) compared to participants receiving BPaL in TB-PRACTECAL trial (n=60) experienced higher levels of grade 3 to 5 adverse events (21% vs 20%), i.e., 7% relative increase (aRR=1.07, 95%CI 0.62 to 1.88). **Considering this research evidence and the additional considerations, the GDG judged that BPaLM may have small undesirable effects and noted the very low certainty of the evidence.**	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies **x Don't know**	Additional evidence was presented to the ERC by the review team from data relating to WHO sub-PICO 7.2 provided by Gregory Fox. For sub-PICO 7.2, the comparison of BPaLM arm from TB-PRACTECAL only in participants with fluoroquinolone -resistant TB (n = 11) vs. BPaL from the ZeNix 600-26 arm in participants with fluoroquinolone-resistant TB (n = 33), BPaLM was associated with statistically significant less treatment success (unadjusted RR 0.82; 95% CI 0.52, 0.95) and higher rates of treatment failure/recurrence (RD 0.18, 95% CI 0.05, 0.48). There was no difference in mortality, loss-to-follow-up or amplification of resistance. Based on point estimate, with wide confidence interval crossing no difference, BPaLM in this population was also associated with more grade 3 ≥ adverse events (aRR 1.19; 95% CI 0.34, 4.21).	

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with BPaL (Lzd 600mg/300mg)	Risk difference with BPaLM
Adverse events	207 (1 RCT)	⨁◯◯◯ Very low[abcdefg]	**RR 1.07** (0.61 to 1.88)	Study population 196 per 1 000	**14 more per 1 000** (76 fewer to 173 more)

The ERC considered that the possible increased risk of treatment failure and reduced treatment success reported in the additional research presented may have occurred as a result of chance (noting the small sample size), however, an alternate explanation is that the reduction in Linezolid dosing from 600mg to 300mg at 16 weeks in the BPaLM arm in TB PRACTECAL as compared to 600mg of Linezolid used for 26 weeks in the ZeNix trial may account for this difference in outcomes in the fluoroquinolone resistant population.

However, based on the wide confidence intervals that cross no effect for adverse events, in the comparison of the BPaLM and BPaL arms in TB-PRACTECAL, and the potential for more undesirable effects when used in those with fluoroquinolone resistance, the ERC judged that it is currently not known how substantial the undesirable effects of the intervention are.

PICO 7 Comparison 7.2	BPaLM (FQ-r) vs BPaL (FQ-r)
Intervention	BPaLM (FQ-r) TB-PRACTECAL
Comparator	BPaL (Zenix 600-26)
Time of follow-up	18 months post treatment initiation

	Regimens		Outcome measures					Propensity score model
	BPaLM	BPaL	Unadj. RR	(95% CI)	Adj. RR (or RD)	(95% CI)	p-value	Covariates included in mod
	n (%)	n (%)						
Total	11	33						
Outcomes								
Treatment success	9 (82%)	33 (100%)	0.82	(0.52, 0.95)			0.0581	Age, sex, HIV status, ART treatmen AFB smear, previous DRTB treatme
Failure & recurrence	2 (18%)	0 (0%)	0.18	(0.05, 0.48) RD			0.0581	As above
Death	0 (0%)	0 (0%)	0	(-0.11, 0.26)RD			1	As above
Loss to follow-up	0 (0%)	0 (0%)	0	(-0.11, 0.26)RD			1	As above
Grade 3 or more AE	5/18 (28%)	5 (15%)	1.83	(0.61, 5.5)	1.19	(0.34, 4.21)	0.7854	
Amplified resistance	0/18 (0%)	0 (0%)	0	(-0.11, 0.18)				† Adjustment not possible

The University of Sydney

*Sensitivity estimates for aRR for treatment success

Certainty of evidence: What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline panel**		
x Very low ○ Low ○ Moderate ○ High ○ No included studies	**Research Evidence** Confidence limits were wide for most estimates. Certainty was rated *very low*. Risk of bias was serious or very serious, for different outcomes. There was a lack of blinding, early termination of the trial for benefit, measured confounding and likely unmeasured confounding and small event numbers precluding adjustment for some comparisons. These concerns resulted in downgrading by one or two levels depending upon outcome. We did not downgrade for inconsistency. We downgraded for indirectness due to differences in population and the comparator regimen by one level. Imprecision was serious or very serious according to outcome, with a small number of events for some outcomes resulting downgrading by one to two levels according to outcomes.	

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)
Treatment success	122 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]
Failure and recurrence	122 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]
Death	122 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,g]
Lost to follow up	122 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]
Adverse events	207 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]
Amplification of drug resistance	207 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]

a. An imbalance in measured covariates (gender, past TB treatment, past DR-TB treatment, smear positivity, culture positivity and FQ-S proportion) likely arises from the small number of participants in each group. While the adjusted analyses will account for measured confounding, unmeasured confounding is also likely.
b. Small numbers of events in some outcomes precludes adjustment in some comparisons
c. A lack of blinding of patients, caregivers and those adjudicating outcomes may introduce bias in the conduct of the trial. Higher loss to follow-up was noted in the comparator group, which is an that may be influenced by patient or clinician knowledge of the regimen.
d. The trial was stopped early for benefit, with few events (<200). This can introduce bias. Formal stopping rules do not reduce bias (GRADE Handbook, 2013).
e. Multiple comparator regimens were used, varying across site. This may explain some of the inconsistency in the point estimates for treatment outcomes seen between countries (Belarus, South Africa and Uzbekistan). The decision whether to downgrade is a difficult decision. Confidence limits for these estimates do overlap, and so we have chosen not to downgrade for inconsistency.
f. A single trial. Serious indirectness (i) Populations: Differences in population of a trial and population to which guidelines will apply. (ii) Comparator: Some comparator regimens are sub-optimal, not according with the WHO standard of care (at the time or presently) and vary by country. Downgraded one level.
g. The number of participants in both intervention and comparator groups was small (n=62 and n=60). Very few events in the outcomes of interest, causing very serious imprecision. We downgraded two levels for imprecision for some outcomes, and one level for others.

• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
x Very low ○ Low ○ Moderate ○ High ○ No included studies	The ERC agrees with the WHO GDG panel judgement that the overall certainty of the evidence of the effects is very low.	
Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Important uncertainty or variability ○ Possibly important uncertainty or variability **x Probably no important uncertainty or variability** ○ No important uncertainty or variability ○ No known undesirable outcomes	**Research Evidence** No evidence research searched for. Higher treatment efficacy, shorter duration of treatment, lower pill burden and less adverse events are usually valued by patients. The panel judged that there was probably no important uncertainty or variability in how much people value the main outcomes.	Higher treatment efficacy, shorter duration of treatment, lower pill burden and less adverse events are usually valued by patients.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		

○ Important uncertainty or variability ○ Possibly important uncertainty or variability **x Probably no important uncertainty or variability** ○ No important uncertainty or variability ○ No known undesirable outcomes	No additional research evidence was presented to the ERC by the review team. The ERC agrees with the WHO GDG judgment that there is probably no important uncertainty or variability in how much people value the main outcomes.	
Balance of effects: Does the balance between desirable and undesirable effects favour the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison **x Probably favours the intervention** ○ Favours the intervention ○ Varies ○ Don't know	**Research Evidence** Nil additional The GDG judged the benefits of BPaLM to be moderate and the undesirable effects to be small compared to BPaL. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaLM.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Favours the comparison ○ Probably favours the comparison **x Does not**	Considering the previous ERC judgements, that the size of desirable and undesirable effects of the BPaLM intervention in comparison to the BPaL intervention is unknown, the ERC judged that based on the currently available data (or lack thereof) the balance of undesirable and desirable effects does not favour the intervention or the comparison. However, clinicians in the review team had concern that many patients may require termination of treatment with linezolid as a result of intolerance, in which case a treatment would only comprise two drugs. Therefore, the committee suggested that a fluoroquinolone be included in the regimen initially, and be continued for the duration of treatment if fluoroquinolone resistance is excluded. This recommendation is based on expert opinion rather than the data presented by WHO. In those	

favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	whom fluoroquinolone resistance is detected, the fluoroquinolone may be omitted from the regimen. The ERC deliberated whether levofloxacin should be recommended rather than moxifloxacin as the fluoroquinolone of choice. The primary consideration by the Committee in support of levofloxacin over moxifloxacin as the fluoroquinolone of choice is the better safety profile of levofloxacin, specifically with regard to cardiotoxicity (specifically reduced QTc prolonging effects) which is well-documented in the literature. (20-22) In terms of the relative efficacy of levofloxacin and moxifloxacin, the consideration of interchangeability was based primarily on expert opinion, and supported by two publications.(23, 24)	

Resources required: How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline panel**		
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings **x Varies** ○ Don't know	**Research Evidence** Nil additional	**Additional considerations** The cost savings from improved health outcomes were felt to be an important consideration as they could be substantial. However, the panel also felt that some of the cost will vary e.g., the savings from improved health outcomes will depend on underlying fluoroquinolone resistance prevalence. Cost may also be affected by access to fluoroquinolone DST and accordingly the ability to drop Moxi if resistance is found. Therefore, the GDG judged the resources required to vary.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		

○ Large costs ○ Moderate costs **x Negligible costs and savings** ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**The ERC considered the normative cost analysis conducted by review team. For more information consult Appendix 3.** Appendix 3.xlsx **Normative cost analysis based on specific direct costs** (Sensitivity analysis excl.clinic visit costs) The differences in cost between BPaLM and BPaL were considered negligible.	

Regimen	Drug costs (ZAR)	Bacteriological tests (Costs in ZAR)	Other lab tests (Costs in ZAR)	Clinic visit costs (ZAR)	Total costs per patient treated incl. clinic visit costs (ZAR)	Total costs per patient treated excl. clinic visit costs (ZAR)
Short oral course (Min)	11 437,70	1 058,58	472,42	2 680,79	15 649,49	12 968,70
Short oral course (Max)	13 650,99	1 058,58	472,42	2 680,79	17 862,78	15 181,99
BPaL (Lzd_Adjusted dose)	11 710,64	705,72	2 158,89	2 632,56	17 207,81	14 575,25
BPaLM (Lzd_Adjusted dose)	12 307,88	705,72	2 158,89	2 632,56	17 805,05	15 172,49
BPaLM (Lzd_Standard)	11 787,08	705,72	2 158,89	2 632,56	17 284,25	14 651,69
Long course 1 (Basic)	27 159,16	2 117,16	783,55	4 407,60	34 467,47	30 059,87
Long course 2	49 601,58	2 117,16	2 028,07	6 581,40	60 328,21	53 746,81

Note:
Where weight calibrated dosing is recommended, drug costs have been applied at the maximum weight band/adult dose
1 US$ equivalent to R18.30
Drug calculations all based on a 28 day cycle per month
Diagnostic Xpert, microscopy, culture and DST not included in costs for bacteriological tests
Clinic visits classified according to nature of clinical visits and based on secondary data representing a fully decentralised model.

Certainty of evidence of resource requirements: What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline panel**		
x Very low ○ Low ○ Moderate ○ High ○ No included studies	**Research Evidence** Nil	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Very low ○ Low **x Moderate** ○ High ○ No included studies	The ERC considered the certainty of evidence of resource requirements to be moderate considering the normative cost analysis performed by the review team is locally relevant.	

Cost effectiveness: Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies **x No included studies**	**Research Evidence** The cost-effectiveness study embedded in TB-PRACTECAL trial (Sweeney et al.) compared BPaL regimens to other longer regimens, therefore may not be useful for comparison between BPaL and BPaLM	Both regimens are of 6 months duration.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies **x No included studies**	Nil additional research comparing the cost-effectiveness of BPaLM to BPaL was available for presentation to the ER.	

Equity: What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Reduced ○ Probably reduced **x Probably no impact** ○ Probably increased ○ Increased ○ Varies ○ Don't know	**Research Evidence** No research evidence searched for. Implementation in some countries may be hampered by lack of availability of DST and that could have an impact on equitable roll out if DST for moxifloxacin is a requirement for implementation. However, the WHO GDG judged that the intervention would probably have no impact on health equity over the comparison.	The panel considered the treatment duration and the ability to decentralize treatment (to enable access for remote, underserviced settings and disadvantaged populations) to affect equity.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Reduced ○ Probably reduced **x Probably no impact** ○ Probably increased ○ Increased ○ Varies ○ Don't know	Considering that both the intervention and the comparison are of similar durations, and not significantly complex, the ERC judged that they are likely to have the same impact on equity.	
Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ No ○ Probably no **x Probably yes** ○ Yes ○ Varies ○ Don't know	**Research Evidence** No research evidence searched for. The panel considered patients and health care providers as key stakeholders. The panel considered the following aspects as critical with regards to acceptability: regimen duration and drug safety monitoring needs (both relating to necessary travel, loss of income and general disruption of the life of patients; workload for the health care system), needs for drug susceptibility testing. The panel judged that the BPaLM regimen would probably be acceptable.	Both regimens are 6month regimens, only difference is Moxifloxacin in BPaLM.

• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ No ○ Probably no **x Probably yes** ○ Yes ○ Varies ○ Don't know	No additional evidence was presented to ERC committee. Considering previous judgements that BPaLM (EtD and PICO c) is probably acceptable to key stakeholder and that BPaL (EtD and PICO a) is probably acceptable to key stakeholders, the ERC judged that BPaLM (when compared to BPaL) would probably be acceptable to key stakeholders .	
Feasibility: Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ No ○ Probably no **x Probably yes** ○ Yes ○ Varies ○ Don't know	**Research Evidence** No research evidence searched for. The panel noted that rapid DST to moxifloxacin is not available in all settings and that this is a potential barrier to implementation. The panel judged that implementation is probably feasible.	The panel considered the following aspects to affect feasibility (i.e., to be potential barriers to implementation): requirements for drug safety monitoring and requirements for drug susceptibility testing. Both BPaLM and BPaL are 6month regimens, only difference is Moxifloxacin in BPaLM.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ No ○ Probably no **x Probably yes** ○ Yes ○ Varies ○ Don't know	The ERC considered the issues raised by the WHO GDG. Based on the indirect evidence of high feasibility of BPaL in preXDR-TB reported by van de Berg et al. and South Africa's ability to perform genotypic testing for fluoroquinolone resistance , the ERC judged the intervention (BPaLM) to be feasible. The ERC heard from the NDOH TB programme that feasibility could be impacted if the level of prescriber be restricted to medical officer only, as clinical nurse practitioners and clinical associates are important human resources for decentralized care.	

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	23 March 2023	JT, NG, SE, FB, NN, GM, MM, JN, TK, KC	Initial ERC discussion took place on 16th March 2023, with ongoing discussion and updated ERC decision at an extraordinary meeting of the ERC on 23 March 2023, where a conditional recommendation for the use of the BPaLM in the treatment of drug resistant TB without fluoroquinolone resistance was suggested. The recommendation is conditional and based only on the expert opinion and not on data presented by the WHO GDG. Furthermore, levofloxacin could be used instead of moxifloxacin as fluoroquinolone of choice for inclusion in the revised regimen.

5. Recommendations

Through the GRADE adolopment process, the following recommendation has been adapted from the WHO by the PHC/Adult hospital level Committee:

1. We suggest the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600mg) and a fluoroquinolone rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients. (Conditional recommendation, very low certainty of evidence). Levofloxacin is to be used instead of moxifloxacin as fluoroquinolone of choice, for inclusion in the revised regimen.

The PHC/Adult hospital level committee has adopted the following remarks relevant to the recommendation above from the WHO:

2. Drug susceptibility testing (DST) for fluoroquinolones is strongly encouraged in people with MDR/RR-TB, and although it should not delay initiation of the BPaLM, results of the test should guide the decision on whether the fluoroquinolone can be retained or should be dropped from the regimen – in cases of documented resistance to fluoroquinolones, BPaL without the fluoroquinolone would be initiated or continued.
3. This recommendation applies to the following:
    a. People with MDR/RR-TB or with MDR/RR-TB and resistance to fluoroquinolones (pre-XDR-TB).
    b. People with confirmed pulmonary TB and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular and disseminated (miliary) TB.
    c. Adults and adolescents aged 14 years and older.
    d. All people regardless of HIV status.
    e. Patients with less than 1-month previous exposure to bedaquiline, linezolid, pretomanid or delamanid. When exposure is greater than 1 month, these patients may still receive these regimens if resistance to the specific medicines with such exposure has been ruled out.
4. This recommendation does not apply to pregnant and breastfeeding women owing to limited evidence on the safety of pretomanid.
5. The recommended dose of linezolid is 600 mg once daily.

6. References

1. Ismail NA, Mvusi L, Nanoo A, Dreyer A, Omar SV, Babatunde S, et al. Prevalence of drug-resistant tuberculosis and imputed burden in South Africa: a national and sub-national cross-sectional survey. Lancet Infect Dis. 2018;18(7):779-87. 10.1016/S1473-3099(18)30222-6. https://www.ncbi.nlm.nih.gov/pubmed/29685458.
2. Global tuberculosis report 2022. Geneva: World Health Organization. 2022. https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022/tb-disease-burden/2-3-drug-resistant-tb.
3. Ndjeka N, Schnippel K, Master I, Meintjes G, Maartens G, Romero R, et al. High treatment success rate for multidrug-resistant and extensively drug-resistant tuberculosis using a bedaquiline-containing treatment regimen. Eur Respir J. 2018;52(6). DOI: 10.1183/13993003.01528-2018. https://www.ncbi.nlm.nih.gov/pubmed/30361246.
4. South African Department of Health. Management of rifampicin-resistant tuberculosis: A clinical reference guide. 2019. https://www.health.gov.za/wp-content/uploads/2020/11/management-of-rifampicin-resistant-tb-booklet-0220-v11.pdf.
5. Tack I, Dumicho A, Ohler L, Shigayeva A, Bulti AB, White K, et al. Safety and Effectiveness of an All-Oral, Bedaquiline-Based, Shorter Treatment Regimen for Rifampicin-Resistant Tuberculosis in High Human Immunodeficiency Virus (HIV) Burden Rural South Africa: A Retrospective Cohort Analysis. Clinical Infectious Diseases. 2020;73(9):e3563-e71. 10.1093/cid/ciaa1894. https://doi.org/10.1093/cid/ciaa1894.
6. Jaspard M, Butel N, El Helali N, Marigot-Outtandy D, Guillot H, Peytavin G, et al. Linezolid-Associated Neurologic Adverse Events in Patients with Multidrug-Resistant Tuberculosis, France. Emerg Infect Dis. 2020;26(8):1792-800. 10.3201/eid2608.191499.
7. WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment 2022, IGO. update. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0. https://www.who.int/publications/i/item/9789240063129.
8. World Health Organization. Target regimen profiles for TB treatment: candidates: rifampicin-susceptible, rifampicin resistant and pan-TB treatment regimens. 2016(WHO/HTM/TB/2016.16). https://apps.who.int/iris/handle/10665/250044.
9. Schünemann HJ, Wiercioch W, Brozek J, Etxeandia-Ikobaltzeta I, Mustafa RA, Manja V, et al. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. J Clin Epidemiol. 2017;81:101-10. 10.1016/j.jclinepi.2016.09.009.
10. Florez ID, Amer YS, McCaul M, Lavis JN, Brouwers M. Guidelines developed under pressure. The case of the COVID-19 low-quality "rapid" guidelines and potential solutions. J Clin Epidemiol. 2022;142:194-9. 10.1016/j.jclinepi.2021.11.012. https://www.ncbi.nlm.nih.gov/pubmed/34780983.
11. McCaul M, Tovey D, Young T, Welch V, Dewidar O, Goetghebeur M, et al. Resources supporting trustworthy, rapid and equitable evidence synthesis and guideline development: results from the COVID-19 evidence network to support decision-making (COVID-END). J Clin Epidemiol. 2022;151:88-95. 10.1016/j.jclinepi.2022.07.008. https://www.ncbi.nlm.nih.gov/pubmed/35868494.
12. Schünemann HJ, Wiercioch W, Etxeandia I, Falavigna M, Santesso N, Mustafa R, et al. Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise. Cmaj. 2014;186(3):E123-42. 10.1503/cmaj.131237.
13. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ. 2010;182(18):E839-42. 10.1503/cmaj.090449. https://www.ncbi.nlm.nih.gov/pubmed/20603348.
14. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008. 10.1136/bmj.j4008. https://www.bmj.com/content/bmj/358/bmj.j4008.full.pdf.
15. Conradie F, Diacon AH, Ngubane N, Howell P, Everitt D, Crook A, et al. Treatment of Highly Drug-Resistant Pulmonary Tuberculosis. New England Journal of Medicine. 2020;382(10):893-902. 10.1056/NEJMoa1901814. https://www.nejm.org/doi/full/10.1056/NEJMoa1901814.
16. Conradie F, Bagdasaryan TR, Borisov S, Howell P, Mikiashvili L, Ngubane N, et al. Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis. New England Journal of Medicine. 2022;387(9):810-23. 10.1056/NEJMoa2119430. https://www.nejm.org/doi/full/10.1056/NEJMoa2119430.

17. Nyang'wa BT, Berry C, Kazounis E, Motta I, Parpieva N, Tigay Z, et al. A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis. New England Journal of Medicine. 2022;387(25):2331-43. 10.1056/NEJMoa2117166. https://www.nejm.org/doi/full/10.1056/NEJMoa2117166.
18. Gomez GB, Siapka M, Conradie F, Ndjeka N, Garfin AMC, Lomtadze N, et al. Cost-effectiveness of bedaquiline, pretomanid and linezolid for treatment of extensively drug-resistant tuberculosis in South Africa, Georgia and the Philippines. BMJ Open. 2021;11(12):e051521. 10.1136/bmjopen-2021-051521.
19. Sweeney S, Berry C, Kazounis E, Motta I, Vassall A, Dodd M, et al. Cost-effectiveness of short, oral treatment regimens for rifampicin resistant tuberculosis. PLOS Global Public Health. 2022;2(12):e0001337. 10.1371/journal.pgph.0001337. https://doi.org/10.1371/journal.pgph.0001337.
20. Täubel Jörg, Prasad Krishna, Rosano Giuseppe, Ferber Georg, Wibberley Helen, Cole Samuel Thomas, et al. Effects of the Fluoroquinolones Moxifloxacin and Levofloxacin on the QT Subintervals: Sex Differences in Ventricular Repolarization. The Journal of Clinical Pharmacology. 2020;60(3):400-8. https://doi.org/10.1002/jcph.1534. https://accp1.onlinelibrary.wiley.com/doi/abs/10.1002/jcph.1534.
21. Tsikouris James P., Peeters Michael J., Cox Craig D., Meyerrose Gary E., Seifert Charles F. Effects of Three Fluoroquinolones on QT Analysis After Standard Treatment Courses. Annals of Noninvasive Electrocardiology. 2006;11(1):52-6. https://doi.org/10.1111/j.1542-474X.2006.00082.x. https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1542-474X.2006.00082.x.
22. Noel G. J., Natarajan J., Chien S., Hunt T. L., Goodman D. B., Abels R. Effects of three fluoroquinolones on QT interval in healthy adults after single doses. Clin Pharmacol Ther. 2003;73(4):292-303. 10.1016/s0009-9236(03)00009-2.
23. Koh WJ, Lee SH, Kang YA, Lee CH, Choi JC, Lee JH, et al. Comparison of levofloxacin versus moxifloxacin for multidrug-resistant tuberculosis. Am J Respir Crit Care Med. 2013;188(7):858-64. 10.1164/rccm.201303-0604OC. https://www.ncbi.nlm.nih.gov/pubmed/23927582.
24. Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR TB treatment, Ahmad N, Ahuja SD, Akkerman OW, Alffenaar JC, Anderson LF, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet. 2018;392(10150):821-34. 10.1016/S0140-6736(18)31644-1. https://www.ncbi.nlm.nih.gov/pubmed/30215381.

7. Appendix 1

A critical group appraisal of: WHO consolidated guidelines on TB using the AGREE II Instrument

Created with the AGREE II Online Guideline Appraisal Tool.

No endorsement of the content of this document by the AGREE Research Trust should be implied.

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Date: 20 February 2023

URL of this appraisal: http://www.agreetrust.org/group-appraisal/18838

Guideline URL: https://www.who.int/publications/i/item/9789240063129

Comments

Domain 1. Scope and Purpose

Item 1

- Appraiser 2: \"This evidence review aims to evaluate the efficacy and safety of novel short-course oral regimens to treat MDR/RR-TB, in comparison to the 2020 WHO- recommended regimens. This will be undertaken by conducting analyses of data from clinical trials and individual patient data meta-analyses of cohorts treated for MDR/RR-TB in programmatic settings.\" p313 Annexes. \

  "This current module on DR-TB treatment provides specific recommendations on the treatment of DR-TB, including use of regimens for rifampicin-susceptible, isoniazid- resistant TB (Hr-TB), all-oral shorter regimens for MDR/RR-TB, longer regimens for MDR/RR-TB, monitoring patient response to MDR/RR-TB treatment, starting ART in patients on second-line anti-TB regimens and undertaking surgery for patients on MDR-TB treatment.\" p3
- Appraiser 3: \"provide specific recommendations on the treatment of DR-TB, including use of regimens for rifampicin-susceptible, isoniazid resistant TB (Hr-TB), all-oral shorter regimens for MDR/RR-TB, longer regimens for MDR/RR-TB, monitoring patient response to MDR/RR-TB treatment, starting ART in patients on second-line anti-TB regimens and undertaking surgery for patients on MDR-TB treatment.\"

  Health intent: Treatment, monitoring, timing of ART initiation, use of surgery. Expected benefit: Not clearly stated; to inform national TB programmes and assist in policy development, reduced adverse effects associated with DR-TB treatment and shorten treatment duration. Targets: Patients with MDR/RR-TB and Hr-TB. Well written. Expected benefit or outcome not easy to find in the guideline.

Item 2

- Appraiser 2: Annex
  Population: Yes (p 313)
  Intervention: Yes (p 313)
  Comparator: Yes (p 314)
  Outcome: Yes (p 316)
  Context: inclusion criteria p 315, worldwide
- Appraiser 3: PICO questions including target population, intervention, comparator are clearly stated and easily found in each respective section. Health care setting/context is not explicitly stated.
  PICO subquestions for Section 1 are not found in guideline document but can be found in the annexes document.

Item 3

Appraiser 2: Pages 313 and 315 include population, as well as inclusion and exclusion criteria

- Appraiser 3: Target population and clinical condition: All eople with DR-TB, Hr-TB.
  No gender or age exclusions listed. No exclusions of specific severity or stages of disease. No exclusions of certain populations or comorbidites.

  The lack of exclusionary criteria is not specifically highlighted in the guideline, but assumed based on the recommendations.

Domain 2. Stakeholder Involvement

Item 4

- Appraiser 2: Web Annex 1. Methods and expert panels - page 7 Name: YES
  Discipline/content expertise (e.g., neurosurgeon, methodologist): YES Institution (e.g., St. Peter's hospital): YES
  Geographical location (e.g., Seattle, WA): YES
  Description of the member's role in the guideline development group: YES Appraiser 3: For
- each member of guideline development group name, discipline/content expertise, institution and geographical location where stated. The description the members specific role in guideline development was not found.

  Item easily found at start of the guideline. Members are appropriate match for the topic and scope. Methodological experts included in the development group.

Item 5

- Appraiser 2: Web Annex 1. Table A1.3 - perspectives from patients with recommendation.

  ONE former MDR-TB Patient was included in the guideline development group. Not

  really sufficient information.
- Appraiser 3: \"The methods used to develop and formulate the recommendations complied with WHO standards for guideline development and were based on up-to- date evidence reviews, complemented with additional information on values and preferences, feasibility and acceptability, and cost.\"

  End-user\'s and former DR-TB patient are noted to have been included in the guideline development group and as external reviewers. However, there is no clear statement on additional strategies used to capture patients/public views and preferences.

  This item was not easy to find in the guideline but is noted in the methods section of the annexe document.

Item 6

Appraiser 2: Yes - p5 of module 4

- Appraiser 3: Page 5: policy makers in ministries of health, or managers of NTPs who formulate country-specific TB treatment guidelines or are involved in the planning of TB treatment programmes. For use by health professional, including doctors, nurse, educators.

  Clear, concise and well written. Appropriate for scope of guideline.

Domain 3. Rigour of Development

Item 7

- Appraiser 2: \"Evidence gathering and analysis
  Evidence provided for the GDG review on using 6-month novel regimens was from the TB-PRACTECAL trial (evidence on using BPaLM, BPaLC, BPaL regimens), ZeNix trial (evidence on using the BPaL regimen with difference dosing schemes of linezolid use) and Nix-TB study (evidence on using the BPaL regimen). Evidence on using a new 9- month shorter regimen was from the programmatic data provided by the National TB Programme in South Africa. In addition, evidence was available on the use of other treatment regimens that were used as external comparators required for comparisons with the intervention regimens. The evidence included data on the use of WHO recommended shorter all- oral bedaquiline-containing regimen, which were from the programmatic implementation provided by South Africa; and WHO recommended longer regimens, which were provided by several country programmes from Belarus, Republic of Moldova, Georgia, Russian Federation, India, South Africa, and Somalia; or cohort studies (EndTB studies) provided by Médecins Sans Frontières and Partners in Health.
  In preparation to the guidelines update, WHO/GTB also received the data from the Newer and Emerging Treatment for MDR/RR-TB (NExT) trial that was a phase II/III open-label randomized controlled trial evaluating the effectiveness of an all-oral 6–9- month regimen for treatment of MDR-TB in South Africa (21), against a local standard of care regimen at the time. Sharing of the data by the principal Investigator and colleagues in the University of Cape Town and the South African Medical Research Council, is gratefully acknowledged\"

  No search methods, no search strategy BUT data collated from various large trials and in collaboration with large TB programmes
- Appraiser 3: For the updated section of the guideline (section 1 and 2) no strategy for the search of evidence is provided. Evidence was obtained through collaboration and engagement with NTPs, researchers and TB alliance as well as the WHO call for data.

  Evidence for section 3, 4,5 obtained from meta-analysis of IPD. No search strategy provided.

Item 8

- Appraiser 2: Annex p 315
  A5.2 Eligibility for inclusion in this evidence review

  Annex p 314
  Regimens excluded from analyses

  Also included in the GL page 3
- Appraiser 3: No description on criteria for evidence selection in guideline document. Web Annexes describe eligibility criteria for dataset inclusion and participant exclusion. Datasets from a public call for data were included.

Item 9

- Appraiser 2: GRADE evidence summary tables available with five GRADE domains and reasons
- Appraiser 3: The WHO Guideline Development process uses specific criteria to assess the characteristics of a body of evidence, such as within-study bias (methodological quality), consistency, precision, directness or applicability of the evidence, and others.

  The strengths and limitations of body of evidence are assessed, well written and clear and concisely described in the Web annex document in the Methods section and GRADE evidence summary tables but not in the main guideline.

Item 10

- Appraiser 2: GRADE EtD tables available for each PICO with recommendations Appraiser 3:
- A formal process and evidence-to-decision framework was used to arrive at recommendations. Decisions reached through discussion and consensus, where consensus through discussion not reached, the GDG voted on decisions. Here, decisions were made based on the vote of the majority.
  (information from annex. - not easily found.)

Item 11

- Appraiser 2: Yes, included in EtD
- Appraiser 3: Supporting data and report of benefits included in the Etd frameworks in the web annexes per PICO and also in the guideline. Recommendations do reflect considerations of both benefits, harms and risks. This discussion is integral to the document.

Item 12

- Appraiser 2: EtD available with link to evidence
- Appraiser 3: Each recommendation is linked to a discussion of the key evidence in the evidence-to-decision frameworks in the annexes document. Evidence summaries are provided for each sub-PICO in the guideline. Where evidence is lacking it is clearly stated in the guideline that recommendations are based on consensus of the guideline development group.

Item 13

- Appraiser 2: An External review group is listed (Web Annex 1 page 7), there is a specific acknowledgment statement (GL page vi), otherwise scanty information as to what the external review group did
- Appraiser 3: An external review group was assembled to review the updated recommendations based on the inputs of the guideline development group. External review group members are listed with qualifications and affiliation and are appropriate.
  Not easily found in the guideline, but available in web annex document. No indication of how information provided by review group was used by guideline development group. No indication of the purpose or intent of the review, methods undertaken or a summary of key findings.

Item 14

- Appraiser 2: This guideline is an update. No timescale found around when the next update will be
- Appraiser 3: No clear statement of when guideline will be update, the explicit time interval or criteria to guide decisions or methodology of updating procedure.

Domain 4. Clarity of Presentation

Item 15

- Appraiser 2: EtD tables - recommendations provided with remarks around applicability

  Recommendations available in GL, also clear what updates/changes have been made from previous GLs
- Appraiser 3: The recommendations are concrete and precise, specifically in the remarks underlying each recommendation.

Item 16

- Appraiser 2: Extensive information available in EtDs - not necessarily alternatives thus rated down slightly. Recommendations in GL also quite specific
- Appraiser 3: Different options for management are presented: either BPAL, BPALM or BPLAC rather than SOC.
  Different options for LZD dosing and BDQ dosing is presented.
  Specific recommendations are made for children, pregnant women, HIV positive patients and patients with extrapulmonary TB. This information can be found under appropriate headings in the guideline.

Item 17

- Appraiser 2: Yes, once the correct PICO is found.
- Appraiser 3: Recommendations are summarised in a box at the start of the guideline and are clear and concise.

Domain 5. Applicability

Item 18

- Appraiser 2: Within the EtDs and GL, the guideline panel discussed acceptability, feasibility, equity, cost-effectiveness. required resources, balance of effects, etc.

  There are also implementation and subgroup considerations.
- Appraiser 3: In Web Annexes document facilitators and barriers discussed in EtD frameworks that assessed acceptability, feasibility required resources, cost effectiveness etc.

Item 19

- Appraiser 2: There are implementation and subgroup considerations listed with each PICO in the EtD but these do not necessarily provide sufficient information to actually implement.
- Appraiser 3: An implementation section is found in the guideline. No summary documents, algorithms or check lists are found, although a summary of the recommendations is listed at the start of the guideline.

  Some references to guideline facilitators for example for sections \"Care and Support\" - reference supplied to WHO Consolidated guidelines on tuberculosis: Module 4: Treatment - tuberculosis care and support\"

  Appendices do not contain useful implementation resources.

Item 20

- Appraiser 2: Yes - in the EtD, cost effectiveness and feasiblility have been considered. Appraiser
- 3: Regimen costs were estimated in US$ for regimens based on GDF prices. Studies of cost-effectiveness of regimens were included in the guideline.

Resource implications are considered in the EtD framework.
It does not appear that any health economist were part of guideline development group.

Item 21

- Appraiser 2: Yes, monitoring and evaluation section available in the EtDs
- Appraiser 3: No clear schedule of monitoring of relevant clinical and laboratory tests is provided, besides the following:

  1. Recommend monitoring patients with monthly sputum cultures
  2. Patients should be followed up for 12 months after the completion of treatment for possible relapse with sputum culture and smear.
  3. Test samples of patients with no bacteriological conversion after month 4 on BPaLM/BpAL regimen with DST.
  4. ECG should be done at baseline prior to start of treatment.

Domain 6. Editorial Independence

Item 22

- Appraiser 2: The WHO is the funding agency through grants from USAID. WHO is also the publisher. No statement on influence.
- Appraiser 3: Statement that update was funded by grants provided to WHO by USAID. No statement that funding body did not influence content of guideline.

Item 23

- Appraiser 2: Web Annex 2: declarations of interest. Also listed in EtD where a GDG member was excluded in specific PICOs due to competing interests
- Appraiser 3: A description of competing interests is found in the Web Annexes document. The methods by which competing interests were sough was not clear.

  WHO policy is noted to have been applied in the EtD frameworks to recuse panel members with potential-conflicts of interest.

Overall Assessment

- Appraiser 2: Recommended for use for adolopment
- Appraiser 3: 1. No information provided regarding systematic search for evidence.
  2. Lack of implementation resources
  3. Complicated, information for AGREE II assessment not always easily found in the document.
  4. Clearer descriptions on role, contributions and findings of end users, external reviewers should be provided.
  5. More specific monitoring criteria should be described.

Created online at www.agreetrust.org 20 February 2023

A critical group appraisal of: WHO consolidated guidelines on TB using the AGREE II Instrument

Created with the AGREE II Online Guideline Appraisal Tool.

No endorsement of the content of this document by the AGREE Research Trust should be implied.

Co-ordinator: Tasha Gloeck

Email: natasha.gloeck@mrc.ac.za

Date: 20 February 2023

URL of this appraisal: http://www.agreetrust.org/group-appraisal/18838

Guideline URL: https://www.who.int/publications/i/item/9789240063129

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	OA 1	OA 2
86%	78%	63%	89%	65%	67%	83%	Yes - 1, Yes with modifications - 1, No - 0

Domain 1. Scope and Purpose		
	Appraiser 2	Appraiser 3
Item 1	6	5
Item 2	7	6
Item 3	7	6
Domain 2. Stakeholder Involvement		
	Appraiser 2	Appraiser 3
Item 4	7	6
Item 5	5	4
Item 6	6	6
Domain 3. Rigour of Development		
	Appraiser 2	Appraiser 3
Item 7	4	1
Item 8	5	6
Item 9	6	6
Item 10	7	5
Item 11	6	6
Item 12	7	6
Item 13	5	3
Item 14	2	1
Domain 4. Clarity of Presentation		
	Appraiser 2	Appraiser 3
Item 15	7	6
Item 16	6	7
Item 17	6	6
Domain 5. Applicability		
	Appraiser 2	Appraiser 3

Item 18	6	6
Item 19	4	2
Item 20	6	5
Item 21	6	4
Domain 6. Editorial Independence		
	Appraiser 2	Appraiser 3
Item 22	4	3
Item 23	7	6
Overall Assessment		
	Appraiser 2	Appraiser 3
OA1	6	6

Created online at www.agreetrust.org 20 February 2023

8. Appendix 2

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AMSTAR Checklist

Printer Friendly Version

Article Name:
WHO consolidated guidelines on tuberculosis

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
- ☑ Population
- ☑ Intervention
- ☑ Comparator group
- ☑ Outcome

Optional (recommended)
- ☑ Timeframe for follow up

- ☑ Yes
- ☐ No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:
- ☑ review question(s)
- ☐ a search strategy
- ☑ inclusion/exclusion criteria
- ☑ a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:
- ☐ a meta-analysis/synthesis plan, if appropriate, and
- ☐ a plan for investigating causes of heterogeneity
- ☐ a plan for investigating causes of heterogeneity

- ☐ Yes
- ☑ Partial Yes
- ☐ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:

For Partial Yes (ALL the following):	For Yes, should also have ALL the following:	
☐ described populations	☑ described population in detail	☐ Yes ☐ Partial Yes ☑ No
☐ described interventions	☑ described intervention in detail (including doses where relevant)	
☐ described comparators	☑ described comparator in detail (including doses where relevant)	
☐ described outcomes	☑ described study's setting	
☐ described research designs	☑ timeframe for follow-up	

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from	For Yes, must also have assessed RoB from:	
☐ unconcealed allocation, and	☐ allocation sequence that was not truly random, and	☐ Yes ☐ Partial Yes ☑ No ☐ Includes only NRSI
☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	

NRSI

For Partial Yes, must have assessed RoB:	For Yes, must also have assessed RoB:	
☐ from confounding, and	☐ methods used to ascertain exposures and outcomes, and	☐ Yes ☐ Partial Yes ☑ No ☐ Includes only RCTs
☐ from selection bias	☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes

☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies	☐ Yes ☑ No

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes:

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For Yes:

☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☐ Yes ☐ No ☑ No meta-analysis conducted

---

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes:

☐ The authors reported no competing interests OR ☑ The authors described their funding sources and how they managed potential conflicts of interest	☑ Yes ☐ No

---

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

Assess Article

AMSTAR 2 Results

Printer Friendly Version

Article Name: WHO consolidated guidelines on tuberculosis - module 4

WHO consolidated guidelines on tuberculosis - module 4 is a Critially Low quality review

1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes Yes Yes Yes Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	YesYes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes Yes
4. Did the review authors use a comprehensive literature search strategy?	No
5. Did the review authors perform study selection in duplicate?	No
6. Did the review authors perform data extraction in duplicate?	No
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No
8. Did the review authors describe the included studies in adequate detail?	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the	

review? **RCT**	Yes
NRSI	
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? **RCT**	Yes
NRSI	
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

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9. Appendix 3

Normative cost analysis based on specific direct costs						Sensitivity analysis excl.clinic vist costs
Regimen	Drug costs (ZAR)	Bacteriological tests (Costs in ZAR)	Other lab tests (Costs in ZAR)	Clinic visit costs (ZAR)	Total costs per patient treated incl. clinic visit costs (ZAR)	Total costs per patient treated excl. clinic visit costs (ZAR)
Short oral course (Min)	11 437,70	1 058,58	472,42	2 680,79	15 649,49	12 968,70
Short oral course (Max)	13 650,99	1 058,58	472,42	2 680,79	17 862,78	15 181,99
BPaL (Lzd_Adjusted dose)	11 710,64	705,72	2 158,89	2 632,56	17 207,81	14 575,25
BPaLM (Lzd_Adjusted dose)	12 307,88	705,72	2 158,89	2 632,56	17 805,05	15 172,49
BPaLM (Lzd_Standard)	11 787,08	705,72	2 158,89	2 632,56	17 284,25	14 651,69
Long course 1 (Basic)	27 159,16	2 117,16	783,55	4 407,60	34 467,47	30 059,87
Long course 2	49 601,58	2 117,16	2 028,07	6 581,40	60 328,21	53 746,81

Note:

Where weight calibrated dosing is recommended, drug costs have been applied at the maximum weight band/adult dose

1 US$ equivalent to R18.30

Drug calculations all based on a 28 day cycle per month

Diagnostic Xpert, microscopy, culture and DST not included in costs for bacteriological tests

Clinic visits classified according to nature of clinical visits and based on secondary data representing a fully decentralised model.

Resource requirement for Sub-PICO 4.1: BPaL vs. WHO_Long in pulmonary preXDR TB and Sub-PICO 5.2: BPaL vs WHO_Long in pulmonary MDR/RR-TB						
Regimen	Drug costs (ZAR)	Bacteriological tests (Costs in ZAR)	Other lab tests (Costs in ZAR)	Clinic visit costs (ZAR)	Total costs per patient treated incl. clinic visit costs (ZAR)	Total costs per patient treated excl. clinic visit costs (ZAR)
BPaL (Lzd_Adjusted dose)	11 710,64	705,72	2 158,89	2 632,56	17 207,81	14 575,25
BPaLM (Lzd_Adjusted dose)	12 307,88	705,72	2 158,89	2 632,56	17 805,05	15 172,49
BPaLM (Lzd_Standard)	11 787,08	705,72	2 158,89	2 632,56	17 284,25	14 651,69
Long course 1 (Basic)	27 159,16	2 117,16	783,55	4 407,60	34 467,47	30 059,87
Long course 2	49 601,58	2 117,16	2 028,07	6 581,40	60 328,21	53 746,81

Resource requirement for Sub-PICO 5.3: BPaL vs. SA_new in MDR/RR-TB						
Regimen	Drug costs (ZAR)	Bacteriological tests (Costs in ZAR)	Other lab tests (Costs in ZAR)	Clinic visit costs (ZAR)	Total costs per patient treated incl. clinic visit costs (ZAR)	Total costs per patient treated excl. clinic visit costs (ZAR)
BPaL (Lzd_Adjusted dose)	11 710,64	705,72	2 158,89	2 632,56	17 207,81	14 575,25
BPaLM (Lzd_Adjusted dose)	12 307,88	705,72	2 158,89	2 632,56	17 805,05	15 172,49
BPaLM (Lzd_Standard)	11 787,08	705,72	2 158,89	2 632,56	17 284,25	14 651,69
Short oral course (Min)	11 437,70	1 058,58	472,42	2 680,79	15 649,49	12 968,70
Short oral course (Max)	13 650,99	1 058,58	472,42	2 680,79	17 862,78	15 181,99