National Institute for Health and Clinical Excellence

Multiple Technology Appraisal (MTA)

Colistimethate sodium powder and tobramycin powder for inhalation for the treatment of pseudomonas lung infection in cystic fibrosis

Response to consultee and commentator comments on the second draft scope

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background information	Association of Respiratory Nurse Specialists	Accurate	Comment noted. No changes to the scope required
	British Thoracic Society	yes this is satisfactory	Comment noted. No changes to the scope required
	Forest Laboratories UK Ltd.	There were over 8,500 people with cystic fibrosis in the UK. Each week, five babies are born with Cystic Fibrosis in UK. (Source: NHS choices)	Comment noted. The scope has been amended accordingly.
	NHSQIS	The history of the use of antibiotics in Cystic Fibrosis therapy via the inhaled route is long and complex. On a general basis, it is relatively inconvenient for patients to take nebulised antibiotics as this is a major intrusion into their daily lives. The reality is that the vast majority of patients as they get older have to take such therapies as they get older have to take such therapies in order to improve their lung function. The problem with the agent Colistin is that it is very controversial. It has the capacity to reduce the bacterial burden in Cystic Fibrosis but it has not been shown to improve short term lung function. The key advantage of this agent is that it does not seem to induce resistance in the manner that other agents do and this is it's key therapeutic advantage over other nebulised treatments.	Comment noted. The scope is only intended to provide a general overview of the condition and the technologies of interest. Factors such as those described will be captured within the framework of a full appraisal. No changes to the scope required.

Section	Consultees	Comments	Action
	Novartis	The background section is not entirely accurate with regard to the management of Pseudomonas aeruginosa infection in patients with cystic fibrosis. Antibiotics are not just used to "suppress bacterial growth". Rather, the aims of treatment are broadly three-fold:- 1. Erradication of intermittent acute Pseudomonas aeruginosa infections 2. Suppression of Pseudomonas aeruginosa infection (with long-term therapy) in patients who have become chronically infected (i.e. colonised patients). 3. Treatment of acute exacerbations in patients chronically infected with Pseudomonas aeruginosa (usually with i.v. antibiotic therapy).	Comment noted. The scope has been amended accordingly.
	Profile Pharma	The background of the condition of cystic fibrosis is appropriate.	Comment noted. No changes to the scope required
	Royal College of Nursing	This information seems accurate and appropriate. It would be helpful to date figures regarding UK deaths of cystic fibrosis (CF), 2005 is quoted as 97 deaths. It is considered that there were about 100 deaths in 2009 according to the UK CF database (Port CF). Might be good to get more up to date statistics.	Comment noted. The scope has been amended accordingly.
	Royal College of Paediatrics and Child Health	We note there is still confusion about the terms colonistation and infection. There is no such thing as colonisation of the CF airway. Bacteria present are always harmful. The CF airway should be considered as either intermittently infected or chronically infected. Management of CF airways infection requires aggressive treatment of intermittent infection to delay or ideally prevent chronic infection. Once chronic infection with mucoid Ps aeruginosa has occurred, it is impossible to clear. The aim of treatment then is to suppress the infection in a way that minimises lung damage, with the minimum of side effects. We think that the information should include the fact that most children with CF in the UK are currently given nebulised colistin for first isolation of Pseudomonas and when chronically colonised, and that comparatively few are given nebulised tobramicin because of the cost.	Comment noted. The scope has been amended accordingly. Comments noted. The scope is only intended to provide a general overview of the way Pseudomonas aeruginosa lung infection is managed. No changes have been made to the scope

Section	Consultees	Comments	Action
	Royal College of Pathologists	The background information fails to properly distinguish between 'Early P. aeruginosa Colonisation' in which inhaled antibiotics are given as short courses in order to eradicate (i.e. achieve microbiological cure) the organism and 'Chronic P. aeruginosa Infection' in which inhaled antibiotics are given on a long-term basis to control rather than cure the infection. The information should make it much clearer that there are two distinct approaches to therapy. This then makes the interpretation of the different outcome measures somewhat easier for readers to understand.	Comment noted. The background of the scope has been amended accordingly. However, the scope is only intended to provide a general overview of the way Pseudomonas aeruginosa lung infection is managed.
The technology/ intervention	Association of Respiratory Nurse Specialists	Yes	Comment noted. No changes to the scope required
	British Thoracic Society	yes	Comment noted. No changes to the scope required
	Forest Laboratories	Colistimethate sodium dry powder market authorisation application has been made to the EMA [redacted]	Comment noted. No changes to the scope required
	Novartis	The descriptions of the two technologies appear to be accurate. However, it is important to note that the tobramycin dry power (TOBI Podhaler) is formulated using new PulmoSphere technology. This technology has been specifically designed to offer good dispersibility and lung deposition, thus helping to overcome some of the challenges that can occur when using traditional technologies for formulating a dry powder antibiotic for inhalation.	Comment noted. The scope is intended to provide a brief description of the technologies. No changes have been made to the scope.

Section	Consultees	Comments	Action
	Profile Pharma	The information on the technologies is not adequate. There is no information in the public domain on the particle size characteristics of the drug delivered for both devices. Efficacy for these inhaled antibiotics requires that they are delivered to the correct part of the lung. Without knowledge of the lung deposition by radio-imaging or of the particle size of the inhaled particles little or no comment can be made about the likely efficacy of the treatment. No comparative depositional data have been provided comparing these tecnologies and current nebuliser technology. Little information is supplied over and above the fact that the dry powder formualtions will be inhaled by patients over the age of six years. Acceptable lung functon criteris to operate the Turbospin and Podhaler have not been supplied. The dose to be administered, number of capsules the dose will require, average time taken to administer a dose and the number of doses per day are important considerations when considering advantages over the comparators.	Comment noted. The scope is intended to provide a brief description of the technologies. The details of how the technologies should be used will be captured within the framework of a full appraisal and guidance will be issued in accordance with the licensed indications of the technologies. No changes have been made to the scope.
	Royal College of Nursing	Description of technologies is brief, with little detail of the device to be used or number of treatments per day required. Yes - currently colistin is first line choice of nebulised medication but some patients will be intolerant of this (get a wheezy or tight chest) and healthcare professionals would then try tobramycin via nebuliser. Patients who currently nebulise antibiotics will be keen to try these new devices, as they will be much quicker and easier for them to use	Comment noted. The scope is intended to provide a brief description of the technologies. The details of how the technologies should be used will be captured within the framework of a full appraisal. No changes have been made to the scope
	Royal College of Paediatrics and Child Health	Yes However, there needs to be more discussion of patient preference for dry powder inhalation, in terms of its speed, and the likelihood of better compliance.	Comment noted. The scope is intended to provide a brief description of the technologies. Details about patient preference will be captured within the framework of a full appraisal. No changes have been made to the scope

Section	Consultees	Comments	Action
	Royal College of Pathologists	The description of the technology would benefit from pointing out what is currently used in clinical practice (e.g. nebulisation devices) and what advantages the new dry powder formulations could bring (e.g. portability, faster speed of drug administration, better compliance, etc) in comparison.	Comment noted. The scope specifies that current treatment options include the use of inhaled antibiotics (such as nebulised colistimethate sodium or tobramycin). The scope is intended to provide a brief description of the technologies. Details of advantages to patients will be captured within the framework of a full appraisal.
Population	Association of Respiratory Nurse Specialists	Population group accurate	Comment noted. No changes to the scope required
	British Thoracic Society	population size to be studied is unclear	Comment noted. Full details of the population will be captured within the framework of a full appraisal. No changes have been made to the scope.
	Forest Laboratories	A more appropiate definition is patients aged 6 years and over with cystic fibrosis and Pseudomonas aeruginosa pulmonary infection.	Comment noted. The definition of the population in the scope has been changed to “People aged 6 years and over with cystic fibrosis and chronic Pseudomonas aeruginosa pulmonary infection”.

Section	Consultees	Comments	Action
	Novartis	Splitting the population into those with intermittent and chronic infection may be problematic for this proposed Multiple Technology Appraisal (MTA). As stated in the section of the scope on "the technologies", the CHMP positive opinion for TOBI Podhaler covers "suppressive therapy of chronic pulmonary infection due to Pseudomonas aeruginosa in adults and children aged 6 years and older with cystic fibrosis". Our understanding is that Colobreathe studies have included different patient populations. If this leads to an indication for Colobreathe that is different to the indication for TOBI Podhaler, there may be an issue regarding the existence of a common population for an MTA.	Comment noted. The definition of the population in the scope has been changed to “People aged 6 years and over with cystic fibrosis and chronic Pseudomonas aeruginosa pulmonary infection”.
	Profile Pharma	The "Technologies" section indicates that both dry powder products can be used in the management of chronic infections, yet the "population" section addresses patients aged 6 years and over with intermittent and chronic Pseudomonas aeruginosa infections. From the limited data in the public domain no work appears to have been undertaken investigating efficacy in early intermittent infection. All abstracts relate to chronically infected patients.	Comment noted. The definition of the population in the scope has been changed to “People aged 6 years and over with cystic fibrosis and chronic Pseudomonas aeruginosa pulmonary infection”.
	Royal College of Nursing	Yes	Comment noted. No changes to the scope required
	Royal College of Paediatrics and Child Health	Yes We think that children under 12 years should probably be considered separately from adolescents and adults. We note that children under 6 years would not be able to use a dry powder inhaler.	Comment noted. Subgroup by number of prior therapies has been identified as the only subgroup for whom the technologies may be particularly clinically or cost effective and in accordance with the Methods Guide. In addition, guidance will only be issued in accordance with the licensed indications of the technologies.

Section	Consultees	Comments	Action
	Royal College of Pathologists	The population is poorly and inaccurately defined. The outcome measures talk about 'Intermittent infection' and 'Chronic infection' but offer no robust definition of either of these. There are published, validated clinical definitions of both of these (Leeds Criteria) available. The European Cystic Fibrosis Society has developed a Clinical Trials Network. Part of its function is to agree definitions for trial enrolment and this includes those to be enrolled into trials of inhaled therapy for early eradication and chronic infection. NICE should not be looking to re-invent the wheel. By applying standard definitions to all future clinical trials it will allow greater comparison of their results. I would suggest that NICE consult with the ECFS CTN regarding their definitions. The term 'Intermittent' is also misleading. Many of the individuals who could be enrolled into the study may never have grown P. aeruginosa (defined as 'Never' by Leeds Criteria) or have grown it more than 12 months ago (defined as 'Free' by Leeds Criteria). These two groups should be included in those suitable for entry into a trial of early eradication therapy	Comment noted. The background of the scope has been amended, however it is only intended to provide a brief overview of the condition and the technologies of interest. Full details will be captured within the framework of the appraisal.
Comparators	Association of Respiratory Nurse Specialists	Colistimethate sodium & tobramycin for nebulised inhalation are the current standard treatment available on NHS - which can be time consuming. Currently no other alternative, although inhalation may be the best alternative , as less time required to administer & one would assume less equipment required & medication to be supplied & stored.	Comment noted. No changes to the scope required
	British Thoracic Society	yes these 2 antibiotics are the commonest used in inhaled/nebulised form in CF Need to compare against current practice of nebulised colo and tobra. if just the 2 powders are compared, this will not give the answers needed	Comment noted. The comparators in the scope include antibiotics for nebulised inhalation, including colistimethate sodium powder for nebulised inhalation and tobramycin for nebulised inhalation.

Section	Consultees	Comments	Action
	Forest Laboratories	The most commonly used treatments are nebulised colistimethate sodium and tobramycin for nebulisation (TOBI). However, TOBI is the only treatment with this specific indication -"chronic pulmonary infection due to Pseudomonas aeruginosa in cystic fibrosis (CF) patients aged 6 years and older". And it is the only product with good quality clinical evidence to provide a strong basis for comparison .Colistimethate sodium for nebulisation is suggested as as a comparator, but TOBI is the most appropriate comparator for the two new products being appraised..	Comment noted. The comparators in the scope include: Colistimethate sodium powder and tobramycin dry powder compared with each other, antibiotics for nebulised inhalation, including colistimethate sodium for nebulised inhalation and tobramycin for nebulised inhalation.
	Novartis	The nebulised treatments currently available in the UK are two proprietary formulations of colistimethate sodium (Colomycin and Promixin), two proprietary formulations of tobramycin (TOBI and Bramitob) and aztreonam (Cayston). The latter (indicated for the suppressive therapy of chronic Psuedomonas aeruginosa infection) is not named in the scope, either as an intervention or a comparator, which is an obvious omission.	Comment noted. The comparators in the scope now include: Colistimethate sodium and tobramycin dry powder compared with each other, antibiotics for nebulised inhalation, including colistimethate sodium for nebulised inhalation and tobramycin for nebulised inhalation. Therefore the scope does rule out other nebulised treatments being included as comparators in the appraisal if the evidence is available.

Section	Consultees	Comments	Action
	Profile Pharma	No. The dry powder colistimethate sodium (Colobreathe) clinical trials should have compared Colobreathe to the recognised first line inhaled antibiotic therapy, which is nebulised colistimethate sodium solution, as per the recommendations of the report of the UK Cystic Fibrosis Trust Antibiotic Working Group, entitled Antibiotic Treatment for Cystic Fibrosis published September 2002 and May 2009 (see attached to covering e-mail). This study compared a continuous antibiotic therapy (Colobreathe) with a cyclical therapy month on month off (tobramycin solution for inhalation). The comparators listed are: Forest Laboratories UK (colistimethate sodium powder for inhalation). This has no MA and is the subjects of this assessment and therefore should be removed. The comparator needs to include colistimethate sodium 1 to 2 million IU in solution manufactured by Forest Laboratories UK. Novartis (TOBI podhaler). This has no MA and therefore should be removed. The comparator needs to include TOBI 300 mg in 5 mL of solution. Manufactured by Novartis. In addition, there is now a new approved inhaled antibiotic aztreonam (75 mg), (Cayston, Gilead Pharma), for the treatment of pseudomonas aeuriginosa in cystic fibrosis. Comparison with this product should also be considered. The information in the public domain indicates that the studies conducted used older jet nebulisers and not modern nebulisers that have been shown to be more efficient and reduce treatment times.	Comment noted. The comparators in the scope now include: Colistimethate sodium and tobramycin dry powder compared with each other, antibiotics for nebulised inhalation, including colistimethate sodium for nebulised inhalation and tobramycin for nebulised inhalation. Therefore the scope does not rule out other nebulised treatments being included as comparators in the appraisal if the evidence is available.

Section	Consultees	Comments	Action
	Profile Pharma	Little information on the comparative efficacy of the two treatments are available. The data in the public domain does not provide information on the comparative lung doses of the different methods of delivery. It is estimated that nebulised systems deliver approximately 25 to 50 mg to the lung of currently licensed nebulised antibiotics. The dry powder inhalers have a loaded dose of 112 and 125 mg. There is no information on the extent or the fate of the additional 50 to 100 mg of drug. The "wasted" non respirable fraction of the drug is in the body and may, in the case of tobramycin, be absorbed from the gastro-intestinal tract. The non-respirable drug may cause safety and resistance issues. The affect of any drug swallowed into the GI tract on gut flora does need to be considered.	Comment noted. The scope is intended to provide a brief overview of the condition and the technologies of interest. Details such as these will be captured within the framework of the appraisal.
	Royal College of Nursing	Colistin or tobramycin have been nebulised via a compressor machine for many years as an anti-pseudomonal treatment for CF. They have never before been available as a dry powder. Gentamicin and tazocin is occasionally used for a minority of patients. Colistin is normally used as first line treatment due to cost, but for those who are intolerant of Colistin or who do not respond to it, tobramycin is an option.	Comment noted. The comparators in the scope now include: Colistimethate sodium and tobramycin dry powder compared with each other, antibiotics for nebulised inhalation, including colistimethate sodium for nebulised inhalation and tobramycin for nebulised inhalation. Therefore the scope does rule out other nebulised treatments being included as comparators in the appraisal if the evidence is available.
	Royal College of Paediatrics and Child Health	Yes	Comment noted. No changes to the scope required

Section	Consultees	Comments	Action
	Royal College of Pathologists	Both these drugs (colistin and tobramycin) are the most widely used inhaled antibiotics currently used in the NHS. These devices will be offering an alternative method of delivery. Whilst there are a number of other antibiotics entering the market place (e.g. aztreonam lysine) or nearing entry (e.g. liposomal amikacin, some quinolones) none of these are established (or are likely to be established in the short-to-medium term (i.e. over the next five years)	Comment noted. The comparators in the scope now include: Colistimethate sodium and tobramycin dry powder compared with each other, antibiotics for nebulised inhalation, including colistimethate sodium for nebulised inhalation and tobramycin for nebulised inhalation. Therefore the scope does not rule out other nebulised treatments being included as comparators in the appraisal if the evidence is available.
Outcomes	Association of Respiratory Nurse Specialists	Yes	Comment noted. No changes to the scope required
	British Thoracic Society	Clearly this needs to be adequately powered to detect any real differences. For example, what measures of lung function are to be used, how often etc. For elimination of infection, is this based on sputum culture, cough swab (and is there an agreed way of taking them) and /or serology. Patient preference does not seem to be recorded but shoudl be included - perhaps it is under health related quality of life.	Comment noted. No changes to the scope required Patient preference is a component of the health related quality of life outcome

Section	Consultees	Comments	Action
	Forest Laboratories	For both intermittent and chronic Pseudomonas aeruginosa infection along with outcome measures already outlined in the 'draft scope', the following should be added: 1. antimicrobial sensitivity of respiratory tract	The outcome “antimicrobial sensitivity of respiratory tract” will fall within the general outcome of “rate and extent of microbial response”.
	NHSQIS	Under "outcomes" I would couple with "reduction in hospital admissions" with "reduction in infective exacerbations" - because not all exacerbations lead to hospital admission..	Reduction in hospital admissions will be included in economic evaluation component of the appraisal if appropriate. Reduction in infective exacerbations will fall within the general outcome of “frequency and severity of acute exacerbations”.

Section	Consultees	Comments	Action
	Novartis	Our comments are focussed on the outcomes for chronic Pseudomonas infection in accordance with the anticipated licence indication wording for TOBI Podhaler:- 1. Lung function - this is an appropriate outcome measure in this population. 2. Respiratory symptoms - this is an appropriate outcome measure in this population 3. Frequency and time to acute exacerbations - these are appropriate outcome measures in this population 4. Body mass index - it is not clear why this outcome measure has been included in the scope. Cystic fibrosis is a multisystem condition that is managed by mutlidisciplinary healthcare teams. Body mass index is often lower in cystic fibrosis patients than in the general population and may be an indicator of general health. However, it is debatable whether it is an appropriate outcome measure when considering the effects of antibiotic treatment in isolation. Our suggestion would be to remove this from the scope. 5. Health-related quality of life - this is an appropriate outcome measure in this population. 6. Adverse events of treatment (including rate of resistance to antibiotic treatment) - these are appropriate outcome measures in this population. Outcome measures that are not included for patients with chronic Pseudomonas aeruginosa infection that should be considered for inclusion are as follows:- 1. Treatment satisfaction - for example, patient-reported satisfaction with a dry-powder inhaler treatment vs. a nebulised treatment. 2. Sputum density of Pseudomonas aeruginosa - this is an outcome measure that is frequently included in clinical trials of cystic fibrosis antibiotics. 3. Hospitalisation for acute exacerbations - this was included in the original Colobreathe scope but does not appear in this version. However, hospitalisation for acute exacerbations remains a relevant outcome measure in CF.	Comments noted. The outcome “Body mass index” has now been excluded from the scope. Treatment satisfaction and patient preference are components of the health related quality of life outcome. “Rate and extent of microbial response (for example sputum density of Pseudomonas aeruginosa)” is in the scope. Reduction in hospital admissions will be included in the economic evaluation component of the appraisal if appropriate

Section	Consultees	Comments	Action
	Profile Pharma	An important consideration is the development of resistance by the bacteria to the two antibiotics. In 2003 the resistance to tobramcyin was evaluated at 10.1% and the resistance to colistimethate sodium was evalauted to be 3.1% (Pitt et al 2003). This study used 417 isolates. A more recent paper studying the resistance of 1844 isolates of P. aeruginosa obtained from 22 CF patients receiving alternate therapy with inhaled tobramycin and colistin, estimated the resistance to tobramycin to be 27.5%. In contrast, all isolates were susceptible to colistimethate sodium (Valenza 2010). The propensity for resistance has to be considered when considering the comparative benefits of the formulations. It is not clear how resistance will be assessed. Resistance is a global as well as local issues and must take into account trends over time. (See above)	Comment noted. The outcome adverse events of treatment (including rate of resistance to antibiotic treatment) has now been included in the scope.
	Profile Pharma	Clarity is required regarding how lung function will be assessed. It is not apparent if both the new technologies in this appraisal have been compared with modern nebulisers in terms of the impact on reducing treatment burden for patients with CF e.g.modern nebulisers can deliver a dose of colistimethate sodium in 3 to 4.5 minutes (e-flow rapid nebuliser and I-neb nebuliser) (Colistimethate sodium nebuliser solution SmPCs).	Comment noted. The scope is only intended to provide a general overview of the condition and the technologies of interest. Factors such as those described will be captured within the framework of a full appraisal. No changes made to the scope.
	Profile Pharma	Patient reported outcomes need to be measured against appropriate modern comparative nebulised therapy as they are portable, quicker and less noisy versus older mains driven nebulisers.	Patient reported outcomes such as treatment satisfaction and patient preference are components of the health related quality of life outcome
	Profile Pharma	In addition, objective measurement of compliance and adherence to inhalation therapy are vital with any new technology (McNamara et al Journal of Cystic Fibrosis 2009, 8 259-263 see attached covering e-mail).	Adherence to treatment will be included in the economic evaluation component of the appraisal if appropriate.

Section	Consultees	Comments	Action
	Profile Pharma	Additional endpoints to consider: Sputum volume might be worth assessing. Occurrence of other infections (non PA), development of resistance to the antibiotics used by non-target bacteria.	The outcome “sputum volume”” will fall within the general outcome of “Rate and extent of microbial response (for example sputum density of Pseudomonas aeruginosa)
	Profile Pharma	In relation to potential toxic effects, particularly in relation to the relative doses, the incidence of hyperreactivity and cough following Colobreathe and Tobi Podhaler administration, needs to be considered in comparison to nebulised colistimethate sodium and tobramycin	These outcomes will fall within the general outcome “adverse events of treatment (including rate of resistance to antibiotic treatment).
	Royal College of Nursing	We consider that "adherence to treatment" should be added as another outcome measure, as there could be potentially quite a dramatic improvement in adherence for patients using this device.	Comment noted. Adherence to treatment will be included in the economic evaluation component of the appraisal if appropriate
	Royal College of Paediatrics and Child Health	Yes This mentions "eradication of the organism". We recommend adding another bullet point: "reduction in colony count".	Comment noted. Reduction in colony count will be incorporated within the general outcome “Rate and extent of microbial response (for example sputum density of *Pseudomonas aeruginosa*) now included in the scope.

Section	Consultees	Comments	Action
	Royal College of Pathologists	There is no clear definition of 'successful eradication'. It is also not clear whether the trial will include some element of molecular detection (e.g. PCR) or insist that more invasive procedures (e.g. induced sputum, broncho-alveolar lavage) are done to exclude the continued presence of P. aeruginosa, particularly in those patients unable to expectorate. Some recent studies of early eradication therapies have used 'median time to recurrence' (i.e. 'failure') rather than a time measurement relating to negative cultures (i.e. 'success'). Whilst median time to recurrence is an objective measure that allows clinically relevant comparisons to be made, the timescale for this is indeterminate and may be several years, given that the typical success rate of early eradication regimens is currently about 80%. One may then look at the time for the first quartile to recur or indeed look at the recurrence rate at a fixed time point (e.g. 1 year, 2 years) but this will require statistical advice to determine the required number of participants to deliver sufficient power to the study.	Comment noted. Reduction in colony count, including eradication and time to recurrence will be incorporated within the general outcome "Rate and extent of microbial response (for example sputum density of *Pseudomonas aeruginosa*) now included in the scope.
Economic analysis	Association of Respiratory Nurse Specialists	No idea of the expected costs of inhaled medication, however the cost benefit analysis should take into consideration the time spent on administering treatments, ie. will take up to 5 minutes to administer rather than 20 minutes (2 -3 times daily), remembering that this is not done in isolation but amongst multiple other treatments that people with Cystic Fibrosis have to complete on a day to day basis when well, let alone when they have an exacerbation	Comment noted. The scope is intended to provide a brief overview of the condition and technologies, full details will be captured within the framework of the appraisal. No changes to the scope required.
	British Thoracic Society	Quality adjusted life year may be difficult to assess in CF	Comment noted. The scope is intended to provide a brief overview of the condition and technologies, full details and exploration of quality of life with CF will be captured within the framework of the appraisal. No changes to the scope required.

Section	Consultees	Comments	Action
	Profile Pharma	The time horizon is not specified. the development of resistance does need a long time horizon.	Comment noted. The scope is intended to provide a brief overview of the condition and technologies, full details and exploration of the time horizon will be captured within the framework of the appraisal. No changes to the scope required.
	Royal College of Nursing	There is no mention of cost of the these new technologies. TOBI (tobramycin preservative-free) has historically been much more expensive than colistin.	Comment noted. The scope is intended to provide a brief overview of the condition and technologies, full details and exploration of the total costs of the technologies will be captured within the framework of the appraisal. No changes to the scope required.
	Royal College of Pathologists	This is alluded to above. A shorter trial will require a larger number of subjects to be enrolled to generate meaningful comparisons, particularly if aiming to show superiority of one product over another. This will obviously impact on the funding required.	Comment noted. No changes to the scope required.
Equality and Diversity	Association of Respiratory Nurse Specialists	Pricing. Budget holders across different PCT/GP fund holders, will often decline to prescribe expensive medications. No requirement for expensive equipment to nebuliser treatments - compressors, administartion sets, syringes, needles & sharps boxes Potentially easier to use & less maintenance. More portable, smaller quantity of medication required for supply & storage	Comment noted. The scope is intended to provide a brief overview of the condition and technologies, full details such as those described will be captured within the framework of the appraisal. No changes to the scope required.

Section	Consultees	Comments	Action
	British Thoracic Society	no concerns here	Comment noted. No changes to the scope required.
	Royal College of Nursing	In Scotland, adult CF care is funded by the National Services Division, which is a Scottish Executive Government department. This money is ring fenced and used solely for the care of CF patients. As a result, all adult patients in Scotland are treated in the same way and are not affected by "postcode lotteries". The National Service Division do require national and standardised protocols for antibiotic treatment, and would currently see nebulised colistin as first line therapy to be followed by TOBI should it be necessary. All adult patients in Scotland with CF are treated at one of the three main specialist centres as well as being regularly reviewed at a district hospital as necessary.	Comment noted. No changes to the scope required.
	Royal College of Pathologists	The devices are small, portable and easy to use. They should pose no problems to study participants unless they suffer from a disability that impairs their ability to manipulate the device effectively.	Comment noted. The scope has been amended accordingly.
Other considerations	Association of Respiratory Nurse Specialists	If people have difficulty manipulating inhaler device, they also tend to have difficulty in putting nebuliser together & cleaning equipment as well. For those living in areas affected by frequent disruptions to electricity supply	Comment noted. The scope has been amended accordingly and consideration will be given to the ability of people with disabilities in manipulation of the devices.
	British Thoracic Society	The delivery device will speed up treatment and potentially improve compliance. .	Comment noted. Adherence to treatment will be included in the economic evaluation component of the appraisal if appropriate

Section	Consultees	Comments	Action
	Profile Pharma	The appropriateness of comparing Colobreathe to nebulised tobramycin as opposed to nebulised colistimethate sodium. Nebulised tobramycin is administered for chronically colonised pseudomonas Cystic Fibrosis patients on a 28 day cycle, with 28 days on and 28 days off. Nebulised colistimethate sodium is used on a continuous basis. If Colobreathe uses the same treatment regimen then this is an inappropriate comparator.	Comment noted. The technologies will be evaluated in accordance with their recommended treatment duration(s) specified in their licence indications.
	Royal College of Pathologists	The current proposal is likely to be very challenging for trial organisers and staff in CF Centres, particularly as it suggests that both early eradication and chronic infection comparative studies will be conducted with two drugs with at least two different methods of delivery (dry powder and conventional therapy). It is not clear if the intention is to perform these simultaneously or in a particular order of priority.	Comment noted. The comparators in the scope include: Colistimethate sodium powder and tobramycin dry powder compared with each other, antibiotics for nebulised inhalation, including colistimethate sodium for nebulised inhalation and tobramycin for nebulised inhalation.
Questions for consultation	Association of Respiratory Nurse Specialists	These drugs are the standard treatment for Pseudomonas aeruginosa infection. To be able to administer the theraputic dosage in a less technical way would make this treatment faster & easier, this could lead to improved compliance with treatment. In future this treatment could be used by other patients with respiratory diseases such as Bronchiectasis & COPD, who have infective exacerbations or are chronically colonised with Peudomonas aeruginosa. To stop a postcode lottery in the prescribing of the inhaled treatments, the cost needs to be the same or less than the nebulised treatments.	Comment noted. No changes to the scope required. Comment noted. The technologies will be evaluated in accordance with their licence indications. The relative costs of the technologies will be taken into consideration during the economic evaluation component of the appraisal.

Section	Consultees	Comments	Action
	Association of Respiratory Nurse Specialists	There is a strong correlation between weight loss & lung function. As the appetite decreases when patients get chest infections and their body's calorie requirement increases to try & help fight the infection. If bacteria are adqeuatley treated the appetite improves & their nutritional state improves, allowing for improvement in lung function Although inhalers have been used for many years the advent of inhaled antibiotics via the inhaler device, shows that more efficent delivery systems are becoming available & are for the patient benefit	Comment noted. Improvements in lung function will be captured within the outcome “lung function” which is included in the scope. Comment noted. The appraisal will evaluate Colistimethate sodium powder for inhalation (used in conjunction with the Turbospin device) and tobramycin powder for inhalation (used in conjunction with the TOBIPodhaler device).
	British Thoracic Society	The delivery device will speed up treatment and potentially improve compliance.	Comment noted. Adherence to treatment will be included in the economic evaluation component of the appraisal if appropriate
	Forest Laboratories	Yes. We do believe it as a step change because it is replacing treatment in five to six minutes instead of 20 minutes, twice a day with nebulised treatments,a reduction of 72%. In the pivotal phase 3 trial, Colistimethate sodium dry powder has shown favourable 'ease of use' and treatment preference compared to TOBI, but these are not captured explicitly by any of the EQ5D constructs. Data available are: 1. Phase 3 study COLO/DPI/02/06 report 2. Examing the feasibility of mapping the CFQ-R to EQ5D	Comment noted. All available data will be considered in the context of the appraisal. No changes to the scope required

Section	Consultees	Comments	Action
	NHSQIS	(1) I am a little surprised that Colistin dry powder is being taken out of context. There are to be a flurry of applications for UK licenses in the next year or two. These include an alternative dry powder antibiotic inhaler (Tobramycin - Novartis) and a range of nebulised antibiotics (most imminent Cayston - Gilead, nebulised aztreonam – but 4-5 others in phase 2 and above). I would have thought it timely to look at 'Inhaled antibiotic therapies in cystic fibrosis', without limiting to a single as yet unlicensed therapy. (2) It would be important to acknowledge patient preference. CF is a huge burden of disease, with many therapies. Clinicians face great pressure to minimise the burden of therapy to achieve improved adherence. It is likely that dry powder preparations will be preferred by patients and so whilst not an overriding outcome it should be acknowledged and noted (and would not necessarily come out from QOL).	Comment noted. During the scoping workshop for the 1ST draft of the scope, consultees agreed the appraisal should be through the MTA process looking at the two powders for inhalation technologies with anticipated licenses. Comment noted. The scope is intended to provide a brief overview of the condition and technologies, full details and exploration of quality of life with CF will be captured within the framework of the appraisal. No changes to the scope required.
	NHSQIS	Dry powder antibiotics especially colomycin will be a huge advance in the management of CF patients, currently they are asked to take nebulised colomycin and because it takes 15-30 minutes to do twice a day adherence is very poor. Colomycin is an excellent anti-pseudomonal drug and resistance is not common. There are two scenarios for this drug, treatment of first isolates of pseudomonas and long term treatment of chronically colonised CF patients. The suggested NICE guideline is not probably relevant. Suggest CF Trust antibiotic guidelines. I think that a critical analysis will be to compare adherence with dry powder and nebulised therapy, because if adherence improves then there will be major savings in terms of exacerbations, courses of ivs, hospital admissions, possibly life expectancy, and improved quality of life will follow on from not having to use nebulised therapies.	Comment noted. Adherence to treatment will be included in the economic evaluation component of the appraisal if appropriate

Section	Consultees	Comments	Action
	NHSQIS	Anti-pseudomonal antibiotics used for CF patients vary. We use oral antibiotics such as Ciprofloxacin together with Nebulised anti - pseudomonal antibiotics (e.g Colomycin and TOBI) in pseudomonas eradication protocols [Ref 1 pages 29-30]. We also would use Ciprofloxacin for exacerbations of CF in those patients who have isolated pseudomonas. Intravenous anti-pseudomonal antibiotics e.g Ceftazidime and Tobramcyin are used together for more significant exacerbations of CF in those patients who have isolated pseudomonas and are also used in some circumstances as regular courses for those who are chronically colonised with pseudomonas. Regular intravenous courses on antibiotics reduce the load of pseudomonas in the lungs of patients with CF and therefore reduce inflammation and damage. Nebulised anti- pseudomonal antibiotics have been shown to slow the decline in lung function, to reduce exacerbations and improve lung function [Ref 1 page 25]. They have the advantages of delivering the antibiotic directly to the lungs thereby leading to maximal killing of bacteria. They can be given at home. The disadvantages of nebulised therapy are that they are given usually twice a day every day for many months, the nebulised treatment can a significant amount of time and some of the nebulisers are not very portable. Children and adults with CF have a large burden of care including chest physiotherapy, pancreatic replacement therapy in the form of enzymes taken with all meals and antibiotics and other CF treatment. If their nebulised therapy could be replaced by the inhalation of a dry powder antibiotic this would lead to a significant reduction in the burden of care for many CF patients as the dry powder device would be significantly faster and hopefully easier to use. CF patients who are chronically colonised with pseudomonas or those on eradication regimens would benefit equally from a dry powder antibiotic.	Comment noted. The comparators in the scope now include: Colistimethate sodium and tobramycin dry powder compared with each other, antibiotics for nebulised inhalation, including colistimethate sodium for nebulised inhalation and tobramycin for nebulised inhalation. Therefore the scope does rule out other nebulised treatments being included as comparators in the appraisal if the evidence is available.

Section	Consultees	Comments	Action
	NHSQIS	Colistin has been used for a long time by the nebulised route (many trials; but actually many are poor or of short duration - thus its use in Europe reflect mor "tradition" than exceptional evidence base; indeed it is not used in the USA, through lack of evidence). However, most Cf clinicians believe it has value andit is one of the treatments used to reduce exacerbation frequency in patients colonised by P aeruginosa. The new powder formulation is obviously not a new drug but potentially an easier delivery system. Also, nebulised colomycin can cause adverse effects on the airways, and so a new formulation may have advantages there, also. Thus, the proposed scope is challenging but appropriate for evaluating the powder delivery system. (I would be concerned that there are insufficient data to be able to answer all of the questions; but they are reasonable questions.	Comments noted. No changes to the scope required.

Section	Consultees	Comments	Action
	NHSQIS	There are some theoretical and technical issues that need to be considered when evaluating the drug. First amongst these is that it might be beneficial for the patient not to be able not to require nebulised treatment and to have an inhaled preparation. The second interesting aspect of this drug is that the way in which it acts might theoretically improve the efficiency and efficacy of action of other agents that act on bacterial species. Personal View: It is uncommon to use more than one nebulised agent or inhaled agent at the same time but I have never seen the logic behind this idea. For example, it is common place now in Cystic Fibrosis intravenous therapy to use more than one agent to prevent resistance occurring. It seems to me that similar considerations might apply to the inhaled use of two agents at the same time. However, further work will have to be done to evaluate this. So to answer your specific questions first of all what is the most appropriate antibiotic for the treatment of Pseudomonas aeruginosa? The short answer is the two market leaders for use are Tobramycin and Colistin and both can be nebulised. However this is relatively inconvenient as a route. Your second question was are there any sub groups of people in whom there technology is expected to be more clinically effective and cost effective and should these groups be examined separately. In my opinion, the use of eradication therapy at first isolation is a critical use of these agents. Typically 50% of the children after a first isolation of the Pseudomonas are clear of the bacterium after a combination of intravenous and inhaled therapy. 50% of those keep the bacterium away without needing further courses of eradication therapy whereas the other half require multiple rounds of therapy and then, often the Pseudomonas gets hold in the Lung. The net result is that the rising incidence of persistent infection increases from 8 to about 16% through childhood. These are the children that will benefit the most through such therapies.	Comments noted. The scope is intended to provide a brief overview of the condition and technologies, factors such as those described will be captured within the framework of the appraisal. No changes to the scope required. Comment noted. The scope has been amended accordingly.

Section	Consultees	Comments	Action
	CONT…	However, in Intensive Care and in other settings as the lung is damaged from other disease, these agents might also be of benefit for such patients. I am thinking particularly those with Ciliary Dyskenisia and these may also benefit in future years.	
	Novartis	One of the existing nebulised formulations of tobramycin is TOBI, originally launched in the UK in 1999. TOBI has been a Novartis product since the acquisition of Chiron in 2006. TOBI Podhaler was developed by Novartis as a dry-powder inhaler alternative to nebulised TOBI. The main benefit of this new formulation is that it allows faster and more convenient administration of tobramycin. Clinical trial evidence shows that TOBI Podhaler has non-inferior efficacy to TOBI (on FEV1 % predicted) and a faster administration time (LSM = 5.6 mins per administration for TOBI Podhaler vs. LSM = 19.7 mins for TOBI, LSM difference = 14.1 mins, $p<0.0001$). However, based on the non-inferiority design, there will be no QALY gains based on comparative efficacy alone. Patients may also benefit from reduced time setting up, cleaning and disinfecting their nebulisers, as well as from the portability and lack of requirement for product refrigeration. These benefits may have an impact on health-related quality of life. Outside the QALY calculation, the reduced administraton time may have an impact on productivity. However, these benefits are difficult to quantify.	Comments noted. The factors highlighted will be captured in the framework of the appraisal. No changes to the scope required.
	Profile Pharma	In short no. Both tobramycin and colistimethate sodium are currently available, delivered now via a modern nebuliser e.g. E-fow rapid and I-neb. It is unlikley that the dry powder versions will provide greater efficacy or cost effectiveness. The highly selective outcome measures such as "treatment satisfaction" need to be critically appraised against more clinically relevant outcome measure in CF and consideration needs to be given to the fact that modern nebulisers have rapidly replaced compressor nebuliser systems that have been used in these studies to deliver the comparator drug. Any claims of superiority in treatment satisfaction using dry powders is now not applicable to modern nebulisers that patients use today to deliver antibiotics.	Comments noted. The outcomes in the scope have been amended.

Section	Consultees	Comments	Action
	Royal College of Nursing	Yes, we do consider this technology to be innovative in the treatment of CF. It would need to be priced comptetively compared to current therapy and be as effective and well tolerated as current therapy. However, the benefits to the patients could be very significant in terms of adherence, quality of life and length of time between chest exacerbations. There is a significant problem currently with compliance with CF patients which this new technology could help to address.	Comments noted. Factors such as those highlighted will be considered in the appraisal. No changes to the scope required.
	Royal College of Paediatrics and Child Health	Dry powder antibiotics may be more efficacious than nebulised ones, but we doubt it. Their main advantage will be convenience of use. This is a major step advance to patients with CF who have a heavy and tiem consuming burden of treatment. Nebulisation, including cleaning and sterilising equipment, is especially time consuming. The current standard therapy for treatment of pseudomonal airway infection is either nebulised colomycin or tobromycin, with or without oral colomycin, with or without a 2 week course of anti-pseudomonal iv antibiotics (usually aminoglycoside plus beta-lactam). We note the technologies are innovative, and likely to be more portable than nebulised treatment. Cost effectiveness should be examined in comparison with the use of the newer faster nebuliser devices avaialable for promixin (Ineb) and TOBI (eflow). It would be important to build in monitoring of compliance. This is already possible with the Ineb and is very useful, showing variability in the number of prescribed nebulised doses actually delivered from as low as 20% to as high as 110% in individual patients. We are not aware of any trials comparing these dry powder devices with the use of promixin via the Ineb. We assume these manufacturers have only compared existing nebulised antibiotics made by them with their own dry powder alternatives.	Comments noted. The administration routes of the technologies (including cost and associated health-related quality of life) will be considered in the context of the appraisal. No changes to the scope required.

Section	Consultees	Comments	Action
	Royal College of Pathologists	There is no doubt that dry power formulations of these two drugs do offer the potential to improve delivery and compliance with inhaled antibiotic therapy in cystic fibrosis. This also raises the possibility that these products may also offer advantages to other patient groups who are chronically infected with P. aeruginosa e.g. bronchiectasis, COPD. Another theoretical benefit of these devices is a claim by the manufacturers that they do not require cleaning between use. Poor cleaning of conventional nebuliser equipment has resulted in their contamination with other potential pathogens (e.g. mycobacteria, environmental Gram negative bacilli, and fungi). However, this aspect does require further study	Comments noted. The administration routes of the technologies (including cost and associated health-related quality of life) will be considered in the context of the appraisal. No changes to the scope required.
	British Thoracic Society	Need to consider fact that new nebulisers s are v quick (ineb, eflow) Should consider eradication of 1st PsA growth as well as treatment of chronic infection	Comment noted. The outcomes in the scope have been amended.
	Forest Laboratories	TOBI is the only product currently licensed for this indication, however, Colistimethate sodium for nebulised inhalation and Tobramycin for nebulised inhalation are currently standard of care in Pseudomonas aeruginosa lung infection in cystic fibrosis. .	Comment noted. The comparators in the scope now include: Colistimethate sodium and tobramycin dry powder compared with each other, antibiotics for nebulised inhalation, including colistimethate sodium for nebulised inhalation and tobramycin for nebulised inhalation.

Section	Consultees	Comments	Action
	Forest Laboratories	2. Phase 3 trial data suggests that the clinical and cost-effectiveness benefits of colistimethate sodium powder for inhalation are significant across the whole patient population, but appear to be greatest in children aged 6-17 years.	Comment noted. Subgroup by number of prior therapies has been identified as the only subgroup for whom the technologies may be particularly clinically or cost effective and in accordance with the Methods Guide.
	Forest Laboratories	3. The current body of evidence shows that there is a correlation between 'weight gain' and 'mortality' in cystic fibrosis. Therefore, weight and BMI are appropiate outcome measures	It was agreed that BMI, as a surrogate outcome, should be excluded as an outcome in the scope.
	Forest Laboratories	3. In our view technology is truly innovative in the sense of 'ease of use' of the inhaler which will potentially have bearing on compliance and thereby on clinical and HRQoL markers	Comments noted. The administration routes of the technologies (including cost and associated health-related quality of life) will be considered in the context of the appraisal. No changes to the scope required.
	NHSQIS	References included, but not reproduced here	Comment noted.

Section	Consultees	Comments	Action
	Novartis	1. Most appropriate antibiotics used for the treatment of Pseudomonas aeruginosa infection - Information on the use of antibiotics for the treatment of Pseudomonas aeruginosa infection in cystic fibrosis can be found in the Cystic Fibrosis Trust consensus document on "Antibiotic Treatment for Cystic Fibrosis" (3rd Edition, May 2009) and "Cystic Fibrosis in Children and Adults: The Leeds Method of Management" (Revised Edition, Number 7, 2008). In general, UK clinical practice has been to use inhaled colistin first line for chronic infection and inhaled tobramycin second line. Some centres have been known to use colistin during tobramycin "off-cycles". 2. Subgroups - No comments. 3. Eliminating unlawful discrimination and promoting equality - No comments. 4. Nutritional status/BMI as an outcome measure - please see comments in the section on outcomes.	Comment noted. No further changes to the scope required.
	Novartis	We understand that the Cystic Fibrosis Trust and Department of Health are currently working on a Payment by Results (PbR) inititiative (http://www.cftrust.org.uk/aboutus/what_we_do/improvingcare/pbr). A mandatory national tariff for Cystic Fibrosis based on an annual/banded package of care is scheduled to be implemented by April 2011. Should the tariff include antibiotic drug costs, this may limit the value of a NICE MTA. A previous MTA of drugs for the treatment of pulmonary aterial hypertension was terminated part way through in similar circumstances "because NHS specialised commissioners have now put in place agreed arrangements for the supply of targeted therapies for all patients affected at the most severe stages of the condition" (http://www.nice.org.uk/nicemedia/live/11708/43721/43721.pdf).	Comment noted. This topic has been referred as an MTA to NICE by the Department of Health. No changes to the scope required.

Section	Consultees	Comments	Action
	Profile Pharma	The use of Colobreathe, or Tobi Podhaler could only replace a single therapy. It will not replace the need for the majority of Cystic Fibrosis patients who will still require a nebuliser system to deliver other inhaled therapies e.g mucolytics/bronchodilators/other antibiotics. Modern nebuliser technology has resulted in virtually silent, portable nebuliser systems that deliver quickly with minimal environmental exposure. In addition some inhalation devices have the capability of monitoring breathing patterns, providing feedback for training purposes and electronic monitoring to allow clinicians to work with patients to improve adherence in line with the recommendations of the UK Cystic Fibrosis Trust Antibiotic Working Group, entitled Antibiotic Treatment for Cystic Fibrosis published May 2009 (see attached to covering e-mail)	Comment noted. The scope is intended to provide a brief overview of the condition and the technologies of interest. No changes to the scope have been made.
	Royal College of Nursing	1 The most appropriate antibiotics used for treatment of CF (nebulised) are colistin and tobramycin (TOBI or Bramitob). These latter two antibiotics are very expensive and are not used as first line therapy. In Grampian, for instance, they also use gentamicin and tazocin in a couple of patients. 2 Some of the patients tend to react to nebulised colistin (usually tight throat/wheeze) and these patients will be tried with TOBI. The wheeze can occasionally be controlled by dissolving the colistin powder in 2.5mls salbutamol and nebulising them simultaneously. They have also had patients who have not tolerated TOBI or Bramitob and for this group, they tend not to use nebulisation therapy. It is possible that using colistin as a DPI via an inhaler may reduce/prevent intolerances (this might require further studies). 3 As previously stated, in Scotland, all adult patients are treated on an equal basis due to the national funding of the CF service by the National Services Division. 4 BMI probably would be an appropriate outcome measure. There is consistent evidence to show that fewer chest infections result in better nutritional status and a higher BMI results in fewer exacerbations.	Comment noted. The comparators in the scope are nebulised antibiotics. The routes of administration of the technologies will be considered in the appraisal. It was agreed that BMI, as a surrogate outcome, should be excluded as an outcome in the scope

Section	Consultees	Comments	Action
	Royal College of Paediatrics and Child Health	It would be very helpful if NICE could consider use of dry powder antibiotics both for the eradication of intermittent infection and the suppression of chronic mucoid infection. We think that trials comparing the dry powder devices to placebo alone would not be appropriate in most cases of Pseudomonas infection, so the trials would have to show equivalance to the previously prescribed nebulised antibiotics. Historical evidence for the efficacy of nebulised colistin in CF is quite weak; evidence for the efficacy of nebulised tobramicin is better.	Comments noted. NICE will issue guidance in accordance with the licensed indications of the technologies. All relevant evidence will be considered in the appraisal.
	Royal College of Paediatrics and Child Health	We think that the draft scope does not read clearly. Is NICE proposing to assess co-administration of tobramycin and colistimethate? Or to simply compare the two separately? If the former, then as there is potential for interaction at the neuromuscular junction, the potential for a synergistic microbiological benefit could be affected by a drug-drug interaction. On page 2, it should read Acinetobacter baumannii not Acinetobacter baumanii.	Comments noted. The scope now specifies that Colistimethate sodium and tobramycin dry powder will be appraised as separate interventions. In addition, they will be compared with each other. The scope has been amended accordingly.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Cystic Fibrosis Trust
Department of Health
Welsh Assembly Government
United Kingdom Clinical Pharmacy Association (UKCPA)