MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
29 05 2019 and 30 05 2019

Agenda Item No	03.1
National Programme	Blood and Infection
Clinical Reference Group	Infectious Diseases
URN	1837

Title
Treatment for defined patients with MDR-TB and XDR-TB including bedaquiline and delamanid

Actions Requested	1. Support the policy proposition
	2. Recommend the relative priority

Proposition
Routinely commissioned. This policy updates the current policy position and extends access for treatment in line with the latest WHO 2018 Guidelines and newly reviewed evidence. MDR-TB poses a significant public health risk because although the number of people newly diagnosed with TB has decreased in previous years, the proportion of people with MDR-TB has not (PHE, 2018). Widening the availability of these drugs will provide a public health benefit as they are more effective, easier to administer and have less severe side effect profile than current alternative treatments.

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

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes / Head of Mental Health Programme confirms the proposal is supported by an: Impact Assessment; Stakeholder Engagement Report; Equality Impact and Assessment Report; Clinical Policy Proposition. The relevant National Programme of Care Board 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 Clinical Programmes Director (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 Impact and Assessment Report

1 ADULTS

1.1 Bedaquiline for more than six months versus bedaquiline for less than six months in multi-drug resistant tuberculosis		
No	**Outcome measures**	**Summary from evidence review**
1.	Survival	Survival is the proportion of participants alive at the end of a study. Guglielmetti et al 2017 reported a mortality rate after less than 190 days bedaquiline (dose not reported) of 0/12 (0%) and after more than 190 days bedaquiline (dose not reported) of 1/33 (3%), p=1.0. The avoidance of mortality is of very high value to patients. This study does not indicate that more patients survive after courses of bedaquiline of more than 190 days, compared with courses shorter than 190 days. 11% of patients were lost to follow-up during treatment and this rate increased during post-therapeutic follow-up, though data are not reported. This may bias the study, with poor outcomes in those on prolonged treatment being less likely to be reported, a particular problem as the study was retrospective. The study was small and lacked a reported power calculation. It was too small to detect all but large differences between the two groups. Those receiving prolonged treatment were more often previously treated for TB (data not reported, p<0.001). They were more likely to have XDR-TB, bilateral lung involvement, cavitary TB and strains with resistance to a greater number of drugs, although none of these differences reached statistical significance. Patients in the prolonged treatment group were more frequently sputum culture-positive at treatment start (p=0.048). These factors likely biased the study against the group receiving prolonged treatment. The six

		months treatment period specified in the PICO is about 182 days, slightly less than the 190-day cut-off used in this study.
2.	Progression free survival	Not reported
3.	Mobility	Not reported
4.	Self-care	Not reported
5.	Usual activities	Not reported
6.	Pain	Not reported
7.	Anxiety / Depression	Not reported
8.	Replacement of more toxic treatment	Not reported
9.	Dependency on care giver / supporting independence	Not reported
10.	Safety	See below
11.	Delivery of intervention	Not reported
No	**Outcome measures**	**Summary from evidence review**
1.	Cure	The authors do not define cure, but usually cure of TB means that that treatment was completed with at least five consecutive negative cultures during the last 12 months. Guglielmetti et al 2017 reported a cure rate after less than 190 days bedaquiline (dose not reported) of 7/12 (58%) and after more than 190 days bedaquiline (dose not reported) of 27/33 (82%), p=0.13. Cure is of very high value to patients. This study does not indicate that more patients are cured by courses of bedaquiline of more than 190 days, compared with courses shorter than 190 days. See above for details and limitations of Guglielmetti et al 2017.
2.	Treatment completion	The authors do not define treatment completion, but usually it occurs when treatment is completed but there are fewer than five cultures performed during the last 12 months. Guglielmetti et al 2017 reported a treatment completion rate after less than 190 days bedaquiline (dose not reported) of 2/12 (17%) and after more than 190 days bedaquiline (dose not reported) of 0/33 (0%), p=0.067.

		Treatment completion without confirmed cure is an indication of compliance and may be associated with cure. Its value to patients is dependent on whether cure occurred. This study does not indicate that more patients' complete courses of bedaquiline of more than 190 days, compared with courses shorter than 190 days. See above for details and limitations of Guglielmetti et al 2017.
3.	Treatment failure	The authors do not define treatment failure, but usually it means that a patient had two or more positive cultures among five collected during the final 12 months of treatment or has a positive culture among the final three sputum cultures collected. Guglielmetti et al 2017 reported a treatment failure rate after less than 190 days bedaquiline (dose not reported) of 1/12 (8%) and after more than 190 days bedaquiline (dose not reported) of 2/33 (6%), p=1.0. Treatment failure is likely to lead to recurrent symptoms and possibly fatal progression, so avoiding it is likely to be of high value to patients. This study does not indicate that fewer patients have treatment failure after courses of bedaquiline of more than 190 days, compared with courses shorter than 190 days. See above for details and limitations of Guglielmetti et al 2017.
4.	Time to sputum smear conversion	Time to sputum smear conversion is the elapsed time between treatment starting and the first sputum sample free of TB on microscopy. Guglielmetti et al 2017 reported a median time to sputum smear conversion after less than 190 days bedaquiline (dose not reported) of 71 days and after more than 190 days bedaquiline (dose not reported) of 110 days, p=0.002. Earlier sputum smear conversion indicates the earlier elimination of TB from sputum and may be associated with earlier remission of symptoms. If so, it is of value to patients. It may also indicate an earlier end to a patient's infectivity to others. This study might appear to indicate that sputum smear conversion occurs earlier after courses of bedaquiline of more than 190 days, compared with courses shorter than 190 days. However, this result is not reliable: multivariate analysis

		showed that there were differences in confounding variables between the two groups, and it is likely these biased this result. Both groups of patients had received the same treatment at the median time of conversion, further undermining any claim that longer treatment accelerates sputum conversion. See above for details and limitations of Guglielmetti et al 2017.
5.	Time to sputum culture conversion	Time to sputum culture conversion is the elapsed time between treatment starting and the first sputum sample free of TB on culture. Guglielmetti et al 2017 reported a median time to sputum culture conversion after less than 190 days bedaquiline (dose not reported) of 71 days and after more than 190 days bedaquiline (dose not reported) of 91 days, p=0.021. Earlier sputum culture conversion indicates the earlier elimination of viable TB from sputum and may be associated with earlier remission of symptoms. If so, it is of value to patients. It may also indicate an earlier end to a patient's infectivity to others. This study might appear to indicate that sputum culture conversion occurs earlier after courses of bedaquiline of more than 190 days, compared with courses shorter than 190 days. However, this result is not reliable: multivariate analysis showed that differences in sputum culture conversion arose from differences in confounding variables between the two groups (see below). Both groups of patients had received the same treatment at the median time of conversion, further undermining any claim that longer treatment accelerates sputum conversion. See above for details and limitations of Guglielmetti et al 2017.
6.	Odds of culture conversion after multivariate adjustment (factors not reported)	The odds of culture conversion after multivariate adjustment indicate whether treatment duration is associated with the probability of TB being cultured from a sputum sample, adjusting for potential confounders. The authors do not report which potential confounders they selected for adjustment. Guglielmetti et al 2017 do not report an odds ratio comparing less than 190 days bedaquiline (dose not reported) and more than 190 days bedaquiline (dose not reported), but state that p=0.702. Sputum culture conversion indicates the elimination of viable TB from sputum and may be associated with remission of

		symptoms. If so, it is of value to patients. It may also indicate an earlier end to a patient's infectivity to others. This study indicates that sputum culture conversion is no more likely after courses of bedaquiline of more than 190 days, compared with courses shorter than 190 days, once confounding variables are taken into account. See above for details and limitations of Guglielmetti et al 2017.
7.	Severe adverse effects	Severe adverse effects are defined in this study as those causing severe, life-threatening or fatal effects. Guglielmetti et al 2017 reported rate of severe adverse effects after less than 190 days bedaquiline (dose not reported) of 5/12 (42%) and after more than 190 days bedaquiline (dose not reported) of 23/33 (70%), p=0.163. Avoiding severe adverse effects is likely to be of high value to patients. This study does not indicate a difference in rates of severe adverse effects after courses of bedaquiline of more than 190 days, compared with courses shorter than 190 days. See above for details and limitations of Guglielmetti et al 2017.
8.	Prolongation of the corrected QT interval of more than 500ms	Prolongation of the corrected QT interval of more than 500ms is an electrocardiographic abnormality associated with bedaquiline and delamanid. Guglielmetti et al 2017 reported rate of prolongation of the corrected QT interval after less than 190 days bedaquiline (dose not reported) of 0/12 (0%) and after more than 190 days bedaquiline (dose not reported) of 5/33 (15%), p=0.303. Prolongation of the corrected QT interval may lead to symptomatic cardiac arrhythmias, so its avoidance is likely to be of value to patients. This study does not indicate a difference in rates of prolongation of the corrected QT interval after courses of bedaquiline of more than 190 days, compared with courses shorter than 190 days. See above for details and limitations of Guglielmetti et al 2017.

1.2 Delamanid for more than six months versus delamanid for less than six months in multi-drug resistant tuberculosis

No	Outcome measures	Summary from evidence review
1.	Survival	Survival is the proportion of participants alive at the end of a study. Skripconoka et al 2013 reported a mortality rate after delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months of 2/192 (1.0%) and after delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months of 19/229 (8.3%), p<0.001. The avoidance of mortality is of very high value to patients. This study may indicate that fewer participants died when treated with delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months, compared with delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months. Short-term treatment was only received by those who completed the first of two studies reported by Skripconoka et al 2013 but did not enter the second one. The authors report no data comparing these participants with those who entered the second study. If they had more severe TB (perhaps making their initial response to delamanid less marked) or had a worse prognosis for some other reason such as homelessness or social exclusion, that might explain both their non-participation in the second study and their worse results. These possible associations cast doubt on the reliability of the study by confounding the relationship between long-term treatment with delamanid and better outcomes and mean the former may not be the cause of the latter.
2.	Progression free survival	Not reported
3.	Mobility	Not reported
4.	Self-care	Not reported
5.	Usual activities	Not reported
6.	Pain	Not reported
7.	Anxiety / Depression	Not reported
8.	Replacement of more toxic treatment	Not reported
9.	Dependency on care giver / supporting independence	Not reported
10.	Safety	Not reported
11.	Delivery of intervention	Not reported

No	Outcome measures	Summary from evidence review
1.	Cure	The authors define cure as meaning that treatment was completed with at least five consecutive negative cultures during the last 12 months. Skripconoka et al 2013 reported a cure rate after delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months of 110/192 (57.3%) and after delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months of 111/229 (48.5%), p≥0.05. Cure is of very high value to patients. This study does not indicate that more patients are cured by courses of delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months, compared with delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months. See above for details and limitations of Skripconoka et al 2013.
2.	Treatment completion	The authors define treatment completion as meaning that the participant finished all courses of drug therapy recommended but had fewer than five cultures performed during the last 12 months. Skripconoka et al 2013 reported a treatment completion rate after delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months of 33/192 (17.2%) and after delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months of 15/229 (6.6%), p<0.001. Treatment completion without confirmed cure is an indication of compliance and may be associated with cure. Its value to patients is dependent on whether cure occurred. This study may indicate that more patients completed treatment with delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months, compared with delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months. See above for details and limitations of Skripconoka et al 2013.
3.	Treatment failure	The authors define treatment failure as meaning that the participant had two or more positive cultures among five collected during the final 12 months, or a positive culture among the final three sputum cultures collected from the patient.

		Skripconoka et al 2013 reported a treatment failure rate after delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months of 32/192 (16.7%) and after delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months of 26/229 (11.4%), p≥0.05. Treatment failure is likely to lead to recurrent symptoms and possibly fatal progression, so avoiding it is likely to be of high value to patients. This study does not indicate that more patients have treatment failure with courses of delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months, compared with delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months. See above for details and limitations of Skripconoka et al 2013.
4.	Default from treatment	The authors define treatment default as meaning that treatment was interrupted for more than two consecutive months for any reason without medical approval. Skripconoka et al 2013 reported a treatment default rate after delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months of 15/192 (7.8%) and after delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months of 58/229 (25.3%), p<0.001. Treatment default may lead to recurrent symptoms and possibly fatal progression, so avoiding it is likely to be of high value to patients. This study may indicate that more patients have defaulted from treatment with courses of delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months, compared with delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months. See above for details and limitations of Skripconoka et al 2013.

1.2 Delamanid for more than six months in multi-drug resistant tuberculosis (no comparator)		
No	**Outcome measures**	**Summary from evidence review**
1.	Survival	Not reported
2.	Progression free survival	Not reported
3.	Mobility	Not reported
4.	Self-care	Not reported

5.	Usual activities	Not reported
6.	Pain	Not reported
7.	Anxiety / Depression	Not reported
8.	Replacement of more toxic treatment	Not reported
9.	Dependency on care giver / supporting independence	Not reported
10.	Safety	Not reported
11.	Delivery of intervention	Not reported
No	**Outcome measures**	**Summary from evidence review**
1.	Cure	The authors do not define cure. Chang et al 2018 reported a cure rate after delamanid 100mg twice daily for “one to two months”, then 200mg daily of 9/11 (82%). Cure is of very high value to patients. The small size of this study and the lack of controls make it difficult to draw conclusions from this study relevant to this review’s research questions.

1.3 Bedaquiline and delamanid for more than six months in multi-drug resistant tuberculosis (no comparator)		
No	**Outcome measures**	**Summary from evidence review**
1.	Survival	Not reported
2.	Progression free survival	Not reported
3.	Mobility	Not reported
4.	Self-care	Not reported
5.	Usual activities	Not reported
6.	Pain	Not reported
7.	Anxiety / Depression	Not reported
8.	Replacement of more toxic treatment	Not reported
9.	Dependency on care giver /	Not reported

	supporting independence	
10.	Safety	Prolongation of the corrected QT interval of more than 500ms is an electrocardiographic abnormality associated with bedaquiline and delamanid. Guglielmetti et al 2018 reported a rate of prolongation of the corrected QT interval of more than 500ms after bedaquiline (dose not reported, treatment period variable) and delamanid (dose not reported, treatment period variable) of 2/3 (67%). Prolongation of the corrected QT interval may lead to symptomatic cardiac arrhythmias, so its avoidance is likely to be of value to patients The small size of this case series and the lack of controls make it difficult to draw conclusions from this study relevant to this review's research questions.
11.	Delivery of intervention	Not reported
No	**Outcome measures**	**Summary from evidence review**
1.	Cure	The authors do not define cure, but usually it means that treatment was completed with at least five consecutive negative cultures during the last 12 months. Guglielmetti et al 2018 reported a cure rate after bedaquiline (dose not reported, treatment period variable) and delamanid (dose not reported, treatment period variable) of 3/3 (100%). Cure is of very high value to patients. See above for details and limitations of Guglielmetti et al 2018.
2.	Sputum culture conversion	Sputum culture conversion is the disappearance of TB from cultures of sputum. Guglielmetti et al 2018 reported a sputum conversion rate after bedaquiline (dose not reported, treatment period variable) and delamanid (dose not reported, treatment period variable) of 3/3 (100%). Sputum culture conversion indicates a higher probability of cure, so is of high value to patients. See above for details and limitations of Guglielmetti et al 2018.

1.4 Bedaquiline and delamanid sequential use in multi-drug resistant tuberculosis (no comparator)		
No	**Outcome measures**	**Summary from evidence review**
1.	Survival	Not reported
2.	Progression free survival	Not reported
3.	Mobility	Not reported
4.	Self-care	Not reported
5.	Usual activities	Not reported
6.	Pain	Not reported
7.	Anxiety / Depression	Not reported
8.	Replacement of more toxic treatment	Not reported
9.	Dependency on care giver / supporting independence	Not reported
10.	Safety	Prolongation of the corrected QT interval of more than 500ms is an electrocardiographic abnormality associated with bedaquiline and delamanid. Guglielmetti et al 2018 reported a rate of prolongation of the corrected QT interval of more than 500ms after bedaquiline (dose not reported, treatment period variable) and delamanid (dose not reported, treatment period variable) of 0/2 (0%). Prolongation of the corrected QT interval may lead to symptomatic cardiac arrhythmias, so its avoidance is likely to be of value to patients This case series provides little reliable information on the relationship between use of bedaquiline and/or delamanid, and outcomes. Both participants were “exposed” to a combination of bedaquiline and delamanid for at least 30 days; exposure was defined as the sum of the duration of concomitant treatment and, for the patients receiving sequential treatment, the duration of a washout period for one drug after stopping it, while taking the other drug. Bedaquiline washout was 180 days and delamanid washout was 5 days. Two aspects of the paper make interpretation difficult. First, it is not clear the extent to which the washout period should be regarded as part of treatment as specified in the PICO. The prescribing physician had withdrawn bedaquiline, so the patient was no longer being actively treated with it. Notwithstanding the long half-life of bedaquiline, tissue concentrations were falling and its effect diminishing. It is

		unclear whether inclusion of washout periods is a reliable way of assessing the effect of sequential prescription of the two drugs of interest. Second, for one participant, the reported duration of exposure to both drugs was 109 days, less than bedaquiline's washout period, which appears incompatible with the authors' definition of total exposure. So it is unclear if the authors applied their definitions consistently. For these reasons, it is unclear if the participants fall within the scope of the PICO. These issues, the small size of the study and the lack of controls make it difficult to draw conclusions from this study relevant to this review's research questions.
11.	Delivery of intervention	Not reported
No	**Outcome measures**	**Summary from evidence review**
1.	Cure	The authors do not define cure, but usually it means that treatment was completed with at least five consecutive negative cultures during the last 12 months. Guglielmetti et al 2018 reported a cure rate after bedaquiline (dose not reported, treatment period variable) and delamanid (dose not reported, treatment period variable) of 2/2 (100%). Cure is of very high value to patients. See above for details and limitations of Guglielmetti et al 2018.
2.	Sputum culture conversion	Sputum culture conversion is the disappearance of TB from cultures of sputum. Guglielmetti et al 2018 reported a sputum conversion rate after bedaquiline (dose not reported, treatment period variable) and delamanid (dose not reported, treatment period variable) of 1/1 (100%). One participant had negative sputum culture at the start of treatment, so the denominator is 1, not 2. Sputum culture conversion indicates a higher probability of cure, so is of high value to patients. See above for details and limitations of Guglielmetti et al 2018.

2 CHILDREN

2.1 Bedaquiline in multi-drug resistant tuberculosis no comparator		
No	**Outcome measures**	**Summary from evidence review**

1.	Survival	Not reported
2.	Progression free survival	Not reported
3.	Mobility	Not reported
4.	Self-care	Not reported
5.	Usual activities	Not reported
6.	Pain	Not reported
7.	Anxiety / Depression	Not reported
8.	Replacement of more toxic treatment	Not reported
9.	Dependency on care giver / supporting independence	Not reported
10.	Safety	Prolongation of the corrected QT interval of more than 500ms or >60ms change from baseline plus torsade de pointes, polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia is an electrocardiographic (ECG) abnormality associated with bedaquiline and delamanid. Achar al 2017 reported a rate of this ECG abnormality of 5/27 (19%) in children and adolescents treated with bedaquiline. No patient experienced symptoms attributable to ECG abnormalities during treatment with bedaquiline. Prolongation of the corrected QT interval or other ECG abnormalities may lead to symptomatic cardiac arrhythmias, so its avoidance is likely to be of value to patients. This small uncontrolled study indicates a possible rate of QT interval prolongation in children and adolescents treated with bedaquiline. However, the absence of controls and the potential role of other drugs in causing this adverse effect limit what can be concluded.
11.	Delivery of intervention	Not reported

No	**Outcome measures**	**Summary from evidence review**
1.	Culture negative sputum when reported	Culture negativity occurs when mycobacteria are not grown when sputum from a patient is cultured. Achar et al 2017 reported a rate of culture negativity of 23/23 (100%). Culture conversion indicates the elimination of viable mycobacteria from sputum and may be associated with earlier

		remission of symptoms. If so, it is of value to patients. It may also indicate an earlier end to a patient's infectivity to others. This small uncontrolled study suggests that treatment regimens that include bedaquiline for six months are effective in eliminating viable mycobacteria from sputum. Since 10/27 (37%) of participants were culture-negative at inception, the 100% culture-negative rate after treatment does not imply that all these patients were rendered culture-negative by treatment or indicate how important bedaquiline was in achieving that outcome.

2.2 Delamanid in multi-drug resistant tuberculosis no comparator		
No	**Outcome measures**	**Summary from evidence review**
1.	Survival	Not reported
2.	Progression free survival	Not reported
3.	Mobility	Not reported
4.	Self-care	Not reported
5.	Usual activities	Not reported
6.	Pain	Not reported
7.	Anxiety / Depression	Not reported
8.	Replacement of more toxic treatment	Not reported
9.	Dependency on care giver / supporting independence	Not reported
10.	Safety	Tadolini et al 2016 reported but did not define adverse effects more severe than "mild". Tadolini et al 2016 reported that one participant (out of 16 children and adolescents treated with delamanid) had adverse effects more severe than "mild". This participant was receiving eight anti-TB drugs and experienced severe vomiting, renal impairment and severe electrolyte disturbances with a corrected QT interval prolongation >500 ms. Delamanid was discontinued. After management of vomiting and electrolyte imbalance correction, the patient was able to complete delamanid treatment without further QT prolongation. The avoidance of severe adverse effects is of high value to patients.

		This study indicates the potential for severe adverse reactions from anti-TB drugs, though it is unclear the extent to which delamanid caused the reported effect.
11.	Delivery of intervention	Not reported
No	**Outcome measures**	**Summary from evidence review**
1.	Culture negative sputum when reported	Culture negativity occurs when mycobacteria are not grown when sputum from a patient is cultured. Tadolini et al 2016 reported a rate of culture negativity of 13/16 (81%). Culture conversion indicates the elimination of viable mycobacteria from sputum and may be associated with earlier remission of symptoms. If so, it is of value to patients. It may also indicate an earlier end to a patient's infectivity to others. This small uncontrolled study suggests that treatment regimes that include delamanid are effective in eliminating viable mycobacteria from sputum. Of the 16 participants, only one participant had completed TB treatment. Six had completed 24 weeks of delamanid and ten were still receiving delamanid, of whom three had recently started on delamanid. The results do not indicate whether these patients were rendered culture-negative by treatment, or how important delamanid was in achieving that outcome.

2.3 Bedaquiline and delamanid in multi-drug resistant tuberculosis		
No	**Outcome measures**	**Summary from evidence review**
1.	Survival	Not reported
2.	Progression free survival	Not reported
3.	Mobility	Not reported
4.	Self-care	Not reported
5.	Usual activities	Not reported
6.	Pain	Not reported
7.	Anxiety / Depression	Not reported
8.	Replacement of more toxic treatment	Not reported
9.	Dependency on care giver / supporting independence	Not reported

10.	Safety	Not reported
11.	Delivery of intervention	Not reported

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
This policy recommends use of these two products outside their current marketing authorisations as additions to regimens for multi drug resistant TB. Namely in patients over 65 and under 18, for treatments beyond 6 months and sequentially. An existing policy recommends use within their marketing authorisations. They are a tariff exclusion.

Considerations from review by National Programme of Care
1) The proposal received the full support of the Blood and Infection PoC Board on the 28th March 2019 The PoC Board noted that: Further evidence considered was taken from the recommendations within the updated WHO 2018 guidelines. The 2018 update of the WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis has been used to inform this policy proposition in conjunction with the evidence review.