NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Association of Chartered Physiotherapists in Cystic Fibrosis (ACPCF)	The ACPCF believes that the relevant evidence has been considered in the appraisal of the two above treatments for the treatment of pseudomonas lung infection in CF. Long-term inhaled antibiotics are core components of comprehensive CF care in suppressing pseudomonas. Traditionally, these have only been available in nebulised forms which have required dilution and mixing of the antibiotic (Colistimethate) or storing in the refrigerator (Tobramycin) plus assembly of the equipment (nebuliser system) and then connection to an air compressor, all of which results in additional time required by the patient or family to prepare the nebuliser before the inhalation can begin. Even with the latest nebuliser technology typical inhalation times are 5-10 mins for Colistimethate and 8-15mins for Tobramycin. All of the nebuliser component parts then need to be washed and dried after each use and sterilised weekly, which adds significantly to the treatment burden for patients.	Comment noted. The Committee considered the treatment burden associated with cystic fibrosis and heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5
Association of Chartered Physiotherapists in Cystic Fibrosis (ACPCF)	The development of dry powder forms of the two most commonly used inhaled antibiotics is of significant benefit to the CF population. They are quick and simple to use and dramatically reduce the complete inhalation time with minimal set up or cleaning required. As the dry powder tobramycin has been available since September 2011, we have noticed a significant interest from patients who have been prescribed this, as it is so much simpler and quicker to take than the nebulised form, as well as being completely portable and with the benefit of equivalent efficacy to the nebulised form. We have noticed markedly improved adherence to these important treatments. As we encourage patients to be independent and to optimise their quality of life the availability of dry powder inhaled drugs to them is vital.	Comment noted. The benefits of dry powder formulations from the patient and clinician perspective in improving treatment adherence were acknowledged by the Committee. See FAD sections 4.3.5 and 4.3.6
Association of Chartered Physiotherapists in Cystic Fibrosis (ACPCF)	In addition to the benefits to the patients and families, it must also be appreciated the benefits to the health-care provider. Nebulised drugs require regular equipment provision and health professional time to service and test equipment on a regular basis. By making the two most common inhaled antibiotics in CF available as dry powders, there is a large reduction in nebuliser consumable component parts and health professional time required, thereby freeing up time for other clinical tasks.	Comment noted.

Consultee	Comment	Response
Association of Chartered Physiotherapists in Cystic Fibrosis (ACPCF)	As tobramycin is licensed for use as a 28 day on/off cycle, then it is advantageous for patients who use an alternative inhaled antibiotic during the off cycle to be able to use a dry powder, such as Colistimethate. Patients with CF have a high burden of several treatments including regular daily physiotherapy which is time-consuming and hence adherence is challenged due to time restrictions. Any treatment advances that increase the 'free time' available to patients, while not compromising on efficacy of treatments is advantageous.	Comment noted. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5
Association of Chartered Physiotherapists in Cystic Fibrosis (ACPCF)	While we applaud the positive draft recommendation for dry powder inhaled tobramycin and appreciate the larger body of evidence in support, we would urge the committee to reconsider the draft negative opinion for Colistimethate dry powder as an advance in the treatment of pseudomonas lung infection in CF.	Comment noted. See FAD section 1 for the final recommendations.
Clinical Expert	Having already provided to you an expert written personal statement with regard to the ongoing multiple technology assessment for colistimethate sodium and tobramycin powder for inhalation for the treatment of pseudomonas lung infection in cystic fibrosis patients, I would now like to take this opportunity to provide my personal comments on the draft assessment report prepared and publicised by NICE on October 24th 2012 (ID342). As an employee of the Cardiff and Vale University Health Board, I am specifically responsible for the care of 238 adult cystic fibrosis patients across Wales. As recognised, the subset of CF patients with chronic pseudomonas aeruginosa infection have a significantly worse prognosis and quality of life than those with intermittent infection as the chronic nature leads to and accelerates the progressive decline in lung function characteristic of CF and is central to the respiratory related morbidity and mortality. The advantages of inhaled antibiotic therapy for PsA infection in CF has been recognised for nearly 40 years. The hypothesis is that an antibiotic delivered directly to the site of infection will be maximally effective, achieving sputum antibiotic levels far in	Comment noted. See FAD section 1. for the final recommendations

Consultee	Comment	Response
	excess of those achievable by intravenous administration without the risks of systemic toxicity. With this in mind, I am delighted NICE have recommended the approval of the tobramycin dry powder inhaler for these patients. However, the decision NOT to recommend the approval of the colistin DPI (Colobreathe) as well gives me significant cause for concern as a prescribing physician.	
Clinical Expert	This concern is driven by the way tobramycin and colistin (nebulised forms) are currently used in clinical practice, where we have seen a move AWAY from the historical norm (colistin as a first line therapy followed by tobramycin for those patients who cannot tolerate colistin or require additional clinical efficacy) TOWARD a treatment regimen of alternating therapy between these two agents on a monthly basis. The reality of this decision therefore, is to provide an individual patient with a DPI treatment in Month 1 and ask that they return to a nebulised formulation in Month 2 – a situation the patient will find totally unacceptable and one which will lead to high rates on non-compliance and poor quality of life in Month 2 which will ultimately result in faster disease progression.	Comment noted. The Committee concluded that some people with cystic fibrosis and chronic pseudomonas lung infection may receive alternating tobramycin and colistimethate treatment in clinical practice, but it had seen no evidence as to the clinical effectiveness of this treatment regimen, and so agreed that it could not consider this issue further. See FAD section 4.3.3
Clinical Expert	Although several guidelines exist when considering antibiotic management in CF patients with cystic fibrosis - typically those issued by the CF Trust (May 2009) and those prepared by The British Thoracic Society Cystic Fibrosis Special Advisory Group – these are focussed on historical prescribing practices given the arbitrary use of 1st and 2nd line recommendations for colistin and tobramycin respectively. Current prescribing, as described above, now tends to focus on an alternating treatment regime in the majority of specialist centres. Perhaps the time has come to reflect the current clinical practise with a revision to these guidelines.	Comment noted. The Committee concluded that some people with cystic fibrosis and chronic pseudomonas lung infection may receive alternating tobramycin and colistimethate treatment in clinical practice, but it had seen no evidence as to the clinical effectiveness of this treatment regimen, and so agreed that it could not consider this issue further. See FAD section 4.3.3
Clinical Expert	As a clinical expert in the UK, I also had the opportunity to participate in the pivotal Colobreathe study (COLO/DPI/02/06) which is described in the ARD. There is no doubt the design and logistics of the study were complex, particularly when a study requiring such large patient numbers can only achieve this by selecting sites from across the whole	Comment noted. The Committee heard from the manufacturer of colistimethate DPI that the EMA had specified at the time of the design of

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	of Europe. Whilst the statistical aspects of the trial are not something on which I can comment, the choice of comparator most definitely is and although nebulised colistin may have been the preferred choice, I can understand the legal, scientific and regulatory rational for not moving forward with this. Specifically, in 2002 at the start of this study, Forest had only 3 actual choices for the comparator arm – placebo, nebulised colistin or nebulised tobramycin. Ethically, the clinical community would not support a placebo arm given the 24 week duration of the trial, nebulised colistin was not registered / approved in several of the countries identified for patient recruitment (given the orphan nature of the disease, recruitment was never going to occur solely in the UK) and thus nebulised tobramycin was the only choice the company could move forward with. Indeed, by using tobramycin as the comparator, one could conclude that Colobreathe is as effective as the current evidence based 'gold standard' since previous studies have demonstrated that nebulised tobramycin is superior to nebulised colistin.	the study that the most appropriate comparator for their pivotal trial should be nebulised tobramycin due to this being the only licensed comparator in all of the study site countries. See FAD section 4.3.4. The Committee noted that the manufacturer of colistimethate sodium DPI had confirmed that there was no trial that compared the effectiveness of colistimethate sodium DPI with nebulised colistimethate sodium. The Committee was therefore unable to reach a conclusion on the clinical and cost effectiveness of colistimethate sodium DPI compared with nebulised colistimethate sodium. See FAD section 4.3.17.
Clinical Expert	In conclusion, if the price of Colobreathe can be moderated to ensure similar alignment to tobramycin podhaler or promixin, then I believe Colobreathe would be a welcome addition to the physician's armamentarium, the patients choice of medication and would ultimately, improve compliance in this patient population. Although I welcome the decision to approve TIP; as an expert in cystic fibrosis with many years experience and looking after a large number of patients I feel that the decision not to approve Colobreathe on the evidence given is a retrograde step in the future care of my patients. I therefore urge NICE to reconsider their decision.	Comment noted. See FAD section 1.2 for the final recommendation on colistimethate sodium DPI.
Cystic Fibrosis Trust	The CF Trust welcomes the initial recommendation from the NICE, following a MultiTechnology Appraisal, that tobramycin dry powder for inhalation (Tobi Podhaler,Novartis) for CF should be an option for use in people with CF. We are pleased that tobramycin dry powder will be recommended for people with CF. It is really good news for the CF community as tobramycin has been found to be effective in treating lung	Comment noted.

Consultee	Comment	Response
	infections in adults and children over the age of six.	
Cystic Fibrosis Trust	It is however, very disappointing that NICE have so far taken the view not to recommend Colobreathe (colistimethate sodium dry powder for inhalation, Forest Laboratories). Colobreathe also treats pseudomonas infections and offers significant patient benefits over current treatment. These benefits include: · An alternate inhaled treatment option for patients who are contraindicated for tobramycin, · Treatment burden is reduced because the drug is administered by inhaler, rather than by nebuliser· Promotes adherence as quick and easy to administer compared to the current nebulised form of colomycin· Treatment is more likely to be effective as patients will take a full dose.	Comment noted. See FAD section 1 for the final recommendations.
Cystic Fibrosis Trust	There is a great need for further choice of treatments for CF to become available, particularly treatments that are quick and easy to use such as powder antibiotics.	Comment noted. The Committee concluded that on balance it could see an additional benefit for people with cystic fibrosis and chronic pseudomonas lung infection of having the choice of a dry powder formulation of anti-pseudomonal drug rather as well as its appropriate nebulised comparator. See FAD section 4.3.13
Cystic Fibrosis Trust	People with CF have a huge burden of care, often having to do hours of treatments and physiotherapy a day. Each treatment that becomes available and is proven to be effective in treating infections and symptoms of CF is a huge step forward in helping people with CF to stay well.	Comment noted. The Committee considered the treatment burden associated with cystic fibrosis. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5

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Cystic Fibrosis Trust	Colobreathe is delivered by an inhaler (like an asthma inhaler), which is an efficient way of delivering the treatment, making it quicker and easier to take than the current nebulised form of colomycin. The new inhaler device makes it much more likely that the full dose of the active ingredient will be administered to the patient, largely due to the ease and speed of the delivery system but also due to less of the drug escaping into the air during nebulisation.	Comment noted.
Cystic Fibrosis Trust	It is crucial for this treatment to be an available prescribing option for those people that do not tolerate or struggle to comply with nebulised therapy. If Colobreathe is not recommended tobramycin will be the only option, which is not appropriate for some due to ototoxicity caused by the effects of aminoglycosides or other contraindications to taking tobramycin.	Comment noted. The Committee acknowledged that there was a group of people who could benefit or were benefitting from nebulised colistimethate sodium but were unable to tolerate it twice daily in its nebulised form. See FAD section 4.3.19
Cystic Fibrosis Trust	Limiting treatment options available will make it more difficult for clinicians to consider what might be the most appropriate treatment for an individual patient and may impinge on their decision to recommend alternating treatments on a monthly basis, as many do currently with the nebulised forms of tobramycin and colomycin. With only one antibiotic available in dry powder form, there is a risk of over reliance on one antibiotic treatment, and a reduction in adherence during the monthly periods assigned to nebulised antibiotic therapies.	Comment noted. The Committee concluded that some people may receive alternating tobramycin and colistimethate treatment in clinical practice, but it had seen no evidence as to the clinical effectiveness of this treatment regimen, and so agreed that it could not consider this issue further. See FAD section 4.3.3. The benefits of dry powder formulations from the patient and clinician perspective including improving treatment adherence were acknowledged by the Committee. See FAD sections 4.3.5 and 4.3.6
Cystic Fibrosis Trust	This prescribing method is clearly outlined in the response by Dr R I Ketchell, Consultant Physician and Director of the Adult Cystic Fibrosis Centre, Wales to this NICE consultation.	Comment noted.

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Cystic Fibrosis Trust	It must also be taken into account that those who do well on colomycin should have the option of reducing their treatment burden through moving onto a more effective and less time consuming delivery method. This should especially be the case if they are not adhering well because of the treatment burden.	Comment noted. The Committee acknowledged that there was a group of people who could benefit or were benefitting from nebulised colistimethate sodium but were unable to tolerate it twice daily in its nebulised form. See FAD section 4.3.19
Cystic Fibrosis Trust	In CF, the overall burden of care is immense, time consuming and exhausting for the patient. Effective innovations must be supported if we are going to help people with CF improve their quality of life and live longer. Innovative dry powder inhalers represent a step change in CF medicine.	Comment noted.
Cystic Fibrosis Trust	The CF Trust supports both therapies and would like NICE to recommend both as prescribing options for CF specialist clinicians. Therefore, the Cystic Fibrosis Trust is of the opinion that the provisional recommendations from NICE regarding Colobreathe are not a sound and suitable basis for guidance to the NHS and serves to severely limit clinicians' prescribing options.	Comment noted. See FAD section 1 for the final recommendations.
Department of Health	I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Comment noted.
Forest	Executive Summary Thank you for the opportunity to comment on this appraisal consultation document (ACD). Cystic fibrosis (CF) is a devastating, genetic, multi-system chronic disease, affecting 8,500 people in the UK, causing significant morbidity and mortality (median age of death of 29 years). Of these CF patients, around one third [~3,200] have chronic PsA infection (which is the main cause of death), requiring highly individualised patient care for effective management. We are encouraged that NICE has discussed and concluded that "…it could see an additional benefit for people with cystic fibrosis and chronic pseudomonas lung infection of having the choice of a dry powder formulation (DPI) of anti-pseudomonal drug rather than its appropriate nebulised comparator." However, given the emerging current clinical	Comments noted.

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	care prescribing practices (see below), it is vital that physician and patient choice are not denied, patient inequality is not promoted and patient mortality and compliance is not compromised by offering only one of the two mainstay antibiotic treatments as a DPI.	
Forest	In Forest's view, inadvertent deficiencies, inaccuracies and oversights in the ACD have contributed to the disappointing recommendation to deny appropriate patients access to colistimethate sodium DPI. This response is provided to clarify and address these deficiencies, inaccuracies and oversights. Furthermore, Forest has noted the comments made by the Appraisal Committee when considering the cost effectiveness of the colistimethate sodium DPI and is in the process of submitting a revised Patient Access Scheme to the Department of Health.	Comments noted.
Forest	Specifically, this response is focussed on further helping the Appraisal Committee understand that: • Current medical practice is moving away from the historical position towards the position articulated by Drs Ketchell and Hull in their statements, the current British Thoracic Society (BTS) guideline and the more recently published European Cystic Fibrosis Society (ECFS) guideline. As of today, there is no clearly identified first-line treatment, with both nebulised tobramycin and colistimethate sodium routinely used depending on local clinical practice and patient need to provide the individualised care necessary for successful management of the condition. Indeed, NICE appears to have already accepted this position in its recent assessment of Mannitol with the Committee concluding "…that best standard of care for cystic fibrosis was complex and tailored to patient needs…"	Comment noted. The Committee considered the current treatment pathway for people with cystic fibrosis with chronic P. aeruginosa lung infection. See FAD sections 4.3.2 and 4.3.3
Forest	• Provision of only one DPI product will deny both physician and patient choice, promote patient inequality and risk reduced compliance with a corresponding potential acceleration in patient mortality since an alternating DPI/nebuliser/DPI/nebuliser treatment paradigm is not feasible for a chronic disease	Comments noted. The Committee concluded that on balance it could see an additional benefit for people with cystic fibrosis and chronic pseudomonas lung infection of having the choice of a dry powder formulation of anti-pseudomonal drug as well as its appropriate nebulised comparator.

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		See FAD section 4.3.13 See FAD section 1 for the final recommendations.
Forest	• The efficacy of colistimethate sodium DPI has been assessed and confirmed to be non-inferior to nebulised tobramycin by the European Medicines Agency (EMA), with European Marketing Authorisation granted on that basis. The current position taken by the Appraisal Committee may be contrary to the principles outlined in the Servier case. Furthermore, the renal safety of colistimethate sodium DPI has been extensively studied in COLO/DPI/02/05 showing that colistimethate sodium DPI is not associated with nephrotoxicity.	Comments noted. See FAD sections 4.3.7 and 4.3.9
Forest	• The pivotal regulatory trial (COLO/DPI/02/06 also known as the FREEDOM trial) for colistimethate sodium DPI has now been published in Thorax, a prestigious peer-reviewed journal. The ACD and the overview document contain a number of factual inaccuracies and misinterpretations regarding the FREEDOM trial which may have hindered the Appraisal Committee's ability to accurately interpret the pivotal trial data. We provide clarification of these in our response.	Comment noted.
Forest	• Numerous, significant factual inaccuracies are present throughout the body of the ACD and within the Overview. These inaccuracies contribute toward the overall recommendation from the Appraisal Committee, given that they influence data interpretation, particularly with regard to the efficacy of colistimethate sodium DPI. We have therefore sought to provide detailed corrections (Key inaccuracies are addressed in Section 5, with the remainder addressed in the Appendix (sections 7.1, 7.2 and 7.3)	Comment noted.
Forest	• Colistimethate sodium DPI offers a vital treatment option for those people with CF who clinically benefit from nebulised colistimethate sodium but either adhere poorly to or do not tolerate well conventional nebuliser therapy. This holds true, whether the product is used as the only inhaled antibiotic or in an alternating pattern with tobramycin DPI and is based on clinical need and judgement. Furthermore for that subgroup of people with CF who are identified as aminoglycoside sensitive or intolerant, it is the only dry powder treatment option that clinicians could utilise. Colistimethate sodium DPI is a simple to use 1 capsule, twice daily system taking less than 60 seconds per treatment (please see	Comments noted. The Committee acknowledged that there was a group of people who could benefit or were benefitting from nebulised colistimethate sodium but were unable to tolerate it twice daily in its nebulised form. See FAD section 4.3.19

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	Appendix, section 7.5 for the UK Patient Information Leaflet). Each 125mg capsule is equivalent to 1.662 mu and is packed in a 28 day pack containing 56 capsules and a single disposable turbo spin inhaler device. The single patient use device requires minimal cleaning and no maintenance and each new pack contains a new device.	
Forest	• It is clear that the evidence base to support economic modelling in this therapy area is limited and unreliable, as referenced by the Assessment Group's feedback on Forest's economic model and highlighted in the Assessment Group's own de novo model. Given this, it would be more appropriate if the Appraisal Committee gave more weight to the clinical data and the views of the physician and patient community in this therapeutic area.	Comments noted.
Forest	• In light of comments made by the Appraisal Committee when considering colistimethate sodium DPI, Forest is in the process of submitting a revised Patient Access Scheme to the Department of Health	Comment noted. The Committee based its decisions on the cost-effectiveness results from analyses incorporating the revised patient access scheme for colistimethate sodium.
Forest	We trust the Appraisal Committee will reconsider their recommendations and recommend the use of colistimethate sodium DPI given the additional clarification and information provided in this response, in conjunction with the revised Patient Access Scheme; enabling appropriate patients to access this effective, innovative treatment. Ultimately, recommending the product for approval provides physicians and patients with the opportunity to continue to individualise patient care using DPI's for optimal outcome, improving patient compliance and promoting choice and equality for people with this rare, devastating, genetic disease.	Comment noted. See FAD section 1.2 for the final recommendations.
Forest	Cystic fibrosis is a rare, devastating chronic disease affecting less than 8,500 patients in England and Wales. Just as our own DNA make-up is unique to us, every CF patient is unique, with the disease manifesting through a range of differing clinical sequelae at different times during their short lives. What is consistent is the impact on morbidity and mortality, along with the need for individualised patient care.	Comment noted
Forest	Although significant clinical guidance exist (CF Trust, The British Thoracic Society Cystic Fibrosis Special Advisory Group, Regional, Local and Hospital publications), it is clear	Comment noted. The Committee considered the current treatment

Consultee	Comment	Response
	that real-life clinical care for people with CF and chronic Pseudomonas aeruginosa (PsA) lung infection continues to evolve.	pathway for people with cystic fibrosis with chronic P. aeruginosa lung infection. See FAD sections 4.3.2 and 4.3.3
Forest	Historically, and in line with much of the existing guidance, treatment of chronic PsA pulmonary infection in people with CF has routinely been initiated using nebulised colistimethate as a first-line therapy, with the option to progress to nebulised tobramycin (second-line) only available to patients in which nebulised colistimethate was contraindicated or in whom additional efficacy was required / the safety profile was unacceptable. However, the Appraisal Committee heard from clinical specialists that current treatment is "…generally patient driven and that the most important outcomes for the patient that influence treatment decisions are the person's quality of life [QoL], treatment burden, maintaining good lung function and reducing the incidence of exacerbations."	Comments noted
Forest	Furthermore, in the recently approved Final Appraisal Determination for Bronchitol (mannitol dry powder for inhalation), "…the Committee concluded that best standard of care for cystic fibrosis was complex and tailored to patient needs…"	Comment noted
Forest	Drs Ketchell and Hull provide personal written expert statements as additional evidence to reflect the way in which nebulised colistimethate sodium and tobramycin are currently used in clinical practice. Here we understand clinical practice is moving away from the historical guideline 'norm' (nebulised colistimethate sodium as a first-line therapy, nebulised tobramycin as a second-line therapy) toward a treatment paradigm in the major specialist centres of alternating therapy on a monthly basis, i.e. Month 1 on nebulised tobramycin, Month 2 on nebulised colistimethate and repeat.	Comment noted. The Committee concluded that some people with cystic fibrosis and chronic pseudomonas lung infection may receive alternating tobramycin and colistimethate sodium treatment in clinical practice. The Committee noted the increased cost of such alternating antibiotic regimens and that it had not been presented with any evidence as to the clinical effectiveness of this approach by the Assessment Group or the manufacturers or during

Consultee	Comment	Response
		consultation. It concluded that because there was no evidence of the clinical effectiveness of using alternating antibiotics, it could therefore not consider this issue further. See FAD section 4.3.3
Forest	Forest have interrogated both the published literature and the UK CF Registry to try and gain an insight into the numerical incidence (either actual absolute numbers or as a percentage) of patients currently treated in this manner. However, it would appear data is not yet reported in this way given the gradual evolution of the clinical care pathway, although a single reference (Iles et al 2003) reported by the School of Health & Related Research Sheffield (ScHARR) in their Assessment Report suggests 49% of patients are treated in this way. The percentage reported in the Iles paper has been supported by one CF centre where 79 of 167 patients (47%) who have pseudomonas infection are treated on an alternating colistimethate sodium/tobramycin antibiotic regime.	Comment noted. The Committee heard from the Assessment Group that information from their clinical experts suggested that less than 25% of people with cystic fibrosis and chronic P. aeruginosa lung infection would receive an alternating therapy regimen. The Committee therefore concluded that some people with cystic fibrosis and chronic pseudomonas lung infection may receive alternating tobramycin and colistimethate sodium treatment in clinical practice. It concluded that because there was no evidence of the clinical effectiveness of using alternating antibiotics, it could not consider this issue further. See FAD section 4.3.3
Forest	In the light of current prescribing practice, the recommendations in the ACD give rise to a scenario where an individual patient is provided with a DPI treatment in Month 1 and then ask to return to a nebulised formulation in Month 2. This is a totally untenable situation in the eyes of the patient (personal written expert statement from Emma Lake, a person with CF) in which she highlights the quality of life and time saving elements of the DPI mechanism of delivery. An alternating DPI/nebuliser/DPI/nebuliser treatment paradigm is	Comment noted. Comment noted. See FAD section 1 for the final recommendations.

Consultee	Comment	Response
	not considered feasible for chronic disease. Furthermore, it is vital that physician and patient choice are not denied, patient inequality is not promoted and patient mortality and compliance is not compromised by offering only one of the two mainstay antibiotic treatments as a DPI.	
Forest	In the ACD, the Appraisal Committee acknowledges the use of these products in monthly treatment cycles and comments that use of nebulised colistimethate sodium in this manner is outside of its approved marketing authorisation, stating that there is no clinical evidence for such approaches to treatment. Forest respectfully disagrees with the Appraisal Committee position. We consider this approach to be entirely consistent with the authorised uses of both nebulised and DPI colistimethate sodium. Colistimethate sodium DPI is authorised for use "…for as long as the physician considers that the patient is obtaining clinical benefit." Cyclical use with other antibiotics is permitted. The authorisations for both nebulised and DPI tobramycin expressly envisage that the products should be taken in alternating cycles of 28 days on treatment followed by 28 days off treatment. Thus, the use of monthly treatment cycles is clearly reflected in 'real-world' prescribing practices, which are consistent with both products' marketing authorisations.	The Committee noted that the use of colistimethate sodium only in the tobramycin 28-day off period or continuous half-dose tobramycin in some people on nebulised tobramycin were outside the respective marketing authorisations, and heard from the clinical specialists that there was no clinical-effectiveness evidence for such approaches to treatment. See FAD section 4.3.2. The Committee concluded that some people with cystic fibrosis and chronic pseudomonas lung infection may receive alternating tobramycin and colistimethate sodium treatment in clinical practice. It concluded that because there was no evidence of the clinical effectiveness of using alternating antibiotics, it could not consider this issue further. See FAD section 4.3.3
Forest	Furthermore, the whole evidenced-based justification for using nebulised colistimethate sodium – reflected in current CF Trust guidance as the perceived first-line therapy – is predicated on Level D evidence, the lowest level of evidence available and usually referred to as non-analytic studies, anecdotal / case reports etc.	Comment noted. The Committee understood that the usual treatment pathway was for nebulised colistimethate sodium to be used first and then nebulised tobramycin

Consultee	Comment	Response
		second. See FAD section 4.3.2.
Forest	Given the evidence presented above, the clinical pathway described in the ACD cannot be confirmed and there remains significant uncertainly around National prescribing practises which are influenced by physician preferences and tailored to meet the needs of the individual concerned. It is clear that both tobramycin DPI and colistimethate sodium DPI have a role to play in the treatment chronic PsA infection of the lung in people with CF. Colistimethate sodium DPI offers a vital treatment option for those CF patients who clinically benefit from colistimethate sodium but either adhere poorly to or do not tolerate well conventional nebuliser therapy. This holds true whether the product is used as the only inhaled antibiotic or in an alternating pattern with tobramycin DPI, based on clinical need and judgement. Furthermore for that subgroup of people with CF who are identified as aminoglycoside sensitive or intolerant, it is the only dry powder treatment option that clinicians could utilise.	Comment noted.
Forest	Provided below, as additional supportive data, are quotes from UK Healthcare providers contained within the Evaluation Report which support the current variability in treatment approaches: • "There are variations in practice as to which of these antibiotics is used more often in different parts of the UK" and that whether DPIs are "…used or not comes down to patient preference." (The Royal College of Paediatrics and Child Health notes) • "The therapeutic options per patient with Cystic Fibrosis are incredibly varied. In addition, the propensity to develop allergies to the various medications whether given by the inhaled route or whether delivered intravenously, can severely limit these options in the older patients." (Healthcare Improvement Scotland in their response to the Technology Appraisal Report) • "Current practice is to use nebulised solutions of the same 2 drugs – colistin and tobramycin. Which is used depends on local practice." (Dr Jeremy Hull, a CF specialist at	Comments noted.

Consultee	Comment	Response
	the John Radcliffe Hospital, Oxford) • "In the UK there has historically been a postcode lottery for prescribing medications and the regional variation is reflected in local care pathways and management protocols, involving specialist pharmacists where required." (The Royal College of Nursing, after describing the situation with antibiotic treatment in Scotland)	
Forest	Conclusion on clinical care pathway Given the evidence presented above, we would ask that the Appraisal Committee reconsider the clinical care pathway as describe in the ACD to reflect the current opinions of the prescribing physicians who treat based on patient need and the Mannitol final appraisal conclusion which already reflects this approach (October 2012). The Appraisal Committee should reconsider the assumption based on the historic use of antibiotics in this therapy area and reappraise; the weight of evidence previously submitted by various parties alongside the evidence provided in this response confirm that variations in current prescribing exist based on patient need and physician preference.	Comment noted. The Committee discussed the comments received during consultation on the ACD regarding the current treatment pathway. See FAD section 4.3.3
Forest	Clarification of colistimethate sodium DPI's pivotal trial design and data The ACD identifies a series of potential concerns around the pivotal FREEDOM clinical trial. The FREEDOM trial can be summarised as a 24 week trial comparing twice daily doses of colistimethate sodium DPI with twice daily doses of tobramycin administered via a nebuliser. FREEDOM was a prospective randomised trial, intending to show that colistimethate sodium DPI was not inferior to nebulised tobramycin using FEV1% predicted (forced expiratory volume at one second) at 24 weeks as the primary endpoint. A trial of this size, in this orphan disease population is by nature complex in design and difficult to administer logistically – a factor which may ultimately have some bearing on why the Appraisal Committee believe both the colistimethate sodium DPI and the tobramycin DPI studies are of poor to moderate quality. In early 2002, Forest began to solicit external views on the trial design (first draft protocol) to mitigate as many of these uncertainties as possible. Contributors to this process included key opinion leaders of the	Comments noted.

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	time (Drs Jim Littlewood, Steve Conway, Christian Koch, Niels Hoiby and Gerd Doring) and the EMA. Using this approach, the final agreed clinical trial design for the FREEDOM trial represented the collective view of not just the Company but also the key opinion leader community across Europe and the pan European regulatory body at the EMA; indeed, all bodies with which it was possible to consult at the time.	
Forest	Colistimethate sodium DPI is clinically effective and non-inferior to nebulised tobramycin The FREEDOM trial provides robust, convincing and credible evidence that colistimethate sodium DPI is non-inferior to nebulised tobramycin solution with respect to FEV1% predicted after 24 weeks of treatment. Furthermore, this conclusion is supported by the EMA who offered a positive opinion for the product which was subsequently adopted by the European Commission who granted Marketing Authorisation for the product following their own clinical and statistical analysis and the world-leading, peer reviewed respiratory journal Thorax who has now published the manuscript for the trial online.	Comment noted. The Committee concluded that the COLO/DPI/02/06 and EAGER trials may have demonstrated that colistimethate sodium DPI and tobramycin DPI were non-inferior to nebulised tobramycin with respect to change in FEV1% within the populations tested and in the manner conducted within each trial, but remained concerned with the uncertain clinical relevance of these findings given the short-term nature of these trials. See FAD section 4.3.9
Forest	We do not believe that the Appraisal Committee has a reasoned cogent basis for reaching a different view from that of the EMA's Committee for Medicinal Products for Human Use (CHMP) given the clinical evidence we have provided. The recent Servier Laboratories Limited vs. National Institute for Health and Clinical Excellence case illustrates the necessity for this.	Comment noted.
Forest	In the ACD, the Assessment Group make several references to the EMA guideline for the clinical development of medicinal products for the treatment of cystic fibrosis (EMEA/CHMP/EWP/9147/2008) As can be seen from the document reference number, this guideline was not drafted until 2008, was not adopted by the CHMP until 2009 and did not come into effect until 2010. Indeed, it was the lack of published guidance in 2002 that led Forest to seek scientific advice on the protocol design at an early stage. Below is a summary, of the key points of our discussion:	Comments noted. The Committee discussed the quality of the 2 key trials. It noted the Assessment Group's critique of the trials, in particular the fact that the manufacturers had not commented in their submissions on the quality of these trials in light of the current EMA

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	(i) EMA endorsed the choice of the surrogate endpoint FEV1 as the primary endpoint for the trial, supported by microbial data from sputum samples and QoL data as secondary endpoints. (ii) EMA endorsed the non-inferiority design of the trial, leaving Forest to determine the appropriate non-inferiority limit and confidence intervals, given that a superiority trial designed to detect a 10% treatment difference using FEV1 as the primary outcome was unfeasible, requiring more than 600 patients. (iii) EMA endorsed the open label (non-blinded) nature of the trial using the following comment "Ideally a double-blinded controlled trial would be preferred, however, this is not feasible in the light of the difficulties of patient recruitment in the target population, practical difficulties for the patient and obvious differences in the administration method". Furthermore, the differing routes of administration (DPI vs. nebulised) were necessary to allow Forest to obtain data on treatment burden and QoL using the CFR-Q (Cystic Fibrosis Questionnaire-Revised), the recommended instrument of the EMA at the time. (iv) EMA instructed the comparator MUST be nebulised tobramycin as this was the only approved treatment for the intended indication available at that time. These recommendations will be described in the sections below.	research guidelines for the development of medicinal products for the treatment of cystic fibrosis. The Committee concluded that the evidence base for assessing the clinical effectiveness of colistimethate sodium and tobramycin DPIs was of, at best, modest quality but that it was the best available. See FAD section 4.3.8
Forest	Non-inferiority studies in CF are new and this is an evolving area. In asthma studies, typically a 5% non-inferiority limit, with 95% confidence interval, have been used. Based on advice from the CF clinical community and the EMA we selected a more challenging non-inferiority limit of 3%.	Comment noted.
Forest	The Statistical Analysis Plan (SAP) was finalised prior to study start and included methodology to account for both the normal and non-normal distribution of the data. Determination of the normality of the data was undertaken using the Shapiro-Wilks test which indicated the data were not normally distributed and therefore the data were analysed with log transformation as well as non-parametrically. With these analyses there is no doubt that the trial provides robust, scientifically credible evidence that colistimethate sodium DPI is non-inferior to nebulised tobramycin solution when	Comment noted

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	assessed using FEV1 as the primary endpoint.	
Forest	It is incorrect that the ACD reports that "colistimethate sodium DPI was marginally less efficacious than tobramycin nebuliser solution..." This conclusion is drawn from a parametric analysis of untransformed data. As the data is not normally distributed, this is a significant error on the part of the Assessment Group which requires correction. Forest believe it is this error alone which leads Appraisal Committee to draw a wrong and different conclusion regarding the clinical efficacy of colistimethate sodium DPI to that presented by EMA in the publically available European public assessment report (EPAR) for the product.	Comment noted. The results of the log-transformed and non-parametric ITT population LOCF data analyses were –0.98% (95% CI –2.74% to 0.86%) and –2.16% (95% CI –2.16% to 1.00%) respectively, suggesting in both cases that colistimethate sodium DPI was non-inferior to nebulised tobramycin. For the PP population the ANCOVA, log-transformed and non-parametric analyses using LOCF data indicated that the non-inferiority hypothesis was satisfied for non-parametric analysis only (ANCOVA –1.49% [95% CI –3.79% to 0.81%], log-transformed –1.10% [95% CI –3.08% to 0.97%] and non-parametric –2.57% [95% CI –2.57% to 1.16%]). See FAD section 4.1.4
Forest	Please Note: Utilisation of the untransformed data and hence the wrong conclusion drawn regarding clinical efficacy is only one of numerous errors contained within the ACD, the Evaluation Report and Overview documents. Please refer to the Appendix (sections 7.1, 7.2 and 7.3) for full details.	Comment noted.
Forest	Nebulised tobramycin was the only appropriate comparator at the time The ACD appears very critical of the comparator choice utilised in the FREEDOM trial, with the Appraisal Committee's key concern being a wish to see data comparing colistimethate sodium DPI with nebulised colistimethate sodium. Initially two choices of comparator were considered – nebulised colistimethate sodium or placebo, however, the	Comment noted. The Committee discussed the appropriate comparators for colistimethate sodium and tobramycin DPIs. It heard from the manufacturer of colistimethate sodium DPI that the EMA had

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	instruction given by EMA to use nebulised tobramycin (as nebulised colistin did not have credible evidence or widespread regulatory approval in this indication) was very influential in our final choice. A detailed explanation is provided below: (i) A placebo control trial was rejected by the clinical community on the grounds of ethics, as physicians did not want to treat patients in such a lengthy (24 week) trial with an agent which would provide no relief. (ii) EMA rejected nebulised colistimethate sodium as the comparator on the grounds that such a trial would be futile, as it would generate indeterminate data against a comparator for which the treatment effect was not known and which was not authorised in the specific indication at the time. Furthermore, the EMA's protocol assistance in September 2002 stated "there are several reasons for seriously questioning the validity of nebulised colistimethate as the active comparator of choice, although it is used in several CF-centres in Europe"; EMA continued: "…nebulised colistimethate is not registered in many EU countries" and "…the efficacy of nebulised colistimethate sodium with regard to FEV1% predicted versus placebo is not sufficiently established in robust clinical trials in the sought indication" and EMA concluded: "Hence, reliance on this comparator for the proof of efficacy and the demonstration of significant benefit appears questionable."	indicated that the most appropriate comparator at the time of the study design for their pivotal trial would be nebulised tobramycin because this was the only licensed comparator in all of the study site countries. See FAD section 4.3.4
Forest	Quality of life is poorer for PsA infected people with CF As recognized by the Appraisal Committee, the subset of CF subjects with chronic PsA infection (estimated to be 3,200 patients) have a significantly worse prognosis and QoL than those with intermittent infection as the chronic nature of the disease leads to and accelerates the progressive decline in lung function characteristic of CF and is central to the respiratory related morbidity and mortality. The advantages of inhaled antibiotic therapy for PsA infection in people with CF have been recognised for nearly 40 years, with the hypothesis that an antibiotic delivered directly to the site of infection will be maximally effective and achieve sputum antibiotic levels far in excess of those achievable by intravenous administration without the risks of systemic toxicity.	Comment noted. The Committee considered the treatment burden associated with cystic fibrosis. See FAD sections 4.3.5 and 4.3.6.

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Forest	Furthermore, the personal written expert testimonies of both Professor Greening and Dr Ketchell describe the advantages to the patient in terms of the potential for improved compliance and reduced treatment burden when medications can be administered via a DPI. These testimonies are further supported with a selection of quotes previously provided to NICE as personal expert statements. • "There is a significant problem currently with compliance by people with CF, which this new technology could help to address." (The Royal College of Nursing) • [DPIs] "…will help with adherence as adults and children with CF already take many medications and treatments and therefore poor compliance is common. Anything that makes the treatment quicker and easier would be helpful to improve adherence and the burden of care." (Emma Lake, a person with CF) • "The technology mainly would aid better compliance which could help more effective eradication and better management of the condition. In turn this could help reduce exacerbations and time spent in hospital. This could help to increase life expectancy, independence and overall quality of life." Emma Lake a person with CF • [DPIs will] "…help with adherence as adults and children with CF already take many medications and treatments and therefore poor compliance is common. Anything that makes the treatment quicker and easier would be helpful to improve adherence and the burden of care." (Lynsey Morton, a person with CF) • "…the convenience of a DPI may result in improved adherence once the patient is used to taking the medication, and is aware of appropriate cough control techniques." (The Association of Chartered Physiotherapists in Cystic Fibrosis (ACPCF) notes that)	Comments noted. The benefits of dry powder formulations from the patient and clinician perspective in improving treatment adherence were acknowledged by the Committee. See FAD sections 4.3.5 and 4.3.6
Forest	It is clear the Appraisal Committee also recognise the value of this improved compliance – both to the patient and to the NHS (in terms of reduced hospital administration, given a lower likelihood of exacerbations) with the Committee concluding that in clinical practice (rather than in clinical trials), "…people with cystic fibrosis may be more likely to comply	Comments noted. The benefits of dry powder formulations from the patient and clinician perspective in improving treatment adherence were

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	with a dry powder for inhalation treatment than a nebulised treatment in view of the speed and convenience of drug delivery."	acknowledged by the Committee. See FAD sections 4.3.5 and 4.3.6.
Forest	The data obtained in FREEDOM provide evidence that colistimethate sodium DPI can address several of the criteria identified by the physician, patient and patient carer community. Overall 120/183 (65.6%) preferred colistimethate sodium DPI to nebulised tobramycin. Of particular note, is the finding in the younger age group (6-12year old) where 25/31 (80.6%) preferred colistimethate sodium DPI.	Comment noted. See above.
Forest	This patient preference data is also supported by data presented in the COLO/DPI/02/05 study which evaluated the safety and tolerability of colistimethate sodium DPI compared to nebulised colistimethate sodium in a small cross over study of 16 patients treated for 28 days with either treatment. Regardless of the sequence in which they used the therapy, all patients rated dry powder inhalers as either 'much easier' (62.5% of patients) or as a 'little easier' (25.0%) to use than nebulised treatment.	Comment noted. See above.
Forest	The tendency for a better ease of use assessment for dry powder inhalation than nebulised treatment was more pronounced in children than in adults i.e.75% of children and 50% of the adults rated dry powders easier than nebulised treatments.	Comment noted. See above.
Forest	With regard to the secondary outcome of QoL (using the Cystic Fibrosis Questionnaire-Revised (CFQ-R)) in the FREEDOM study, patients consistently favoured colistimethate sodium DPI compared to nebulised tobramycin in most domains. Although the study was not powered to detect statistical significance there was a highly statistically significant reduction in the burden of treatment with colistimethate sodium DPI, as measured by the burden of treatment domain.	Comment noted. See above.
Forest	Conclusion on clinical trial design and subsequent analysis In the absence of published, consistent clinical or regulatory guidance in 2002, the final clinical trial design for FREEDOM reflected the output of a series of consultations involving the clinical community in the UK and the European regulators (EMA), with particular regard to the primary endpoint, the choice of comparator, the non-blinded nature of the design and the preferred statistical approach. When analysed correctly, that is, using a log transformed dataset and a non-parametric	Comment noted. The Committee concluded that the COLO/DPI/02/06 and EAGER trials may have demonstrated that colistimethate sodium DPI and tobramycin DPI were non-inferior to nebulised tobramycin with respect to change in FEV1% within the populations tested and in the manner conducted within each

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	approach to account for the non-normal distribution, the FREEDOM trial provides robust, convincing and credible evidence that colistimethate sodium DPI is non-inferior to nebulised tobramycin solution, in respect of the primary endpoint, FEV1 predicted, and this was endorsed by the EMA.	trial, but remained concerned with the uncertain clinical relevance of these findings given the short-term nature of these trials. See FAD section 4.3.9
Forest	FREEDOM clearly shows patients have a preference for colistimethate sodium DPI over a nebulised therapy. In addition, evaluation of data captured through the CFQ-R demonstrates a highly significant superiority in reduction of burden of treatment on colistimethate sodium DPI after four weeks treatment.	Comments noted. The Committee heard from clinical specialists that treatment is generally patient driven and that the most important outcomes for the patient that influence treatment decisions are the person's quality of life, treatment burden, maintaining good lung function and reducing the incidence of exacerbations. See FAD section 4.3.2
Forest	Given the above, and in line with current treatment practices reflecting patient need and physician choice, we believe the Appraisal Committee should consider colistimethate sodium as an appropriate DPI therapy, after nebulised colistimethate sodium, for those patients who: 1. cannot / do not comply with nebulised treatment options 2. cannot tolerate tobramycin due to its toxicity profile 3. require individualised patient care comprising of alternating monthly treatment	Comment noted. See FAD section 1 for the final recommendations. The Committee acknowledged that there was a group of people who could benefit or were benefitting from nebulised colistimethate sodium but were unable to tolerate it twice daily in its nebulised form. See FAD section 4.3.19.
Forest	3 Economic models for treatment of PsA in chronic lung infection in people with cystic fibrosis The Assessment Group feedback on Forest's model and their comments on the Assessment Group's own de novo model clearly illustrate that the evidence base to	Comments noted. The Committee also accepted there were limitations to the Assessment Group's de novo model. See FAD section 4.3.15 The Committee concluded that there

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	support economic modelling in this therapy area is limited and unreliable. , , Specifically, the Assessment Group acknowledged "…that it could not fully resolve the problems regarding the time horizon, the health impact of adverse events or the uncertainty surrounding the QALY [quality-adjusted life year] benefits for colistimethate sodium DPI". For the reasons addressed in more detail below, we believe the Appraisal Committee should be cautious in using the economic assessment resulting from its de novo model as a factor in its decision making.	was a great deal of uncertainty in the modelling of colistimethate sodium DPI and that the most plausible ICERs indicated that with the revised patient access scheme colistimethate sodium DPI resulted in a small QALY loss and a substantial cost saving compared with nebulised tobramycin. See FAD sections 4.3.16 and 4.3.19.
Forest	Direct utility data was not available and given the small differences identified, the utility estimates must be regarded as unreliable Utility assessment in cystic fibrosis is difficult, as NICE itself has acknowledged in the recent appraisal of Mannitol for treating CF, where it states "The Committee concluded that current measures of quality of life may not accurately capture the consequences of having cystic fibrosis and of its treatments."	Comment noted.
Forest	At the request of the EMA, both Forest (COLO/DPI/02/06, FREEDOM) and Novartis (EAGER) used the Cystic Fibrosis Questionnaire-Revised (CFQ-R) as the appropriate quality of life (QoL) measure. Forest undertook a mapping exercise to convert the data from CFQ-R to EQ5-D utilities. While acknowledging that this was a less than perfect approach, it did at least make direct use of the mandated QoL data from the clinical trial.	Comment noted
Forest	The alternative approach, used by the Assessment Group, disregards the specific QoL data derived from the FREEDOM trial and instead uses data derived from a separate study (Bradley et al, 2010) to map EQ5-D utilities to FEV1 bands. It should be noted that that this study was presented as a poster at the European Respiratory Society Conference in 2010, but has not been published in a peer-reviewed journal. Moreover, the published data relates FEV1 to pulmonary exacerbations (severe, mild or none) rather than FEV1 levels per se and was applied to a limited subset of 75 patients from the Bradley study.	Comment noted
Forest	Moreover, most studies relating QoL to levels of FEV1, including those referenced by the Assessment Group, use narrower bands than the three strata (FEV1 >70%, FEV1 from	Comment noted

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	69% to 40% and FEV1 <40%) on which the Assessment Group's model is based. With such broad strata, a relatively small number of patients transitioned from one stratum to another, in either the colistimethate sodium DPI or tobramycin for nebulisation arms, thus weakening the comparative analysis. In addition, it is not clear whether the FEV1 data taken from the FREEDOM trial by the Assessment Group was the (incorrect) untransformed analysis or the correct log-transformed analysis. We therefore believe that this approach is flawed, and clearly there must be some considerable uncertainty in the results.	
Forest	Both approaches to calculating utilities produced minor changes, albeit in opposite directions, in the calculated EQ5-D. Using the Assessment Group's approach there was "...an expected tiny decrease (0.002) in QALYs for colistimethate sodium DPI…" over six months. This was then projected over the patient's lifetime to produce a difference of 0.13. Given the indirect nature of the derivation of the QALY, such small differences must be within the margin of error. In contrast, Forest's mapping approach showed an increase in QALY of 0.031 over one year. This too could be said to fall within the margin of error. However, it is at least consistent with the directly observed CFQ-R data taken from the FREEDOM trial, which showed a favourable impact on quality of life for colistimethate sodium DPI compared to tobramycin for nebulisation in 9 out of the 12 CFQ-R domains.	Comment noted
Forest	Given the very small differences calculated and the uncertainties surrounding either approach, we do not believe that the Appraisal Committee should place any reliance on the cost per QALY calculations. In the ACD, the Assessment Group acknowledged that "…the choice of utility value had the most substantial effect on the cost effectiveness estimates." An additional analysis showing the incremental cost effectiveness ration of colistimethate assuming no QALY decrement would have helped to clarify this.	Comment noted. The Committee concluded that there was a great deal of uncertainty in the modelling of colistimethate sodium DPI and that the most plausible ICERs indicated that with the revised patient access scheme colistimethate sodium DPI resulted in a small QALY loss and a cost saving compared with nebulised tobramycin. See FAD section 4.3.16
Forest	Moreover, the result of using the Assessment Group's approach is to push colistimethate sodium DPI, when compared to tobramycin for nebulisation, into the South West	The Committee concluded that there was a great deal of uncertainty in the

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	quadrant (less expensive but less effective) rather than the South East quadrant (less expensive but more effective). This is inconsistent with the clinical data showing non-inferiority and the directly observed QoL data from the FREEDOM trial.	modelling of colistimethate sodium DPI and that the most plausible ICERs indicated that with the revised patient access scheme colistimethate sodium DPI resulted in a small QALY loss and a substantial cost saving compared with nebulised tobramycin. See FAD sections 4.3.16 and 4.3.19.
Forest	Additionally in both the FREEDOM trial and the EAGER trial, patient preferences were clearly in favour of the dry powder inhalers over the nebulisers, and this should be reflected in the overall conclusion.	Comment noted. The Committee further observed that adherence might be greater with the use of a dry powder inhaler. See FAD section 4.3.19
Forest	The relationship between absolute or relative FEV1 and quality of life is not well established, and at best is weak. Modelling based on this relationship is therefore subject to considerable uncertainty There is considerable debate about the relevant endpoint between absolute FEV1 and relative value of FEV1 as a percentage of predicted FEV1. In the Assessment Group's original report they commented that "…only one study identified attempted to examine whether a statistical association exists between FEV1 and EQ-5D utility." This Johnson et al. study suggests that such a relationship may exist, however the size of the coefficient is very small and is unlikely to be clinically meaningful. This indicates that FEV1, at least within the range of scores assessed within Johnson et al, does not represent a good discriminatory indicator of health-related quality of life (HRQoL). Despite this, the Assessment Group's model bases the assessment of cost effectiveness on bands of absolute FEV1 levels and movement between those levels.	Comment noted. Committee acknowledged comments received during consultation that there are inherent difficulties in quantifying the relationship between FEV1 %and quality of life. See FAD section 4.3.15
Forest	The Assessment Group's model understates the costs associated with nebulised tobramycin	Comment noted. The Committee concluded that some people with cystic fibrosis and chronic

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	The Assessment Group's model assumes that no drug is used during the nebulised tobramycin 'off' months. However the Appraisal Committee acknowledged that the model did not reflect the current clinical pathway, as reflected in statements from clinical specialists and patients to the Appraisal Committee, in that some people on nebulised tobramycin would receive treatment on a continual basis, including nebulised colistimethate in the off months. This clearly understates the cost effectiveness of colistimethate sodium DPI in comparison with nebulised tobramycin.	pseudomonas lung infection may receive alternating tobramycin and colistimethate sodium treatment in clinical practice. The Committee noted the increased cost of such alternating antibiotic regimens and that it had not been presented with any evidence as to the clinical effectiveness of this approach by the Assessment Group or the manufacturers or during consultation. It concluded that considered that as there was no evidence of the clinical effectiveness of using alternating antibiotics, it could therefore not consider this issue further. See FAD section 4.3.3
Forest	The Assessment Group's model may also underestimate the costs associated with nebulisation. An estimate is made that the additional costs of nebulisation (over and above the direct drug costs) amount to £200 per year, but this is based on a personal communications and is not subject to any sensitivity analysis. Our own estimate is that the additional annual costs of nebulisation amount to £385 (estimate based on the manufacturer's recommendations for the Pari e-flow and two filters per day plus one handset). Again this may have resulted in an underestimation of the cost effectiveness of colistimethate sodium DPI in comparison with nebulised tobramycin.	Comment noted.
Forest	The Assessment Group's model does not reflect the wider impact of cystic fibrosis on patients, carers and society The Assessment Group's model fails to take into account the wider societal costs associated with CF. Advances in treatment options and the involvement of all stakeholders - patients, carers, medical profession and the industry - over the past 50 years have resulted in massive improvements in the treatment of CF resulting in an	Comment noted. The NICE reference case specifies that costs will be considered from an NHS and Personal Social Services perspective. See the 'Guide to the methods of technology appraisal' (June 2008).

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	increased lifespan. With this increased lifespan comes an extended treatment burden on patients and their carers, family life, and restricted work opportunities and lost workdays due to treatment demands and exacerbations. The model fails to take these broader societal factors, and the potential benefits offered by DPIs, into account, but the Appraisal Committee could do so.	
Forest	3.5 Summary: None of the five key assumptions within the Assessment Group's model are fully substantiated The Assessment Group's model makes the following key assumptions: (i) "FEV1 measurements are stable and not subject to measurement error" This has not been substantiated. (ii) "HRQoL is assumed to differ by FEV1 strata" The relationship between FEV1 and HRQoL has not been substantiated except at FEV1 levels below 40% of predicted. (This represents only a small part of the patient cohort in the Assessment Group's model.) Moreover the FEV1 strata used in the Assessment Group's model are broader than those typically used in clinical trials. (iii) "Transitions between FEV1 strata are assumed to be independent of patients' previous transitions" This has not been substantiated, especially in relation to the strata used in the Assessment Group's model. (iv) "Colistimethate sodium DPI has no additional benefit over nebulised tobramycin in	Comments noted. The Committee acknowledged that there were limitations of the Assessment Group model See FAD section 4.3.15

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	terms of patient survival" This has not been substantiated. (v) "The costs of follow-up and concomitant medication are equivalent between colistimethate sodium DPI and tobramycin nebulised" This is not true. As identified above, there is substantial evidence that additional medications are used by patients treated with nebulised tobramycin solution in the "off" months. In addition the costs associated with nebulisation may have been underestimated. In conclusion, the evidence base to support economic modelling in this therapy area is limited and unreliable; suggesting that modelled economic outcomes should not play a critical role in the Appraisal Committee's determination. In particular it is inappropriate to assess colistimethate sodium DPI as being both clinically less effective and less cost effective on the basis of small margins in an economic model, and in the face of the established clinical evidence of non-inferiority.	
Forest	Cost Forest has noted the comments made by the Appraisal Committee when considering the cost effectiveness of the colistimethate sodium DPI and is in the process of submitting a revised Patient Access Scheme to the Department of Health.	Comment noted.
Forest	Factual inaccuracies Section 7, provides eight pages of factual inaccuracies occurring throughout the Appraisal Consultation Document, the Evaluation Report and the Overview. Several of the more significant findings feature in all documents and these are pulled forward and clarified / corrected in this section. Those described here are identified as being those which may have impacted on the Appraisal Committee's initial decision.	Comments noted.

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Forest	Page 10 of the ACD (Section 4.1.4) the following text is found; similar related text is present on Page 18 of the Evaluation Report "For the primary end point of mean difference in change in FEV1% predicted after 24 weeks of treatment using logarithmic analysis, the results from the ITT population were -1.16% (95% CI −3.15 to 0.84) suggesting that colistimethate sodium DPI was marginally less efficacious than tobramycin nebuliser solution (because the non-inferiority criteria were not met). However, a predefined non-parametric analysis indicated non-inferiority, with the median difference in change in FEV1% predicted after 24 weeks of treatment being -0.56% (95% CI -2.16 to 1.00)" Correction For the primary end point of mean difference in change in FEV1% predicted after 24 weeks of treatment using logarithmic analysis, the results from the ITT population were -0.97% (95% CI −2.74 to 0.86) suggesting that colistimethate sodium DPI was as efficacious as tobramycin nebuliser solution (because the non-inferiority criteria were met). In addition, a predefined non-parametric analysis confirmed non-inferiority, with the median difference in change in FEV1% predicted after 24 weeks of treatment being -0.56% (95% CI -2.16 to 1.00). Impact of correction – colistimethate sodium DPI would be recognised as non-inferior to nebulised tobramycin	Comment noted. The FAD has been amended accordingly. See FAD section 4.1.4
Forest	On Page 33 of the ACD (Section 4.3.8) the following text can be found: "The Committee noted that the study was powered to detect a minimum change in the difference in FEV1% of -3% (based on the lower bound of a 95% confidence interval of a two-sided t-test) and the results of the ITT population showed that colistimethate sodium DPI had not demonstrated non-inferiority (see section 4.1.7) but that a predefined non-parametric analysis had demonstrated non-inferiority."	Comment noted. The FAD has been amended accordingly. See FAD section 4.1.4

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	Correction The reference to section 4.1.7 should be 4.1.4. Section 4.1.4 has presented the wrong confidence interval for the logarithmic analysis – see comment above – thus the conclusion drawn in section 4.3.8 that non-inferiority has not been demonstrated is incorrect, since non-inferiority has indeed been shown. Impact of correction – confirms non-inferiority has been demonstrated by colistimethate sodium DPI	
Forest	On Page 34 of the ACD (Section 4.3.8) the following text can be found: "Additionally the Committee noted that the results of COLO/DPI/02/06 trial indicated it had failed its primary non-inferiority end point…" Correction Section 4.1.4 has presented the wrong confidence interval for the logarithmic analysis – see comment above – thus the conclusion drawn in section 4.3.8 that non-inferiority has not been demonstrated is incorrect, since non-inferiority has indeed been shown. Impact of correction – confirms the FREEDOM study met its primary endpoint	Comment noted. The Committee noted that the non-inferiority criterion was not met in the pre-defined ANCOVA analysis for the ITT population but it acknowledged that in the logarithmic and non-parametric analyses the non-inferiority criterion had been met in the ITT population for the LOCF analysis. See FAD section 4.3.9
Forest	On Page 384 of the Evaluation Report the following text can be found: "My interpretation of the COLO/DPI/02/06 trial is that it is intrinsically flawed in design. (I observe that the trial has not been published in a peer reviewed publication, which is very surprising. Is this because it has never been submitted [if so why not?] or because referees have rejected it?)." Correction	Comment noted.

Consultee	Comment	Response
	The COLO/DPI/02/06 (FREEDOM) trial has now been published and we are concerned that this statement appears to be imputing motives to Forest which are incorrect and that the clinical specialist is speculating on clinical trial design. The design of the study has been discussed above and is now part of the standard convention in evaluation inhaled antibiotics in CF. Impact of correction – speculation of clinical specialist addressed	
Forest	On Page 384 of the Evaluation Report the following text can be found: "Both interventions should have had the same starting point, and ideally in patients naïve to both drugs, but at least in a balanced selection with regards prior use of either." Correction It seems that the clinical specialist is not aware that a run-in period had to be with a licensed product and at the time of the trial there was no other registered product. Impact of correction – clinical specialist comments addressed	Comment noted
Forest	On Page 52 of the Overview (Appendix B) the following text can be found: Appendix B requires correction for several points regarding the annual cost of various products. Correction The following costs should be inserted. • Colistimethate sodium (non-proprietary) only comes in 1mu vials • Nebulised colomycin should have the annual cost of £1,226.40 1mu and	Comment noted

Consultee	Comment	Response
	£2,255.70 for 2mu • Promixin annual cost should be £3,358 1mu twice daily, £6,716 2mu twice daily Full details of the corrections required are provided for convenience in the Section 7.4 of the Appendix. (Not reported here) Impact of correction – may have an impact on the cost comparison across treatments	
Forest	6 Conclusion Cystic Fibrosis is a devastating, genetic, multi-system chronic disease, affecting 8,500 people in the UK, causing significant morbidity and mortality (median age of death of 29 years). Of these CF patients, around one third [~3,200] have chronic PsA infection, which is the main cause of death, requiring highly individualised patient care for effective management. This document continues to demonstrate the need for patients within this therapeutic area to have the option for individualised, tailored patient care, articulated in the NICE Mannitol Final Appraisal Determination and the written expert statement of Dr Ian Ketchell.	Comment noted.
Forest	Ms Emma Lake (a person with CF) in her own personal written statement identifies the preferences of the patient for medications with improved ease of use and reduced treatment burden, ultimately leading to improved patient compliance and potentially better long term outcomes for suffers. Colistimethate sodium DPI can deliver both of these patient choices.	Comment noted. The benefits of dry powder formulations from the patient and clinician perspective in improving treatment adherence were acknowledged by the Committee. See FAD sections 4.3.5 and 4.3.6
Forest	For physicians who currently individualise patient care by prescribing alternating colistimethate sodium and tobramycin therapy, provision of only a single medication as a DPI will result in an unworkable treatment paradigm (DPI/nebuliser/DPI/nebuliser) that has the potential to limit patient choice and contribute to a decline in lung function.	Comment noted. The Committee concluded that as there was no evidence of the clinical effectiveness of using alternating antibiotics, it could therefore not consider this issue

Consultee	Comment	Response
		further. See FAD section 4.3.3
Forest	This response addresses the factual inaccuracies which may have contributed to the Assessment Group's initial determination of colistimethate sodium DPI's clinical efficacy. Once these inaccuracies are addressed and the determination is made using the correctly identified log transformed dataset, there is no doubt colistimethate sodium DPI has similar efficacy to nebulised tobramycin when using FEV1 as the primary endpoint in a study of 24 weeks.	Comment noted.
Forest	Colistimethate sodium DPI offers a vital treatment option for those CF patients who clinically benefit from colistimethate sodium but either adhere poorly to or do not tolerate well conventional nebuliser therapy. This holds true whether the product is used as the only inhaled antibiotic or in an alternating pattern with tobramycin DPI based on clinical need and judgement. Furthermore, for that subgroup of people with CF who are identified as aminoglycoside sensitive or intolerant, it is the only dry powder treatment option that clinicians could utilise.	Comment noted. The Committee acknowledged that there was a group of people who could benefit or were benefitting from nebulised colistimethate sodium but were unable to tolerate it twice daily in its nebulised form. See FAD section 4.3.19.
Forest	With regard to the proposed economic model, it is clear that the evidence base to support such a model in this therapy area is limited and unreliable, affecting both the initial Forest model and also the Assessment Group's own de novo model. Given this, significantly more weight should be given to the clinical data and the views of the physician and patient community.	Comment noted.
Forest	Forest is in the process of submitting a revised Patient Access Scheme to the Department of Health.	Comment noted.
Forest	We trust the Appraisal Committee will reconsider their recommendations, given the additional clarification and information provided in this response, in conjunction with the revised Patient Access Scheme; enabling appropriate patients to access this effective innovative treatment by recommending colistimethate sodium DPI use. Ultimately, recommending colistimethate sodium DPI for approval will provide physicians and patients with the opportunity to individualise patient care using DPIs for optimal outcome, improving patient compliance and promoting choice & equality for people with this rare, devastating, chronic, genetic disease	Comment noted. See FAD section 1 for the final recommendations.

Consultee	Comment	Response
Healthcare Improvement Scotland	Clinical need and practice section 2.1 The statements in this section although technically correct, have recently been extended to include multiple additional mechanisms that are unrelated to CF as an Ion Transport Disease (ITD). It is important to add that Cystic Fibrosis is also recognised to be a disorder of pathogen sensing and a disorder of cell stress and hyper-inflammation.	Comment noted. The clinical need and practice section aims only to provide a very brief summary of the condition and its management.
Healthcare Improvement Scotland	Section 2.2 1 in 64 people in the United Kingdom who have Cystic Fibrosis are of Asian origin (McCormick et al Eur J Human Genetics) . In addition, increased inter marriage between races is complicating the 'CF as an ITD of whites in Europe' accepted clinical picture. The statement it is much less common in people of African and Caribbean and Asian origin should be removed and replaced with an appropriate statistic. The last paragraph is misleading as it mixes two unrelated issues. The 103 deaths of UK patients with a median age of 29 has advanced by approximately seven years since the year 2000. This median age at death is reflective of care using older therapies and prior to screening that occurred some twenty years ago. It is imperative not to mix this issue up with median survival which for current cohorts, cannot be predicted. For example it is expected that less than 5% of babies diagnosed with Cystic Fibrosis today will die before their 20th birthday.	Comments noted. The clinical need and practice section aims only to provide a very brief general overview of the epidemiology of the condition.
Healthcare Improvement Scotland	Section 2.3 Childhood CF and adult CF differ such that hypertonic saline is not of benefit in childhood. And whilst the statements in section 2.3 are technically correct, it is also important to note that nutrition is one of the major idrivers that relates to pulmonary health in Cystic Fibrosis up to a max BMI (Kastner-Cole et al J Cyst Fibrosis).	Comment noted. The clinical need and practice section aims only to provide a very brief summary of the condition and its management.

Consultee	Comment	Response
Healthcare Improvement Scotland	Section 2.4 The idea that single organisms can be thought of in isolation as pathogenic factors in Cystic Fibrosis, whilst technically true, is not reflective of modern understanding of the condition. The complex microbiology of Cystic Fibrosis is now out of date as it does not include the most crucial understanding that the pseudomonas is stimulated to grow by factors secreted by other pathogens. The words complex micro-biome are key. For example, the role of viruses such as Rhinovirus which persists in Cystic Fibrosis lungs for unknown reasons should be remembered.	Comment noted. The clinical need and practice section aims only to provide a very brief summary of the condition and its management.
Healthcare Improvement Scotland	Section 2.5 A comment might be added that host factors which vary between patients even with the same genotype in Cystic Fibrosis seem to be important in the transition from no infection through to long term sustained infection (Corvol et al J Cystic Fibrosis)	Comment noted. The clinical need and practice section aims only to provide a very brief summary of the condition and its management.
Healthcare Improvement Scotland	Section 4.1.2 Whilst I can see the use of throat irritation as a complication or side effect of the treatment whether it is with the agent in question or with another dry powder formulation, when a patient coughs it is rather more difficult to be sure that this is actually a side effect. After all should the bacteria be killed and more mucus production and/or a different quality of mucus is produced, the patient may cough in order to clear the mucus from the lung.	Comment noted.
Healthcare Improvement Scotland	Section 4.1.3 and Section 4.1.4 in combination. The work of Taylor-Robinson shows that the intrinsic variability in a given patient in their lung function due to the condition is 5% (random error) so I fail to see how the statement in section 4.1.4 can be supported. There is no difference between the two treatments in my view.	The Committee remained concerned at the uncertain clinical relevance of a small change in FEV_1% predicted given the short-term nature of these trials. See FAD section 4.3.9
Healthcare Improvement Scotland	Section 4.1.5 My comments above apply in that we don't know whether the so called acute	Comment noted.

Consultee	Comment	Response
	exacerbation is actually a benefit of treatment in this condition.	
Healthcare Improvement Scotland	Section 4.1.6 Is it necessary to use dysgeusia? 70% of 'taste' is actually smell!	Comment noted.
Healthcare Improvement Scotland	Section 4.1.7 Given the nature of the condition I could not really understand why quality of life criteria would be of any benefit in this kind of treatment.	Comment noted. Health Related Quality of Life is specified as an outcome in the scope and this data is a key component of the economic evaluation.
Healthcare Improvement Scotland	Combining Sections 4.1.8 and 4.1.9. From my perspective given that the rate of decline of lung function is approximately 1% per year (or less) and that the variability in the measure of lung function is around 5% just as a random variation, it seems that such Studies are never going to reveal any interesting results without much larger numbers and better stratification.	Comment noted. The Committee remained concerned at the uncertain clinical relevance of a small change in FEV_1% predicted given the short-term nature of these trials. See FAD section 4.3.9
Healthcare Improvement Scotland	Section 4.1.10. It is commonly observed that the complex microbiome of the Cystic Fibrosis lung means that resistance that is reported to one particular antibiotic bears no relationship to the clinical outcome which, despite 'resistance' is nonetheless associated with an improvement of lung function and a better weight for the patient. Indeed it is commonly observed that one of the earliest indications of being ill in Cystic Fibrosis is a drop in the weight percentile.	Comment noted.
Healthcare Improvement Scotland	Section 4.1.14. I concur with these conclusions and would suggest that any future evaluations should include a prior assessment using registry data of the number and frequency of outcome related events. This should be readily available given the quality and density of data this	Comment noted.

Consultee	Comment	Response
	is now stored on the registries. New data are available (Boelle et al Orphanet web site, J Rare Disease) on the CF centiles for lung function.	
Healthcare Improvement Scotland	Section 4.2.10. This is a critically important section because it reflects the fact that the state of the Cystic Fibrosis patients, particularly those born after 1986 when proper nutritional therapy became available, is very different from those born before this date who had an early childhood experience of poor growth and poor body mass index. This impacts on lung development. I note that the assessment group did not include a switch between the two different agents and this is an important clinical parameter because patients do change as a result of the development of allergies having been on certain treatments for a long period of time. The clinician is then faced with either trying to desensitise the patient or switching therapy.	Comment noted. The Committee were aware that some people may switch between colistimethate sodium and tobramycin at some point in their lives. However, clinical-effectiveness data on the effect of treatment switching were not available. See FAD section 4.2.10
Novartis	Novartis welcomes the opportunity to comment on the above Appraisal Consultation Document (ACD) and accompanying Evaluation report which were disseminated on 16 October 2012. Novartis is delighted that the preliminary guidance from the Appraisal Committee outlined in the ACD recommends the use of tobramycin inhalation powder. In issuing this preliminary recommendation, the Appraisal Committee has recognised the added benefits of tobramycin inhalation powder for the treatment of chronic pulmonary infection caused by Pseudomonas aeruginosa in people with cystic fibrosis. Futhermore, we are pleased that qualitative parameters have been taken into consideration, primarily around the possibility that patients on dry powder inhalers may be more likely to comply than those on nebulised treatment due to the speed and convenience of drug delivery.	Comment noted.
Novartis	Overall, we found the Appraisal Committee has taken into account all of the relevant evidence and consider, in general, that the summaries of clinical and cost-effectiveness are reasonable interpretations of the evidence. Novartis supports the provisional recommendations as a sound and suitable basis for guidance to the NHS.	Comment noted.

Consultee	Comment	Response
Novartis	Within the Evaluation Report, there are a number of possible points of clarification. However, these comments are unlikely to materially affect the overall conclusions determined by the Appraisal Committee and thus extensive comments have not been put forward. Once again, we are grateful for the opportunity to comment on the ACD and look forward to continued dialogue with NICE.	Comment noted.
Patient Experts	We welcome the initial recommendation from the NICE, that Tobramycin dry powder for inhalation for cystic fibrosis (CF) should be an option. However it is very disappointing to learn that NICE have initially decided not to recommend Colobreathe (colistimethate sodium dry powder for inhalation, Forest Laboratories).	Comment noted. Comment noted. See FAD section 1 for the final recommendations.
Patient Experts	As two consultees to the process - a patient with CF and a parent of a child with CF - we welcome new proven treatments such as Colobreathe that reduce treatment burden and encourage adherence. Dry powdered inhalers will have a meaningful impact on what is currently a relentless treatment regime. These new treatments will make a real difference to the everyday lives of people with CF, by making treatment easier and quicker. Improved adherence, due to decreased treatment burden, has been proven to result in improved health outcomes.	Comments noted. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5 The benefits of dry powder formulations from the patient and clinician perspective in improving treatment adherence were acknowledged by the Committee. See FAD sections 4.3.5 and 4.3.6

Consultee	Comment	Response
Patient Experts	Dry powdered inhalers are also more efficient than many current nebulizer systems due to amount of the drug escaping into the air during nebulisation. These new devices will deliver the full dose using the correct technique.	Comment noted.
Patient Experts	If Tobramycin is the only treatment recommended, this will affect patient and clinician choice. Those who are not able to take or tolerate Tobramycin should similarly be able to be able to reduce their treatment burden. Therefore it is important that both therapies are made available for those with Cystic Fibrosis	Comment noted. See FAD section 1 for the final recommendations.
Royal College of Paediatrics and Child Health	Page 10 I would be grateful for clarification on the statement on page 10 that: For the primary end point of mean difference in change in FEV1% predicted after 24 weeks of treatment using logarithmic analysis, the results from the ITT population were -1.16% (95% CI −3.15 to 0.84) suggesting that colistimethate sodium DPI was marginally less efficacious than tobramycin nebuliser solution (because the non-inferiority criteria were not met). Surely if the confidence intervals range between -3.15 and 0.84, then there are no differences between the two treatments in terms of FEV1. This does appear to be critical since the basis by which NICE has not recommended the use of Colobreathe is that it is less efficacious than nebulised tobramycin. This impression of lack of efficacy seems to be re-inforced by the slightly higher exacerbation rate – but once again this does not seem to be statistically different between the 2 groups.	For the non-inferiority criterion to be met the lower 95% confidence interval must not go below -3 (i.e. 3%). As the results from the ANCOVA analysis had a lower confidence interval of -3.15, non-inferiority was not met. See section 4.3.9 of FAD for further details.
The Royal College of Nursing	**Has the relevant evidence been taken into account?** The ACD is very comprehensive and thorough. We consider that the available evidence seem to have been taken into account accordingly.	Comment noted.
The Royal College of Nursing	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The summaries of clinical and cost effectiveness appear to have been reasonably	Comments noted.

Consultee	Comment	Response
	interpreted. We note the statements in section 4.1.14 that the evidence provided by the two manufacturers was not of a very high quality ("poor to moderate") and that some of the answers required were not available (i.e. the comparator for the study for colistimethate was nebulised tobramycin, whereas nebulised colistimethate would have been more appropriate). We also note the committee's comments that the models used for some of the cost analysis were not up to date or very accurate and as a result that it was difficult for the committee make fully informed comments.	
The Royal College of Nursing	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** We welcome the committee's recommendation that Tobramycin dry powder for inhalation can be used as an option for treating chronic pulmonary infection caused by Pseudomonas aeruginosa in people with cystic fibrosis (CF). We are however, disappointed to note that colistimethate dry powder for inhalation has not been recommended for use in the NHS for treating chronic pulmonary infection caused by Pseudomonas. aeruginosa in people with cystic fibrosis. Some CF patients tolerate nebulised tobramycin better than colistimethate and vice versa so it has always been appropriate to prescribe the medication that "suits" the patient best in the past. In future, CF clinicians will not have the option of deciding between two medications to treat people with P. aeruginosa with CF. It is understood that nebulised colistimethate may still be used, but it is anticipated the dry powder inhalation preparations will be much preferred by patients for ease of use and better adherence. In the limited interpretation of results for both these medications, it would appear that neither appeared to have a statistically significant benefit over the other and it remains uncertain as to whether this is the case.	Comments noted. See FAD section 1 for the final recommendations.

Consultee	Comment	Response
	Further long term trials with appropriate comparators are required. Although neither medication has definitively been proven to be more effective than the equivalent nebulised medication, it is anticipated that many patients will prefer to take the dry powder inhalation preparation over nebulisation for the reasons stated above. The dry powder inhalation medication will also eliminate the need for nebuliser machines and the sundry equipment required to use the machine, thereby reducing costs significantly. Although this was mentioned briefly in the ACD, it does not appear to have been taken into account (4.2.12). This cost saving could have been taken more fully into account (for both medications).	
The Royal College of Nursing	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?** None identified.	Comment noted.
The Royal College of Nursing	**Are there any equality-related issues that need special consideration that are not covered in the appraisal consultation document?** We are not aware of any specific issue at this stage. We would ask that any guidance issued should show that an equality impact analysis has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate	Comment noted. All NICE guidance has an associated equality impact assessment – this will be published on the NICE website alongside the final guidance.

Comments received from members of the public

NHS Professional 1	**Other**	1. A basic fact is that in the UK, the management of CF differs widely from centre to centre in the UK, and also differs widely between children and adults with CF. Whilst there are approaches common to many CF centres, there are a number of very notable differences. For example at centre A, there is considerable use of long term oral corticosteroids, whereas at centre B there is enthusiasm for the use of enteral feeding by gastrostomy. There are notable differences in the enthusiasm for the use of regular 3 monthly intravenous anti-Pseudomonas antibiotics, our own policy being at the enthusiastic end of the spectrum. Maybe the most stark illustration is that the model of care for paediatric patients is treatment by the CF centre for children with live near to a centre, and so-called “shared care” or “networked care” for those who live closest to a district general hospital (DGH). The shared care model provides all basic CF care by the local DGH CF team, with regular input from the regional CF centre team. For example, I visit and conduct a joint CF clinic with the local CF team in Blackpool and Lancaster twice a year, with the result that all patients with CF in those cities are seen by a specialist from the regional CF centre at least twice a year. Between clinic visits there is regular communication between the DGH and regional centre CF teams, and for specialised diagnostic or therapeutic procedures (e.g. bronchoscopy) the patient travels to the regional centre. In contrast, adult regional CF centres have turned their back on any form of shared care, and insist on all patients travelling to the regional centre, even when this involves considerable distances.	Comment noted. The Committee considered the current treatment pathway for people with cystic fibrosis with chronic P. aeruginosa lung infection. See FAD sections 4.3.2 and 4.3.3.

NHS Professional 1	**Other**	Thus the fundamental management of the CF changes in the UK at the age of 18, this change having no evidence in support from RCT's.	Comment noted.
NHS Professional 1	**Other**	2. The study in question, between tobramycin dry powder and colismethate sodium dry powder, has little relevance or applicability to our own management of CF. Comparison of these two treatments implies that they are likely to be used in a similar way, in similar clinical situations. I reality our own use of these two inhaled antibiotics is completely different. Starting with the nebulised drugs, we have used colistimethate by nebuliser for many years, in patients whose lungs are colonised with Pseudomonas aeruginosa. This has been (i) either as part of a so-called "eradication" regimen in children in whom PA has been isolated for the first time, when treatment is given with a combination of oral ciprofloxacin (for 6 weeks) and twice daily nebulised colistimethate, usually for 6-12 months or more, depending upon whether there is a re-growth of PA, or (ii) on a long term basis for patients chronically colonised with PA in whom there are significant symptoms in between the regular 3 monthly courses of intravenous anti-PA antibiotics we give to all patients chronically colonised with PA. Inhaled tobramycin plays no part in either of these regimens, for a number of reasons. One is that despite prolonged use over many years, the development of resistance of PA to colistimethate is extra-ordinarily unusual, so the antibiotic can be given indefinitely without the development of resistance. I can recall only a single case in which this occurred. Another reason is that we	Comments noted. The Committee considered the current treatment pathway for people with cystic fibrosis with chronic *P. aeruginosa* lung infection. See FAD sections 4.3.2 and 4.3.3

		regard intravenous tobramycin as being of particular value, and we greatly rely on its use. An important drawback to the use of nebulised tobramycin is the development of resistance, which is the reason why the drug cannot be administered for more than 1 month at a time. Another drawback to one particular brand of tobramycin, namely TOBI, is that the formulation is irritant and poorly tolerated. As a consequence, we have not used nebulised TOBI for some years, and on the infrequent occasions when we have used nebulised tobramycin we have used the BRAMITOB formulation, which is far less irritant.	
NHS Professional 1	**Other**	Nebulised colistimethate has one major drawback, which is that it requires to be given via a nebuliser, which is time consuming. This is seen by children and families as a huge drawback. A good illustration of this was given by a parent who gave a paper on her experiences as a parent of two children with CF to one of the annual conferences on CF which I have organised for many years at the Royal Society of Medicine. I have attached a copy of the paper. It describes the very time consuming nature of administering nebulised medication to children with CF. This message was rather strikingly emphasised by the speaker explaining how when nebulised DNAse had been commenced in one of her children, the mother admitted that she had actually hoped it would not work because of her concern about the burden of an additional nebulised medication.	Comment noted. The Committee considered the treatment burden associated with cystic fibrosis. See FAD section 4.3.5
NHS Professional 1	**Other**	It is self evident that a dry powder formulation of colistimethate has the potential to make a great deal of difference to our patients and their families, and I would be concerned were this treatment to be unavailable. We are aware, of course, of the availability of a dry powder	Comment noted. See FAD section 1 for the final recommendations.

		formulation of TOBI, but this requires the administration of 4 capsules which has been estimated to take a similar amount of time to the administration of a nebulised dose, but far more importantly the powder cannot be used continuously for more than 4 weeks and is therefore unsuitable for our patients who are receiving long term nebulised colistimethate. A final point is that we reserve nebulised tobramycin for the most severely affected patients, who tend to have poor lung function, making it difficult for them to use the Podhaler device, which as a result I have yet to prescribe or recommend.	
NHS Professional 1	**Other**	In conclusion, the concern is that the limited expert advice that has been offered has failed to reflect what happens in clinical practice, and that the provisional decision will severely limit patient choice.	Comments noted. The Committee considered the current treatment pathway for people with cystic fibrosis with chronic *P. aeruginosa* lung infection. See FAD sections 4.3.2 and 4.3.3.
239 members of the public submitted these comments to NICE, through the web comments system:	**Section 1** (Appraisal Committee's preliminary recommendations)	I agree with the following statement from the Cystic Fibrosis Trust: Colobreathe (colistimethate sodium dry powder for inhalation, Forest Laboratories) should be recommended for the treatment of pseudomonas infections.	Comments noted. See FAD section 1 for the final recommendations.
239 members of the public submitted		The benefits over other treatments include: An alternate inhaled treatment option for patients who are contraindicated for tobramycin	Comment noted. The Committee acknowledged that some people would be amino-glycoside insensitive or otherwise intolerant to tobramycin. However the

these comments to NICE, through the web comments system			Committee agreed that given its understanding of the treatment pathway this group receive colistimethate as a first line treatment and then an alternative treatment to tobramycin once they failed on colistimethate. The Committee therefore concluded that colistimethate DPI did not have a role to play in the treatment of chronic Ps. aeruginosa in people who were insensitive or intolerant to tobramycin. See FAD section 4.3.19
239 members of the public submitted these comments to NICE, through the web comments system		Treatment burden is reduced because the drug is administered by inhaler rather than by nebuliser. Promotes adherence as quick and easy to administer compared to the current nebulised form of colomycin. Treatment is more likely to be effective as patients will take a full dose because of more convenient inhaled delivery mechanism. There is a great need for further choice of treatments for CF to become available, particularly treatments that are quick and easy to use such as dry powder antibiotics. People with CF have a huge burden of care often having to do hours of treatments and physiotherapy a day. Each treatment that becomes available and is proven to be effective in treating infections and symptoms of CF is a huge step forward in helping people with CF to stay well.	The Committee considered the treatment burden associated with cystic fibrosis. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5
239 members of the public submitted these		We are pleased that tobramycin dry powder will be recommended for people with CF. NICE should also recommend Colobreathe for the treatment of pseudomonas infections.	Comment noted. See FAD section 1 for the final recommendations.

comments to NICE, through the web comments system			
Patient 1	**Section 1** (Appraisal Committee's preliminary recommendations)	I am a 33 year old woman with Cystic Fibrosis whom works 40 hours per week and has done for over 15 years. Being able to reduce my treatment time would make a huge improvement to my live. Ensuring I receive adequate dosages also means I will keep infections to a minimum and less time off of work which will ultimately the NHS money and ensure that for as long as possible, I remain an active, tax paying member of society. Â I ask that you strongly consider the quality of life improvements that this product would bring to those actively LIVING with this disease.	The Committee considered the treatment burden associated with cystic fibrosis. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5
Carer 1	**Other**	My son need all the options open to him. The more doors we open for his specialist to choose, then better chances he has. He deserves deserves a better, longer quality of life.	Comment noted. See section 1 of the FAD for the final recommendations
Carer 1	**Section 4** (Evidence and interpretation)	QALY - More options will provide a better QALY outcome for carer - in delaying the total contraindiction point.	Comment noted.

Carer 2	**Section 2** (Clinical need and practice)	Any new drugs that will reduce the burden of treatment and improve quality of life is most welcome. Watching my 18 year old daughter struggle on a daily basis with her punishing regime Â of drug therapy, nebulised treatment & physio is something I would not wish on any parent. If this new drug could be of benefit and speed the drudgery for my daughter even by 5 minutes a day would be fantastic.	The Committee considered the treatment burden associated with cystic fibrosis. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5
Carer 3	**Other**	Our child had cf and would benefit from this greatly	Comment noted.
Patient 2	**Section 2** (Clinical need and practice)	While it is true that CF sufferers have problems with both respiratory and digestive systems, it is the respiratory problems which mainly affect both their quality of life and life expectancy. The digestive problems are often well controlled with modern enteric-coated enzymes which are easily and quickly taken. Anything which makes managing or alleviating respiratory complication easier or quicker therefore has a major impact on the lives of CF sufferers.	Comment noted.
Patient 2	**Section 3** (The technologies)	The fact that different patients respond to different medication in different ways is one reason why there should be as wide a range of treatments as possible available to patients and their medical advisors. As for cost, a better treatment for a CF patient can lead to cost savings for other treatments and procedures which could be necessary if health deteriorates. In the case of my son, and presumably many others, while he is kept well he can continue to work, thereby not claiming unemployment benefit, and contributing Income Tax and National Insurance from his wages.	Comment noted. See FAD section 1 for the final recommendations.

Patient 3		From my own personal perspective as a CF patient, i take both Colymcin and Tobramycin, in 4 weekly alternate cycles. The inhaled tobi is an unbelievable improvement, from what used to take 30 mins to administer, now down to just a few minutes is quite incredible. If colymcin could also be inhaled, this would be massively beneficial too. I also understand that the inhaled form of drug is more effective than the nebulised solution. I strongly urge you to give approval to this, as i know from personal experience how advantageous this would be, as cf patients do have so much treatemnt to fit into their day and any time saving equipment will be hugely welcomed. Many thanks. Andrew	Comment noted. The Committee considered the treatment burden associated with cystic fibrosis. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5
Patient 4	**Section 1** (Appraisal Committee's preliminary recommendations))	As a cf patient, I curently take inhaled tobi and nebulised colymcin, in 4 weekly alternate cycles. It is difficult for me to provide a clinical opinion on this as i am not qualified to do so, suffice to say that time taken to administer oral antibiotics is a big issue and secondl the effectiveness of the treatment. From what i have been advised at the Royal Brompton, the inhaled drug is more effective than the nebulised, in addition to being massively quicker, which as a patient is significantly beneficial.	Comment noted. The Committee considered the treatment burden associated with cystic fibrosis. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5
Patient 4	**Section 2** (Clinical need and practice)	I completely agree with all the above. I also take Azithromycin (3 days per week) in addition to Tobi and Colymcin.	Comment noted.

Patient 4	**Section 3** (The technologies)	The tobi inhaler is just fantastic - i would go as far as to say that it is revolutionary and has reduced the time i take this drug from about 1 hour per day to about 5-10 mins, simply incredible. I am very grateful for this medical advance and for my GP to fund this. If Colistimethate can provide similar benefits, then it has my strong support.	Comment noted.
Patient 4	**Section 4** (Evidence and interpretation)	There is much analysis here and much to digest. I re-iterate my previous comments that inhaled tobi has been hugely beneficial to me, and further inhaled antibiotics, which are both time saving and effective must be beneficial.	Comment noted.
Patient 4	**Section 5** (Implementation)	The sooner the better, as always	Comment noted.
Patient 4	**Section 6** (Proposed recommendations for further research)	I postively welcome all further cf clincial research and indeed am pleased to advise that my company, The Big Yellow Self Storage Company, has chosen cf as our Head Office Charity and i liaise with the cf trust to ensure that all money raised is directed	Comment noted.
Patient 4	**Section 7** (Related NICE guidance)	This seems an awfully long way off - the sooner the better. completely agree with all the above. I also take Azithromycin (3 days per week) in addition to Tobi and Colymcin.	Comment noted.

Carer 3	**Notes**	Please please please reconsider the recommendation for Inhaled Colobreath to be available to people with Cystic Fibrosis. My son is coping with this disease and life at university. The daily burden is huge and this Inhaler would make all the difference to his life. His compliance would be greater and he would stay more well - Thus saving the NHS money. If the research has produced this product, then it should be available.It is mind body and soul destroying to know that its there and would help my son, other sons and all people with CF. Please reconsider.	Comments noted. See FAD section 1 for the final recommendations.
Carer 3	**Section 1** (Appraisal Committee's preliminary recommendations)	Colistimate should be avaialbe. Thise who thinkno t should try making up nebule, sterising equipmemt 2/3/4/ times a day, every day Christmas day, on holiday, when ill. This treatment is a life saver for all the family	The Committee considered the treatment burden associated with cystic fibrosis. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5
Carer 3	**Section 2** (Clinical need and practice)	The compliance using Inhaled Colobreath would be far more frequent and beneficial than nebulising.	Comment noted. The benefits of dry powder formulations in improving treatment adherence were acknowledged by the Committee. See FAD sections 4.3.5 and 4.3.6
Carer 3	**Section 3** (The technologies)	Our child had cf and would benefit from this greatly .	Comment noted.

NHS Professional 2	**Notes**	I think that the dry powder colistimethate is a significant advance in treatment technology for cystic fibrosis patients and should be available for NHS patients. Nebulised colistin is our first line inhaled treatment for patients growing pseudomonas but patients find the nebulisation times too long and the proper care of nebulisers and compressors very onerous. I feel that the availability of the dry powder preparation would greatly enhance the quality of life of these patients and improve adherence to colistin therapy, which is often poor.	Comments noted. See FAD section1 for the final recommendations.
NHS Professional 2	**Section 2** (Clinical need and practice)	The device used in order to administer the antibiotic therapy is likely to be one of the most crucial factors affecting adherence to treatment and longterm outcome after pseudomonas infection	Comment noted. The benefits of dry powder formulations in improving treatment adherence were acknowledged by the Committee. See FAD sections 4.3.5 and 4.3.6
Carer 4	**Section 1** (Appraisal Committee's preliminary recommendations)	My daughter is very ill with cystic fibrosis and has been battling with pseudomonas infection since the age of 5 she is now 18 and is starting to be assessed for transplant. Maybe with better help to fight the pseudomonas infection my daughters health could improve drastically!!! We need every chance we can get we don't want to lose the battle against cf we love our daughter dearly. Please help keep my daughter alive and at home with her family where she belongs!!	Comment noted.

Carer 4	**Section 2** (Clinical need and practice)	I am a full time carer for my daughter who has CF. She is colonised with psuedomonas and aspergillus and regularly grows other bacteria in sputum samples.CF is extremly invasive and significantly impacts on her life.She has a portacath (a permanet indwell indwelling device in her chest, which also necessitates flushing every 28 days)as she needs regular intravenus antiboitics to treat psuedomonas. Her daily routine of medicines, specific CF diet, physiothereapy, nebulisers and inhalers is extremely time consuming and she naturally becomes exasperated from the amount of treatment and the time it all takes. Anything that will help reduce the treatment adherence time will be hugely effective as she is more likely to be encouraged to adhere to her treatments thereby promoting better health and hopefully reducing the requirement and frequency for IV antibiotics and hospital stays. She has periods of depression, as do I due to the intensity of the disease and it's implications. Please help her by recommending and supporting Colobreathe.	Comment noted. The Committee considered the treatment burden associated with cystic fibrosis. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5
Carer 4	**Section 3** (The technologies)	It is proven that these drugs target psuedomonas although the current delivery methods are far from efficient and practical as a nebuliser is needed to administer them. Also it is very time consuming to use and requires an extensive cleaning regime after each use. Standing on it's own this seems rather petty but in conjunction with all the other vital treaments i.e. physio etc it adds up to a substantial amount of time which is at the very least tedious and results in non compliance further resulting in worsening of symptoms then needing MORE treatment and medicines!	The Committee considered the treatment burden associated with cystic fibrosis. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5

Carer 4	**Section 4** (Evidence and interpretation)	When previously using nebulised Colistin over meny years my daughter developed a significant wheeze and cannot tolerate nebulised Tobramycin as it irritates her cough and throat causing lengthy coughing bouts and shortness of breath. She has recently been given the Toby Podhaler which has proven to be ABSOLUTELY AMAZING, in so much as it targets the psuedomonas - keeping it more controlled thereby limiting the lung damage.	Comment noted.
Carer 4	**Section 5** (Implementation)	If this were to be recommended the lives of many people suffering with CF, a chronic life threatening condition would be hugely improved. I believe it is vital to consider the long term rather than short term financial expenditure as it would most certainly encourage CF sufferers to adhere to their extensive treatment regime as it would be less time consuming and invasive.This in turn would reduce the exaserbation of lung disease and consequently hospital admissions.	The Committee considered the treatment burden associated with cystic fibrosis. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5
Carer 4	**Section 6** (Proposed recommendations for further research)	MAnnitol is another wonderful medication to help those with CF please recommend it's availibility on NHS.	Comment noted.
Other 2	**Section 1** (Appraisal Committee's preliminary recommendations)	My granddaughter is a CF sufferer and if there is any way her life can be made easier by having a more effective way of taking a treatment when she is suffering with the pseudomonas infection, then she & her doctors should be able to have that choice.So I really support the statement from the CF Trust , which says that Colobreathe should be recommended for the treatment of pseudomonas infections	The Committee considered the treatment burden associated with cystic fibrosis. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5

Patient 5	**Notes**	I suffer with Cystic Fibrosis, and have been taking nebulised colistin for several years. On top of the various other treatments I have to take, administering this drug is time consuming and to be able to have it as a simple inhaler would improve my quality of life drastically. I do not see any reason that this drug shouldn't be approved immediately, it has been available for years and the NHS are wasting time by not approving it, whilst the lives of thousands of CF sufferers are being detrimentally affected by nothing other than simple bureaucracy. Also, many people with CF (like myself) cannot tolerate nebulised or inhaled tobramycin, and it is not fair that one drug should be approved when another of the same sort isn't!	Comments noted. The Committee considered the treatment burden associated with cystic fibrosis. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5 See FAD section 1 for the final recommendations.
Carer 5	**Section 2** (Clinical need and practice)	My son has Cystic Fibrosis. He manages to maintain a full-time job but finds it difficult to keep up with all his treatment, which includes nebulised Coliston. He would very much welcome a product such as Colobreathe which would make his treatment much easier. As with all people with CF, if he complies with his treatment he is able to stay out of hospital much longer, thus saving the NHS money, and continue working, thus contributing to the economy.	Comment noted.

NHS Professional 2	**Section 1** (Appraisal Committee's preliminary recommendations)	Tobramycin nebulisation can cause significant side effects as the drug may be absorbed. Many patients grow Pseudomonas resistant to Tobramycin while resistance to Colistimethate sodium is unusual. The key study allowing the use of Tobi was based on comparing half dose Colomycin vs nebulised tobramycin in patients previously exposed to the former drug. It was key to compare Colistimethate sodium dry powder to Tobi rather than nebulised colomycin. There are very limited antibiotics and patients find adherence very difficult. The individuals who use the ineb and work need alternatives. Adherence as we have shown is poor and even those individuals who which to be adherent can find it difficult to use nebulisers to to lack of time and convenience. As a doctor I would suggest those prescribing try out all the devices. I did and was amazed as to how unpleasant an Ineb and other nebuliser devices are. Tolerance of various products is variable and we need to have as many products available as possible. Lung deposition of Colistimethate dry powder is excellent and the device is so simple. Infection control is also very important. Fungal and bacterial contamination occurs in all nebuliser devices and disposable systems are key.	Comment noted. See FAD section 1 for the final recommendations.
NHS Professional 2	**Section 2** (Clinical need and practice)	So where is the evidence for azithromycin. What about phage killing and NTM?	Comment noted. The scope of this appraisal was colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis. Evidence was only presented comparing the dry powder formulations with nebulised colistimethate sodium and tobramycin and no other drugs.

NHS Professional 2	**Section 3** (The technologies)	Have the team tested the various devices. They are both very good but one is a lot simpler to use. I agree that cost of Colistimethate sodium dry powder for inhalation needs to be reduced.	Comment noted.
NHS Professional 2	**Section 4** (Evidence and interpretation)	I welcome the decision for TIP but do not agree that the most appropriate comparator for colistimethate sodium DPI would be nebulised colistimethate. This would have gone against all the literature and certainly I would have criticised Forest. Â I also feel that there is too much emphasis on the newer nebulisers as discussed above. Those who are adherent and wish to get on with their life should be able to reduce their infection risk and ease of administration. It is very hard to write the comments as the box is 5 cm long and 3 cm tall.	Comment noted. See FAD section1 for the final recommendations.
NHS Professional 2	**Section 6** (Proposed recommendations for further research)	So where is the evidence for azithromycin. What about phage killing and NTM?	Comment noted. The scope of this appraisal was colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis. Evidence was only presented comparing the dry powder formulations with nebulised colistimethate sodium and tobramycin and no other drugs.

Patient 6	**Notes**	As a CF patient, I know from first hand experience how debilitating Pseudomonas infections can be and how difficult it can be to treat. Any treatment which makes the administration of the drug easier should be welcomed as being connected to an IV three times a day really does limit what you can do and when I have needed to do that, it has meant I needed 2 weeks off work.	Comment noted. The Committee considered the treatment burden associated with cystic fibrosis. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5
Carer 6	**Section 1** (Appraisal Committee's preliminary recommendations)	I concur with the position and recommendation of the Cystic Fibrosis Trust that Colobreathe (colistimethate sodium dry powder for inhalation, Forest Laboratories) should be recommended for the treatment of pseudomonas infections. As a parent of a child with CF I strongly believe that we should have available to CF patients treatments that are effective and reduce the burden of care and improve quality of life. Repeated daily nebulizers (in addition to physiotherapy regimes and oral medications) for multiple medications place a heavy burden on time and effort for patients/carers to administer and manage the treatment. Providing an alternative solution that reduces this effort cost effectively improves quality of life and encourages/facilitates compliance which in turn reduces frequency of hospital submissions. It is the appropriate and correct position to recommend this solution on both moral and total life cycle cost effectivenss grounds.	Comments noted. See FAD section 1 for the final recommendations The Committee considered the treatment burden associated with cystic fibrosis. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5

Public 1	**Section 1** (Appraisal Committee's preliminary recommendations)	My cousin suffered with CF all her life until her death 2 years ago at an incredible age for someone suffering with CF of 35. Â Her life expectancy when she was born was little more than 8 years. Â She fought every day to improve the care for CF sufferers and awareness of the illness. Â Her day to day life towards the end was made incredibly difficult due to the regular need for her nebuliser. Â A drug such as this that could be administered through an inhaler would have made her life much easier. Anything that makes life easier for sufferers of this terrible illness should be made as readily available as possible.	Comment noted. The Committee considered the treatment burden associated with cystic fibrosis. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5
Carer 7	**Notes**	At the age of 7 years my young grandson has had psudomonas twice and treatment is by intravenous anti-biotic under hospitalisation; we all love to see him improve with his treatment but he misses home and a large chunk of education. As Britains most common life-threatening disease CF sufferers need all the help available.	Comment noted.

Other 2	**Section 2** (Clinical need and practice)	Comment from Gilead Sciences UK Ltd. We wish to draw to the attention of the Appraisal Committee that a third inhaled antibiotic is licensed and available for prescription in the UK CaystonÂ® , (aztreonam lysine solution for inhalation) is a monobactam antibiotic indicated for the suppressive therapy of chronic pulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis (CF) aged 6 years and older. It may be used in repeated on/off cycles of 28 days duration. Cayston is administered by nebuliser using the ?e-flow rapid? device and has a significantly shorter administration time of only 2-3 minutes. The safety and efficacy have been extensively demonstrated in a large programme of clinical studies, including a long-term safety study. Â Cayston was shown to be non-inferior to inhaled tobramycin in an active comparator study. Although the addition of Cayston to the current, small range of available inhaled medications for the treatment of pulmonary exacerbations is comparatively recent, we consider that the omission of any reference to this product in the appraisal is an important oversight. Â We would anticipate an acknowledgment of this omission.	Comment noted. The Committee was aware of other products for treatment of chronic *Pseudomonas* infection – however there was no evidence presented comparing them to either colistimethate sodium DPI or tobramycin powder for inhalation as detailed in the final scope for the appraisal issued by NICE.
NHS Professional 3	**Section 1** (Appraisal Committee's preliminary recommendations)	Why dry powder tobramycin but not colistin	Comment noted. See FAD section 1 for the final recommendations.
NHS Professional 3	**Section 2** (Clinical need and practice)	Evidence may be emerging that Azithromicin may be associated with non tuberculous mycopbacterial infection so this strategy may fall in disuse.	Comment noted.

NHS Professional 3	**Section 4** (Evidence and interpretation)	It should be stated that the microbiology of CF is changing rapidly with emerging pathogens especially aspergillus and non tuberculous mycobacteria. These often require multiple antibiotic regimes including nebulised treatment. Together with requirement for mucolytic therapies (Dnase and Hypertonic saline) there is simply not enough time in the day to administer all this nebulised treatment. We simply must replace nebulisation with dry powder devices or we will be forced to stop treatments as we try a guess which pathogen we should treat first. I do not think you have given enough emphasis on reduced treatment time that dry powder devices bring. You have also not mentioned the cost of the actual nebuliser devices in your analysis and the latest devices are not cheap and consumables produce a suprisingly large bill for the NHS. Nebulised treatment is largely frowned on in other areas of respiratory medicine where dry powder alternatives are available and the same should follow in CF	Comment noted. The Committee considered the treatment burden associated with cystic fibrosis. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5
NHS Professional 4	**Section 4** (Evidence and interpretation)	As a clinical psychologist with 22 years experience working with people with cystic fibrosis, much of my work is involved with difficulties associated with adherence to treatment. I am pleased to read that the committee did conclude that the use of dry powder inhaler system would improve quality of life and increase adherence to medication. Greater adherence to daily antibiotics reduces cost of other care such as admissions and added in therapies. The patients and families I work with are eagerly awaiting the availability of an inhaled device for colistin. Parents are keen that this device will reduce their time spent preparing and cleaning the device and people with CF are keen to be able to use something as normal as an inhaler rather than a nebuliser for colistin.	Comment noted. The benefits of dry powder formulations in improving treatment adherence were acknowledged by the Committee. See FAD sections 4.3.5 and 4.3.6

NHS Professional 5	**Section 1** (Appraisal Committee's preliminary recommendations)	It is sad that NICE have decided purely on the basis of cost that Colistimethate shouldn't be recommended. In real practice we get very little resistence to Colistine as opposed to Tobramycin on the basis of its mode of action. Also it is 1 capsule at a time as opposed to 4 capsules. Thus the compliance will decline with passage of time.	Comment noted. See FAD section 1 for the final recommendations
NHS Professional 5	**Section 2** (Clinical need and practice)	As above. Clinically Colistine dry powder is far superior to the Tobramycin dry powder system. Practically, the turbospinhaler is a much easier device to use than the tobramycin podhaler.	Comment noted. See FAD section 1 for the final recommendations
NHS Professional 5	**Section 3** (The technologies)	Though recommendation is a month on and month off, frequently patients are on it continuously, hence encouraging more resistent Pseudomonas to develop.	Comment noted.
NHS Professional 5	**Section 4** (Evidence and interpretation)	Comparative study was done on the basis of EMA requirement for Colistin. May be it should have been more explicit as to what was the best study to do prior to marketting the devices. It would also have been useful to have someone with the knowledge and expertise of CF in the committee.	Comment noted.
NHS Professional 5	**Section 5** (Implementation)	Cost can always be negotiated. If the company doesn't get licence/ NICE recommendation then we are likely to loose an important drug in the treatment of CF in UK. The Forrest are more likely to get European agreement	Comment noted.
NHS Professional 5	**Section 7** (Related NICE guidance)	As above. Clinically Colistine dry powder is far superior to the Tobramycin dry powder system. Practically, the turbospinhaler is a much easier device to use than the tobramycin podhaler.	Comments noted. See FAD section 1 for the final recommendations
Carer 8	**Section 1** (Appraisal Committee's preliminary recommendations)	I have CF and sometimes have reactions to some mediciations. It is therefore important to me to have a number of options available.	Comment noted. See FAD sections 1 for the final recommendations

Carer 9	**Notes**	My daughter really struggles with the high doses of colomycin and the cure is bad mind you the problem worse, please pleae make this available for people like my daughter, she made it to 21, something i never dreamed possible, please let her see more birthdays.	Comments noted. See FAD section 1 for the final recommendations

Patient 7	**Section 1** (Appraisal Committee's preliminary recommendations)	I am a CF patient and the main benefit of dry powder antibiotics to me would be that as it is quick to use and portable, I can take the antibiotic the correct amount of time after my pulmozyme (DNase). It is necessary to wait at least an hour after DNAse before taking nebulised/inhaled antibiotics as the antibiotics reduce the efficacy of the DNase. I have just been prescribed the dry powdered tobramycin inhaler instead of my colomycin nebuliser for alternate months. After just three weeks on this my health has definitely improved. Previously I was did not have enough time or energy (due to coughing fits etc) in the morning to take DNAse, wait an hour and a half (Hour wait + 30mins physio) then nebulised colomycin (15mins + 10mins wash and sterlise) before leaving for work, so I had to just take my colomycin in the morning then DNAse after work. This is not so effective and meant my lungs were not cleared properly all day. Now I do my DNAse and physio before work, then take my TOBI inhaler to work to do anytime during the morning. My health is much improved on this regime! For patients that need colomycin not TOBI, and for patients like me who only take TOBI alternate months, the opportunity to have colobreathe would make a massive difference to both our health (especially for patients that have to do many more nebulisers than myself), and in their quality of life as the majority of CF patients use pulmozyme so experience the same difficulties as me of fitting in the meds at the appropriate times with the right time gaps between them to allow them to work.	Comments noted. The Committee considered the treatment burden associated with cystic fibrosis. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5

Carer 10	**Section 3** (The technologies)	He quicker the technique the more likely a child/person will use this.	Comment noted. The benefits of dry powder formulations in improving treatment adherence were acknowledged by the Committee. See FAD sections 4.3.5 and 4.3.6
Other 3	**Notes**	My Wife and I have an 19 years old Grandchild, who is currently ill with the pseudomonas lung infection bug. It is a further crucial stage of his Young life, one of a series of similar infections that blight sufferer's lives and make every day a battle. Doctors and Clinicians need every possible array of arsenal weapon to keep sufferer's alive. We agree with the C.F. Trust in their support of this treatment.	Comments noted. See FAD section 1 for the final recommendations
Public 2	**Notes**	I have a six year old sister who has had the pseudomonus infection since last year. It is important to keep this at bay and if it flares up who knows how ill she will become. Cystic Fibrosis is such a temperamental illness and infection can make a sufferer seriously decline. I have experienced it and think it's really important that this treatment is offered.	Comments noted. See FAD section 1 for the final recommendations.
Patient 8	**Notes**	This. would make my life so much easier. Any help managing my CF is greatly appriciated and this would help.	Comment noted.

Carer 11	**Section 1** (Appraisal Committee's preliminary recommendations)	MY SON IS RESISTANT TO TOBRAMYCIN so we desperately need NICE to recommend Colobreathe for the treatment of pseudomonas infections. Colobreathe would ease this burden for my family.	Comment noted. The Committee acknowledged that some people would be amino-glycoside insensitive or otherwise intolerant to tobramycin. However the Committee agreed that given its understanding of the treatment pathway this group receive colistimethate as a first line treatment and then an alternative treatment to tobramycin once they failed on colistimethate. The Committee therefore concluded that colistimethate DPI did not have a role to play in the treatment of chronic Ps. aeruginosa in people who were insensitive or intolerant to tobramycin. See FAD section 4.3.19
Carer 11	**Section 3** (The technologies)	My son has multiple resistant pseudo. He is resistant to Tobi he would benefit so much from having Colobreathe	Comments noted. The Committee acknowledged that some people would be amino-glycoside insensitive or otherwise intolerant to tobramycin. However the Committee agreed that given its understanding of the treatment pathway this group receive colistimethate as a first line treatment and then an alternative treatment to tobramycin once they failed on colistimethate. The Committee therefore concluded that colistimethate DPI did not have a role to play in the treatment of chronic Ps. aeruginosa in people who were insensitive or intolerant to tobramycin. See FAD section 4.3.19 See FAD section 1 for the final recommendations.

Patient 9	**Section 1** (Appraisal Committee's preliminary recommendations)	I could copy and paste the CF Trust statement, however thought it important to stress adherence. It's incredibly important, and the burden of nebulisers seems to be poorly understood at times. It isn't just the time taken to nebulise (and the new models are quicker, but not quick) but also the cleaning and care involved. Dry powder inhalers, even if not quite as effective, are going to help with compliance and thus potentially be more effective in the long term.	Commenst noted. The benefits of dry powder formulations in improving treatment adherence were acknowledged by the Committee. See FAD sections 4.3.5 and 4.3.6
Carer 12	**Notes**	My daughter Freya is 10 months old and has CF.	Comment noted.
Carer 13	**Section 1** (Appraisal Committee's preliminary recommendations)	I believe this would improve quality of life being quicker and so much easier to administer than a nebuliser: without the inconvenience of having the extra equipment to assemble, disassemble and wash all the separate parts, changing filters each time, mixing the medicine(having to use syringe/needle to do so then suitably disposal of these), having to use electricity or battery power, sterilising the equipment Â and of course being in a suitable place to do all this.	Comments noted. The Committee considered the treatment burden associated with cystic fibrosis. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5

Carer 14	**Section 4** (Evidence and interpretation)	I am an aunt of an 11 year old with cystic fibrosis whose daily treatment regime involves both physiotherapy and oral and nebulised drugs, lasting several hours. Pseudomonas aeruginosa is a bacterium that has caused recurrent infections. The amount of time taken to administer treatment has increased over time, and also involves fortnightly intravenous drugs every 3 months. The physical discomfort and disruption to education and family life cannot be underestimated for this child and its carers. The Cystic Fibrosis community can see that there is a great need for an increased choice of treatments for CF to become available, and in particular those that are quick and easy to use such as dry powder antibiotics. There are immense benefits to be had from such treatments to enable those with CF to remain well, and to live their lives with less impact from increasingly time-intensive treatment regimes. The Cystic Fibrosis Trust believes that NICE should recommend Colobreathe for treatment of pseudomonas infections, so that people with CF and their clinicians should have the opportunity to assess whether Colobreathe is the right treatment for them. I am fully supportive of this position.	Comment noted. The Committee considered the treatment burden associated with cystic fibrosis. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5

Patient 10	**Section 2** (Clinical need and practice)	As a cf patient and one which has to do 2x daily nebulised colomycin permenantly, to have an the oppotunity for a dry powder inhaler which could potentially be available is fantastic news! It is extreamly hard work to keep well and it takes alot of dedication and energy to adhere to all the required treatment, medication, physio, hospital appointments on top of working full time, and trying to spend quality time with friends and family as well as trying to enjoy life! It is essential that these new treatments can be made available to everyone helping to releive the burden of daily time consuming treatments. This would dramatically improve my quality of life making it easy as possible helping people just like me to get on with life whist keeping well and keeping on top of medication and ultimately keep well for as long as possible. This would help so many patients in so many ways and I urge this to be recommended for the treatment of pseudomonas infections.	Comments noted. The Committee considered the treatment burden associated with cystic fibrosis. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5.
Patient 11	**Notes**	On a personal note the idea of quick and fast treatment is very very appealing. I have a busy work schedule and treatments which take hours, resulting in early 5am starts and late 12am finishes are not ideal and only impede recovery. Something fast and quick like this should be made available for all those who would benefit from it.	Comments noted. The Committee considered the treatment burden associated with cystic fibrosis. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5

Patient 11	**Section 3** (The technologies)	Something fast and quick is greatly needed so patients with CF can live a more normal life, without treatments starting at 5 am and finishing at 12am to ensure we can go to work etc.	Comment noted.
Carer 14	**Notes**	My 7 year old son has Cystic Fibrosis, and after his 3rd case of Pseudomonas he is now on permanent nebulised Colomycin. Anything that is going to make his life more comfortable has got to be tried	Comment noted.
Carer 14	**Section 2** (Clinical need and practice)	My 7 year old son has Cystic Fibrosis and has had Pseudomonas 3 times. He is now permanently on nebulised Colomycin, so anything to ease his burden must be a good thing	Comment noted. The Committee were aware of other products for treatment of chronic *Pseudomonas* infection – however there was no evidence available comparing them to either colistimethate sodium DPI or tobramycin powder for inhalation as detailed in the final scope for the appraisal issued by NICE.
Other 3	**Notes**	I agree with the following statement from the Cystic Fibrosis Trust: Colobreathe should be recommended for the treatment of pseudomonas infections. One of the benefits is that it promotes adherence as quick and easy to administer compared with the current colomycin;this is of particular relevance to young people like my grandson who is about to go into King's Hospital London for several days to help stop the infection or at least slow it down.	See FAD section 1 for the final recommendations.
Carer 15	**Section 1** (Appraisal Committee's preliminary recommendations)	As a parent of a child with CF then any medication which is proven to fight pseudomonas is a welcomed development. This type of infection reduces the quality of life of a person with CF and so prevents them from having a normal as possible. This affects there mental health as well as physical as it prevents them from doing every day things.	Comment noted. The Committee considered the treatment burden associated with cystic fibrosis. See FAD section 4.3.5

Other 4	**Notes**	My granddaughter becomes very poorly when the levels of pseudomonas in her lungs increases. If using an inhaler works efficiently it would save her a great deal of time and keep her lungs working for longer, which may one day enable her to work full time when she finishes her studies.	Comment noted.
NHS Professional 6	**Section 1** (Appraisal Committee's preliminary recommendations)	The Colobreathe study shows surprising clinical responses in both arms, which CF physicians would not have anticipated and probably reflect the treatment naÃ¯ve population recruited. Â Treatments are only efficacious if they are taken and this needs to be the focus of this review. In summary 1.The appraisal has not taken into consideration factors that are important for CF patients and the CF teams that care for them (illustrated in the two expert statements from patients). 2. It has given too much credence to a comparison which is not significant (either statistically or clinically) 3. It has resulted in a recommendation that will led to a monopoly that will result in continued inflated pricing of the Tobramycin dry powder device	Comments noted. The Committee considered the treatment burden associated with cystic fibrosis. See FAD section 4.3.5 See FAD section 1 for the final recommendations.
NHS Professional 6	**Section 2** (Clinical need and practice)	The review mentions the importance of addressing adherence, but does not give this adequate consideration in the document. For CF physicians, sustaining these long term treatments is the biggest challenge we face in maintaining the health and well-being of our patients with chronic airway infection. Â We require a varied armamentarium to achieve this and have anticipated the development of dry powder delivery devices as an important step forward in addressing this challenge.	Comments noted. The benefits of dry powder formulations in improving treatment adherence were acknowledged by the Committee. See FAD sections 4.3.5 and 4.3.6

NHS Professional 6	**Section 3** (The technologies)	I feel very uneasy that the NICE review recommends that one DPI device remains available for the UK CF community. Â This essentially represents a monopoly and is disadvantageous to both patients and the NHS. Â We have already seen how the availability of	Comment noted. See FAD section 1 for the final recommendations.
Carer 16	**Notes**	My son is now three years old and has spent 18 months of his life needing Colomycin administered via a nebuliser. For a baby and toddler anything which can ease the burden of administering medications through a nebuliser is life-changing. Toby would cry so much during the twenty minutes it took to administer a dose that I found it too distressing to continue. he therefore was not benefitting from the therapy prescribed. NICE must allow this formulation to be made available for my son and all those others living with CF.	Comment noted. See FAD section 1 for the final recommendations.

Carer 18	**Notes**	The following is our current experience of nebulisers: I am never confident that the dose dispensed from the current nebuliser is accurate, times of dispersal are erratic: it is fiddly to make up, we get cut by the metal on the vial, I cannot leave anyone else to make the product up, I have to be there to mix it AM and PM; nebulisers require thorough washing and routine steaming or boiling with sterilised water. Â The need for all this plus the pumps, leads, filters and chambers we also have a water steriliser and a steamer. Â It is cumbersome treatment to the point we dont go away and ensure we do not make arrangements that mean we are away from home AM and PM. Â When we have had to go Â away and just one element of the kit has been missed, which has happened, treatment can be missed for days. Â It is life limiting for a condition that is already burdensome. Â a diagnosis of pseudomonas is bad enough but the ensuing upheaval of a nebulised treatment compounds it, an inhaler would be so fantastic and enable my 13year old to get on with her life despite pseudomonas rather than the treatment overburdening her.	Comments noted.

Carer 18	**Section 1** (Appraisal Committee's preliminary recommendations)	My daughter is 14 years old. Â She has had repeated pseudomonas infections since the age of 8. Â The burden of the treatment regime for CF sufferers & their families is immense. Courses of nebulised colistin last for months at a time to eradicate an infection, & involve preparation of the drug, twice daily nebulisers & the sterilisation & care of the equipment each time. This compromises the lifestyle of a young child & their carer, but particularly compromises the lifestyle of a teenager or young adult. It is a huge responsibility for those leaving home for the first time, either short term for a holiday or long term for University. Adherence to treatment would be greatly increased if the burden was reduced with the benefit of inhaled colistin Â (ie:Colobreathe) & the consequence would be a direct improvement in health & recovery from each pseudomonas infection. This in turn would enhance CF sufferers chances of a longer & healthier life & a greater chance of maintaining lung function.	Comments noted. Comment noted. See FAD section 1 for the final recommendations.
Carer 19	**Notes**	the life of a person with cystic fibrosis is hard enough, this drug will help ease the daily burden of treatments currently available	Comment noted. See FAD section 1 for the final recommendations.
Carer 20	**Notes**	I have a 15 year old daughter with Cystic Fibrosis who is treated regularly for damaging lung infections caused by pseudomonas.	Comment noted.

NHS Professional 7	**Section 4** (Evidence and interpretation)	I think it is important not to underestimate the importance of compliance with medication here. This is something that is not assessed in randomised controlled trials where compliance is alway abnormally high, not reflecting the real-life situation we face as CF clinicians. Simplicity of treatment is paramount in some individuals, even when it comes down to 4 capsules twice a day vs. 1 capsule twice a day. A significant minority of patients will only engage with the simplest of treatment regimes, and it is often these patients who take up expensive inpatient time because of exacerbations relating to non-compliance. I feel strongly that having an alternative simple inhaled antibiotic regime for such patients, and those unable to tolerate tobramycin DPI or suffering side effects from long-term aminoglycoside use, is worthwhile. I accept that the colistimethate DPI has undersold itself by failure to properly measure patient preference but I hope that common sense, and perhaps some financial negotiation, may lead to a change in recommendations. The simpler colistimethate DPI is something CF clinicians and patients have been eagerly awaiting for many years.	Comments noted. The benefits of dry powder formulations in improving treatment adherence were acknowledged by the Committee. See FAD sections 4.3.5 and 4.3.6
Public 3	**Notes**	I have relatives with cf and am a uk taxpayer	Comment noted.
Carer 21	**Section 2** (Clinical need and practice)	There is an urgent need for improved treatments to improve quality and extend life for CF patients; the prposed drug will help with this considerably.	Comment noted.
Carer 21	**Section 3** (The technologies)	Because of the possible adverse reactions, there is a need for a new alternative to tobra mycin. The new drug will help with this need.	Comment noted. See FAD section 1 for the final recommendations

Carer 22	**Notes**	I have a young daughter that was re-diagnosed with this today. Although I know she is too young for this treatment at the moment the fact that she may be denied something that could help in the future is extremely upsetting for my whole family. This infection can be hard to get rid of, sometimes not at all, and treatment takes months if not a year so anything that can help is invaluable.	Comment noted. Comments noted. The Committee considered the treatment burden associated with cystic fibrosis. See FAD section 4.3.5 See FAD section 1 for the final recommendations.
Carer 22	**Section 2** (Clinical need and practice)	There is a need for a faster acting drug which will hopefully cut down treatment time	Comment noted.
Patient 12	**Section 1** (Appraisal Committee's preliminary recommendations)	I struggle with treatment times now I have so many nebulisers to take a day as my health gets worse. This is exhausting. By doing it as an inhaler will cut so much time out of my already full day with treatments alone. It will also benefit my health as I sometimes miss nebulisers if im out or struggle to fit it in. As bad as it is if im unwell and tired sometimes I dont do it because it takes too much effort as well as the cleaning washing all the little bits of the neb afterwards. If im out I can take the inhaler in my bag with me. The idea that this could become availiable makes me so happy thinking how much easier it will be, as im sure it will do for others like me. Please do not take this away from us, we have enough to do as it is.	Comments noted. The Committee considered the treatment burden associated with cystic fibrosis. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5

NHS Professional 8	**Section 1** (Appraisal Committee's preliminary recommendations)	The recommendations lose sight of a an unavoidable outcome of this decision: a a significant switch from nebulised TOBI to TOBI podhaler, driven by the patients and their carers for the sake of ease and speed of administration, which promotes adherernce and may improve outcomes of chronic pseudomonal infection. Exclusion of Colobreathe is inappropriate however: 1. the clinical trial evidence used to endorse the Podhaler is not superior to that available for Colobreathe. 2. EMA required new agents to be compared with older drugs within their licensed indication. Nebulised Colistin is a traditional cheap and effective first line therapy in most UK CF centres but it is not licensed for this indication and could not have been used as a comparator for Colobreathe when the Freedom study was first planned and approved in early 2000's. 3. Us clinician need choice of alternatives. TOBI is not as clean as it is first set out to be. Several patients can't tolerate it due to bronchospasm, some have developed oto- and nephrotoxicity on it and can't use it again, and a third group simply do not show benefit Â from it. Restricting access to the only alternative will be to patient detriment.	Comments noted. The Committee heard from the manufacturer of colistimethate sodium DPI that the EMA had indicated that the most appropriate comparator would be nebulised tobramycin because this was the only licensed comparator in all of the study site countries. See FAD section 4.3.4 See FAD section 1 for the final recommendations.

NHS Professional 8	**Section 4** (Evidence and interpretation)	If a majority of patients switch to TOBI podhaler, as they will undoubtedly do, its chronic use will increase the background resistance to tobramycin and limit the useful shelf life of this antibiotic when no new effective antipseudomonal antibiotics are being developed at present (this was seen in most of the original TOBI trials). In contrast, resistance to colistin remains amazingly minimal despite its heavy use in CF. Many clinicians use alternate month colistin and TOBI nebs but this was not considered in the appraisal. I have made use of this fact, applying colistin for IV therapy of pseudomonal infection, nebulised therapy for eradication of first isolate, and for long term suppression of pseudomonas over 7 years in a transplant population including a large cohort of CF with good clinical and microbiological efficacy, tolerability and safety (BTS 2008, ERS 2012, manuscript in prep). Lung transplant recipients endure a huge treatment burden and patients and doctors were looking forward to having access to Colobreathe and TOBI podhaler to simplify treatment.Does a patient discount scheme allow Colobreathe to dominate TOBI nebs or even the podhaler? Negotiated with Forest yet?	Comment noted.

NHS Professional 8	**Section 5** (Implementation)	General point: if we, as a clinical community, are not mindful of the implications of ongoing regulatory restriction of access to new "expensive" therapy based on hypothetical cost effective models (which do not capture real life expense; related to the burden of admissions from exacerbations and length of IV antibiotics in the case of CF), we run the risk of driving Pharma companies away from the UK. They simply will not consider the UK a viable site for conducting clinical trials and may no longer seek approval of new molecules in the UK. Our patients are the only losers in this scheme.	Comment noted.
Carer 23	**Section 1** (Appraisal Committee's preliminary recommendations)	Sadly, my 23 year old daughter lost her life to CF 4 years ago. I know she would want me to support all attempts to improve medical treatment as she had to undergo many tedious, tiring hours of treatment including twice daily nebulisers. As colobreatthe is an alternative, quick medication this relieves CF patients of having to prepare and administer a nebulised treatment when they are exhausted after doing 30 minutes of physiotherapy 2-3 times each day.	Comments noted. The Committee considered the treatment burden associated with cystic fibrosis. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5

Patient 13	**Section 2** (Clinical need and practice)	I have Cystic Fibrosis. I spend several hours a day administering my medication, having rigorous physiotherapy and exercise sessions to keep healthy. I take my Colistimethate nebuliser twice a day. Although each session lasts for around half an hour, it should be taken into consideration that I have to also take other nebulised medication & that the preparations of the solution as well as the cleaning and sterilising of the apparatus take up valuable time. I would love to spend this time every day with with my friends and family, studying, or dancing, which I very much love, rather than being reminded that I have a life-threatening condition. Being able to administer this drug as a dry powder for inhalation would mean that I could take this medication on-the-go. I could travel; go on holiday; camp even! I could spend a day somewhere & not have to miss valuable (and expensive) degree study sessions. I wouldn?t have to leave special occasions early to race home & do my treatments before I need to sleep. The fact of the matter is that it would improve the quality of life that I have. It's stressful to have to plan every day down to the minute. Sometimes I just need to breathe easy	Comments noted. The Committee considered the treatment burden associated with cystic fibrosis. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5
Carer 24	**Section 1** (Appraisal Committee's preliminary recommendations)	If you do not recommend colistimethate sodium dry powder, you will restrict those patients who are unable to use tobramycin because it has caused side effects in the past to a altenative nebulised colistine which takes a considerable amount of time to mix up and adminsiter, and is difficult to store and requires additional equipement to mix up and administer, which is costly and inconvenient.	Comments noted. The Committee considered the treatment burden associated with cystic fibrosis. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5

Other 4	**Notes**	Our Son has CF. I believe it would be MORALLY wrong to deny our son and any CF sufferers any treatment which may give him and others a better quality of life.PLEASE make this available.	Comment noted.
Other 4	**Section 1** (Appraisal Committee's preliminary recommendations)	Our Son has CF. I believe it would be MORALLY wrong to deny our son and any CF sufferers any treatment which may give him and others a better quality of life.PLEASE make this available.	Comment noted.
Public 4	**Notes**	I have a friend suffering from cystic fibrosis and she needs all the help she can get. Â She believes this would help her enormously as this drug would save her about 20-30 mins each morning with a noisy machine and mask on her face? and would cut it down to just an inhaler!! Which she feels is very exciting!	Comments noted. The Committee considered the treatment burden associated with cystic fibrosis. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5
Carer 25	**Notes**	I should add to this that my 5 year old daughter suffers from CF. She currently spends up to 2 hours a day receiving treatment, including up to 3 nebulised medication . Anything that could reduce this burden and help her and children like her spend more time being normal children should be encouraged.	Comments noted. The Committee considered the treatment burden associated with cystic fibrosis. The Committee heard from patient experts how time-consuming treatment can be. The Committee concluded that reducing the time that people with cystic fibrosis spend receiving treatment would be beneficial in improving the quality of life of people with cystic fibrosis and their families. See FAD section 4.3.5

NHS Professional 9	**Section 1** (Appraisal Committee's preliminary recommendations)	Antibiotic resistance is much commoner with tobramycin than colistin. A dry powder form of colistin would be of benefit to the tobramycin resistant Â patient who's poorly compliant with nebulised medication	Comments noted. See FAD section 1 for the final recommendations
NHS Professional 9	**Section 2** (Clinical need and practice)	AS patients are surviving longer antibiotic resistance will become more of a problem and need to swap inhaled anti-pseudomonal antibiotics will become common. A dry powder alternative for our least resistant antibiotic (i.e. colistin) should be available	Comment noted.
NHS Professional 9	**Section 3** (The technologies)	having to take 1 capsule of colistin dry powder compared with 4 capsules of tobramycin dry powder would improve compliance particularly in our adolescent / teenage patients	Comment noted. The benefits of dry powder formulations from the patient and clinician perspective in improving treatment adherence were acknowledged by the Committee. See FAD sections 4.3.5 and 4.3.6
Carer 26	**Notes**	Simple : This is for children dying! If my tax can go to India any other countries for stupid reasons and Illegal immigrants can have free HIV/AIDS treatment, then please advise what's NICE's argument is over these drugs?	Comment noted.
Carer 27	**Notes**	I have two children with cf who this would benefit	Comment noted.
Carer 28	**Notes**	As a parent of a person with Cystic Fibrosis who has had chronic lung infection with Pseudomonas I obviously think that any treatment that could help my daughter live longer without the need for a lung transplant has to be worthwhile. Â People with Cystic Fibrosis do not choose their lifestyle (as maybe alcoholics or drug users) - their life is affected from the moment they are born and if any medicine can give them an improved quality of life then they should have access to it. Please listen to the families living with Cystic Fibrosis and help them help themselves to a longer life.	Comment noted.

Carer 28	**Section 2** (Clinical need and practice)	I agree with the following statement from the Cystic Fibrosis Trust: Colobreathe (colistimethate sodium dry powder for inhalation, Forest Laboratories) should be recommended for the treatment of pseudomonas infections. The benefits over other treatments.	Comment noted.
Carer 29	**Notes**	I have a daughter with cf. do you...?? Please think again as if you had a loved one with cf you might reconsider this awful decision... You can contact me anytime to discuss	Comments noted. See FAD section 1 for the final recommendations
Carer 30	**Section 1** (Appraisal Committee's preliminary recommendations)	We need this drug	Comment noted.
Carer 30	**Section 2** (Clinical need and practice)	We need this drug	Comment noted.
Carer 30	**Section 3** (The technologies)	We need this drug	Comment noted.
Carer 30	**Section 4** (Evidence and interpretation)	We need this drug	Comment noted.
Carer 30	**Section 5** (Implementation)	We need this drug	Comment noted.
Carer 30	**Section 6** (Proposed recommendations for further research)	We need this drug	Comment noted.
Carer 30	**Section 7** (Related NICE guidance)	We need this drug	Comment noted.

Carer 31	**Section 2** (Clinical need and practice)	my daughter is chronically infected with P aeruginosa and as a result suffers the acute exacerbations associated with it. Against enormous odd she is a university student living away from home and working hard on her studies. She cannot manage home based IV treatment in a shared student accommodation. Hospital admission for IV treatment is a huge cost to the NHS and could be avoided with a home treatment which limited the huge burden associated with nebulised antibiotics. Colobreathe would free this burden and enable my child to manage her studies and in future become a hardworking tax paying employee contributing back to society. Please please help my daughter and other young people with this dreadful disease to have improved quality of life by agreeing to the provision of this drug asap.	Comment noted.
NHS Professional 10	**Section 1** (Appraisal Committee's preliminary recommendations)	The failure to support colistin DPI is wrong for patients with CF. Â In clinic they are desparate for options that reduce their treatment burden, allowing them to lead more normal lives (college, work etc). Â Their decisions are often between one or the other, and DPI colistin gives them this option, greatly improving their Quality of Life.	Comment noted. See FAD section 1 for the final recommendations
NHS Professional 10	**Section 2** (Clinical need and practice)	The current research is recognising that the CF airway microbiology is about much more than Pseudomonas. Â Please see Stressman et al Thorax 2012, and Daniels et al Journal of Cystic Fibrosis (in press).	Comment noted.
NHS Professional 10	**Section 4** (Evidence and interpretation)	Colistin DPI has been compared and shown to be efective against the clinical Gold standard of wet Tobramycin. Â Whether or not it is effective against wet colistin is irrelevant, as this has never been defined as the gold standard but has been pragmatically accepted by clinicians.	Comment noted. See FAD section 1 for the final recommendations

Patient 13	**Notes**	I have had cf all my life and been through so much. Anything that could help my illness would be a great help as there is no cure. If this inhalers helps our illness in anyway then please don't stand in the way of it being released to us	Comment noted.
Patient 13	**Section 1** (Appraisal Committee's preliminary recommendations)	Just because something is not recommended doesn't mean that it won't do nothing. Every cystic is different,therefore without giving it to people how are you meant to know	Comment noted.
Patient 13	**Section 2** (Clinical need and practice)	For cystic fibrosis patients, going in hospital for antibiotics is normal, some orals just don't do enough. But then sometimes neither do antibiotics. Cf patients can come resistant to many antibiotics, therefore if the option of these inhalers was there, it could combine with other medicine to fight the p.aeruginosa	Comment noted.
Patient 13	**Section 3** (The technologies)	If these inhalers help cystic fibrosis in anyway, prices should not matter as your helping save people's lives in which there is not a cure.	Comment noted.
Patient 13	**Section 4** (Evidence and interpretation)	I don't think with the evidence given that these inhalers would not be beneficial	Comment noted.
Patient 13	**Section 5** (Implementation)	I think these inhalers should definitely be made available for cystic fibrosis sufferers and on prescription	Comment noted. See FAD sections 1for the final recommendations
Patient 13	**Section 6** (Proposed recommendations for further research)	People with cystic fibrosis like myself would tell how vital this is ,so the quicker you make a decision ,the better	Comment noted.
Patient 13	**Section 7** (Related NICE guidance)	I think making it available as soon as possible is a must	Comment noted.
NHS Professional 11	**Section 4** (Evidence and interpretation)	The finding of the EAGER trial that 20% of P. aeruginosa had an MIC of 8 mg or Â greater should be directly contrasted with the 1.1% rate of resistance for colistimethate; tobramycin is thus likely to be ineffective for a significant number of patient isolates.	Comment noted