CLINICAL PRIORITIES ADVISORY GROUP
21 May 2024

Agenda Item No	2.1
National Programme	Blood and Infection
Clinical Reference Group	Infectious Diseases
URN	2310

Title
BPaLM/BPaL for patients aged ≥14 years with suspected, functional or confirmed rifampicin resistant (RR) tuberculosis (TB), multidrug-resistant (MDR) TB or pre-extensively drug resistant (pre-XDR) TB.

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its approval as an IYSD

Proposition
Service delegation status – NHS England is the responsible commissioner for high-cost TB medicines, including bedaquiline and delamanid. Tuberculosis services are integrated care board (ICB) commissioned, they are not subject to delegation and their status is not changing. The proposition is: Bedaquiline (B), Pretomanid (Pa), Linezolid (L) +/- Moxifloxacin (M) (BPaLM/BPaL) is recommended to be available as a routine commissioning treatment option in patients aged ≥14 years old for suspected, functional or confirmed rifampicin resistant (RR) tuberculosis (TB), multidrug-resistant (MDR) TB and pre-extensively drug resistant (pre-XDR) TB within the criteria set out in this document. The policy proposition is restricted to certain age groups as there is insufficient evidence to confirm safety and/or it is not recommended through the licence authorisation process to be used in those age groups not included in the proposition. The use of bedaquiline for extra-pulmonary TB as part of BPaLM/BPaL, in line with the eligibility criteria in this proposition, is off-label. The use of linezolid as part of BPaLM/BPaL, in line with the eligibility criteria in this proposition, is off-label. The use of moxifloxacin as part of BPaLM/BPaL, in line with the eligibility criteria in this proposition, is off-label. The use of pretomanid as part of BPaLM/BPaL, in line with the eligibility criteria in this proposition, is off-label.

Clinical Panel recommendation
The Clinical Panel recommended that the policy proposition progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Deputy Director of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Deputy Director of Acute Programmes confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Director of Clinical Commissioning (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Engagement Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

In people with suspected, functional or confirmed RR, MDR- or pre-XDR TB, what is the clinical effectiveness and safety of BPaLM/BPaL compared with standard of care?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Sputum culture conversion rates **Certainty of evidence:** Very low to Moderate	Sputum culture conversion rates are an important outcome to patients as sputum culture negativity is an indicator that a patient is non-infectious and could potentially be discharged from hospital. In total, one RCT (Nyang'wa et al 2022) and one prospective case series (Conradie et al 2020) provided evidence relating to sputum culture conversion rates in people with RR TB treated

Outcome	Evidence statement
	with either BPaL or BPaLM (Nyang'wa et al 2022), and in people with MDR TB (pre)XDR TB[1]treated with BPaL (Conradie et al 2020). **At 12 weeks follow-up** *BPaLM vs SC* One RCT (Nyang'wa et al 2022) reported a higher conversion rate among people treated with BPaLM (85/96, 88.5%) compared with SC (78/99,78.8%); p not reported. HR for time to conversion favoured BPaLM: 1.59 (95% CI 1.18 to 2.14). RD adjusted for site was 9.2% higher with BPaLM (95% CI –1.6% to 20.1%); p not reported; RR adjusted for site was 1.12 (95% CI 0.99 to 1.27); p not reported. (**LOW)** *BPaL vs SC* One RCT (Nyang'wa et al 2022) reported a higher conversion rate among people treated with BPaL (73/90 81.1%) compared with SC (78/99,78.8%); p not reported. HR for time to conversion not reported. RD adjusted for site was 3.9% higher with BPaL (95% CI –8.0% to 15.9%); p not reported; RR adjusted for site was 1.04 (95% CI 0.90 to 1.20); p not reported. (**MODERATE)** **At 16 weeks follow-up** One prospective case series (Conradie et al 2020) reported that 30/31 (96.8%) of people with MDR TB and 61/62 (98.4%) of people with **(pre)**XDR TB (overall cohort: 91/93, 97.8%) treated with BPaL had sputum culture conversion. (**VERY LOW)** **At 108 weeks follow-up** *BPaLM vs SC* One RCT (Nyang'wa et al 2022) reported HR for time to conversion adjusted for site as: 1.49 (95% CI 1.10 to 2.01). 91[2] people on BPaLM converted compared to 85 on SC (denominators unclear). No p value reported. (**LOW)** *BPaL vs SC* One RCT (Nyang'wa et al 2022) reported HR for time to conversion adjusted for site as: 1.05 (95% CI 0.77 to 1.44). 82 people on BPaL converted compared to 85 on SC (denominators unclear). No p value reported. (**VERY LOW)**

[1] People described here as (pre)XDR TB were described in the Conradie et al 2020 study as having XDR TB. However, they meet the current WHO criteria for pre-XDR TB so were considered to meet the population description in the PICO for this review.

[2] Actual number of people converting is larger than total N for 108 weeks; this is assumed to include the larger cohort.

Outcome	Evidence statement
	For BPaLM vs SC: one RCT provided low certainty evidence of a higher sputum conversion rate with BPaLM compared with SC for RR TB at 12 weeks and at 108 weeks (statistical significance not reported). **For BPaL: one RCT provided moderate certainty evidence of a higher sputum conversion rate with BPaL compared with SC for RR TB at 12 weeks but very low certainty evidence of little difference between groups at 108 weeks (statistical significance not reported). One prospective case series reported very low certainty evidence of a 97.8% conversion rate in people with MDR or (pre)XDR TB after 16 weeks of BPaL treatment.**
Unfavourable treatment outcome **Certainty of evidence:** Very low to Moderate	This outcome is important to patients as it provides an indication of how effective and tolerable the treatment regimen is. It is a composite measure which may include death, treatment failure, treatment discontinuation, loss to follow-up or recurrence of tuberculosis. In total, one RCT (Nyang'wa et al 2022), one arm of a prospective randomised uncontrolled trial (Conradie et al 2022) and one prospective case series (Conradie et al 2020) provided evidence relating to unfavourable treatment outcome in people with RR TB, MDR TB or (pre)XDR TB. **At 26 weeks/6 months follow-up** One randomised uncontrolled trial (Conradie et al 2022) reported that, across all four arms with different linezolid dosages, **4/21 (19.0%) people with MDR TB and 4/83 (4.8%) people with pre-XDR TB treated with BPaL had an unfavourable treatment outcome[3]. In the 600mg/26-week linezolid dosage arm specifically, 1/4 (25%) people with MDR TB and 2/22 (9.1%) people with pre-XDR TB had an unfavourable outcome.** (**VERY LOW)** One prospective case series (Conradie et al 2020) reported that **3/38 (7.9%) people with MDR TB and 8/71 (11.3%) people with (pre)XDR TB (11/109 (10.1%) overall) treated with BPaL had an unfavourable treatment outcome.** (**VERY LOW)** **At 72 weeks follow-up** *BPaLM vs SC* One RCT (Nyang'wa et al 2022) reported an unfavourable status[4] in *statistically significantly* fewer people with RR TB treated with BPaLM (17/72, 23.6%) compared with 39/73 (53.4%) receiving SC (RD: -30% (96.6% CI –46%

[3] Unfavourable outcome defined as treatment failure (clinical or bacteriologic) or disease relapse in both Conradie et al 2020 and Conradie et al 2022.

[4] Unfavourable status defined as a composite of death, treatment failure, treatment discontinuation, loss to follow-up, or recurrence of tuberculosis.

Outcome	Evidence statement
	to –14%)[5]. The RR adjusted for site gave a lower risk of an unfavourable status with BPaLM for the mITT population (RR 0.24, 0.11 to 0.52). No p values reported. (**MODERATE)** *BPaL vs SC* One RCT (Nyang'wa et al 2022) reported an unfavourable status in 24/70 (34.3%) of people with RR TB treated with BPaL compared with 39/73 (53.4%) receiving SC (RD: -19% (95% CI –36% to –2%). The RR adjusted for site gave a lower risk[6] of an unfavourable status with BPaL for the mITT population (RR 0.47, 0.28 to 0.80). No p values reported. (**MODERATE)** **At 108 weeks follow-up** *BPaLM vs SC* One RCT (Nyang'wa et al 2022) reported the unadjusted RD for an unfavourable status for people with RR TB (ITT population) as -50.0% (95% CI -69.2% to -30.9%), and a RR of 0.19 (95% CI 0.08 to 0.51). No p values reported. (**MODERATE)** *BPaL vs SC* One RCT (Nyang'wa et al 2022) reported the unadjusted RD for an unfavourable status for people with RR TB as -33.6% (95% CI -55.2% to -12.0%), and a RR of 0.46 (95% CI 0.26 to 0.82). No p values reported. (**LOW)** **For BPaLM vs SC: one RCT provided moderate certainty evidence of a *statistically significantly* lower risk of an unfavourable status in people with RR TB treated with BPaLM compared to SC at 72 weeks, and moderate certainty evidence of a lower risk at 108 weeks (statistical significance not reported).** **For BPaL: two uncontrolled studies provided very low certainty evidence that between 5% and 25%[7] of people with**

[5] Nyang'wa et al 2022 state that: *"A noninferiority margin of 12 percentage points as the upper boundary of the confidence interval was determined to be a reasonable clinical and public health trade-off limit, given the benefits of a shorter treatment duration, decreased pill burden and regimen cost, and the all-oral nature of the investigational regimens."* This was assumed to indicate clinical and statistical significance.

[6] Nyang'wa et al 2022 note that "*Confidence intervals for the BPaLC group and BPaL group as compared with the standard-care group are two-sided and were not adjusted for multiplicity and should not be used to infer relative treatment effects."* Results were therefore not described as statistically significant even if the 95% confidence interval excluded no effect.

[7] Based on the linezolid 600mg/26-week arm only of Conradie et al 2022. Across all linezolid dosages, 19% of people with MDR TB had an unfavourable outcome.

Outcome	Evidence statement
	MDR TB or pre-XDR TB had an unfavourable outcome at 6 months follow-up. One RCT provided moderate certainty evidence of a lower risk of an unfavourable status with BPaL compared to SC for RR TB at 72 and low certainty evidence of a lower risk at 108 weeks (statistical significance not reported).
Treatment completion rates **Certainty of evidence:** Very low to Low	Adherence to treatment is important to patients as it provides an indication of how the treatment is tolerated. If a treatment has adherence challenges, it can increase the risk of treatment failure and drug resistance. In total, one RCT (Nyang'wa et al 2022) and one prospective case series (Conradie et al 2020) provided evidence relating to treatment completion rates in people with RR TB treated with either BPaL or BPaLM (Nyang'wa et al 2022), and in people with MDR TB and (pre)XDR TB treated with BPaL (Conradie et al 2020). **At 6 months follow-up** One prospective case series reported that 1/71 (1.4%) people with (pre)XDR TB treated with BPaL withdrew their consent to continue in the study (1/109, 0.9% of the whole cohort). Excluding 7 people who died and 2 who relapsed, authors reported that *"All surviving participants completed 26 weeks (including two who extended to 39 weeks) of treatment with allowable interruptions of up to 35 consecutive days, and none had the regimen permanently discontinued."* (**VERY LOW)** **At 72 weeks follow-up** *BPaLM vs SC* One RCT (Nyang'wa et al 2022) reported fewer people with RR TB discontinuing BPaLM early (15/72, 20.8%) compared with those on SC (35/73, 47.9%). Statistical significance not reported (**LOW)**. Of those who discontinued, 0/15 in the BPaLM group did so due to adherence issues, compared with 3/35 (8.6%) in the SC arm. Statistical significance not reported. (**VERY LOW)** *BPaL vs SC* One RCT (Nyang'wa et al 2022) reported fewer people with RR TB discontinuing BPaL early (18/70 (26%) compared with those on SC 35/73 (47.9%) (**LOW)**. Of those who discontinued, 2/18 (11.1%) in the BPaL group did so due to adherence issues, compared with 3/35 (8.6%) in the SC arm. Statistical significance not reported. (**LOW)** **One prospective case series provided very low certainty evidence of all surviving MDR/(pre)XDR TB patients completing treatment with BPaL at 6 months follow-up,**

Outcome	Evidence statement
	other than one who withdrew consent. One RCT provided low certainty evidence of a higher completion rate at 72 weeks in people with RR who received either BPaLM or BPaL compared with SC (statistical significance not reported).
Important outcomes	
Quality of life **Certainty of evidence:** Not reported	Quality of life (QOL) is important to patients as it provides an indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. Validated tools for general quality of life measurements are important patient reported outcome measures to help inform patient-centred decision making and inform health policy. None of the included studies reported this outcome.
Treatment failure and disease recurrence **Certainty of evidence:** Very low	This outcome is important to patients because it can result in further treatment being required which will impact on patient satisfaction as well as any potential drug side effects from further treatment. There is also a negative public health impact associated with treatment failure. This is a composite outcome, as the terms treatment failure and disease recurrence are used interchangeably in some studies. In total, one RCT (Nyang'wa et al 2022) and one prospective case series (Conradie et al 2020) provided evidence relating to treatment failure and disease recurrence. **At 6 months follow-up** One prospective case series (Conradie et al 2020) reported that 1/38 (2.6%) people with MDR TB and 1/71 (1.4%) people with (pre)XDR TB treated with BPaL (2/109, 1.8% overall) relapsed at 6 months. (**VERY LOW)** **At 72 weeks follow-up** *BPaLM vs SC* No RR TB patients treated with either BPaLM (0/72) or SC (0/73) failed treatment at 72 weeks in the RCT. (**VERY LOW)** No RR TB patients treated with either BPaLM (0/72) or SC (0/73) had disease recurrence at 72 weeks in the RCT. (**VERY LOW)** **At 72 weeks follow-up** *BPaL vs SC* No RR TB patients treated with either BPaL (0/70) or SC (0/73) failed treatment at 72 weeks in the RCT. (**VERY LOW)** 3 RR TB patients treated with BPaL (3/72, 4.2%) and none on SC (0/73) had disease recurrence at 72 weeks in the RCT. (**VERY LOW)**

Outcome	Evidence statement
	For people with MDR/(pre)XDR TB, one prospective case series provided very low certainty evidence that < 2% relapsed by six months. One RCT provided very low certainty evidence that no RR TB patients taking BPaLM, BPaL or SC failed treatment at 72 weeks, although 4% of those taking BPaL (and none on BPaLM or SC) had disease recurrence by 72 weeks.
Amplification of drug resistance **Certainty of evidence:** Very low	This is an important outcome to patients as increased levels of drug resistance may results in changes to their treatment regimen and longer treatment duration. In total, one prospective case series (Conradie et al 2020) provided evidence relevant to the PICO-specific population of people with MDR TB and pre-XDR TB. **At 6 months follow-up:** 1/109 (0.9%) people treated with BPaL had a change in bedaquiline resistance gene Rv0678, from wild type at baseline to a 138-139insG variant in the late isolate. **(VERY LOW)** **For people with pre-XDR TB or MDR TB treated with BPaL, amplification of drug resistance was reported in 0.9% of patients at 6 months follow-up.**
Safety	
Safety outcomes **Certainty of evidence:** Very low to Moderate	Safety of BPaL/BPaLM is important to patients as it allows comparison of treatment approaches. In total, one RCT (Nyang'wa et al 2022) and one prospective case series (Conradie et al 2020) reported safety outcomes for people with RR TB, MDR TB and pre-XDR TB. **At 6 months follow-up** One prospective case series (Conradie et al 2020) reported that all patients with MDR/(pre)XDR TB experienced at least one AE (109/109, 100%) **(VERY LOW)** ○ Peripheral neuropathy was reported by 88/109 (80.7%). ○ Optic neuritis was reported by 2/109 (1.8%). ○ 52/109 (47.7%) had myelosuppression, 40/52 (76.9%) of whom had anaemia (36.7% of all patients). ○ Aminotransferase increases were reported in 17/109 (15.6%), of whom 12 had ALT elevation and 11 had AST elevation to > 3x ULN. ○ 8/109 (7.3%) patients had hepatic AE leading to regimen interruption (then resumed). ○ No patients had QTcF > 480 msec. One prospective case series (Conradie et al 2020) reported that 62/109 (56.9%) patients with MDR/(pre)XDR TB experienced at least one grade 3 or 4 AE and 19/109

Outcome	Evidence statement
	(17.4%) had at least one grade 3 or 4 SAE. There were 6/109 (5.5%) deaths. **(VERY LOW)** **At 72 weeks follow-up** *BPaLM vs SC* One RCT (Nyang'wa et al 2022) reported that *statistically significantly* fewer people with RR TB treated with BPaLM (14/72, 19.4%) had at least one SAE or AE of at least grade 3 compared with those receiving SC (43/73 (58.9%). RD: -40% (96.6% CI -55% to -24%). No p value reported. (**MODERATE)** In terms of specific SAE/grade ≥3 AE, one RCT (Nyang'wa et al 2022) reported: o A lower incidence of hepatic disorders in people with RR TB on BPaLM (3/72, 4.2%) compared with those on SC (8/73, 11.0%). o QTcF prolongation was reported by fewer people with RR TB on BPaLM (1/72, 1.4%) compared with those on SC (10/73, 13.7%). o Rates of decreased creatinine renal clearance were lower among people taking BPaLM (1/72, 1.4%) compared with SC (5/73, 6.8%). o Rates of anaemia were also lower in those taking BPaLM (2/72, 2.8%) compared with SC (6/73, 8.2%). o Similar rates of neutropaenia were reported in both groups (BPaLM: 3/72, 4.2%) vs SC: 2/73, 2.7%). o No patients in either group reported optic neuropathy. (**MODERATE)** **Fewer people with RR TB taking BPaLM discontinued due to AE (5/72, 6.9%) compared with those on SC (**17/73, 23.3%). Statistical significance not reported. (**LOW)** No RR TB patients taking BPaLM (0/72) had died by 72-week follow-up, compared with 7/73 (9.6%) on SC (4 considered to be treatment-related, 0 TB-related). (**LOW)** **At 72 weeks follow-up** *BPaL vs SC* One RCT (Nyang'wa et al 2022) reported that fewer people with RR TB treated with BPaL (15/69, 21.7%) had at least one SAE or AE of at least grade 3 compared with those receiving SC (43/73 (58.9%). RD: -37% (95% CI -52% to -22%). No p value reported. (**MODERATE)** In terms of specific SAE/grade ≥3 AE, one RCT (Nyang'wa et al 2022) reported: o A lower incidence of hepatic disorders in people with RR TB on BPaL (2/69, 2.9%) compared with those on SC (8/73, 11.0%).

Outcome	Evidence statement
	○ No RR TB patients on BPaL had QTcF prolongation (0/69, 0%) compared with those on SC (10/73, 13.7%). ○ Rates of decreased creatinine renal clearance were lower among people taking BPaL (2/69, 2.9%) compared with SC (5/73, 6.8%). ○ Rates of anaemia were lower in those taking BPaL (1/69, 1.4%) compared with SC (6/73, 8.2%). ○ No patients on BPaL reported neutropaenia (0/69, 0%) compared with two patients on SC: 2/73, 2.7%). ○ No patients in either group reported optic neuropathy. (**MODERATE)** Fewer people with RR TB taking BPaL discontinued due to AE (5/70, 7.1%) compared with those on SC **(**17/73, 23.3%). Statistical significance not reported. (**LOW)** One RR TB patient taking BPaL (1/70, 1.4%) had died by 72-week follow-up (not treatment-related or TB-related), compared with 7/73 (9.6%) on SC (4 considered to be treatment-related, 0 TB-related (**MODERATE)** **At 108 weeks follow-up[8]** *BPaLM vs SC* One RCT (Nyang'wa et al 2022) reported a *statistically significantly*[9] lower incidence of patients with at least one SAE or AE of at least grade 3 in the BPaLM group compared with those receiving SC (RD adjusted for randomisation site: -35.3%, 96.6% CI -56.2% to -14.3%). P not reported. (**MODERATE)** **Other time points** One RCT (Nyang'wa et al 2022) reported similar numbers of people with RR TB who experienced an AE of any grade by the date of study termination (duration not defined) either on BPaLM (142/151, 94.0%), BPaL 120/122 (98.4%) or SC 145/150 (96.7%). **One prospective case series provided very low certainty evidence that all patients with MDR/ (pre)XDR TB treated with BPaL experienced at least one AE during 6 months follow-up, the most common being peripheral neuropathy or myelosuppression, and 19/109 (17.4%) had at least one grade 3 or 4 SAE.** **One RCT provided moderate certainty evidence of *statistically significantly* fewer people on BPaLM for RR TB having at least one SAE or AE of at least grade 3 compared**

[8] This outcome was not reported for the BPaL group.

[9] This result was reported with a 96.6% confidence interval and met the study definition of statistically significant.

Outcome	Evidence statement
	with those receiving SC at either 72 weeks or 108 weeks follow-up, and moderate certainty evidence of fewer SAE or AE of at least grade 3 among people with RR TB treated with BPaL compared with SC at 72 weeks (statistical significance not reported). **One RCT provided low certainty evidence that fewer people taking either BPaLM or BPaL discontinued by 72 weeks due to adverse events compared with those on SC (statistical significance not reported). The RCT provided low to moderate certainty evidence of a higher number of treatment-related deaths among people with RR TB on SC compared with either BPaLM or BPaL (statistical significance not reported).** **In terms of specific SAE or ≥ grade 3 AE, one RCT provided moderate certainty evidence that, at 72 weeks, hepatic disorders, QTcF prolongation, decreased creatinine renal clearance, and anaemia were all less common in people treated with either BPaLM or BPaL compared with those receiving SC, although similar rates of neutropaenia were reported in both BPaLM and SC groups (statistical significance not reported).**
Abbreviations AE: adverse events; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BPAL: bedaquiline, pretomanid, and linezolid; BPaLM: BPAL+ moxifloxacin; CI: confidence interval; HR: hazard ratio; ITT: intention-to-treat; MDR: multidrug-resistant TB; mITT: modified ITT; QTcF: QT interval calculated with Fridericia's formula; RCT: randomised controlled trial; RD: risk difference; RR: risk ratio; RR TB: rifampicin-resistant TB; SAE: serious adverse events; SC: standard care; ULN: upper limit of normal range; XDR TB: extensively drug resistant TB	

From the evidence selected, are there any subgroups of patients that may benefit from BPaLM/BPaL more than the wider population of interest?

Outcome	Evidence statement
Unfavourable treatment outcome by subgroup	One RCT (Nyang'wa et al 2022) reported that the proportion of RR TB patients with an unfavourable treatment outcome at 72 weeks (BPaLM vs SC) did not vary by age, sex, HIV infection, sputum smear status, the presence of cavities on chest radiographs, fluoroquinolone resistance, or country of recruitment. The RD (96.6% CI) for BPaLM vs SC for the subgroups was: Sex (F vs M): -29.3% (-53.9% to -4.6%) vs -42.9% (-63.1% to -22.8%) Country (S Africa vs Uzbekistan): -7.6% (-42.2% to 27.0%) vs -41.7% (-61.1% to -22.3%); Belarus not calculable HIV status (negative vs positive): -44.7% (-61.3% to -28.1%) vs -11.4% (-48.5% to 25.6%) Cavity present (absent vs present): -38.8% (-66.7% to -11.0%) vs -37.7% (-56.4% to -19.0%)

	Previous TB treatment (no vs yes): -30.1% (-50.7% to -9.5%) vs -47.6% (-70.9% to -24.2%) Smear positivity (negative vs positive): -53.4% (-82.2% to -24.6%) vs -31.5% (-50.1% to -12.9%) Current smoker (no vs yes): -31.6% (-50.7% to -12.5%) vs not calculable Fluoroquinolone resistance (sensitive vs resistant): -45.3% (-63.7% to -26.9%) vs -17.3% (-45.1% to 10.5%) Isoniazid resistance (sensitive vs resistant): -46.7% (-115.7% to 22.4%) vs -37.2% (-53.6% to -20.8%) One RCT reported
Adverse events results by HIV status	One prospective case series (Conradie et al 2020) reported AE results for the combined population of MDR TB and (pre)XDR TB for people who were HIV positive vs those who were HIV negative. People who were HIV positive had similar safety outcomes as those who were HIV negative, although the rate of grade 3 or 4 AE was slightly higher among people who were HIV positive: AE: 53/53 (100%) vs 56/56 (100%) AE leading to death: 3/53 (5.7%) vs 3/56 (5.4%) SAE: 10/53 (18.9%) vs 9/56 (16.1%) Grade 3 or 4 AE: 27/53 (50.9%) vs 35/56 (62.5%)

Abbreviations
AE: adverse events; BPAL: bedaquiline, pretomanid, and linezolid; BPaLM: BPAL+ moxifloxacin; CI: confidence interval; F: female; HIV: human immunodeficiency virus; M: male; MDR: multidrug-resistant TB; RCT: randomised controlled trial; RD: risk difference; RR TB: rifampicin-resistant TB; SAE: serious adverse events; SC: standard care; TB: tuberculosis; XDR TB: extensively drug resistant TB

From the evidence selected, what was the treatment duration of the BPaLM/BPaL regimen?

Outcome	Evidence statement
Treatment duration	Patients in one RCT (Nyang'wa et al 2022) had a 24-week BPaLM or BPaL regimen. Both the randomised uncontrolled trial (Conradie et al 2022) and the prospective case series (Conradie et al 2020) gave patients 26 weeks of bedaquiline and pretomanid, but either 26 weeks or 9 weeks of linezolid (in Conradie et al 2022) or linezolid for up to 26 weeks (Conradie et al 2020).
Abbreviations BPAL: bedaquiline, pretomanid, and linezolid; BPaLM: BPAL+ moxifloxacin; RCT: randomised controlled trial	

In people with suspected, functional or confirmed RR, MDR- or pre-XDR TB, what is the cost effectiveness of BPaLM/BPaL compared with standard of care?

Outcome	Evidence statement
Cost effectiveness **Incremental cost per person** **Incremental cost per DALY saved** **Incremental cost** **DALYs averted**	In total, two analyses provided evidence for the cost effectiveness of BPaLM/BPaL compared to SC. One analysis (Sweeney et al 2022) applied treatment effects from TB-PRACTECAL (Nyang'wa et al 2022) to data for people with RR TB in India, South Africa, the Philippines and Georgia. The analysis used a Markov model with a 20-year time horizon and a provider's perspective, with costs reported in 2019 USD and a 3% discount rate. One analysis (Gomez et al 2021) applied treatment effects from Nix TB (Conradie et al 2020) to data for people with MDR/XDR TB in South Africa, the Philippines and Georgia. The analysis used a Markov model with a lifetime horizon (treatment outcomes modelled for 5 years but costs and included until death) and a provider's perspective, with costs reported in 2018 USD and a 3% discount rate. The analysis was presented for two scenarios: 1) XDR TB patients, 2) XDR TB and people with MDR TB who have failed or are intolerant to their MDR TB treatments. Only scenario 2 is considered here. **RR TB:** One analysis (Sweeney et al 2022) estimated that BPaLM would save \$80 to \$997 per person and avert 0.7 to 1.3 DALYs per person in the countries included in the analysis. Savings with BPaL ranged from \$112 to \$1173 per person, but with fewer DALYs averted (0.0 to 0.4 DALYs per person). The authors calculated that, at a willingness-to-pay per DALY averted of 0.5 GDP per capita, BPaLM is the preferred regimen in all countries studied. **MDR/XDR TB**:

Outcome	Evidence statement
	One analysis (Gomez et al 2021) reported that, compared with SC, incremental costs of BPaL ranged from $ -336,950 (-337,480 to -336,420)[10] in Georgia to $ −2,546,098 (-2,542,254 to -2,549,942) in the Philippines. Corresponding DALYs averted ranged from 830 DALYs (819 to 841) in Georgia to 15,416 DALYs (15,214 to 15,618) in South Africa. Authors concluded that BPaL for XDR-TB is likely to be cost saving in all study settings when pretomanid is priced at the Global Drug Facility list price, with increased savings and clinical benefits when BPaL treatment is extended to MDR TB treatment failure and treatment intolerant patients. Although both studies used the provider perspective, costs in the UK may be different, so the cost of the intervention compared to standard care may not be generalisable to the UK NHS setting. There was also large variation in cost estimates for different countries, which introduces uncertainty about generalisability to the NHS in England.

Abbreviations
BPAL: bedaquiline, pretomanid, and linezolid; BPaLM: BPAL+ moxifloxacin; DALY: disability-adjusted life year; GDP: gross domestic product; MDR TB: multidrug-resistant TB; RR TB: rifampicin-resistant TB; SC: standard care; USD: US dollars; XDR TB: extensively drug resistant TB

Patient Impact Summary

The condition has the following impacts on the patient's everyday life:

- **mobility:** Patients have no problems with mobility
- **ability to provide self-care:** Patients have no problems in washing or dressing
- **undertaking usual activities:** Patients have moderate problems in doing their usual activities
- **experience of pain/discomfort:** Patients have moderate pain or discomfort
- **experience of anxiety/depression:** Patients are severely anxious or depressed

Further details of impact upon patients:

The standard care treatment may only have a limited impact on mobility, washing or dressing. However, the drugs used can have side effects including severe nausea, loss of appetite and extreme fatigue. The numerous pills can be very difficult to take and can leave patients feeling unwell most of the time. This can make it difficult to do normal activities such as cooking, socializing, or working full days. Additional side effects may include pain, discomfort, frequent stomach aches, frequent loose and painful bowel movements. Patients may become depressed throughout the treatment and in some cases may experience suicidal ideation.

[10] The meaning of the numbers in brackets is not clear in the Gomez et al 2021 study.

Further details of impact upon carers:
Some patients may require carers to help them to manage unwanted side effects which can continue throughout treatment (standard care is at least 9 months of treatment and can extend up to 24 months).

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
The clinical commissioning proposition recommends the combination of bedaquiline, pretomanid and linezolid, with or without moxifloxacin as a treatment option in people aged 14 years and over for suspected, functional or confirmed rifampicin resistant tuberculosis (TB), multidrug-resistant (MDR) TB and pre-extensively drug resistant (pre-XDR) TB. Bedaquiline is licensed for use as part of an appropriate combination regimen for pulmonary MDR-TB when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. Use of bedaquiline for extra-pulmonary TB as part of BPaLM/BPaL is off-label. Use of pretomanid is off-label when used as part of BPaLM regimen; and for use in RR TB and pre-XDR TB when used as part of BPaL regimen. Use of both linezolid and moxifloxacin is off-label. Where medicines are used off-label, Trust policy regarding unlicensed medicines should apply. Bedaquiline and pretomanid are on the NHS Payment Scheme Annex A, that is, they are excluded drugs. Linezolid and moxifloxacin are both in tariff. Healthcare professionals should consult the January 2024 Drug Safety Update when prescribing fluoroquinolone antibiotics (moxifloxacin) - https://www.gov.uk/drug-safety-update/fluoroquinolone-antibiotics-must-now-only-be-prescribed-when-other-commonly-recommended-antibiotics-are-inappropriate

Considerations from review by National Programme of Care
The proposal received the full support of the Blood and Infection PoC on the 26th March 2024