Engagement Report

Topic details

Title of policy or policy statement:	Nebulised liposomal amikacin for the treatment of non-tuberculous mycobacterial pulmonary disease caused by mycobacterium avium complex refractory to current treatment options (adults and post pubescent children)
Programme of Care:	Internal Medicine
Clinical Reference Group:	Specialised Respiratory
URN:	2111

1. Summary

This report summarises the feedback NHS England received from engagement during the development of this policy proposition, and how this feedback has been considered. There have been 7 forms completed and received.

2. Background

Nebulised liposomal amikacin is recommended to be available as a routine commissioning treatment option for adults and post pubescent children with non-tuberculous mycobacterial pulmonary disease (NTMPD) caused by mycobacterium avium complex (MAC) that is refractory to the current guidance-based treatment (GBT). The treatment is in addition to GBT and is aimed to be delivered through homecare arrangements). Liposomal amikacin is administered by oral inhalation via a nebuliser and is licenced in the UK for adults.

Currently, a few patients with NTMPD MAC do not require treatment. Unlike tuberculosis (TB), diagnosis of the disease does not necessitate treatment (Cowman et al 2019). For patients that require treatment, the current UK GBT has been set by the British Thoracic Society and includes rifampicin, ethambutol, azithromycin or clarithromycin (Haworth et al BTS Guidelines 2017). Currently, if there is culture conversion the treatment continues for at least 12 months.

Around 60% of patients with NTMPD caused by MAC receive treatment with GBT and around 40% of these will be refractory to GBT (Kwak et al. 2017), thus requiring the addition of nebulised amikacin.

Treatment with nebulised liposomal amikacin, as part of a combination antimicrobial regimen, should be continued for 12 months after sputum culture conversion. Treatment should not continue beyond a maximum of 6 months if sputum culture conversion has

not been confirmed by then. The maximum duration of treatment should not exceed 18 months.

Adults and post pubescent children should meet all the following inclusion criteria:

- diagnosis of NTMPD caused by MAC using sputum, induced sputum, bronchial washings, bronchoalveolar lavage or transbronchial biopsy samples (if sputum cultures are negative but clinical suspicion of NTM infection is high, CT-directed bronchial washings to obtain targeted samples can be used) (Haworth et al BTS Guidelines 2017) that:
    - have been treated with GBT for at least 6 months AND
    - have failed to show sputum culture conversion.

Exclusion criteria

- Individuals with cystic fibrosis.
- Treatment should not be initiated or should be temporarily interrupted in patients with any of the following:
    - hypersensitivity reaction to aminoglycosides
    - hypersensitivity to soya
    - co-administration with any aminoglycoside administered via any route of administration
    - severe renal impairment.

Starting criteria

Nebulised liposomal amikacin should be initiated and managed by physicians with significant experience in the treatment of refractory NTMPD due to MAC. The prescribing organisation is responsible for the ongoing prescribing of the treatment and the facilitation of homecare arrangements.

Stopping criteria

A decision to stop using nebulised liposomal amikacin should be made by the clinician with significant experience in managing refractory NTMPD due to MAC, along with the patient and carers (if applicable) using the following criteria:

- No culture conversion or worsening symptoms, by 6 months
- Adverse events where harm exceeds benefit at any time during treatment.

This policy proposition has been developed by a Policy Working Group made up of a Clinical Lead, a Public Health Lead, a Lead Commissioner, 3 Pharmacists, a patient participation volunteer, 3 clinicians with significant experience in managing NTMPD due to MAC.

3. Engagement

NHS England has a duty under Section 13Q of the NHS Act 2006 (as amended) to 'make arrangements' to involve the public in commissioning. Full guidance is available in the Statement of Arrangements and Guidance on Patient and Public Participation in Commissioning. In addition, NHS England has a legal duty to promote equality under the Equality Act (2010) and reduce health inequalities under the Health and Social Care Act (2012).

The policy proposition was sent for stakeholder testing for 2 weeks from 18/2/2022 to 4/3/2022. The comments have then been shared with the Policy Working Group to

enable full consideration of feedback and to support a decision on whether any changes to the proposition might be recommended.

Respondents were asked the following questions:

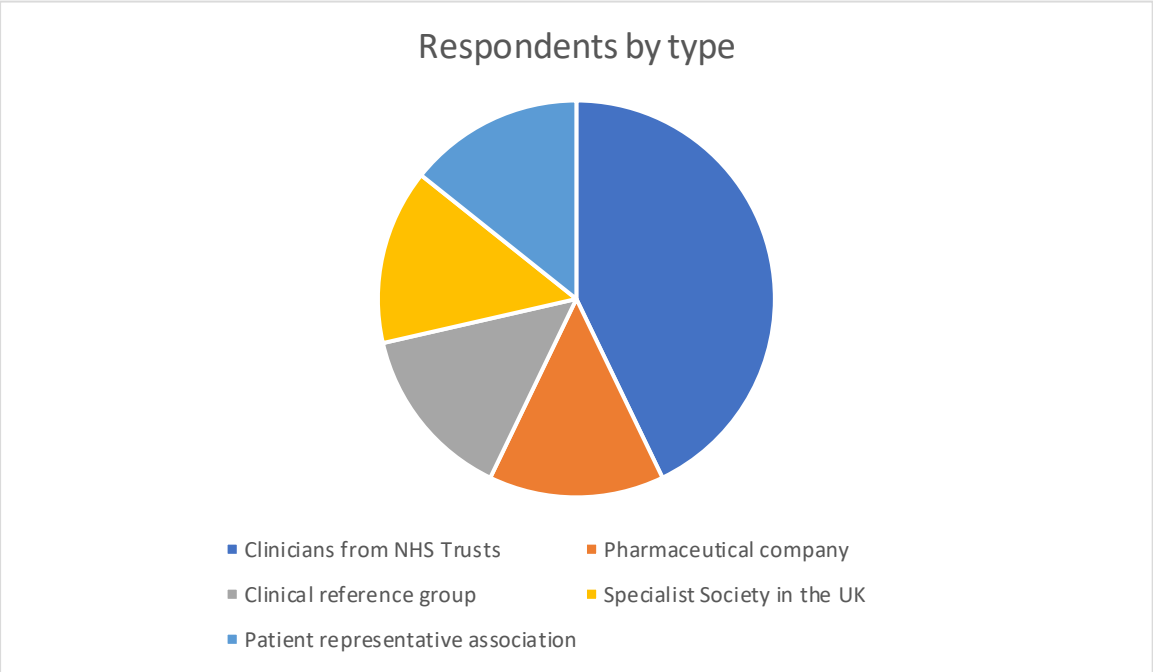
- Do you support the proposition for nebulised liposomal amikacin for the treatment of non-tuberculous mycobacterial pulmonary disease caused by mycobacterium avium complex refractory to current treatment options (adults and post pubescent children) to be available through routine commissioning based on the evidence review and within the criteria set out in this document?
- Do you believe that there is any additional information that we should have considered in the evidence review? If so, please give brief details.
- Do you believe that there are any potential positive and/or negative impacts on patient care as a result of making this treatment option available? If so, please give details.
- Do you have any further comments on the proposition? If Yes, please describe below, in no more than 500 words, any further comments on the proposed changes to the document as part of this initial 'sense check'.
- Please declare any conflict of interests relating to this document or service area.
- Do you support the Equality and Health Inequalities Impact Assessment?

A 13Q assessment has been completed following stakeholder testing.

The Programme of Care has decided that the proposition offers a clear and positive impact on patient treatment, by potentially making a new treatment available which widens the range of treatment options without disrupting current care or limiting patient choice, and therefore further public consultation was not required. This decision has been assured by the Patient Public Voice Advisory Group.

4. Engagement Results

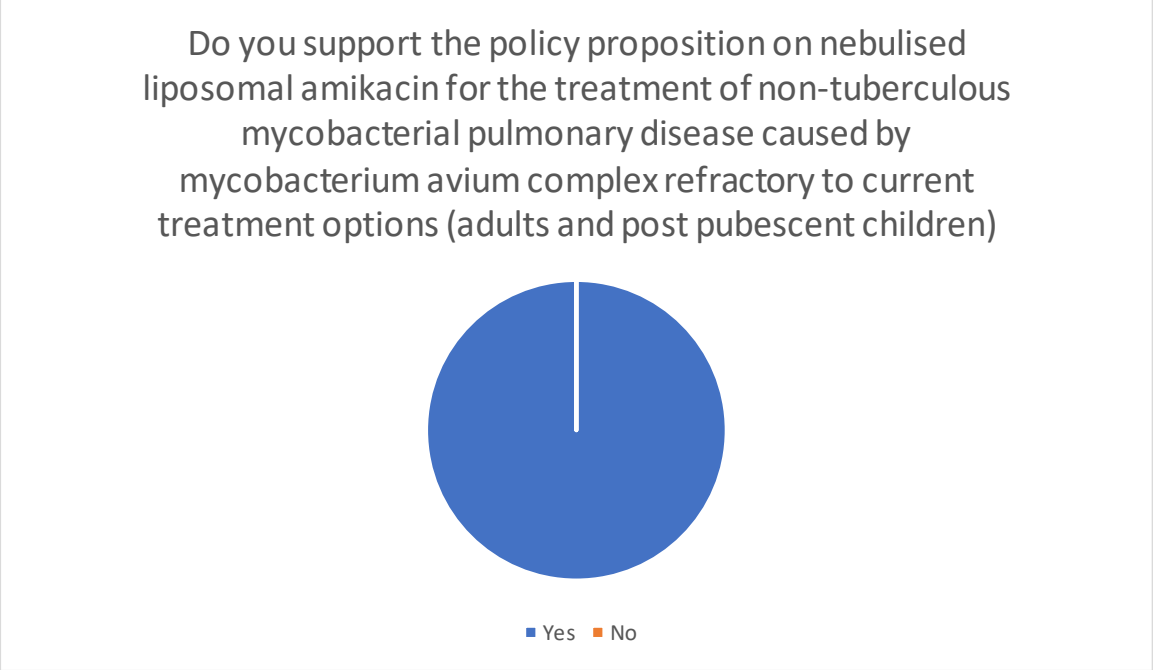
There were 7 responses received: 3 from clinicians representing an NHS organisation treating patients with NTM MAC pulmonary disease, 1 from a pharmaceutical company, 1 from a specialist medical society (British Thoracic Society), 1 from the NTM Patient Care UK and 1 from the Respiratory Clinical Reference Group (CRG)



In line with the 13Q assessment it was deemed that further public consultation was not required.

5. How has feedback been considered?

Responses to engagement have been reviewed by the Policy Working Group and the Internal Medicine PoC. All the respondents supported the policy proposition



The following themes were raised during engagement:

Keys themes in feedback	NHS England Response
Relevant Evidence	
First, we suggest under the 'executive summary and plain language section' the following paragraph: This new policy proposition proposes the use of an aminoglycoside called amikacin to be given through a device producing a fine spray of the drug to be inhaled (nebulised liposomal amikacin). This delivery through inhalation minimises damage to the kidneys and ears (M Shirley 2019). Is replaced with: This new policy proposition proposes the use of a liposomal formulation of the aminoglycoside amikacin to be given through a specifically designed nebuliser device which enables the delivery of the drug as an inhalation solution. This method of administration can provide advantages for drug delivery to the lung tissue, including localised activity and the ability to reach deep into the lungs, enhanced delivery of amikacin to intracellular space (macrophages) in the lung where the infecting NTM reside, and improved pharmacokinetics and tolerability (Chalmers JD et al. Eur Respir Rev. 2021 Jul	Thank you for your comment. This has now been discussed with our Medicines Lead and in order to future proof the policy, the fact that it specifically refers to

20;30(161):210010). Delivery through inhalation minimises damage to the kidneys and ears (M Shirley 2019). Second, the 'links and other policies section' would benefit from the inclusion of: ATS/ERS/ESCMID/IDSA Society Guidelines 2020, which are the authoritative and up-to-date global guidelines referred to by UK clinicians and experts and includes contributions by a panel of experts from leading international respiratory medicine and infectious diseases societies. These Guidelines refer specifically to Nebulised Liposomal Amikacin (referred to as ALIS) as follows: 'In patients with MAC pulmonary disease who have failed therapy after at least 6 months of guideline-based therapy, the guideline recommends the addition of ALIS to the treatment regimen rather than a standard oral regimen, only (strong recommendation, moderate certainty in estimates of effect)'. https://www.idsociety.org/practice-guideline/nontuberculous-mycobacterial-ntm-diseases/ Third, the 'Epidemiology and needs assessment' section refers to the UK NTMPD prevalence rates only. We recommend the incidence rate is added to allow for a clearer understanding of the future patient population. After the current prevalent patient population have received therapy with nebulised liposomal amikacin (in the initial few years from availability of the product), the number of newly eligible patients will be driven by incidence of the disease. Incidence rate has been reported to be approximately ¼ of the prevalence rate (Axson E, et al. Eur J Clin Microbiol Infect Dis. 2018 Sep;37(9):1795-1803). Therefore, the presumed prevalent population that could benefit from Nebulised Liposomal Amikacin is approximately 346 patients, with the data suggesting that the incident patient population eligible for treatment is approximately 87 patients per year. It is worth noting that the above data refers to specific UK data, the estimates for incidence and prevalence do vary depending upon which trial data and parameters are used; identification of an isolate vs. clinically relevant disease, the geographical setting in the world and the sample size. The following paper outlines this view-point and references the data available from the EU and USA. (van Ingen J, et al Expert Review of Respiratory Medicine, 2021 Oct, Vol. 15:1387-1401) https://www.tandfonline.com/doi/full/10.1080/17476348.2021.1987891	nebulised liposomal amikacin is adequate. We clarified though on the document that it needs to be used within its marketing authorisation arrangements. Thank you for your comment; those guidelines have been added on the appropriate section of the policy proposition document. Thank you for your comment; this information will be considered during the integrated impact assessment process. Thank you for the submitted papers. Those have been reviewed by our Public Health Lead. Only those after 2011 considered since that covers the evidence review period. No new evidence was identified.
Nebulised Liposomal Amikacin would offer a clear pathway of care for the patient population. It is the first inhaled antibiotic indicated for the	Thank you for the submitted

treatment of NTM lung infections caused by MAC in adults with limited treatment options who do not have CF (SMPC). Achieving sustained culture conversion allows patients to stop all antibiotic therapy, thereby eliminating the burden of side effects associated with multidrug antibiotic combination therapy (Haworth CS et al. British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). Thorax. 2017 Nov;72(Suppl 2):ii1–64.). Studies reported removing of the infection is associated with reduced lung function decline, reduced progression of lung tissue damage, and improved survival prognosis (Griffith DE et al. Am J Respir Crit Care Med. 2006 Oct 15;174(8):928–34; Jenkins PA et al. Thorax. 2008 Jul 1;63(7):627–34; Pan S-W et al. 2017 Sep 15;65(6):927–34; Ito Y et al. :8; Park HY, Chest. 2016 Dec;150(6):1222–32).	papers. Those have been reviewed by our Public Health Lead. Only those after 2011 considered since that covers the evidence review period. No new evidence was identified.
Better cost-effectiveness analysis	Thank you for your comment; the evidence review has not identified any relevant cost-effectiveness data, but the integrated impact analysis and the financial modelling provide an economic evaluation of the policy proposition.
Impact Assessment	
Positive impact: Availability of a new effective therapeutic option for a patient group (refractory MAC-PD) that is very difficult to manage due to limited other therapeutic options so far. This applies to a relatively large patient cohort (>30% of all MAC-PD patients on active treatment) for whom currently no effective add on therapy exists at the moment Use of conventional / non liposomal amikacin has a high failure rate due to high rate of intolerance, side effects and inability of many elderly patients to technically cope with the nebulizer based drug delivery No real negative impact except that treatment of MAC-PD will become even more nursing intensive if up to 40% of MAC-PD patients end up on this new treatment (Need for audiometry, U+E monitoring and practical support using the proposed treatment) . At the moment NTM-PD patients are often looked after and supported by TB nursing teams who are not officially commissioned or resourced to deal with non MTB work. Therefore the care of NTM-PD puts considerable strain on TB	Thank you for your comment and for your positive remarks. Thank you for your comment; this is considered as part of the normal secondary care monitoring.

services which is not officially recognised in work force planning nationally and locally. Do need to consider the conflicting evidence regarding functional capacity (6MWT) and respiratory function, although the severity of the underlying lung disease may limit these findings Disappointing re the data on improved quality of life measures, mortality and adherence to treatment	Thank you for your comment; the evidence review is based on available data. On the EHIA form the Policy Working Group has expressed the importance of further research and data collection.
The medicine is a new formulation of an older drug that was traditionally given via an intra-muscular or intra-venous (IV) route. More recently it has also been given through a nebuliser, and so is administered directly into the lung (this is with the sterile IV formulation). Most of the feedback received from patients regarding their understanding or expectation of nebulised liposomal amikacin was positive. They regarded it as another much-needed drug to be used in the treatment of MAC. Due to patients' concern about side effects with currently available existing treatments, they viewed the nebulised liposomal amikacin favourably if it had less side effects than those currently in use. Note: We were able to speak to patients who had been treated with IV Amikacin, and IV Amikacin given in a nebuliser, but not to anyone who had used nebulised liposomal Amikacin. The patient experiences below are characteristic of the IV preparation, where there is considerable concern about the drug causing hearing loss; in particular in older people. This effect is reported less often with the inhaled version, however breathing in the drug using the nebuliser might be expected to lead to more local upper airway and lung side effects, such as altered voice, sore throat and cough; and in some cases, as described below, more severe local reactions: Below we have included some comments provided by NTM patients that describe the impact of treatments or reflect current treatment pathways. Patient comment "I was first diagnosed with NTM (MAC) in 2008. Over the years, I have been on & off treatment, mostly the usual 3 antibiotics, with intravenous Amikacin added in just over 3 years ago for a couple of months with oral Linezolid & Clofazimine & I think Metronidazole. Sadly, I have never managed to clear the MAC despite always having been compliant with taking the meds as prescribed. (My nursing background understands how important this is). In March 2021, had just over a week as an inpatient in the respiratory ward as I had picked up a severe secondary chest infection. Whilst there, I had a PICC line inserted for two weeks of Tazocin & recommenced on IV Amikacin. The Amikacin was stopped after around 8 weeks due to a	Thank you for your comments. The patient feedback on the condition and the proposed policy is extremely valuable to NHS England and provides insight on a condition that is very difficult to treat. This information is now recorded on the engagement report.

decrease in hearing levels. I was also recommenced on Ethambutol, Rifampicin & Azithromycin whilst in hospital, the oral antibiotics are still ongoing." The comment below shows where inhaled Amikacin currently sits within a therapeutic strategy (ie after IV Amikacin as well as several other drugs). We presume this might change with the availability of liposomal nebulised amikacin. Patient comment "Following discussions with a regional centre, my local consultant has applied for funding for oral Bedaquiline and if successful, this will be given with Clofazimine, Ethambutol, Isoniazid & nebulised Amikacin in place of the usual three. I am due to see my respiratory nurse next week to commence Amikacin. They are also planning to do a blood test for systemic Amikacin levels & hearing tests as well as an ECG. (I think I am the first person in my town to have the nebulised Amikacin as my nurse said she has never started anyone on it before)." There was some delay in obtaining Bedaquiline and so the patient started nebulised non-liposomal Amikacin "I experienced haemoptysis with the inhaled (non-liposomal) form of amikacin and therefore the treatment was stopped. I am currently on 6 month course of bedaquiline. I am fully supportive of the NHSEI proposal as I feel any opportunity to offer another NTM treatment which may have reduced side effects could benefit NTM patients." Patient comment "I tolerated the two year three-drug treatment and I understand that this is still the currently used method of treatment for MAC victims though many have been less fortunate in their recoveries. At the time of the start of my treatment, and to date, I have been of the belief that this was/is the sole chosen form/combination of treatment. No other choice of treatment was offered to me and the Patient Group members I liaised with, were, to my knowledge, all being treated in the same way. Success/experiences managing this condition, therefore, were varied." Patient comment "The new drug liposomal nebulised amikacin sounds interesting. If it's gentler on your body then it's something I would prefer to try if and when I need treatment." Patient comment "From what I understand about nebulised liposomal amikacin, it is preferable to the non-liposomal formulation of amikacin as it is less harmful and more effective. I have MAC and from October 2018 to June 2020 I was on Azithromycin, Ethambutol and Rifampicin. My sputum tests did become negative (I don't recall now exactly when, but a few months into treatment) and stayed negative. However, having been off the meds from June 2020, in March 2021 I had a follow-up CT scan which looked worse than 6 months previously and a sputum test from April 2021 showed the infection had come back/hadn't gone. So, I went back on the same 3 drugs in June 2021	

which I am still taking with the addition of Isoniazid and Pyridoxine in September 2021. My doctor applied to the drug company at that time explaining my case and to request the nebulised liposomal amikacin for me but she was turned down. So, I had the non-liposomal formulation as IV using a picc line for 5 weeks but my hearing tests showed evidence of ototoxicity, so this was then stopped. Last week I had another hearing test which showed my hearing was the same as at that time, which is being taken as my new baseline, and the plan is to start me on nebulised amikacin (non-liposomal formulation) when the clinic next makes an appointment for me with ongoing hearing monitoring and blood tests. If the nebulised liposomal amikacin is more effective and less harmful, I would certainly think it is worth making available on the NHS and ideally in time for me to use it! The other drugs were effective to a degree in treating the bug but it seems may not have eradicated it, so I would think it in the long term worth considering adding this treatment on the grounds it may prevent further lung damage (I have bronchiectasis as well as alpha 1 antitrypsin deficiency so this is very important too otherwise my risk of getting these infections only increases) as well as reducing the need for long-term drugs which carry their own additional cost." Patient comment "I have Mycobacterium chimaera.I take 1300mg ethambutol, 600mg rifampicin and 500mg azithromycin, i have also had IV amikacin back in July 2020.They tried me on inhaled amikacin & I had a really bad reaction to it & ended up in Resuscitation[in the Emergency Department]. I would never try it again & I wouldn't recommend it to anyone either."	
Positive impacts. There are a number of patients with refractory M.avium pulmonary disease where this treatment has the potential to improve quality of life and clinical outcome. It may prevent hospital admissions. It would be a significant addition to the therapeutic options for patients with refractory pulmonary mycobacterium avium complex infection, and can be anticipated to provide clinical benefit to this group	Thank you for your positive comment.
At present, there is no funded licensed treatment option for patients who are failing on standard therapy for pulmonary MAC disease. Patients are often escalated onto combinations of antibiotics associated with high risk of toxicity and side-effects, with lack of good quality clinical studies to support treatment outcomes with secondary antibiotics. Nebulised liposomal amikacin is formulated to be delivered by nebulisation. The existing intravenous preparation of amikacin is not formulated or licensed for delivery by inhalation. Nebulised liposomal amikacin therefore offers a salvage therapy for patients with pulmonary MAC disease with evidence from recent clinical studies (used to support the evidence review for the document) to support both its use and safety.	Thank you for your positive comment.
NTM Patient Care UK agrees that the Patient Impact Summary presents a true reflection of the patient and carers lived experience of this condition. However, we would also like to add; MAC is a chronic illness that causes marked respiratory symptoms such as cough, sputum	Thank you for your input. The Patient Impact form has been updated to

production, and breathlessness; as well as long-term fatigue and malaise. This results in low mood, and impaired quality of life. People with MAC often report that they are very limited by the condition - whether this is because they are coughing for large amounts of the day (often to the point of retching to bring up sticky sputum), or because their chronic sputum production feels socially-disabling and discourages them from going outside their home. In addition, a frequent need for antibiotics in many cases means that they become accepting of symptoms which others would not. For example, coughing small amounts of blood is not unusual and only leads to starting home antibiotics once the symptom persists for more than a few days or is excessive. In other words, patients "carry on" assuming that this is what is to be expected in this condition. This is also not helped by the constant fatigue that patients will feel. It is usually not so much that they have to remain in bed, but enough to limit what they can do. The small number of studies currently performed on measures of depression indicate that inevitably people with MAC lung disease have a low mood and commonly report symptoms of depression. Some of the patients that contact NTM Patient Care UK have been on medication for many years and their NTM/MAC infection has had very significant impact on their quality of life. The long-term health issues can often in turn impact on their family and carers as well. The, often, constant coughing associated with MAC/NTM pulmonary disease can cause issues with sleep deprivation which can potentially be associated with fatigue and depression. The quote below from an NTM patient that is involved with NTM Patient Care UK clearly demonstrates this impact on all aspects of their life; Patient comment “I have been treated with oral meds for 2 years now since my diagnosis and I am still testing positive. The quality of my life has now diminished considerably and, as I will be 77 in May, I am unable to enjoy an important last few years of my life (I am coping and existing, not living).Having been a very active person previously, enjoying my family, my retirement and travel this is hard for me and the Impact on my family is huge.	include those comments.
Yes. There should be mechanisms to ensure that access does not differ in different regions or population groups. It is also important to ensure that patients living outside of the catchment area of major treatment centres have a clear pathway to access this treatment.	Thank you for your comment. The secondary care centres delivering the treatment are responsible for ensuring homecare arrangements. This will reduce the need for hospital attendances. The publication of the policy will assist with raising

	awareness to the public and the clinicians
Current Patient Pathway	
The licencing of liposomal amikacin and subsequent increased control of pulmonary MAC, may reduce the need for longer term therapy with other antibiotics with their attendant side effects. Such side effects can include a risk of visual loss due to ethambutol - which appears related to cumulative dose.	Thank you for your positive comment.
I welcome the approval of neb amikacin for the treatment of NTM in this difficult to treat group & think it will be a very valuable addition to our treatment options	Thank you for the positive comment.
Potential impact on equality and health inequalities	
All 7 responders supported the Equality and Health Inequalities impact assessment	Nil required.
Changes/addition to policy	
The proposed implementation criteria for the use of nebulised liposomal amikacin state that this would be provided alongside guideline-based therapy (GBT) in cases where patients have not culture converted following six months of GBT. However the proposal does not explicitly define GBT. A significant proportion of patients with pulmonary Mycobacterium avium disease do not tolerate one or more of the drugs included in the standard three-drug GBT of a Macrolide, Ethambutol and Rifampicin - and BTS guidelines do not provide recommendations to alternatives to this standard. In the CONVERT study (Griffith, AJRCCM 2018), which is probably the main evidence-base for the NHSE recommendation, only around two-thirds of patients at enrolment were on standard GBT as defined by BTS guidelines. Hence it is important to clarify whether nebulised liposomal amikacin will only be available for patients who have tolerated six-months of "standard" GBT and not culture converted, or could this be a treatment option also for those on non-standard regimens due to eg drug intolerance, as in the CONVERT study? Would more flexibility be possible to enable the latter group to access Arikayce? This is important to recognise now as otherwise a situation could arise where patients who might benefit from the drug are inadvertently barred from using it because of a technical issue relating to treatment definitions of what drugs they need to be on to be defined as eligible for Arikayce. One way of resolving this might be that patients (with refractory MAC on a non-standard drug regimen and being considered for Arikayce) are discussed at a specialist MDT with expertise in NTM management prior to the drug being used. Furthermore, whilst we expect that this drug would be prescribed following discussion with specialist NTM services, the precise arrangements for this are likely to vary around the country, but would also involve an MDT discussion.	GBT covers alterations in medication as required, so the broader term of GBT is implemented. The prior approval form is not restrictive on that point. The issue of the MDT has been considered and it was felt that 'clinicians with significant experience in managing NTM MAC pulmonary disease' would be less restrictive and easier to implement.
Inclusion criteria – has the committee considered inclusion for patients who may have received less than 6 months of conventional guideline based therapy due to inability to tolerate the oral antibiotic combination used in guideline based therapy, or pre-existing allergy to a number of antibiotics that are regarded as conventional guideline based therapy?	Thank you for your comment. This has been reviewed by our Medicines Lead. The policy proposition is

	based on available evidence (refractory to GBT disease). For cases of macrolide resistance, the GBT has relevant treatment options. Unfortunately, nebulised liposomal amikacin cannot be used without GBT based on the current evidence. This can be revisited if in the future there are studies looking nebulised liposomal amikacin as a monotherapy.

6. Has anything been changed in the policy proposition as a result of the stakeholder testing and consultation?

The following change(s) based on the engagement responses has (have) been made to the policy proposition:

- The policy document has been updated to include the ATS/ERS/ESCMID/IDSA Clinical Practice Guideline 2020, from Daley et al 2020
- The policy document has been updated to state that the nebulised liposomal amikacin will be used within the marketing authorisation arrangements
- The patient impact form has been updated to include the impact of recurrent and persistent cough to the social life, mental health and sleep patterns of the patients and their carers.

7. Are there any remaining concerns outstanding following the consultation that have not been resolved in the final policy proposition?

Nil.