National Institute for Health and Clinical Excellence

Colistimethate sodium powder and tobramycin powder for inhalation for the treatment of pseudomonas lung infection in cystic fibrosis [ID342]

Assessment Report

Commercial in Confidence stripped version for consultation

Produced by: School of Health & Related Research Sheffield (ScHARR)

STRICTLY CONFIDENTIAL

Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence – Assessment Report

Colistimethate sodium powder and tobramycin powder for inhalation for the treatment of *Pseudomonas aeruginosa* lung infection in cystic fibrosis

Produced by ScHARR, The University of Sheffield

Authors Paul Tappenden, Senior Research Fellow, ScHARR
Sue Harnan, Research Fellow, ScHARR
Lesley Uttley, Research Associate, ScHARR
Matthew Mildred, Research Assistant, ScHARR
Chris Carroll, Senior Lecturer, ScHARR
Anna Cantrell, Information Specialist, ScHARR

Correspondence to Dr Paul Tappenden
Senior Research Fellow
Health Economics and Decision Science
School of Health and Related Research
University of Sheffield
Regent Court
30 Regent Street
Sheffield S1 4DA
p.tappenden@sheffield.ac.uk

Date completed 13th March 2012

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 10/08/01.

Declared competing interests of the authors

None.

Declared competing interests of the clinical advisors/peer reviewers

Keith Brownlee has attended a Novartis Advisory board on future developments in cystic fibrosis in 2010 and received a fee and travel expenses for a lecture given at the East Anglia Cystic Fibrosis Club in 2010 from Forest Laboratories. Dr Diana Bilton is the chair of the UK CF Registry Committee and is involved in assisting the design of registry surveillance of patients receiving Colobreathe. Diana is also Chief Investigator on the Insmed trial of once daily nebulised Arikace for CF and was Chief Investigator of a trial of Aztreonam versus tobramycin. Diana is also Chief Investigator of a planned study on the effects of TOBIPodhaler on treatment burden, quality of life and adherence. None of the other advisors or peer reviewers have any conflicts of interest to declare.

Acknowledgements We would like to thank the following individuals for providing considerable input into this assessment: Professor Chris Taylor (Sheffield Children's NHS Foundation Trust), Dr Martin Walshaw (Liverpool Heart and Chest Hospital NHS Foundation Trust) and Dr Keith Brownlee (Leeds Teaching Hospitals NHS Trust). We would like to thank Forest Laboratories and Novartis Pharmaceuticals for providing additional data requested throughout the course of the assessment. Thanks also to Elaine Gunn and the CF Registry for providing patient-level data to inform the economic analysis. We would also like to thank Dr Diana Bilton and Rod Taylor for their helpful comments on the draft report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Tappenden P, Harnan S, Uttley L, Mildred M, Carroll C, Cantrell. Colistimethate sodium powder and tobramycin powder for inhalation for the treatment of *Pseudomonas aeruginosa* lung infection in cystic fibrosis. Technology Assessment Report: Final report to the National Institute for Health and Clinical Excellence.

Contributions of authors

Paul Tappenden acted as Principal Investigator for this assessment. Anna Cantrell developed the electronic search strategies. Sue Harnan, Lesley Uttley and Chris Carroll undertook the review of clinical effectiveness. Paul Tappenden and Matthew Mildred undertook the health economic review and developed the Assessment Group model.

About ScHARR

The School of Health and Related Research (ScHARR) is one of the twelve departments that comprise the Faculty of Medicine, Dentistry and Health at the University of Sheffield. ScHARR specialises in health services and public health research, and the application of health economics and decision science to the development of health services and the improvement of public health.

The ScHARR Technology Assessment Group (ScHARR-TAG) synthesises research on the clinical effectiveness and cost-effectiveness of healthcare interventions for the NIHR Health Technology Assessment Programme on behalf of a range of policy makers, including the National Institute for Health and Clinical Excellence (NICE). ScHARR-TAG is part of a wider collaboration of a number of units from other regions including Southampton Health Technology Assessment Centre (SHTAC), University of Southampton; Aberdeen Health Technology Assessment Group (Aberdeen HTA Group), University of Aberdeen; Liverpool Reviews & Implementation Group (LRiG), University of Liverpool; Peninsular Technology Assessment Group (PenTAG), University of Exeter; Centre for Reviews and Dissemination (CRD) and Centre for Health Economics (CHE), University of York; Warwick Evidence, University of Warwick; the BMJ Group and Kleijnen Systematic Reviews.

Word count: 65,125 words

TABLE OF CONTENTS

TABLES AND FIGURES

1. DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader.

Dominated (simple)	Where an intervention is less effective and more expensive than its comparator.
Dominated (extended)	Where the incremental cost-effectiveness ratio for a given treatment alternative is higher than that of the next more effective comparator.
Meta-analysis	A statistical method by which the results of a number of studies are pooled to give a combined summary statistic.
Relative risk	Ratio of the probability of an event occurring in an exposed group relative to a non-exposed or control group.
Surrogate outcome	An intermediate outcome which is intended to substitute for and be predictive of a final patient-relevant clinical outcome.

LIST OF ABBREVIATIONS

AAD	Adaptive Aerosol Delivery
AHRQ	Agency for Healthcare Research and Quality
ATP	Adenosine triphosphate
BMI	Body mass index
BNF	British National Formulary
BSAC	British Society for Antimicrobial Chemotherapy
CEAC	Cost-effectiveness acceptability curve
CF	Cystic fibrosis
CFQ	Cystic Fibrosis Questionnaire
CFTR	Cystic fibrosis transmembrane conductance regulator
CFU	Colony forming units
CHE	Centre for Health Economics
CHMP	Committee for Medicinal Products for Human Use
CHQ	Child Health Questionnaire
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
CRD	Centre for Reviews and Dissemination
CRDQ	Chronic Respiratory Disease Questionnaire
CT	Computerised tomography
DARE	Database of Abstracts of Reviews of Effects
DNA	Deoxyribonucleic acid
DPI	Dry powder for inhalation
EAGER	Establish A new Gold standard Efficacy and safety with tobramycin in cystic fibrosis
EMA	European Medicines Agency
EQ-5D	Euroqol 5-Dimension
FEF_{25-75}	Forced expiratory flow (at 25-75% of vital capacity)
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HRQoL	Health-related quality of life
HUI-2	Health utilities index mark 2
ICER	Incremental cost-effectiveness ratio
ICU	Intensive Care Unit
ITT	Intention to treat

LOCF	Last observation carried forward
MIC	Minimum inhibitory concentration
MLE	Maximum likelihood estimation
MRI	Magnetic Resonance Imaging
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
OLS	Ordinary least squares
PbR	Payment by Results
PEP	Positive Expiratory Pressure
PP	Per protocol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
RCT	Randomised controlled trial
SD	Standard deviation
SE	Standard error
SF-6D	Short form 6 dimensions
SG	Standard gamble
TNS	Tobramycin nebuliser solution
TTO	Time trade off
UK	United Kingdom
US	United States
VAS	Visual analogue scale
VBA	Visual Basic for Applications

2. EXECUTIVE SUMMARY

2.1 Background

Cystic fibrosis (CF) is an inherited condition characterised by the abnormal transport of Cl- across transporting epithelia. This leads to the production of thick sticky mucus in the lungs, pancreas, liver, intestine, and reproductive tract, and an increase in the salt content in sweat. Amongst other problems, people with CF experience recurrent respiratory infections and have difficulties digesting food. CF affects over 9,000 children and young adults in the UK. In 2010, CF was recorded as the cause of death in 103 cases in England and Wales. Whilst CF limits life expectancy, more people with the condition are living longer. More than half of the CF sufferers in the UK are older than 16 years of age. People with CF are susceptible to lung infections. This is thought to be because the thick mucus makes it difficult for the body to clear inhaled bacteria, and because people with CF have an increased airway inflammatory response to pathogens. The most common bacterial infection is *Pseudomonas aeruginosa*. In 2010, around 37.5% of UK patients had chronic *Pseudomonas aeruginosa*. In the early stages of disease, treatment aims to prevent initial infection with *Pseudomonas aeruginosa*, or to eradicate new and intermittent infections. If bacterial infection is not successfully prevented or treated, a chronic infection can develop whereby bacterial microenvironments known as biofilms form. Biofilms are difficult for immune cells and antibiotics to penetrate. Treatment of chronic infections involves regular use of nebulised antibiotics such as tobramycin and colistimethate sodium to prevent flare-ups (known as exacerbations) and to stabilize lung function and enhance quality of life. Treatment is time consuming for patients, with administration of nebulised antibiotics taking up to an hour per day during good health and longer during periods of ill health. Exacerbations lead to progressive respiratory failure, have a substantial negative impact upon a patient's quality of life and are usually treated using intravenous antibiotics.

2.2 Objectives

The overall aim of this assessment is to evaluate the clinical effectiveness and cost-effectiveness of colistimethate sodium dry powder for inhalation (DPI) and tobramycin DPI for the treatment of *Pseudomonas aeruginosa* lung infection in cystic fibrosis.

2.3 Methods

A systematic literature review was conducted of the clinical effectiveness and cost-effectiveness of colistimethate sodium DPI and tobramycin DPI within their licensed or anticipated licensed indications for the treatment of chronic *Pseudomonas aeruginosa* lung infection in cystic fibrosis. Electronic bibliographic databases were searched in February and March 2011 (MEDLINE, MEDLINE in-Process, EMBASE, Cochrane Library databases, CINAHL, Web of Science and Conference Proceedings Citation Index, BIOSIS Previews). Ongoing and unpublished studies were

searched for in relevant databases. The bibliographies of relevant systematic reviews and the manufacturers' submissions were also handsearched. Randomised controlled trials were selected for inclusion in the review if they included at least one of the interventions of interest, selected only people aged 6 years or over with CF and chronic *Pseudomonas aeruginosa* pulmonary infection, compared the intervention to the other intervention or to nebulised tobramycin or nebulised colistimethate sodium and reported at least one of the following outcomes: rate and extent of microbial response (for example sputum density of *Pseudomonas aeruginosa*); lung function; respiratory symptoms; frequency and severity of acute exacerbations; health-related quality of life; and adverse events of treatment (including rate of resistance to antibiotic treatment). Data were extracted using a standardised form. Critical appraisal was performed using the CRD criteria, the CONSORT statement for non-inferiority trials and criteria taken from the EMA research guidelines for CF. Study selection, data extraction and critical appraisal were performed by one reviewer and checked by a second reviewer. The broader evidence network for a mixed treatment comparison was also examined, but was not included in the review. A meta-analysis was planned subject to the availability of suitable data.

Existing economic evidence available from the literature and evidence submitted to NICE by the manufacturers of colistimethate sodium DPI was critically appraised. Additional systematic reviews were undertaken to examine the credibility of potential relationships between intermediate endpoints and final outcomes. In addition, a *de novo* health economic model was developed to assess the cost-effectiveness of colistimethate sodium DPI versus nebulised tobramycin. The Assessment Group model takes the form of a state transition model to estimate transitions between three FEV_1 strata ([1] FEV_1 70-99% [2] FEV_1 40-69% and [3] FEV_1 <40%). 24-week transition probabilities were estimated based on FEV_1 changes those observed within the COL/DPI/02/06 trial. Different levels of HRQoL are assumed for each health state. Treatment duration, which is assumed to be directly related to survival duration, is assumed to be exactly equivalent between the competing treatment options. Costs include those associated with drug acquisition, nebuliser consumables and the management of exacerbations. The model was evaluated probabilistically over a short-term horizon (24-week duration) and a lifetime horizon using standard decision rules. The analysis was repeated over six prices for colistimethate sodium DPI. Insufficient data were available to produce a full economic evaluation of tobramycin DPI versus any comparator. Instead, a crude threshold analysis was undertaken to estimate the necessary QALY gain that tobramycin DPI would need to produce in order to be cost-effective given its incremental lifetime cost.

2.4 Results

Clinical effectiveness results

Three trials were included in the review of clinical effectiveness. Both colistimethate sodium DPI and tobramycin DPI were reported to be non-inferior to nebulised tobramycin in pivotal Phase III trials for the outcome FEV_1%. A small trial comparing colistimethate sodium DPI to nebulised colistimethate sodium in a younger, healthier cohort of patients showed no significant change in lung function in either arm, but was primarily a safety trial.

The quality of the included studies was generally poor to moderate. None of the trials scored well on all risk of bias items, with blinding and non-adherence to the EMA research guidelines[1] being key problems. This could lead to selection bias and reporting bias for subjective outcomes such as adverse events, inaccuracies and imprecision in the results, and may limit the generalisability of the study. Follow up was nearly adequate to detect effects in respiratory efficacy, but not long enough to detect slowing of the rate of decline in respiratory function, according to EMA research guidelines.

As FEV_1% is a surrogate outcome, the EMA recommend that it should be considered alongside microbiological outcomes and harder clinically relevant outcomes such as frequency of exacerbations and antibiotic use. [redacted] tobramycin DPI [redacted] appeared to result in more people experiencing at least one exacerbation (as indicated by the surrogate outcome "lung disorders" in the EAGER trial) than nebulised tobramycin, but less time on antibiotics. Sputum density was only available from the EAGER trial and supported the direction of effect seen in FEV_1%. Resistance of around 20% was reported for tobramycin arms across both key trials; this was $\leq$ 1.1% for colistimethate sodium DPI in the COL/DPI/02/06 trial. Adverse events were mostly similar between arms within trials, except for cough which was higher in both DPI arms. More patients in the DPI arms withdrew due to adverse events in both trials. The statistical and clinical significance of the changes seen in sputum density, exacerbations, resistance and adverse event data is not known. There was no direct preference-based assessment of health-related quality of life within any of the trials included in the review.

It was not possible to draw any firm conclusions as to the relative efficacy of any intervention compared with any other intervention (except where there was direct evidence comparing to nebulised tobramycin) due to missing data, uncertain comparability of patient characteristics and incompatible populations used when analysing the data.

Cost-effectiveness results

The results of the health economic analysis suggest that colistimethate sodium DPI is expected to produce fewer QALYs than nebulised tobramycin, both in the short-term and over a lifetime horizon. If the price of colistimethate sodium DPI is set at one of the prices which is higher than that of nebulised tobramycin, it is expected to be more expensive and hence dominated by nebulised tobramycin. If the price of colistimethate sodium DPI is set at £9.11, the incremental cost-effectiveness of nebulised tobramycin versus colistimethate sodium DPI is expected to be in the range £126,000 to £277,000 per QALY gained. If the price of colistimethate sodium DPI is set at £10.60, the incremental cost-effectiveness of nebulised tobramycin versus colistimethate sodium DPI is expected to be in the range £24,000 to £50,000 per QALY gained. The range of sensitivity analyses suggest that in those cases where colistimethate sodium DPI offers a positive QALY gain, prices above parity with nebulised tobramycin result in a very high cost per QALY ratio.

Given the incremental discounted lifetime cost of tobramycin DPI versus nebulised tobramycin, the Assessment Group model suggests that it is not possible for tobramycin DPI to have an incremental cost-effectiveness ratio that is better than £30,000 per QALY gained.

2.5 Discussion

A key strength of this assessment is that the systematic review has been conducted to a high standard including comprehensive search strategies with study selection, data extraction and quality assessment checked by a second reviewer. The assessment is limited by the small number of trials available, and methodological weaknesses and incompatibilities within the trials which limit the between-trial comparability. There are variations in the definition and measurement of the key outcomes, due to non-compliance with EMA research guidelines. None of the trials included a preference-based health-related quality of life instrument.

The health economic model developed within this assessment was based on clinical opinion regarding current treatment pathways and systematic reviews of evidence relating to the plausibility of relationships between intermediate and final endpoints (rather than pure assumption). The model was populated using the best available evidence and was peer reviewed by several individuals with clinical and methodological expertise.

The Assessment Group model involves extrapolation of FEV_1 estimates within the COLO/DPI/02/06 trial. Within this analysis, the observable period is 24-weeks in duration whilst the extrapolated period is around 43 years (when <1% patients are still alive). The considerable uncertainty surrounding the short-term evidence base inevitably results in uncertainty surrounding the long-term cost-effectiveness of colistimethate sodium DPI. One particular strength of the assessment is that the model analysis considers the impact of this extrapolation on the cost-effectiveness of treatment. In

addition, uncertainty surrounding the appropriate method of health state valuation is explored by applying a variety of health utility estimates within the model.

A key anticipated benefit of colistimethate sodium DPI and tobramycin DPI concern the increased convenience afforded by reduced treatment administration time as compared against nebulised antibiotics. This may be expected to increase compliance with treatment. In addition, the DPIs are more portable than nebulisers which may also make them a more convenient option. The DPIs may also result in savings in terms of the time associated with cleaning traditional nebulisers. These aspects of benefit may represent "process utilities." However, none of the clinical trials attempted to capture these potential effects using a preference-based instrument. Furthermore, the available evidence does not support the argument for increased compliance with DPIs. As a consequence, this potential effect is not reflected in the health economic analysis. It should be also noted that newer nebulisers such as the I-neb and eFlow devices also allow for faster treatment delivery than conventional nebulisers. The incremental benefits of this aspect of DPI delivery therefore remain unclear.

The key uncertainties within this assessment are:

- The relative efficacy and safety profiles of colistimethate sodium DPI and tobramycin DPI
- The long-term efficacy of treatment using colistimethate sodium DPI and tobramycin DPI versus current standard nebulised therapies
- The validity of the relationship between short-term impact on lung function and longer-term final patient outcomes (mortality and health-related quality of life)
- The long-term impact of DPI treatment on patient survival
- Long-term treatment compliance with DPIs
- The clinical relevance of resistance to antibiotics and its impact upon treatment efficacy
- The trade-off between ease/speed of drug administration using the inhaler devices and adverse events (and the impact of both on patients' quality of life)

2.6 Conclusions

Both DPI formulations have been shown to be non-inferior to nebulised tobramycin as measured by FEV_1%. However, the results of these trials should be interpreted with caution due to the means by which the results were analysed, the length of follow up, and concerns about the ability of FEV_1% to accurately represent changes in lung health. The impact of resistance to tobramycin is not known. When considered alongside other outcomes, it would appear possible that when compared to nebulised treatment, patients on DPI formulations [redacted], but less time on antibiotics, more cough adverse events and may be more likely to not tolerate the treatment. As

such, based on the clinical evidence, the advantages and non-inferiority of DPI treatments compared to nebulised tobramycin remain unclear when all relevant outcomes are considered. Inevitably, the cost-effectiveness of the dry powder formulations is subject to considerable uncertainty. The Assessment Group model suggests that colistimethate sodium is expected to produce fewer QALYs than nebulised tobramycin. Depending on the price adopted for colistimethate sodium DPI, this results either in a situation whereby colistimethate sodium DPI is dominated by nebulised tobramycin, or one whereby the incremental cost-effectiveness of nebulised tobramycin versus colistimethate sodium DPI is in the range £24,000 to £277,000 per QALY gained (South-West quadrant). The economic analysis also suggests that given its price, it is highly unlikely that tobramycin DPI has an incremental cost-effectiveness ratio below £30,000 per QALY gained when compared against nebulised tobramycin.

3. BACKGROUND

3.1. Description of the health problem

3.1.1 Brief statement of the health problem

Cystic fibrosis (CF) is an inherited disease which shortens life expectancy and severely affects the health-related quality of life (HRQoL) of patients. CF is characterised by abnormal ion movement across transporting epithelia. This leads to the production of thick sticky mucus in the lungs, pancreas, liver, intestine, and reproductive tract, and an increase in the salt content in sweat. People with CF have problems with digestion, which can affect growth and body mass index, and are prone to lung infections by a range of pathogens including *Staphylococcus aureus, Pseudomonas aeruginosa,* and *Burkholderia cepacia*. This is thought to be because the thick mucus makes it difficult for the body to clear inhaled bacteria, and because people with CF have an increased airway inflammatory response to pathogens.[2] Whilst both digestive problems and lung infections contribute to morbidity and mortality, respiratory tract infections with *Pseudomonas aeruginosa* have been shown to be a major risk factor contributing to mortality.[3]

In the early stages of disease, management aims to identify and vigorously treat infection[4] and thereby limit structural changes which may predispose a patient to chronic infection with *Pseudomonas aeruginosa*. If bacterial infection is not successfully prevented or treated, a chronic infection/colonisation can develop, whereby bacterial microenvironments known as biofilms form within the bronchial tree. Biofilms are difficult for immune cells and antibiotics to penetrate, and once established, are associated with clinical deterioration and ultimately increased mortality.[3] Treatment of chronic infection typically involves regular use of nebulised antibiotics such as tobramycin and colistimethate sodium to suppress bacterial growth and prevent flare-ups (known as exacerbations) and to maintain lung function and quality of life. Treatment can be time consuming for patients, with administration of nebulised antibiotics taking up to an hour per day during good health and longer during periods of ill health.[2] Newer nebulisers such as the PARI eFlow® rapid nebuliser, or the I-neb™ Adaptive Aerosol Delivery (AAD) system may allow for more rapid administration of treatment. Pulmonary exacerbations may have a substantial negative impact upon a patient's quality of life[5] and are usually treated using intravenous antibiotics, either in hospital, at home or in a combination of these settings.[6]

3.1.2 Aetiology and pathology

Cystic fibrosis is an autosomal recessive disorder where both copies of the gene which code for a protein called the cystic fibrosis transmembrane conductance regulator (CFTR) contain a mutation. Over 1,600 different mutations of the gene have been identified, causing different changes to the

function of the protein, and hence different severities of disease in the individual. The most common mutation is the deletion of phenylalanine at codon 508. This deletion was present in an estimated 91.3% of the mutant alleles in the UK in 2010.[7]

CFTR is a large (~170kDa) multidomain protein belonging to the ATP binding cassette (ABC) family of membrane transporters.[8] It is located in the cell membrane of various cells in the body, including epithelial cells in the respiratory tract, pancreas, liver, intestine, and reproductive tract, where it regulates fluid secretion. CFTR acts as an ion channel which utilises the energy released by the binding and hydrolysis of adenosine triphosphate (ATP) to open. When open, chloride ions pass across the cell membrane by diffusion in the direction of their electrochemical gradient.[9] When functional, this promotes efflux of chloride ions from the cell into the extracellular fluid. Sodium ions and water follow by a paracellular route (between cells rather than through cells) and hence the volume of liquid on the epithelial surface is regulated. In cystic fibrosis, impaired CFTR function is most commonly thought to lead to a decrease in the surface liquid volume of epithelial cells (although there are theories which also consider reduced antibacterial properties of mucous and increased mucin secretion as putative mediators of the characteristics of cystic fibrosis). In the epithelia of the airways, these changes result in a decrease in mucocilliary clearance in the respiratory tract, which is the body's primary defence against invading pathogens. People with cystic fibrosis are more prone to respiratory infections as a result. In addition, people with cystic fibrosis have an excessive inflammatory response. The aetiology of this is unknown,[10] but along with the damage caused by respiratory infections, it leads to bronchiectasis and obstructive pulmonary disease, the primary causes of death amongst people with cystic fibrosis.

Expression of the CFTR gene in the body is widespread, and symptoms are not confined to lung disease. Reproductive function in both males and females may be disrupted (although there is conflicting evidence in women). Exocrine tissues in the pancreas are also affected, where abnormal mucous can block and damage pancreatic ducts. This process starts *in utero* and causes a decrease in the secretion of digestive juices which contain the enzymes, bicarbonate and water which are essential to digestion, which in turn leads to malabsorption of ingested food, and malnutrition. Ultimately, damage to the pancreatic tissue can also lead to destruction of the pancreatic β cells in the islets of Langerhans.[11] These endocrine cells normally secrete insulin into the blood stream, and their absence leads to diabetes mellitus. It is thought that this has a negative impact on lung disease, as lung function is affected by maintaining a normal body weight. This is also associated with a negative impact upon survival. Insulin replacement therapy improves both lung function and body mass.[11]

Children with CF are born without lung infection, but from the moment they are born they are exposed to pathogens, and become infected over time. Common infections include *Staphylococcus*

aureus, Haemophilus influenza, Pseudomonas aeruginosa and *Burkholderia cepacia* complex. *Pseudomonas aeruginosa* is the most prevalent infection, with 37.5% of patients of all ages having a chronic infection in 2010.[7] Between the ages 20 and 49 years, between 55% and 65% patients have chronic *Pseudomonas aeruginosa* infection. *Pseudomonas aeruginosa* infection starts as an intermittent infection with non-mucoid variants of the bacterium. Studies suggest that this phenotype can be eradicated by anti-pseudomonal antibiotics,[12,13] and current practice is to treat all incidences of infection energetically, with the aim of clearing the infection from the respiratory tract using oral or nebulised antibiotics (or both, depending on the UK centre).[4] However, over time, intermittent infections develop into colonisation. Chronic infection is associated with increased mortality and morbidity.[14] The environmental pressures imposed on the bacteria by the conditions within the cystic fibrosis lung are thought to drive the conversion of the non-mucoid phenotype to the mucoid phenotype which secretes large quantities of alginate exopolysaccharide and forms biofilms. Biofilms are aggregates of cells set in an extracellular matrix composed largely of the alginate secreted by the mucoid phenotype. It is hypothesised that these slippery biofilms grow in microaerophilic or anaerobic environments created by the thick mucus characteristic of cystic fibrosis. Other factors present in cystic fibrosis lungs, such as actin, DNA and decreased bacteriocidal secretions are also thought to contribute to the formation of the biofilms.[15] The biofilms are very resistant to antibiotic treatment,[16] and once a chronic mucoid infection has been established, eradication is not possible. Acquisition of this phenotype is again associated with the worsening of symptoms[17] and a considerably worse prognosis.[18]

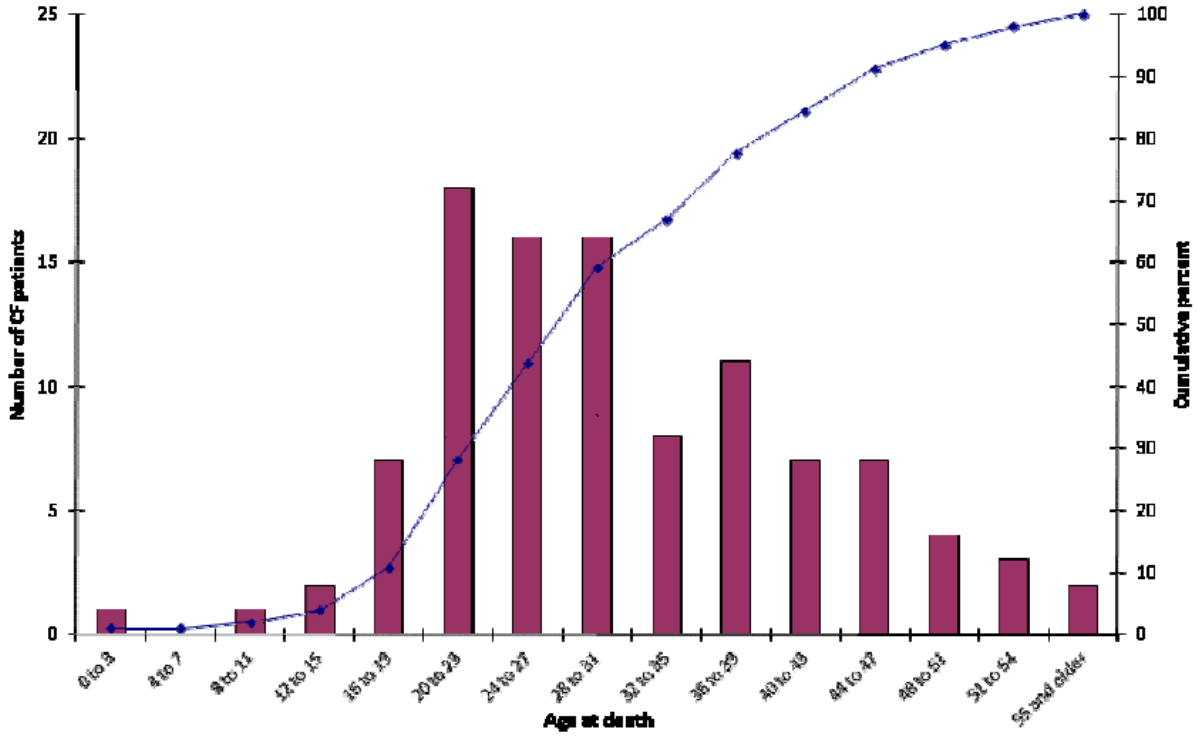
Once bacterial colonisation is established, patients experience a gradual deterioration in lung function as lung tissue is damaged by the infection, which ultimately results in atlectasis (diminished lung volume), severe bronchiectasis, respiratory failure and death.[2] Patients experience increasingly frequent respiratory exacerbations which severely affect quality of life and are usually treated with intravenous (i.v.) antibiotics and may require admission to hospital. Episodes of haemoptysis and pneumothorax may also occur. Historically there have been differences in the diagnostic criteria for determining an exacerbation. These events have usually been characterised by an acute worsening of symptoms such as increased cough, increased expectoration, decreased tolerance to physical activity, loss of weight or appetite and a deterioration in respiratory function. A marked increase in airway bacterial load (in CFU/ml) has been cited as a criterion that may indicate an exacerbation[1] but is subject to some contention. Although Forced Expiratory Volume in one second (FEV_1%) usually improves with treatment, Wagener *et al* demonstrated a progressive decrease in the best FEV_1% recorded in the 180 days after the exacerbation compared to the best FEV_1% recorded in the year prior to the exacerbation.[19] The authors interpret this as being suggestive of an overall decline in FEV_1% associated with each exacerbation. In 2011 the EuroCareCF Working Group published a proposed definition for exacerbations.[20]

Patients in the end stages of lung disease may be assessed for lung or lung and heart transplant, and may be added to the transplant waiting list. Owing to the systemic nature of the disease, transplants for other organs may also be necessary. In the UK in 2010, 169 patients were evaluated and 82 accepted onto the transplant list.[7] Kidney transplants are sometimes needed as a consequence of the toxicity of the high dose aminoglycoside antibiotics used to treat exacerbations. Once a lung transplant has taken place, the risk of death for people with cystic fibrosis is the same as the risk of death for all lung transplants. However, not all patients are fortunate enough to find an appropriate donor in time, and only 27 patients within the CF Registry eventually received a bilateral lung or heart and lung transplant in the UK in 2010.[7]

3.1.3 Prognosis

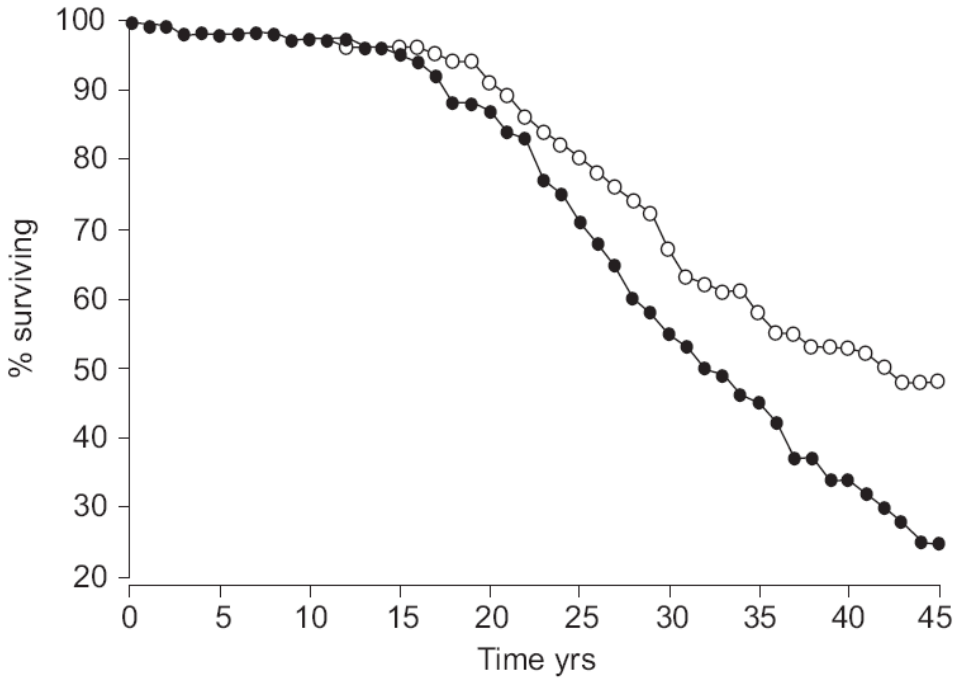
The impact of CF on survival is substantial. In 2010, 103 deaths were recorded in UK patients with cystic fibrosis held within the CF Registry; the median age at death was 29 years (min = 0 years; max = 61 years).[7] Figure 1 shows the age distribution of deaths in CF patients based on 2010 data.

Figure 1: Age distribution of deaths in patients with cystic fibrosis[7]



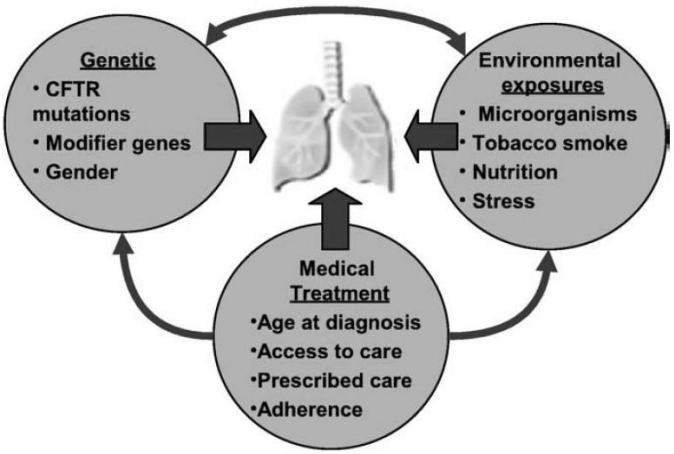
Whilst more people with the condition are living longer than in previous decades, only half of those patients living with cystic fibrosis are likely to live beyond their late 30s. Figure 2 shows recent estimates of survival for males and females with cystic fibrosis based on a large UK-based cohort study.[21] Similar actuarial survival estimates are not currently available from the CF Registry.

Figure 2: Survival UK cystic fibrosis population by sex, 2003[22]



It has been suggested that a number of other factors such as genetics, medical treatment and environmental exposures may interdependently influence prognosis, as illustrated in Figure 3.

Figure 3: Multi-factorial causes of variability in outcomes[23]



3.1.4 Epidemiology – incidence and prevalence

According to 2010 estimates from the Cystic Fibrosis Trust, over 9,300 people in the UK have cystic fibrosis. Complete data on 7,937 of these individuals are available from the UK Cystic Fibrosis Registry for this year. The majority of cystic fibrosis cases are diagnosed by neonatal screening or during early infancy. Around 55.5% of those included in the registry are over 16 years of age and the

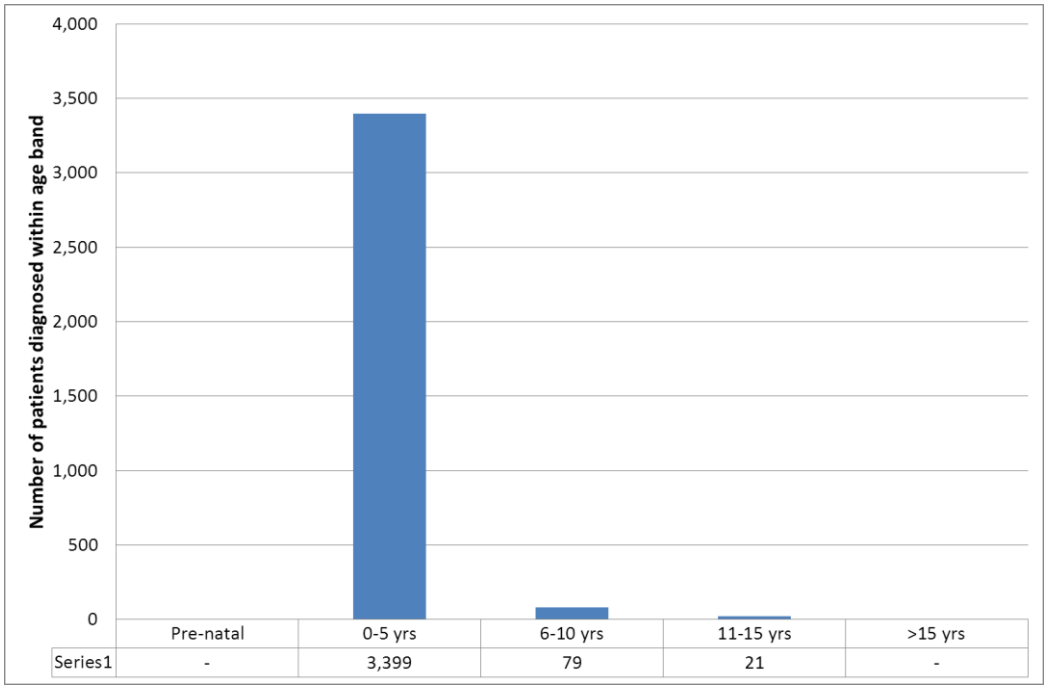
incidence is spread evenly between males and females. For UK patients registered as having cystic fibrosis, approximately 82.2% are located in England, 3.9% in Wales, 4.7% in Scotland and 9.3% in Northern Ireland (see Table 1).

Table 1: Number of patients registered at cystic fibrosis units/centres in the UK[24]

	Number	Number patients registered at paediatric clinics/ centres	Percentage	Number patients registered at adult clinics/centres	Percentage
United Kingdom	9,336	4,475	47.93%	4,861	52.07%
England	7,640	3627	47.47%	4,013	52.53%
Wales	366	217	59.29%	149	40.71%
Scotland	883	407	46.09%	476	53.91%
Northern Ireland	447	224	50.11%	223	49.89%

According to the CF Trust, approximately five babies are born with CF each week. For the period 2007 to 2010, between 235 and 301 new cases of cystic fibrosis were registered each year. Around 1 in 25 people are thought to be carriers of the CF gene although this prevalence estimate is limited to Caucasian people living predominantly in Europe and America. Incidence in other races is less common but is increasingly being reported.[2] Figure 4 shows the age distribution of those patients for whom data are available within the 2010 Cystic Fibrosis Registry Report.

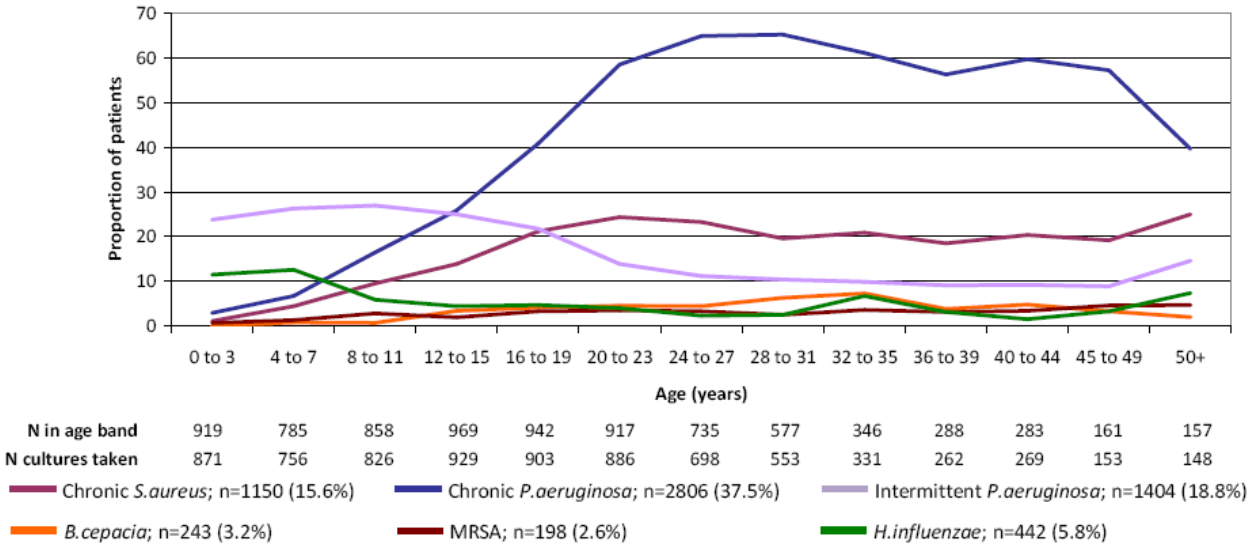
Figure 4: Age at diagnosis of cystic fibrosis based on 2010 estimates[7]



The prevalence of lung infection amongst the broader cystic fibrosis population is high. Around 37.5% of people living with CF are infected with chronic *Pseudomonas aeruginosa*. Age-specific

prevalence rates of *Pseudomonas* infection are shown in Figure 5. The rate of *Pseudomonas aeruginosa* infection increases markedly with increasing age, up to around 25-30 years of age, with slightly lower rates in older age groups. These lower rates may be due to these patients having less severe mutations which make them less likely to develop colonisation.

Figure 5: Prevalence of cystic fibrosis lung infections by age group in 2010[7]



3.1.5 Impact of health problem

Cystic fibrosis has a significant impact upon the survival and quality of life of patients. The disease also impacts upon carers and requires a considerable commitment of health care resources. In 2003, an analysis of data from 196 adult cystic fibrosis patients attending the Manchester CF Unit reported that 113 (57.6%) patients were attending work or study, however 1,799 days were lost due to sickness.[6] More recently, based on an analysis of complete data records from patients aged over 16, the Cystic Fibrosis Trust reported that 69.7% of patients are in work or studying. Whilst 18.5% were reported to be unemployed, only 5.6% of patients classed themselves as "disabled."[7] Patients require monitoring and treatment by the NHS for the duration of their lives. Additionally, two young lives a week are lost to CF which represents a significant impact on the families of CF sufferers. As the UK's most common life-threatening inherited disease, cystic fibrosis continues to present a considerable cost burden for the NHS.

3.1.6 Measuring disease in cystic fibrosis

Patients with cystic fibrosis can be broadly categorised into early stage, intermediate stage and end stage with complications. Early stage patients are characterised by no infection with *Pseudomonas aeruginosa*, or intermittent infection which can usually be eradicated using antibiotics. Intermediate stage patients (FEV_1~30 to 70% predicted) have chronic infection with *Pseudomonas aeruginosa* or

other less common organisms, whilst end stage patients (FEV_1 < 30% predicted) suffer from severe haemoptysis, pneumothorax and respiratory failure.[2] Patients have routine check-ups to monitor the status and stage of their disease. Measurements during these check-ups usually include, amongst other things, assessment of bacterial infection and measurement of lung function, both of which contribute to treatment planning and prognosis. In some centres sputum tests are not performed routinely.

In the context of clinical trials, the Committee for Medicinal Products for Human Use (CHMP) research guidelines for the development of new medicinal products for cystic fibrosis[1] recommend additional disease measures to gauge the efficacy of interventions. These include measuring rates of microbial resistance, the number of acute exacerbations and the patient's health-related quality of life. FEV_1 is recommended as the primary endpoint for studies investigating CF treatments; however a microbiological primary endpoint is also considered necessary for confirmatory trials.[1]

Measuring microbiological indicators of infection

The presence of a microbial infection is ascertained using sputum colony density. This measurement is also recommended as a secondary endpoint for clinical trials assessing safety and/or efficacy of antipseudomonal antibiotics.[1]

Sputum culture in CF patients requires the collection of a sample of sputum which is subsequently cultured and analysed in a clinical laboratory.[25] Sputum samples can be obtained either spontaneously (through expectoration) or can be induced by the use of throat swabs; naso-pharyngeal aspiration (a small catheter through the nostril); or through inhalation of nebulised hypertonic saline to induce expectoration. In spontaneous expectoration the sample may be optimised by chest physiotherapy or by using bronchodilators and/or an rhDNase aerosol.[26] Clinical analysis of the sputum sample may be assayed for bacterial density, cell count and differential inflammatory markers before and after treatment with antibiotics. These measurements can be quantified in colony forming units (CFU) per gram of sputum and can be used to assess the clinical efficacy of antipseudomonal antibiotics. These measurements would not however be routinely taken from cystic fibrosis patients in clinical practice.

Chronic lung colonisation is defined by the European Medicines Agency (EMA) as the 'presence of *Pseudomonas aeruginosa* in the bronchial tree for at least 6 months, based on at least three positive cultures with at least one month between them without direct (inflammation, fever etc.) or indirect (specific antibody response) signs of infection and tissue damage.'[27]

Measuring rates of resistance

Microbial response can also include analyses of resistance through minimum inhibitory concentration (MIC) of isolates or break-point analysis. Clinical trials for antipseudomonal antibiotics often use the

MIC_{50} (minimum inhibitory concentration required to inhibit the growth of 50% of organisms in culture). Sputum samples are analysed for evidence of resistance or susceptibility to the drug in question according to established MIC breakpoints. The British Society for Antimicrobial Chemotherapy (BSAC) publish breakpoints, which are discriminatory antimicrobial concentrations used in the interpretation of results of susceptibility testing to define isolates as susceptible, intermediate or resistant. At the time at which the trials assessed in this report were completed, the breakpoints were ≤ 4mg/L = susceptible, 6mg/L = intermediate susceptible, ≥ 8mg/L = resistant for colistimethate sodium, and ≤ 2mg/L = susceptible, 4 to 6mg/L = intermediate susceptible, ≥ 8mg/L = resistant for tobramycin. In February 2008, the MIC breakpoints for colistimethate sodium and tobramycin changed. The current breakpoints are ≤4mg/L for susceptibility and >4mg/L for resistance for both tobramycin and colistin.[28] There are now no intermediate breakpoints for tobramycin and colistin.

Whilst these breakpoints are well established, and assessment of microbial resistance is recommended in the EMA research guidelines[1] and are required by NICE for the purpose of this assessment, the relevance of MIC susceptibility breakpoints to inhaled antibiotics is debated. There are two main reasons why the breakpoints may not be relevant: 1) Breakpoints are established primarily in relation to antibiotic concentrations achievable in the blood stream. Because many antibiotics are toxic above a certain blood concentration, the therapeutic window is necessarily limited by this toxicity, and the breakpoints are correspondingly low. Antibiotics delievered by inhalation can reach far higher concentrations in the lung without causing the same toxic levels in the bloodstream, and the therapeutic window extends to a much higher concentration. Therefore, higher breakpoints may be more relevant in this context. 2) Breakpoints are established by culturing samples *in vitro* then testing the susceptibility of the organisms. Phenotype (characteristics of the organism in response to their environment) plays a significant part in resistance. Infection with *Pseudomonas aeruginosa* in the cystic fibrosis lung often involves the formation of biofilms with the mucoid phenotype (which are more resistant to antibiotics) in reponse to the environment of the lung. Cultured organisms removed from the environment of the lung display a different phenotype, and therefore a different level of susceptibility to the antibiotic, making the relevance of the cultured organisms' susceptibility questionable.

Whilst the phenotype may be different *in vivo*, and whilst higher concentrations can be achieved in the lung, an increase in the MIC_{50} may still be an indicator that more resistant genotypes are being selected for by the antibiotic, and may therefore still have some relevance in indicating increased resistance.

Finally, as currently this is the established measure for susceptibility, and it is required by the EMA and listed in the NICE scope, this outcome will be reported for consideration.

Measuring lung function

The widespread availability of spirometers and the availability of standardised methods for assessment[29,30] make spirometry the preferred method of measurement of lung function. Spirometry can be reliably performed by children over five or six years of age, and provides a number of potentially useful measurements. FEV_1 is defined as "the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration, expressed in litres at body temperature (i.e. 37°C), ambient pressure and saturated with water vapour (BTPS)."[29] It is converted by use of an equation (e.g. Knudson)[31] to a percentage of the normal predicted value for a healthy person of the same age, sex and height to give the "FEV_1% predicted" or FEV_1%. There are a number of such equations that can be used,[31-35] which will affect the FEV_1% calculated. There does not appear to be a consensus with respect to which equation should be considered most appropriate.

There are, however, some problems with FEV_1 as a measure of the pulmonary health of people with CF. Primarily, FEV_1 is a global assessment of lung function, and is largely insensitive to localised disease. Additionally, it is influenced by respiratory muscle strength, which in turn is sensitive to nutritional status. To address these issues, there are other spirometry measurements and other technologies which are increasingly being used to assess lung function. Forced vital capacity (FVC) is defined as "the maximal volume of air exhaled with maximally forced effort from a maximal inspiration... expressed in litres (BTPS)"[29], and the mean forced expiratory flow during the middle half of the FVC is known as $FEF_{25–75\%}$. Decreases in $FEF_{25–75\%}$ are thought to provide the earliest indications of obstructive pulmonary disease.[36] These obstructive changes later become evident in FEV_1% readings, and will eventually have an impact on FVC. Computerised tomography (CT) and magnetic resonance imaging (MRI) can also be used to assess lung disease.[37] CT is considered the gold standard, however this exposes the patient to a significant dose of radiation and its use is therefore limited as life expectancy increases.[38] MRI is thought to have lower specificity for small airway disease, but may be comparable or even superior for imaging some other indicators of lung disease.[37]

Whilst there may be a role for $FEF_{25–75\%}$, and CT and MRI may be useful in certain circumstances, FEV_1% is currently the recommended primary endpoint for clinical trials,[1] and, owing to the number of studies linking FEV_1% (either absolute readings or slope of decline) to prognosis,[3,39-43] a key indicator of disease progression used to monitor patients' health.

Measuring acute exacerbations

The EMA defines an exacerbation as the onset of an acute episode of clinical deterioration when the patient is in a stable state. The definition of clinical deterioration has recently been revisited by the

EuroCareCF Working Group.[20] Clinical deterioration is defined by the EMA[27] by the presence of at least 3 of the following new clinical findings:

- increased cough;
- increased expectoration (volume and purulence);
- decreased tolerance to effort or physical activity;
- loss of weight or loss of appetite;
- deterioration of respiratory function (FEV_1, FVC), and;
- a marked increase in airway bacterial load (in CFU/ml) during routine monitoring.

There is a lack of clear recommendations for clinical trials with respect to the definition of acute exacerbations and how they should be measured. Frequently, the corresponding measurement for acute exacerbations is 'mean time to first additional antipseudomonal antibiotic use' as well as the duration of this reactive treatment and/or whether the rescue medication was intravenous or not. 'Hospitalisations' and 'length of hospital stay' are also used as measures under the acute exacerbation outcome. More recently, there has been a general decrease in hospitalising patients for treatment[23] and a trend towards more patients being treated at home.[44] Consequently, the use of 'hospitalisation' as a surrogate measure for acute exacerbation may be unreliable. The most robust data currently are likely to be the number of acute exacerbations and the duration of i.v. use, though these measures are also subject to a degree of random error.

There are currently, therefore, several methods of measuring outcomes for acute exacerbation. A clear recommendation regarding how to measure acute exacerbation has yet to be adopted. This judgment requires consensus on reporting the number of acute exacerbation events or the number of patients who experienced an acute exacerbation. Recommendations for measuring acute exacerbations in clinical trials should also consider that these outcomes could be measured as the percentage change from baseline or in terms of absolute event rates.

Measuring health-related quality of life

As cystic fibrosis is incurable, interventions often aim to improve both the quality and duration of a patient's life. To date, four measures specific to cystic fibrosis have been developed[45-48] to overcome a perceived lack of sensitivity of generic HRQoL measures, such as the EQ-5D and SF-6D, to aspects of the disease which are important to people with cystic fibrosis. The Cystic Fibrosis Questionnaire (CFQ) was developed and validated by a French group[46] and exists in different formats for children and adults. A translated version validated in an American cohort[49,50] is also available and is in common use. This questionnaire is supported by the EMA research guidelines as an outcome measure,[1] which should be recorded at least three to six months into therapy. These are not

preference-based measures and do not allow the calculation of health utility scores. The use of generic health status measures such as the EQ-5D have been very limited in the measurement and valuation of different states of health for cystic fibrosis patients (the available evidence is reviewed in Section 6).

3.2. Current service provision

3.2.1 Management of disease

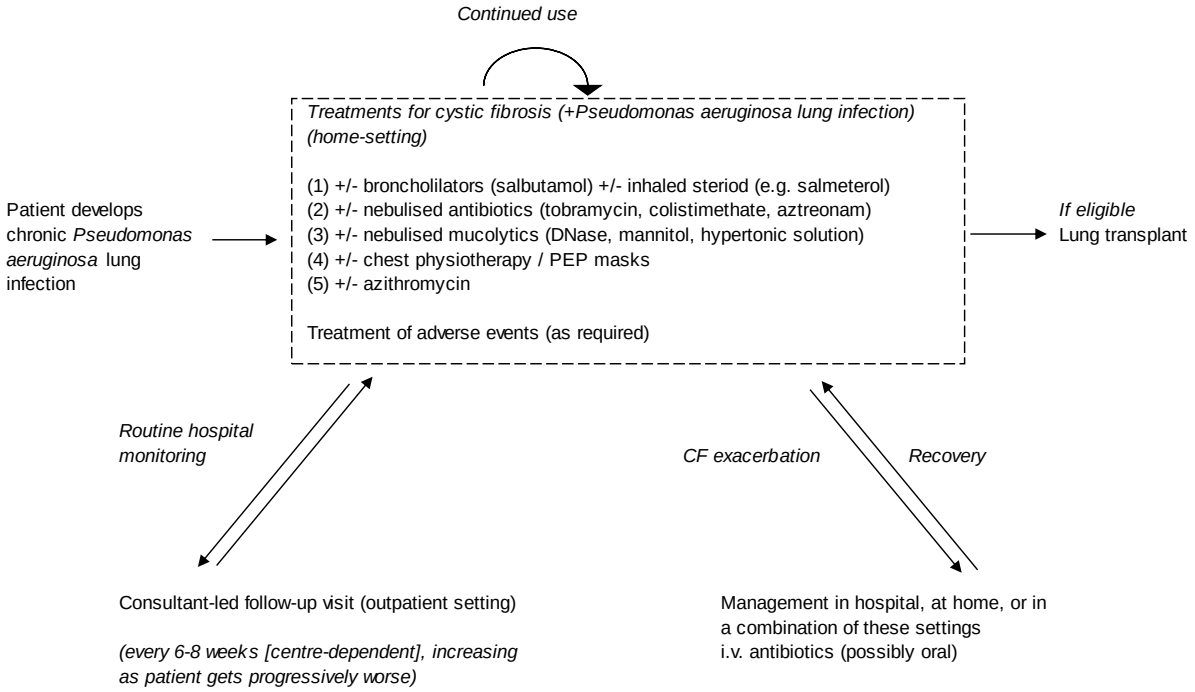
The care of most patients in the UK is co-ordinated by a tertiary cystic fibrosis centre, with formal "shared care" with local clinics. Further, primary care teams may also play a role in the surveillance and early treatment of infection, the provision of dietary and nutritional support, and the provision of social and psychological support for patients and their families.[2] A wide range of treatments may be required at various stages of the disease including physiotherapy, pharmacological therapies, educational advice and surgical interventions for certain complications.

There are two main stages of *Pseudomonas aeruginosa* lung infection, each of which requires a different approach to treatment. The first stage is characterised by intermittent growths of both mucoid and non-mucoid *Pseudomonas aeruginosa* and typically develops during infancy and childhood. This can be treated and sometimes eradicated with antibiotics to maintain respiratory function. Colonisation develops subsequently, and may be associated with mucoid change: it is a marker of reduced survival. Chronic infection cannot be eradicated by antibiotics as biofilm formation prevents antibiotics from working effectively. Acute exacerbations characterised by an acute decrease in respiratory function occur and become more frequent as the disease progresses. It is thought that acute exacerbations may contribute to a stepwise decrease in lung function, with FEV_1% failing to return to pre-exacerbation baseline values. However, evidence to support this theory remains limited. At this stage, for most patients, continuous antibiotic use will be required.

3.2.2 Current management pathways for patients with chronic Pseudomonas aeruginosa infection

Figure 6 presents a general management pathway for cystic fibrosis patients with chronic *Pseudomonas aeruginosa* lung infection. This is intended to be representative of the UK Cystic Fibrosis Trust Guidelines[4] which in turn reflects usual clinical practice in the majority of UK cystic fibrosis centres. There is likely to be some variation in practice across some of the smaller centres and specific antibiotic choices may differ by centre according local bacterial sensitivities. Generally speaking, decisions concerning the use of particular treatments tends to be more related to severity than age, therefore treatment use is broadly similar across both paediatric and adult populations.[7]

Figure 6: Treatment pathway for patients with chronic *Pseudomonas aeruginosa*



Continuous drug treatments

Following chronic infection with *Pseudomonas aeruginosa*, all patients will be offered ongoing nebulised antibiotic treatment, which takes place in the home setting. In a small proportion of patients (around 10-15%) with *Pseudomonas aeruginosa* lung infection may not receive nebulised antibiotic therapy (see Table 2). Current antibiotic treatment options include colistimethate sodium, tobramycin and less commonly, aztreonam. Colistimethate sodium is given every day. Tobramycin and aztreonam differ in that each 28-day treatment cycle is followed by a 28-day period which does not include the use of these drugs. The current guidelines from the Cystic Fibrosis Trust recommend initial treatment using colistin; tobramycin is recommended if colistin is not tolerated or if clinical progress is unsatisfactory.[4] In practice, some patients whose lung function fails to stabilise on monotherapy may receive 28 days of treatment using colistimethate sodium followed by 28 days of treatment using tobramycin as an ongoing repeated sequence.

Concomitant therapies

A number of concomitant treatments may be used alongside nebulised antibiotics. A considerable proportion of CF patients exhibit a degree of airway reversibility (asthma-like changes) and will be treated with bronchodilators (e.g. salbutamol) plus inhaled steroids (e.g. salmeterol xinafoate/fluticasone propionate). This is often administered as a combination inhaler, with up to 50% of CF patients receiving inhalers for this reason. The inhaled drugs for *Pseudomonas aeruginosa*

infection result in bronchospasm (narrowing of the airways) in a proportion of patients. In these patients, a bronchodilator is given before the inhaled antibiotics with prophylactic intent. In addition, patients with chronic *Pseudomonas aerugnosa* infection typically receive macrolides (most commonly azithromycin). These are given between 3 and 7 times per week on an ongoing basis, and are used for their anti-inflammatory properties with the intention of arresting the decline in lung function (however there is conflicting evidence concerning their efficacy[51-53]). Patients may also receive mucolytics (e.g. RhDnase, mannitol, or hypertonic saline) with the intention of reducing the viscosity, adherence and tenacity of the sputum and to aid efficient clearance.[54] In addition, many cystic fibrosis centres would advocate some form of airway clearance using either traditional percussion/drainage via chest physiotherapy or using Positive Expiratory Pressure (PEP) devices.

Follow-up

Patients are invited to attend routine follow-up to monitor progression of the disease and to inform decisions regarding treatment. For children, follow-up appointments are usually every six to eight weeks. However, the frequency of follow-up visits typically increases as the disease progresses. Adults in Band 3 or Band 4 (see Appendix 1) may be supervised more closely. Band 5 patients may be in hospital more or less continuously.

Adverse events and the management of exacerbations

Adverse events should be reported to the CF care team and may be an indication for stopping or modifying therapy. However, patients experiencing exacerbations will require further antibiotic treatment administered intravenously. Many centres now deliver i.v. antibiotics in part at home. Hospital admissions for the management of adverse events are more common in adult centres whereby patients are likely to be more severely ill.

Lung transplantation

A small proportion of patients are eligible for lung transplantation. Most of these patients will no longer require inhaled antibiotics, however anti-rejection therapies and treatments for other organs affected by CF will still be required.

3.2.3 Current usage

Table 2 shows current registry estimates of antibiotic use amongst patients with chronic *Pseudomonas aeruginosa* infection. The data suggest that approximately 78.8% of individuals with chronic *Pseudomonas aeruginosa* infection receive at least one antibiotic. The Cystic Fibrosis Registry states that around 90% of patients with chronic *Pseudomonas aeruginosa* should be prescribed one or more of these treatments.[7]

Table 2: Current antibiotic use among patients with chronic *Pseudomonas aeruginosa*[7]

Drug(s)	Overall	Percentage	< 16 years	Percentage	≥ 16 years	Percentage
Tobramycin solution	691	24.63%	97	22.05%	594	25.11%
Other aminoglycoside	66	2.35%	15	3.41%	51	2.16%
Colistin	1237	44.08%	238	54.09%	999	42.22%
Promixin	726	25.87%	119	27.05%	607	25.66%
At least one of the above	2212	78.83%	383	87.05%	1829	77.30%
Patients with chronic *Pseudomonas aeruginosa*	2806	100.00%	440	100.00%	2366	100.00%

Recent UK-relevant cost estimates relating to the treatment of cystic fibrosis are limited. A recent UK cost of illness study undertaken in the East of England estimated the mean annual cost of treating 174 patients to be £1,040,087 (£5,976 per patient).[55] Multiplying this estimate up to the current number of patients in the CF registry yields a crude annual cost of around £57 million for CF patients in England and Wales. The true cost to the NHS may however be considerably higher (Personal communication: Diana Bilton, Consultant Physician / Honorary Senior Lecturer, Department of Respiratory Medicine, Royal Brompton Hospital).

3.2.4 Variations in services and uncertainties about best practice

It has been noted elsewhere that many aspects of current practice in the management of cystic fibrosis has evolved without being subjected to high quality clinical trials.[2] This may be partly a result of the rarity of the disease and associated difficulties with recruitment to clinical trials, as well as variations between patients in terms of how the disease manifests and is treated. With respect to interventions for the management of lung infection, long-term clinical and mortality benefits of treatments are rarely available.

There is currently no NICE guidance relating to the detection, diagnosis or management of patients with cystic fibrosis. A Single Technology Appraisal of Mannitol dry powder for inhalation for the treatment of CF is in progress and is subject to review following a recent positive CHMP opinion.[56] This ongoing appraisal does not specifically relate to the management of patients with *Pseudomonas aeruginosa* lung infection.

Since 1st April 2011, the Department of Health has adopted a "Payment by Results" (PbR) tariff for patients with cystic fibrosis. This will link 'activity' to funding received, whereby money will follow the patient through their hospital journey, paying for treatment and care (excluding drugs) received along the way.[25]

3.3. Description of technologies under assessment

3.3.1 Summary of interventions and comparators

This assessment includes two interventions which are delivered as a dry powder for inhalation (DPI): colistimethate sodium DPI (Colobreathe® [plus Turbospin®], Forest Laboratories) and tobramycin DPI (TOBI® [plus Podhaler®], Novartis Pharmaceuticals). The antibiotics colistimethate sodium and tobramycin also represent the relevant comparators for the assessment, albeit in nebulised form.

Colistimethate sodium (Colobreathe / colomycin / colistin) belongs to the polymyxin group and is a cyclic polypeptide antibiotic derived from *Bacillus polymyxa* var. *colistinus.* Colistimethate sodium works by disrupting the structure of the bacterial cell membrane in a detergent-like way by changing its permeability, leading to bacterial death. It is also thought to act intracellularly to precipitate rhibosomes and other cytoplasmic components. Colistimethate sodium is active against aerobic Gram-negative organisms including: *Pseudomonas aeruginosa*, *Acinetobacter baumanii*, and *Klebsiella pneumoniae.* Forest Laboratories currently market colistin sulphate (Colomycin) as a tablet or syrup and colistimethate sodium as a powder for injection or nebulisation. Profile Pharma currently market colistimethate sodium (Promixin) as a powder for intravenous injection or for inhalation specifically using an I-neb (Philips Respironics) device. Colobreathe (which is also colistimethate sodium) is available as 125mg hard capsules and is administered specifically using the Turbospin inhaler device. It is anticipated that both the treatment and the Turbospin device will be marketed and packaged together.

The summary of product characteristics(SmPC) (http://www.ema.europa.eu/) lists the following adverse events for colistimethate sodium DPI: unpleasant taste (dysgeusia), cough, throat irritation, dyspnoea, dysphonia, coughing, bronchospasm, balance disorder, headache, tinnitus, heamoptysis, asthma, wheezing, chest discomfort, lower respiratory tract infection, productive cough, crackles lung, vomiting, nausea, arthralgia, pyrexia, asthenia, fatigue, forced expiratory volume decreased, drug hypersensitivity, weight fluctuation, decreased appetite, ear congestion, chest pain, dysphonia exacerbated, pharyngolaryngeal pain, epistaxis, sputum purulent, abnormal chest sound, increased upper airway secretion, diarrhoea, toothache, salivary hypersecretion, flatulence, proteinuria, and thirst. Sore throat or mouth (probably due to candida albicans infection or hypersensitivity) has been reported for nebulised colistimethate sodium and the SmPC states that this may occur with Colobreathe also. Adverse events listed in The Electronic Medicines Compendium (http://www.medicines.org.uk/) for the nebulised form also include bronchospasm, cough, hypersensitivity reactions, and skin rash or rashes.

Tobramycin belongs to the aminoglycoside group of antibiotics and is obtained from cultures of *Streptomyces tenebrarius.* It enters susceptible bacterial cells via a complex active transport mechanism and acts by binding irreversibly to the 30S ribosomal subunit. It is thought that this interferes with essential steps in protein synthesis and consequently affects the permeability of the cell membrane, though there is some suggestion that it may also act directly on the cell membrane.[57] Once the cell envelope becomes compromised, cell death follows. It also acts to induce misreading of the genetic code of the mRNA template, resulting in incorporation of incorrect amino acids which can result in cellular malfunction. Two tobramycin nebuliser solution products are available: Novartis currently market TOBI® nebuliser solution, and Chiesi market Bramitob® nebuliser solution. TOBI DPI is available as 28mg capsules and is administered specifically using the Podhaler device. Both the treatment and device are marketed and packaged together.

Adverse events listed by The Electronic Medicines Compendium (http://www.medicines.org.uk/) for tobramycin DPI include: hearing loss, tinnitus, haemoptysis, epistaxis, dyspnoea, dysphonia, productive cough, cough, wheezing, rales, chest discomfort, nasal congestion, bronchospasm, oropharyngeal pain, vomiting, diarrhoea, throat irritation, nausea, dysgeusia, rash, musculoskeletal chest pain and pyrexia. Cough was the most frequent adverse reaction. With respect to nebulised tobramycin, adverse events reported in controlled clinical trials include dysphonia and tinnitus. Adverse events reported in the post-marketing phase include: laryngitis, oral candidiasis, fungal infection, lymphadenopathy, hypersensitivity, anorexia, headache, dizziness, aphonia, somnolence, tinnitus, hearing loss, ear disorder, ear pain, dysphonia, dyspnoea, cough, pharyngitis, bronchospasm, chest discomfort, lung disorder, productive cough, haemoptysis, epistaxis, rhinitis, asthma, hyperventilation, hypoxia, sinusitis, dysgeusia, nausea, mouth ulceration, vomiting, diarrhoea, abdominal pain, rash, urticaria, pruritus, back pain, asthenia, pyrexia, chest pain, pain, malaise and pulmonary function test decreased.

3.3.2 Place in the treatment pathway

Both interventions are to be used for the ongoing treatment of chronic *Pseudomonas aeruginosa*, as described in Section 3.2. One of the principal anticipated benefits of the interventions is that they are quicker to use and are portable which means that they can be self-administered by the patient as indicated, thereby avoiding time required for inhalation using a nebuliser. The DPIs may also result in savings in terms of the time associated with cleaning traditional nebulisers. It is hypothesised that these benefits may lead to improvements in compliance to treatment.

3.3.3 Identification of important sub-groups

Specific subgroups have not been identified *a priori* within this appraisal. Consideration was given within this assessment to evidence relating to those groups of individuals for whom these therapies may be particularly clinically effective or cost-effective.

3.3.4 Current usage in the NHS

TOBI used in conjunction with the Podhaler device was granted full marketing authorisation by the EMA in 2011. TOBI Podhaler is indicated for the suppressive therapy of chronic pulmonary infection due to *Pseudomonas aeruginosa* in adults and children aged 6 years and older with cystic fibrosis. The Podhaler inhaler device bears an initial date of CE Marking of 28 July 2005. The Novartis submission states that this date is noted on the EC Declaration of Conformity to the EU Medical Device Directive 93/42/EEC as amended for this Class I device.[58]

Colobreathe used in conjunction with the Turbospin device was granted full marketing authorisation by the EMA in February 2012. Colobreathe is indicated for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis aged 6 years and older.

3.3.5 Anticipated costs associated with the intervention

Table 3 summarises the acquisition costs associated with the interventions and comparators based on list prices from the British National Formulary (BNF) 62.[59]

Table 3: Expected costs associated with interventions and comparators

Generic name	Trade name	Manufacturer	Indication	Form of administration	Cost per unit	Cost per 28 days of treatment
Colistimethate sodium	Promixin®	Profile	Adult and child over 2 years, 1–2 million units twice daily; increased to 2 million units 3 times daily for subsequent respiratory isolates of *Pseudomonas aeruginosa*	Powder for nebuliser solution	1 million-unit vial = £4.60	£257.60 (1 million units per dose twice daily) to £772.80 (2 million units per dose three times daily)
	Colomycin®	Forest		Powder for injection or nebuliser solution	(1) 1 million-unit vial = £1.68; (2) 2 million-unit vial = £3.09	£94.08 (1 million units per dose twice daily) to £259.66 (2 million units per dose three times daily)
	Colobreathe® +Turbospin®	Forest	125mg twice daily	Dry powder for inhalation	[redacted]	
Tobramycin	Bramitob®	Chiesi	Adult and child over 6 years, 300 mg every 12 hours for 28 days, subsequent courses repeated after 28-day interval without tobramycin nebuliser solution	Powder for nebuliser solution	75 mg/mL, net price 56 × 4-mL (300-mg) unit = £1187.00	£1,187.00
	TOBI®	Novartis		Powder for nebuliser solution	60 mg/mL, net price 56 × 5-mL (300-mg) unit = £1187.20	£1,187.20
	TOBI® + Podhaler®	Novartis	Adult and child over 6 years, 112 mg every 12 hours for 28 days, subsequent courses repeated after 28-day interval without tobramycin inhalation powder	Dry powder for inhalation	224 x 28mg capsules + 5 podhalers = £1790.00 56 x 28mg capsules + 1 podhaler = £447.50	£1,790
Aztreonam	Cayston®	Gilead	Adult over 18 years, 75 mg 3 times daily (at least 4 hours apart) for 28 days; if additional courses required, a minimum of 28 days without aztreonam nebuliser solution recommended between courses	Powder for nebuliser solution	84 × 75 mg vials (with solvent and nebuliser handset) = £2,566.80	£2,566.80

4. DEFINITION OF THE DECISION PROBLEM

4.1 Overall aims and objectives of the assessment

This assessment addresses the question *"what is the clinical effectiveness and cost-effectiveness of colistimethate sodium DPI and tobramycin DPI for the treatment of Pseudomonas aeruginosa lung infection in cystic fibrosis as compared against current treatments?"*

Specifically, the objectives of the assessment are:

(1) To assess the clinical effectiveness of colistimethate sodium DPI and tobramycin DPI for the treatment of *Pseudomonas aeruginosa* lung infection in terms of lung function, microbial response, respiratory symptoms and the frequency/severity of acute exacerbations.

(2) To assess the adverse event profile associated with colistimethate sodium DPI and tobramycin DPI.

(3) To estimate the incremental cost-effectiveness of colistimethate sodium DPI and tobramycin DPI as compared against current standard treatments for the treatment of *Pseudomonas aeruginosa* lung infection.

4.2 Decision problem

4.2.1 Interventions

Two interventions are included in this assessment:

(1) Colistimethate sodium DPI used in conjunction with the Turbospin device.

(2) Tobramycin DPI used in conjunction with the TOBIPodhaler device.

4.2.2 Populations and subgroups

The population for the assessment will include people aged 6 years and over with cystic fibrosis and chronic *Pseudomonas aeruginosa* pulmonary colonisation. Subgroups are considered according to the available evidence.

4.2.3 Relevant comparators

The interventions are compared against each other. Other relevant comparators include antibiotics used for nebulised inhalation, including colistimethate sodium for nebulised inhalation and tobramycin for nebulised inhalation. The availability of evidence of the effectiveness of other less commonly used nebulised antibiotics (e.g. aztreonam) with antipseudomonal activity is also considered within the assessment.

4.2.4 Outcomes

The following outcomes are considered within this assessment.

- Rate and extent of microbial response (for example sputum density of *Pseudomonas aeruginosa*)
- Lung function measured in terms of forced expiratory volume (FEV_1)
- Respiratory symptoms
- Frequency and severity of acute exacerbations
- Health-related quality of life (HRQoL)
- Adverse events of treatment (including rate of resistance to antibiotic treatment)
- Cost-effectiveness measured in terms of the incremental cost per quality adjusted life year (QALY) gained.

5. CLINICAL EFFECTIVENESS

This section presents the methods and results of a systematic review of clinical effectiveness of colistimethate sodium DPI and tobramycin DPI in comparison to currently used nebulised treatments. Section 5.1 presents the methods of the review. Section 5.2 presents details of the characteristics and quality of the included studies. Section 5.3 presents the assessment of clinical effectiveness.

5.1 Methods for reviewing clinical effectiveness

5.1.1 Identification of studies

A comprehensive search was undertaken to systematically identify literature relating to the clinical effectiveness of colistimethate sodium DPI and tobramycin DPI for the treatment of *Pseudomonas aeruginosa* in cystic fibrosis. The search strategy comprised the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Handsearching of bibliographies of retrieved papers.

The following electronic databases were searched from inception for published trials and systematic reviews:

- MEDLINE: Ovid. 1950-present
- MEDLINE in-Process and Other Non-Indexed Citations: Ovid. 1950-present
- EMBASE: Ovid. 1980-present
- Cochrane Library: Wiley Interscience
    - Cochrane Database of Systematic Reviews (CDSR). 1996-present
    - Database of Abstracts of Reviews of Effects (DARE). 1995-present
    - Cochrane Central Register of Controlled Trials (CCRT). 1995-present
    - Cochrane Methodology Register. 1904-present
    - Health Technology Assessment Database (HTA). 1995-present
    - NHS Economic Evaluation Database (NHS EED). 1995-present
- CINAHL: EBSCO. 1982-present
- Web of Science Citation Index: Web of Knowledge. 1899-present
- Conference Proceedings Citation Index: Web of Knowledge. 1990-present
- BIOSIS Previews: Web of Knowledge. 1969-present

Additional searches were carried out for unpublished studies (e.g. ongoing, completed)**:**

- Agency for Healthcare Research and Quality (AHRQ)

- Bandolier
- Centre for Health Economics (CHE); University of York
- Clinical Trials.gov
- Current Controlled Trials
- The National Research Register Archive: NIHR. 2000-2007
- The MetaRegister of Controlled Trials: Springer Science + Business Media. 2000-present.

Manufacturers' submissions received by NICE, as well as any relevant systematic reviews were also handsearched in order to identify any further clinical trials.

The MEDLINE search strategy is presented in Appendix 2. The search strategy combined freetext and MeSH (Medical subject headings) or thesaurus terms relating to cystic fibrosis, with freetext and MeSH or thesaurus terms relating to *Pseudomonas aeruginosa*, relevant antibiotics and classes of antibiotics and the devices and comparator devices of interest. The search strategy was translated across all databases. No date or language restrictions were applied. Literature searches were conducted during February and March 2011. References were collected in a bibliographic management database, and duplicates removed.

5.1.2 Inclusion and exclusion criteria

Inclusion and exclusion criteria were based on the scope provided by NICE.[60] These are set out below.

5.1.2.1 Inclusion criteria

Studies were included if they satisfied the following criteria.

Interventions

Studies assessing the effectiveness of colistimethate sodium DPI (used in conjunction with the Turbospin device) or tobramycin DPI (used in conjunction with the TOBIPodhaler device) were included.

Population

Studies including only people aged six years and over with cystic fibrosis and chronic *Pseudomonas aeruginosa* pulmonary infection were selected. Children under six years of age were excluded from the assessment as they are subject to different treatment regimens, methods of assessment of lung function differ, and licensing has not been sought for this age group.

Comparators

Acceptable comparators were: i) the comparator intervention, or ii) other antipseudomonal antibiotics for nebulised inhalation including as a minimum colistimethate sodium for nebulised inhalation or tobramycin for nebulised inhalation.

Outcomes

Outcomes to be considered by the review were: rate and extent of microbial response (for example sputum density of *Pseudomonas aeruginosa*); lung function; respiratory symptoms; frequency and severity of acute exacerbations; health-related quality of life (HRQoL); and adverse events of treatment (including rate of resistance to antibiotic treatment). Compliance was also considered as a *post-hoc* addition to the outcomes set out in the NICE scope, as it became evident that this was of relevance to the claims made for the interventions by the manufacturers.

Study types

Randomised controlled trials (RCTs) were included in the assessment. Data from non-randomised studies were considered, but were not included as evidence was available from RCTs.

Systematic reviews were included if they provided additional data for RCTs meeting the inclusion criteria (that is, unavailable from published trial reports). Other systematic reviews identified were not included but were checked for RCTs that met the inclusion criteria of this review.

5.1.2.2 Exclusion criteria

The following were excluded: studies based on animal models; preclinical and biological studies; non RCTs; editorials, opinion pieces; reports published as meeting abstracts only where insufficient details were reported to allow inclusion; studies only published in languages other than English; studies with vasoactive drugs not within their licensed indications; studies in which the population was not restricted to cystic fibrosis, unless data for just this population was presented, and; studies that did not present data for the included outcomes.

Based on the above inclusion/exclusion criteria, study selection was conducted by one reviewer (SH, CC or LU) and checked by a second reviewer (SH, CC or LU). In the first instance, titles and abstracts were examined for inclusion. The full manuscripts of citations judged to be potentially relevant were retrieved and further assessed for inclusion.

Scoping searches indicated that a head-to-head trial of the two interventions was unlikely to be available. In anticipation of this, studies which could potentially contribute to a network meta-analysis were also identified on the basis of their abstract and title. Studies were considered potentially useful if they assessed the efficacy of nebulised antibiotics in the target population for the target condition, and reported relevant outcomes. Key study characteristics of the wider network of evidence were extracted by one reviewer. Based on these characteristics, the available network of evidence was constructed. Were viable networks possible, only studies that could contribute to this network would be included in the review. Were a network not possible, only studies providing direct comparisons with at least one intervention and at least one comparator listed in the inclusion criteria were included in the review.

5.1.3 Data extraction and critical appraisal strategy

Data were extracted without blinding either to authors or journal. Data were extracted by one reviewer using a standardised form and checked by a second reviewer. Where multiple publications of the same study were identified, quality assessment and data extraction were based on all relevant publications, and listed as a single study. The quality of included studies was assessed according to three sets of criteria. The purpose of quality assessment was to provide a narrative account of trial quality for the reader, and to inform subgroup analyses (where data allow). In order to assess the risk of bias, items listed in the NHS CRD report[61] were used and were scored as "yes", "no" or "unclear." To assess the clinical relevance and quality of the studies, items were generated from the EMA research recommendations.[1] Two trials were non-inferiority trials; a separate quality assessment form[62] specific to this type of study was also used.

5.1.4 Data synthesis methods

The pre-specified outcomes were tabulated and discussed within a descriptive synthesis. Where populations, interventions, outcome measures and available data were comparable and statistical synthesis was considered appropriate, classical meta-analysis or network meta-analysis was planned using Bayesian techniques, or Review Manager® software (The Cochrane Collaboration, version 5.0 http://.ims.cochrane.org/revman). If sufficient trials were available, sensitivity analysis was planned to examine whether the removal of poor quality trials influenced the results of the meta-analysis. Consideration was also given to subgroup analyses based on study characteristics.

5.2 Results

5.2.1 Quantity and quality of research available

The search retrieved 743 potentially relevant citations (734 from searches of electronic databases, 9 from secondary searches of relevant reviews, articles and sponsors submissions). Of these, 723 were excluded at the title and abstract stage, leaving 20 potentially includable citations.

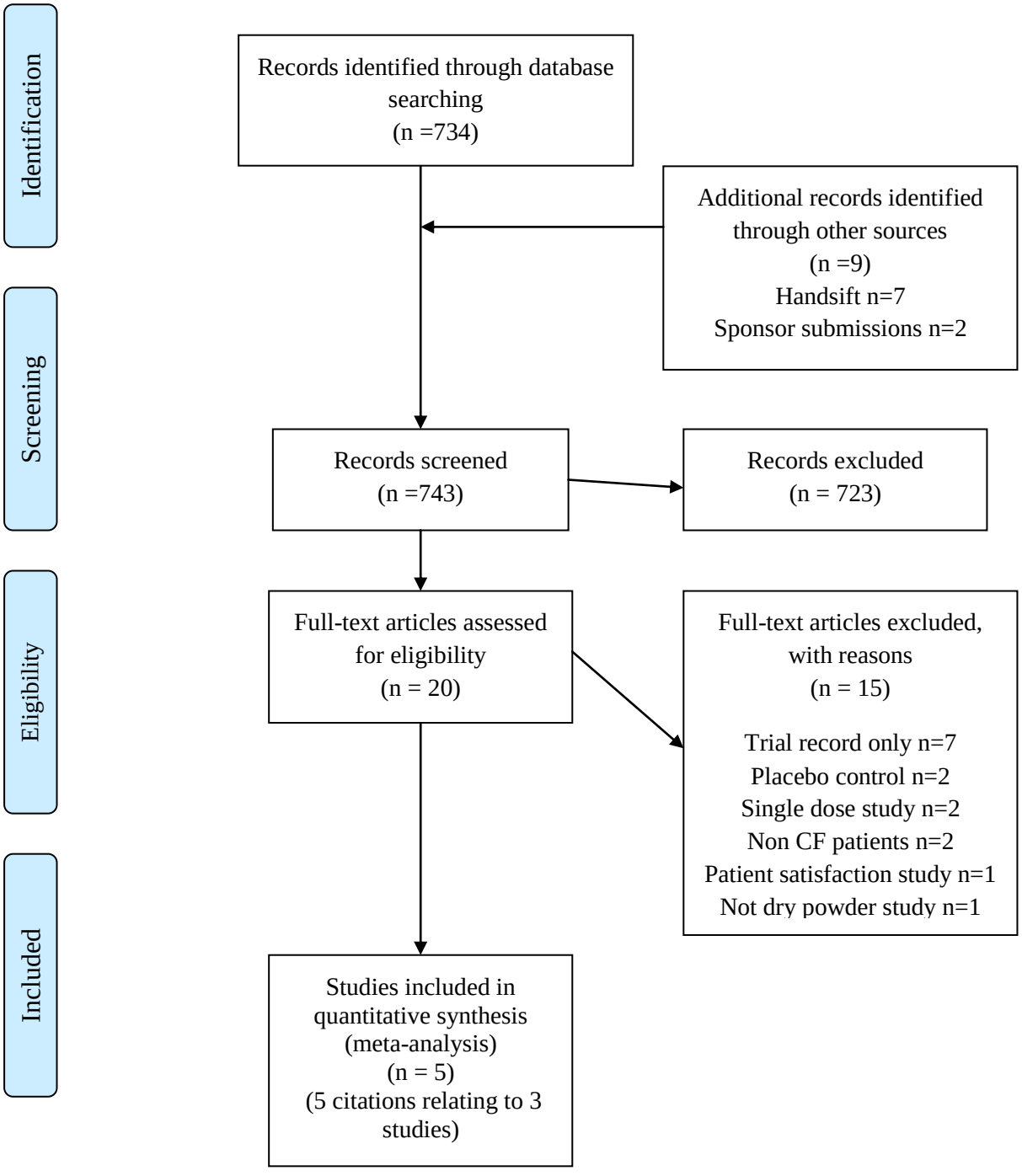
The full texts of the 20 articles were obtained for scrutiny. 15 did not meet the inclusion criteria and were excluded (Appendix 3). Three studies comparing colistimethate sodium DPI or tobramycin DPI with a nebulised antibiotic were included in the review. One study was of tobramycin DPI in combination with the TobiPodhaler,[58,63] and two studies were of colistimethate sodium DPI in combination with the Turbospin device.[64] Information about the three trials included in the systematic review was available from five sources as indicated in Figure 7. These comprise one published journal article,[63] two conference abstracts[65,66] and the two manufacturers' submissions to NICE,[58,64] with subsequent clarifications. It should be noted that data for the pivotal colistimethate sodium DPI trial, study COLO/DPI/02/06,[64] were available from the manufacturer's submission,[64] the Clincial Study Report,[67] the trial protocol[68] and personal communication/clarifications only. None of this information was available in the public domain. The search process is summarised using a PRISMA diagram in Figure 7.

To assess the viability of a network meta-analysis, key study characteristic data were extracted from an additional 13 studies, from 16 citations.[63-65,69-81] Owing to clinical heterogeneity between the studies and incompleteness of the evidence network, a network meta-analysis was not performed (see Appendix 4).

5.2.2 Study characteristics

The included trials and the treatments assessed are summarised in Table 4. All studies were open label, multicentre studies, two of which were multinational studies.[64] The EAGER trial[63] was a large trial (n=533) which compared tobramcyin DPI to nebulised tobramycin. The COLO/DPI/02/06 trial[64] was slightly smaller (n=380) and compared colistimethate sodium DPI with nebulised tobramycin. Both these trials were powered to detect clinically relevant changes in FEV_1%. The COLO/DPI/02/05 trial was much smaller (n=16) and compared colistimethate sodium DPI against nebulised colistimethate sodium. The EAGER trial[63] and COLO/DPI/02/06[64] studies were both of 24 weeks duration, whilst COLO/DPI/02/05[64] was a crossover trial which reported outcome data at 4 weeks (before crossover) and 8 weeks only (after crossover).

Figure 7: Flow diagram of study inclusion (adapted from PRISMA)



5.2.3 Interventions and comparators

Intervention and comparator dosing complied with current UK licensing (http://www.medicines.org.uk/EMC/medicine/). In the two trials of colistimethate sodium DPI (studies COLO/DPI/02/06[64] and COLO/DPI/02/05[64]), patients took colistimethate sodium DPI treatment every day throughout the study. In both the EAGER trial[63] and the COLO/DPI/02/06 trial, [64] the dosing pattern for nebulised tobramycin was cycles of 28 days on treatment followed by 28 days off treatment, for 3 cycles. Within the EAGER trial,[63] the same treatment approach was used for tobramycin DPI. This administration cycle is standard practice for tobramycin[59] with the aim of preventing antibiotic resistance.

Table 4: Summary of included studies

Study name and sources of information	Source of funding	Study design	Dates study undertaken	Study location	Intervention	Comparator	Duration of trial	Treatment schedule
EAGER trial Konstan *et al* 2011;[63] TBM100C2302 manufacturer's submission; [58] manufacturer's clarifications	Novartis Pharmaceuticals	RCT, open label N=533	Feb 2006 - March 2009	127 centres in 15 countries [including North America, Europe, Australia, Israel and Latin America]	Tobramycin dry powder for inhallation T-326 Inhaler 112mg b.i.d	Tobramycin inhalation solution PARI LC Plus jet nebuliser 300mg/5ml b.i.d	24 weeks	Int & comp: 28 days on treatment followed by 28 days off treatment
COLO/DPI/02/06 manufacturer's submission;[64] manufacturer's clarifications	Forest Laboratories UK Ltd	RCT, open label N=380	NR (last patient visit 14 Aug 2007)	66 centres in European Union countries, Russia and the Ukraine	Colistimethate sodium dry powder for inhallation Turbospin device 125mg b.i.d	Tobramycin inhalation solution PARI LC Plus jet nebuliser 300mg/5ml b.i.d	24 weeks	Int: continuous treatment Comp: 28 days on treatment followed by 28 days off treatment
COLO/DPI/02/05 Davies *et al* 2004; manufacturer's submission; [64] manufacturer's clarifications	Forest Laboratories UK Ltd	RCT, open label with crossover N=16	NR	3 centres in the UK	Colistimethate sodium dry powder for inhallation Turbospin device 125mg b.i.d	Colistimethate sodium solution Device: NR 2MU b.i.d	8 weeks	Int & comp: continuous treatment

RCT, randomised controlled trial; NR, not reported; b.i.d, twice daily; Int, intervention; Comp, comparator.

5.2.4 Inclusion and exclusion criteria

Inclusion and exclusion criteria are summarised and compared in Table 5. Criteria seem largely compatible between the two major trials (EAGER[63] and COLO/DPI/02/06[64], though criteria for COLO/DPI/02/06[64] were complicated. Inclusion and exclusion critera are not reported in full here (please refer to manufacturers' submissions for more details).

The EAGER[63] trial and trial COLO/DPI/02/06[64] selected patients with "confirmed" or "documented" CF who were clinically stable, and aged 6 years or older, whilst COLO/DPI/02/05[64] selected patients who were eight years or older. Patients in the EAGER[63] trial and trial COLO/DPI/02/06[64] had to have an FEV_1% value 25 or above, up to 75%, whereas in the COLO/DPI/02/05[64,65] no upper limit for FEV_1% was set. Patients in all trials continued with usual CF treatments (except other routine antipsudomonal treatments). Patients in all three trials had a chronic *Pseudomonas aeruginosa* infection. The criteria used to define a chronic infection did not meet with EMA recommendations[1] in any trial, as all called for only two positive cultures in the last six months, rather than three. In the case of the COLO/DPI/02/06 trial,[64] three positive cultures were required in the last six months, but patients could also qualify with only two in the last two months. As such, it is unclear whether the trials have truely selected chronically infected patients, and how comparable the degree of infection is between the two trials.

The COLO/DPI/02/06 trial[64] had a run-in period whereby participants were required to have received 16 weeks (two cycles) of nebulised tobramycin prior to beginning the trial. Tobramycin has been documented to peak rapidly in efficacy in the first cycle of treatment with the effect not being sustained over time.[74] Therefore, the run-in phase was intended to eliminate this short-term change in FEV_1% predicted. In addition, this run-in phase was intended to exclude any patients who could not tolerate tobramycin. In comparison, the EAGER trial[63] had a wash-out period of any systemic or inhaled antipseudomonal antibiotics for 28 days prior to randomisation, which ensured that patients already on tobramycin complied with the standard dosing schedule of 28 days on treatment followed by 28 days off treatment. The difference between these two criteria may result in slightly different populations.

Table 5: Key inclusion and exclusion criteria of included studies

Study	Inclusion criteria	Exclusion criteria
All trials	• Adequate contraceptive methods for female participants • Written informed consent from patient or patient's guardian • Documented diagnosis of CF from a specialist CF unit (genotype and/or positive sweat tests). • Current CF condition had to be clinically stable. • Chronic *Pseudomonas aeruginosa* infection	• Pregnant or breast-feeding patients • Inability to comply with any of the study procedures or the study regimen (including inability to use study devices i.e. during dry powder inhaler and nebuliser training) • Use of an elective course of intravenous antibiotic therapy or investigational drug within 28 days of screen • Acute respiratory exacerbation within 28 days prior to first day of trial medication administration • Patients who were colonised with *Burkholderia cepacia*.
EAGER[63]	• ≥ 6 years old • FEV_1 >25% to <75% predicted based on Knudson equations. Patients with chronic *Pseudomonas aeruginosa* infection (sputum or throat cultures positive for *Pseudomonas aeruginosa* within 6 months of screening and at baseline)	• Use of systemic or inhaled antipseudomonal antibiotics or other drugs which can affect FEV_1% within 28 days prior to study drug administration. • Hemoptysis more than 60 cc within 30 days prior to study. • Hypersensitivity to aminoglycosides or inhaled antibiotics • Serum creatinine 2mg/dL or more, blood urea nitrogen 40 mg/dL or more, or an abnormal urinalysis defined as 2+ or greater proteinuria • Clinically relevant history of hearing loss or chronic tinnitus
COLO/DPI/02/06[64]	• ≥ 6years old • FEV_1 >25 to <75% predicted based on Knudson equations. • Run-in inclusion criteria (patients to receive a minimum of two nebulised tobramycin on/off cycles immediately prior to randomisation) • Non-smokers or a past smoker who had not smoked within the past 12 months • Patients who, on first day of trial medication administration (Visit 1), had ≥ 28 days but ≤ 35 days off tobramycin. • Patients with chronic P. aeruginosa infection (2 or more sputum or throat cultures positive for *Pseudomonas aeruginosa* within 6 months of screening)	
COLO/DPI/02/05[64]	• ≥ 8 years old • FEV_1>25% based on Knudson equation. • Non-smokers or a past smoker who had not smoked within the past 12 months prior to the date of entry.	• Known sensitivity to colistimethate sodium or salbutamol. • Existence of any pre-study medical conditions which, in investigator's judgement, warranted exclusion from the study. • Inability to communicate/co-operate with investigator due to language problems, poor mental development or impaired cerebral function. • Laboratory parameters falling outside the expected normal ranges for CF (Investigator decision). • Patients who, on first day of trial treatment, had less than 28 days off tobramycin. • Patients who had had less than 72-hours washout from other anti-pseudomonal agents. • Patients who were complicated by allergic bronchopulmonary aspergillosis (ABPA). • Patients who were awaiting heart-lung or lung transplantation.

5.2.5 Patient characteristics

The baseline characteristics of patients in the three trials are presented in Table 6. The patients in the COLO/DPI/02/06 trial[64] had a lower mean age than those in the EAGER trial.[63] Mean age was not reported for trial COLO/DPI/02/05.[64] As age and FEV_1% status are thought to have an inverse correlation, it might be expected that the patients in the COLO/DPI/02/06 trial[64] were earlier in their stage of chronic *Pseudomonas* infection than those in the EAGER trial.[63] However the baseline FEV_1% predicted values are similar between these two trials, with the FEV_1% predicted in COLO/DPI/02/06[64] being slightly lower. This may be due to inclusion criteria for chronic infection not being defined according to EMA recommendations.[1] For all trials, this may result in the recruitment of patients with intermittent infections, who may respond differently to treatment than chronically infected patietns. It is also probable that some patients recruited to the COLO/DPI/02/06 trial[64] may be slightly less well than the EAGER trial[63] participants as criteria were more stringent in this population. In both trials, the lack of consistency and conformity with the EMA guidelines[1]may affect generalisability, with the trial populations not being entirely made up of the chronically infected patient population as defined by the EMA and European and French consensus conference.[27]

In line with the potentially slightly poorer health (based on FEV_1% values) of the COLO/DPI/02/06[64] trial patients, the body mass index (BMI) was also, on average, lower than in the EAGER trial.[63] However, it should be noted that these differences have not been subjected to statistical scrutiny and may not be significant. The clinical relevance of differences of this size are also uncertain.

Concomitant medication use could not be compared between trials as little data was provided (after a request for clarification from the Assessment Group) for the EAGER trial. Many allowed medications (for example macrolides and bronchodilators) could affect FEV_1% measurements, and their impact on the trial results are unknown, and may be different between studies.

In terms of prior antipseudomonal use, patients in the COLO/DPI/02/06 trial[64] had all used nebulised trobramycin immediately before the trial, whereas only around 25% of patients in the EAGER trial had used nebulised tobramydin immediately before the trial (with an additional 55% (approximately) having used it within 3 months prior to the trial). As such, patients in the COLO/DPI/02/06[64] trial may have been more tolerant of tobramycin in terms of adverse events, and will have experienced the initial peak in tobramycin FEV_1% results within the first four weeks of the run-in period, rather than during the trial itself. Conversely the EAGER trial[63] had a proportion of patients who are not tobramycin tolerant having never used tobramycin, and a proportion who have not used tobramycin immediately prior to the 28 day wash-out period. Some or all of these patients may have experienced

an initial peak in efficacy (Table 6) during the trial, and may be more likely to experience adverse events associated with tobramycin than patients in the COLO/DPI/02/06[64] trial.

Given that age, BMI, concomitant medications, prior exposure to antipseudomonal antibiotics and FEV_1% all have prognostic value in CF, it is difficult to determine whether these cohorts are comparable in terms of overall health and propensity to benefit from antipseudomonal treatments.

Table 6: Baseline characteristics of participants

Study	Age Mean (sd)		Gender Male/Total (%)		BMI Mean (sd)		FEV_1% predicted Mean		Concomitant and previous treatment	
	Int	Com	Int	Com	Int	Com	Int	Com	Int	Com
EAGER trial[58,63]	26 (11.4) <13 years: 9.1% ≥ 13 years: 90.9 %	25 (10.2) <13 years: 8.6% ≥13 years: 91.4 %	171/308 (55.5 %)	115/209 (55.0 %)	20.7 (4.0)	20.4 (3.5)	53 (SD 15.9, SE 1.11) ≥ 25 <50: 41.6 % ≥50 ≤80*: 58.4 %	53 (SD 14.2, SE 0.81) ≥ 25 <50: 42.6% ≥50 ≤80*: 57.4%	Chronic macrolide use n=187 (60.7%) [redacted] Use of antipseudomonal antibiotics prior to first dose: 1 month : n 78 (25.3%) >1-3 : n 171 (55.5%) >3-6 : n 33 (10.7%) >6 : n 11 (3.6%) Never used: 15 (4.9%) Other** concomitant medications: Proprotion NR	Chronic macrolide use n=125 (59.8%) [redacted] Use of antipseudomonal antibiotics prior to first dose: 1 month : n 46 (22.0%) >1-3 : n 112 (53.6%) >3-6 : n 24 (11.5%) >6 : n 9 (4.3%) Never used : 18 (8.6%) Other**concomitant medications: Proprotion NR*
COLO/DPI/02/06[64]	Mean (sd) 21.3 (9.72)	Mean (sd) 20.9 (9.30)	103/183 (56.3 %)	101/190 (52.9 %)	Mean (sd) 18.67 (3.396)	Mean (sd) 18.46 (3.584)	51.76 (SE 1.02)	50.82 (SE 0.99)	Any medication (93.4%); Mucolytics (74.3%) Selective β2-adrenoreceptor agonists (76.5%) Macrolides (49.7%) Azithromycin 85 (46.4%) Dornase alpha 94 (51.4%) Glucocorticoids 66/183 (36.1%) Anticholinergics 34/183 (18.6%)	Any medication (94.2%); Mucolytics (79.1%) Selective β2-adrenoreceptor agonists (71.2%) Macrolides (51.3%) Azithromycin 97 (50.8%) Dornase alpha 105 (55.0%) Glucocorticoids 67/191 (35.1%) Anticholinergics 39/191 (20.4%)
COLO/DPI/02/05[64]	≥8 to <13 years: 37.5% ≥13 years 62.5%		NR	NR	Overall for participants Mean (sd) 19.99 (4.011)		75.92 (SE 11.86)	79.51 (SE 7.707)	Concomitant:NR Patients were permitted to continue with pre-existing non anti-pseudomonal CF medications. Bronchodilators: refrained from use 4 hours prior to pulmonary function test. Salbutamol administered as rescue medication for bronchoconstriction after either intervention or comparator administration. Previous: all were on nebulised colistimethate sodium	

Int, intervention; Com, comparator; CF, cystic fibrosis; NR, not reported

** Unclear why this is different to the inclusion criteria of ≤75%*

***other medications listed as: adrenergics, bile acid preparations, cephalosporins, corticosteroids, enzyme preparations, fluoroquinolones, mucolytics, multivitamins, non-drug therapies, other aminoglycosides, proprionic acid derivatives, proton pump inhibitors, selective beta2-adrenoreceptor agonists, dornase alpha, anticholinergics, bronchodilators (patients taking short-acting bronchodilators were to take the medication 15 to 90 minutes before inhalation of study drug; patients taking long-acting bronchodilators were to take the medication as prescribed within the preceding 24 hours) and glucocorticoids.*

5.2.6 Study withdrawals

Table 7 shows the number of participants in each arm of each trial and the numbers of participants who withdrew throughout the study. Both trials saw a relatively high drop out rate, and this was higher in the intervention arm of both major trials.[63,64]

Table 8 describes the reasons for withdrawals. In both trials, more patients withdrew due to adverse events than for any other single reason, with withdrawl of consent/patient request the second most common reason. In the EAGER trial,[63] adverse events accounted for proportionately more withdrawals in the tobramycin DPI arm than in the nebulised tobramycin arm. Similarly, more patients withdrew consent for the trial in the DPI arm. In the COLO/DPI/02/06 trial,[64] the same pattern was seen with more patients withdrawing from the colistimethate sodium DPI arm than from the nebulised tobramycin arm due to adverse events, though withdrawals due to patient request were lower in the DPI arm. In this trial, the difference between arms appears larger than in the EAGER trial,[63] though the absolute number of withdrawals is smaller in COLO/DPI/02/06.[64] Differences between the two trials in drop-out numbers may be attributable to differences between patients' tolerance to nebulised tobramycin at baseline; patients who tolerated nebulised tobramycin poorly were likely to have been excluded before randomisation in COLO/DPI/02/06.[64] The Forest submission to NICE[64] reports 16 screening failures, but it is unclear if these patients failed during the run-in period because of lack of tolerance for tobramycin. However, if this was the case, it could account for at least some of the difference in withdrawals between arms, and between the two main studies.

Table 7: Number of participants of included studies

Study	N randomised	N withdrew before medication	N in ITT analsyis	N withdrew after medication or lost to follow-up	N in PP analysis
EAGER trial[63]	Total: 553 Intervention: 329 Control: 224	Total: 36 (6.5%) Intervention: 21 (6.4%) Control: 15 (6.7%)	Total: 517 (93.5%) Intervention: 308 (93.6%) Control: 209 (93.3%)	Total: 121 (21.9%) Intervention: 83 (25.2%) Control: 38 (17.0%)	[redacted]
COLO/DPI/02/06[64]	Total: 380 Intervention:	Total: 7 (1.8%)	Total: 373 (98.2%) Interven	Total: 53 (13.9%) Interven	PP: 298 (78.4%) Intervention: 141 (75.4%) Control: 157 (81.3%)

	187 Control: 193		tion: 183 (97.9%) Control: 190 (98.4%)	tion : 32 (17.1%) Control: 21 (10.9%)	
COLO/DPI/ 02/05[64]	Total: 16 Cross-over study	Total: 0	Total: 16	Total: 3 (18.8%)	Total: 11 (68.8%)

Table 8: Reasons for withdrawal from study after medication

	EAGER trial[63]		COLO/DPI/02/06[64]		COLO/DPI/02/05[64]
	Intervention attrition (n=83/308)	Control attrition (n=38/209)	Intervention attrition (n=32/183)*	Control attrition (n=21/190)*	Attrition throughout cross-over (n=3/16)
Adverse event	40 (13.0%)	17 (8.1%)	18 (9.8%)	3 (1.6%)	1 patient discontinued after receiving dry powder due to cough, throat irritation and unpleasant taste and did not cross-over to nebulised treatment. 2 patients withdrew due to adverse events, having already completed nebulised treatment.
Death	3 (1.0%)	0 (0%)	0 (0%)	2 (1.1%)	
Consent withdrawn	24 (8.0%)	9 (4.3%)	NA	NA	
Patient request	NA	NA	5 (2.7%)	11 (5.8%)	
Lost to follow up	5 (1.6%)	3 (1.4%)	NA	NA	
Administrative reason	1 (1.2%)	0 (0%)	NA	NA	
Protocol violation	6 (0.3%)	5 (2.4%)	1 (0.5%)	0 (0%)	
Lack of efficacy	NA	NA	2 (1.1%)	1 (0.5%)	
Inappropriate enrolment	0 (0%)	1 (0.5%)	NA	NA	
Other	4 (1.3%)	3 (1.4%)	2 (1.1%)	4 (2.1%)	

**Only primary reasons for discontinuations are given. More than one reason could be given per patient withdrawal.*
NA=not applicable

5.2.7 Study end points and outcomes

The outcomes reported across the three studies are documented in Table 9, alongside the outcomes listed in the NICE scope, and the outcomes recommended by the EMA research guidelines.[1]

All outcomes requested by NICE were reported in the two major trials, however, where a study reports that an outcome is measured, this does not necessarily indicate that the study was sufficiently powered to detect a clinically meaningful effect or that the outcome was assessed and reported according to EMA guidelines.[1] The COLO/DPI/02/05 study[64] was a Phase II safety trial and therefore the outcomes are more limited in this eight week trial than the other two larger trials.

Table 9: Outcomes under investigation in the included studies, ordered according to the priority given in the EMA research guidelines

Study	Clinical endpoint	Microbiological endpoint		Clinical endpoint					Biological endpoint	Physical endpoint	Quality of life endpoint	Safety Endpoint	
	Respiratory function	Resistance/ susceptibility		Exacerbations									Laboratory safety
	FEV_1	Sputum density	MIC	No. exacerbations	Time to exacerbation	No. hospitalisations	Hospitalisation duration	No. i.v. treatments	Inflammation or infection markers	BMI changes	HRQoL	Adverse events	Haematology biochemistry /urinanalysis
NICE scope	✓ (lung function)	✓	✓	✓ (frequency and severity)							✓ (preference based)	✓	
EAGER trial[63]	✓*	✓	✓			✓ (patients not events)	✓	****		✓		✓**	✓
COLO/DPI/02/06[64]	✓**		✓	✓***	✓			****		✓	✓ (CFQ-R)	✓	
COLO/DPI/02/05[64]	✓										✓ (CFQ-R)	✓**	✓

**Secondary outcome, but study was powered to detect an effect in this outcome.*
***Primary outcome*
**** Provided after a request by the Assessment Group*
*****Reported number of new antipseudomonal antibiotics, not necessarily IV antibiotics.*

The primary outcome for efficacy trials recommended by the EMA is change in FEV_1%.[1] This outcome is reported by all three trials, and whilst it was not always the primary outcome of the trial, both major trials[58,63,64] were powered to detect clinically relevant changes in FEV_1%. Study COLO/DPI/02/06[64] followed the American Thoracic Society guidelines. The methods by which FEV_1% measurement were made (Table 10) were not clear within either the EAGER trial[63] or trial COLO/DPI/02/05,[64] which may allow a margin for imprecision and/or inaccuracy in the data, and is a potential source of bias in an open label study.

The EMA recommends that data on exacerbations, i.v. treatment and hospitalisations (as listed in Table 9) should be reported alongside FEV_1% to establish clinical benefit to the patients in terms of harder, more clinically relevant outcomes. The EAGER trial[63] did not define an acute exacerbation, and only provided data on a poorly defined adverse event termed "lung disorder". Data only stated how many patients had at least one event, rather than the overall incidence of events (patients could have multiple events within the timescale of the trial). Incidence data were not provided upon request from the Assessment Group. COLO/DPI/02/06[64] fully defined an exacerbation, and provided data on the time to the first event, and data on incidence upon request from the Assessment Group. Additional antibiotic treatments for exacerbation did not have to be i.v. treatments in either trial reporting this outcome.[63,64]

The EMA recommends a microbiological secondary outcome for all trials of broncho-pulmonary infection with a clinical primary outcome (e.g. FEV_1%),[1] and these should include both measures of colony density (e.g. sputum density) and measures of resistance (e.g. minimum inhibitory concentration [MIC] values). The two major trials both report measures of resistance, but only the EAGER trial[63] reports sputum density. Both trials report MIC_{50} for tobramycin (though it is assumed that the MIC values are MIC_{50} and not MIC_{90} in the EAGER trial,[63] based on the quoted breakpoints matching MIC_{50} breakpoints), and COLO/DPI/02/06[64] reports MIC_{50} for colistimethate sodium as well. Both trials provided these data at the old British Society for Antimicrobial Chemotherapy (BSAC) breakpoint of 8mg/L for resistance, but only COLO/DPI/02/06[64] reported this outcome at the new breakpoint issued by BSAC of 4 mg/L.[28] As noted in Section 3.1.6, the relevance of MIC susceptibility breakpoints to inhaled antibiotics is debated due to higher than usual concentrations reaching the lungs, and because colonisation is usually comprised of multiple phenotypes of *Pseudomonas aeruginosa* which have different sensitivities to antibiotics, and have different sensitivity when grown in culture. However, the monitoring of breakpoints has relevance in indicating whether isolates are becoming more resistant as a population, rather than to indicate whether the treatment is likely to be effective at the concentrations delivered. Whilst the clinical and long-term

relevance of increases in MIC_{50} remain unclear, and as the EMA guidelines recommend their use, the MIC_{50} concentrations are presented in this report for consideration.

The EMA recommend that BMI is recorded only in studies at least six months in duration. A low emphasis is placed on this outcome in both major trials, and this outcome is not listed in the NICE scope. Quality of life was not recorded in the EAGER trial, [63] and was recorded using a non-preference-based instrument in COLO/DPI/02/06. [64] All trials aimed to measure adverse events, but it was not clear how this was achieved in either of the major trials (Table 10).

Table 10: Definitions and methods of measurement of main outcomes in EAGER[63] and COLO/DPI/02/06[64]

	EAGER[63]	COLO/DPI/02/06[64]
FEV_1		
Definition	NR (e.g. which equation was used to calculate % predicted).	Equations used to calculate FEV_1% provided in manufacturer's submission.
Method of measurement	Increases in FEV_1 from baseline (pre-dose Day 1) at all scheduled post-treatment visits (weeks 2, 5, 9, 13, 17, 21, 25).* NR - method for measuring FEV_1% and equipment used.	β2-adrenoreceptor agonists at least 2 hours prior to FEV_1% measurement. Performed at the same time of day using suitable validated equipment available at the centre. Testing performed according to ATS guidelines. FEV_1% was calculated as: FEV_1 % predicted = [Highest FEV_1 / predicted FEV_1 (equations given in manufacturer's submission)] * 100.
Acute Exacerbation		
Definition	NR Proxy outcomes include • New antibiotics • Hospitalisation • Lung disorders (AE), generally reported by the investigator as pulmonary or cystic fibrosis exacerbations, but definitions of these are not given.	Protocol-defined: Use of i.v. antibiotics (with or without hospitalisation) plus 4 of: (i) Change in appearance of sputum; (ii) Increased productive cough, dyspnoea, or respiratory rate; (iii) Progressive physical findings (crackles, rhonchi, and air exchange) on chest auscultation; (iv) New (infiltrates) intrusion on chest X-ray; v) Lassitude and decreased exercise tolerance; (vi) Fever (≥ 38°C); (vii) Deterioration of 10% of highest FEV_1 score obtained in the last 6 months; (viii) Decreased appetite; (ix) Emergence of new pathogen in sputum, i.e., a pathogen that caused clinical disease. Non-protocol defined: i.v. antibiotics with less than 4 of above symptoms. Where no symptoms recorded, AEs consulted.
Method of measurement	• patients requiring new AP anitibiotics • of days and type of new antibiotic use • of patients hospitalised for respiratory-related events and % receiving antibiotics (in hospital)	Time from randomisation to first acute respiratory exacerbation (protocol and non-protocol) using the start date of i.v. antibiotic or visit ID at which reported. • patients requiring new AP anitibiotics • ime to first new AP antibiotic

		• of days of new antibiotic use
Microbiological		
Definition	Microbial response: Change in PA density (log10[CFU]/g sputum) from baseline Resistance: Change in PA tobramycin minimum inhibitory concentration (MIC) susceptibility from baseline	Microbial response: NR Resistance: Minimum inhibitory concentration which inhibits 50% or 90% (MIC_{90}) of isolates grown on agar (MIC_{50}). For colistimethate sodium the *a priori* breakpoints applied to MIC_{50} were ≤ 4 mg/L = susceptible, 6 mg/L = intermediate susceptible, ≥ 8 mg/L = resistant. For tobramycin: ≤ 2 mg/L = susceptible, 4-6 mg/L = intermediate susceptible, ≥ 8 mg/L = resistant. For both, the new BSAC breakpoint (≤ 4mg/L = susceptible, > 4mg/L = resistant) was applied *post hoc*.
Method of measurement	Microbial response: Methods of measurement not reported. Expressed as mean reduction in Pa sputum density at 4 and 20 weeks Resistance: *Pseudomonas aeruginosa* tobramycin MIC (Maximum MIC of all Pa bio-types) > 8 μg/mL and ≤ 8 μg/mL	Microbial response: NR Resistance: Determined using the E-test® system (A B Biodisk, Sweden). Pulsed-field gel electrophoresis of DNA determined whether resistance had been selected in the original strain or whether the original organism had been replaced by a resistant variety.
Adverse events		
Definition	Categorised by MedDRA organ class and preferred term.	Any untoward medical occurrence following the intervention, but which did not necessarily have a causal relationship with this treatment. Categorised by MedDRA organ class and preferred term. (Version 7.0) was used by Chiltern to facilitate coding. Classed as definitely, probably or possibly related to study drug or with an 'unknown' relationship. Severity defined as: Mild: Annoyance but easily tolerated. Intermittent or continuous. Moderate: Marked and uncomfortable and/or interfered with every day activities. Not hazardous to health. Severe: Severe discomfort, and/or severely limited/prevented every day activities or was a definite hazard to health.
Method of measurement	"Patient listings" (not defined) were provided for AEs, SAEs, deaths and discontinuations due to AEs. Unclear whether reports of AEs were solicited or volunteered. Assume recorded at every study visit.	All AEs were recorded in the study CRFs, including those volunteered (unclear whether events were also solicited by investigator) by the patient, as well as clinical or laboratory findings.

** Note: some of these time points were not reported in the submission or in the journal article.*
CFU, colony forming unit; FEV_1, forced expiratory volume in one second or forced expiratory volume in one second as a percentage of the expected value according to gender, age and height; CRF, case report forms; ATS, American Thoracic Society; AE, adverse event, SAE, serious adverse event; MedDRA, Medical dictionary for regulatory activities; MIC, minimum inhibitory concentration; AP, antipseudomonal antibiotics; PA, pseudomonas aeruginosa.

5.2.8 Quality assessment

The quality assessment of the three included studies is presented in Table 11. None of the studies performed consistently well for all quality assessment items. Internal validity items (as scored according to the CRD criteria)[61] were addressed reasonably well, with the exception of blinding (due to the open-label trial design). External validity items (scored according to the EMA research guidelines)[1] were less well addressed, with omissions in a number of key recommendations. The two non-inferiority trials (EAGER[63] and COLO/DPI/02/06[64]) did not perform well when analysed using the CONSORT checklist (www.consort-statement.org) for non-inferiority and equivalence trials as a guide.

Risk of bias assessed using CRD criteria[61]

All three studies included in the review stated that participants were randomised to treatment. The method of randomisation was acceptable in the EAGER trial[58,63], but was not clearly described in COLO/DPI/02/06.[64] The EAGER[63] trial also used a modified randomisation method to balance patient characteristics between groups. It is stated in the Forest submission[64] the method of randomisation used in the COLO/DPI/02/05 study[65] was a randomisation list. The EAGER[63]and COLO/DPI/02/06[64] studies adopted a method of allocation concelment using an interactive voice system.

Participants were not blinded to treatment arm in two of the studies (EAGER[63] and COLO/DPI/02/06[64]), although the Forest submission[64] states that FEV_1 data were collected by a blinded investigator. The COLO/DPI/02/05[64] study does not state whether any blinding was attempted.[65] Blinding would have been difficult to achieve in all studies because of differences in the mode of delivery of the two interventions. In addition, there may be a difference in taste between inhalations that would have been difficult to mask or simulate. However, failure to blind participants to treatment can still introduce performance bias, even where blinding is not possible. For example, sensitivity to both the potentially positive and negative effects of a novel treatment can be overestimated or underestimated by patients and carers according to their prior beliefs about a treatment. In this case, performance bias could affect outcomes such as administration of antibiotics for suspected acute exacerbations, as clinicians may be more likely to administer antibiotics to the DPI patients as the efficacy of the intervention was unknown.

Failure to blind the outcome assessor (be this the patient, a member of healthcare staff or an independent outcome assessor) can lead to detection bias, whereby systematic differences in how outcomes are determined can arise due to the influence of prior beliefs about the effects of the treatment in question. Therefore subjectively measured and interpreted data (such as adverse events) should be interpreted with caution.

Table 11: Summary of quality assessment based on CRD criteria[61] and criteria developed from the EMA research guidelines[1]

	EAGER[63]	COLO/DPI /02/05[64]	COLO/DPI/ 02/06[64]
CRD quality assessment items[61]			
Was the method used to generate random allocations adequate?	Y	Y	U
Was the allocation adequately concealed?	Y	U	Y
Were the groups similar at the outset of the study in terms of prognostic factors, e.g. severity of disease?	Y	U	Y
Were the care providers, participants and outcome assessors blind to treatment allocation?	N	N	N
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Y,N	N,NA	Y,Y
Were all planned outcomes reported?	N	Y	N
Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Y,Y,N	Y	Y,Y,Y
EMA research guideline items[1]			
Were patients stratified by severity at inclusion based on respiratory function tests, OR was an upper limit for FEV_1 at inclusion set?	Y,Y	N	Y
Were patients stratified by age in paediatric studies?	NA	Y	NA
Was cystic fibrosis diagnosed by combination of sequential approaches? (see EMA[1] report for list of acceptable techniques, Pg 11-12)	N	N	N
Was chronic lung infection confirmed by presence of *Pseudomonas aeruginosa* in the bronchial tree for at least 6 months based on at least three positive cultures with at least one month between them without direct (inflammation, fever, etc) or indirect (specific antibody response) signs of infection and tissue damage?	N	N	N
Was FEV_1 measured in a standard way?	U	U	Y
Was the primary endpoint appropriately chosen?*	N	U	Y
Was a primary endpoint of FEV_1 supported by a secondary microbiological endpoint? **	N	N	N
If a study endpoint is the efficacy of respiratory function, was the endpoint appropriate?***	N	N	N
If a study endpoint is the slowing of rate of decline in respiratory function, was the endpoint appropriate? *-as previous, but endpoint >1 year (no consensus on how long)*	NA	NA	NA
If a study endpoint was safety, was the endpoint comprehensive?****	N	N	N
If a study endpoint was quality of life, was the endpoint appropriate? *- 3months or more* *-Uses CFQR or other measure validated in CF patients.*	NA	N	Y
If a study endpoint was microbiological (eg sputum density), was the endpoint appropriate? *- 28 day or longer follow-up*	Y	NA	NA
If study recorded acute exacerbation frequency, was an acute exacerbation defined?	N	NA	Y
Is the study classed as a confirmatory trial?	N	N	N
Was the comparator an active control?	Y	Y	Y

** -if FEV_1 is primary endpoint, score Yes; If microbiological (sputum density) or any other endpoint is primary, score No*

*** Should include: potential to select resistant strains AND; sputum density; AND one of: number/time to exacerbation, number of hospitalisations, number of IV treatments, duration of hospitalisations*

**** Was: FEV_1 measured at ≥ 6 months?; Effect size clinically relevant and justified a priori?; Frequency of measurement of FEV_1 justified?*

***** Should include all of: 12-month follow-up: influence on growth and development for children; resistance; hepatic and renal toxicity; Neurotoxicity (ototoxicity, paresthesia, vestibular disturbance)*

Baseline characteristics were reported in all three studies and were similar between groups in terms of age, gender and severity of disease. Study COLO/DPI/02/05[65] do not provide baseline data separately for intervention and control groups and selection bias cannot be assessed in this trial.

Two of the studies[64,65] report that relatively similar numbers of patients in the intervention and control groups dropped out of the study, however data does not support this (Table 7). The EAGER trial[63] reports a somewhat higher attrition in the intervention group (26.9%) compared to the control group (18.2%). It would seem that more evidence was recorded than was reported for some lung function measurements and for BMI in the EAGER trial,[63] which may indicate a degree of reporting bias.

Only the COLO/DPI/02/06[64] and COLO/DPI/02/05[64] studies report figures for both intention to treat (ITT) and per protocol (PP) groups. The EAGER trial[63] reports an ITT analysis only. The EAGER[63] and COLO/DPI/02/06[64] trials reported that more participants were randomised than were reported in the ITT group statistics. For participants to be included in the analysis they had to have received at least one dose of the study drug. This cannot be regarded as true intention to treat analysis as not all randomised participants were included. The EAGER trial did not perform imputation in its ITT analysis, and is therefore at high risk of attrition bias. Study COLO/DPI/02/05[65] reports ITT data which include all the participants who were randomised to treatment but it is not clear whether imputation was performed.

Study quality assessed using EMA research recommendations[1]

All three studies met EMA research recommendations[1] relating to severity of FEV_1% at inclusion. In one study (the EAGER trial[63]), patients were stratified by severity at inclusion based on respiratory function tests, and in two studies an upper limit for FEV_1 at inclusion was set (EAGER[63] and COLO/DPI/02/06[64]). Two studies also stratified patients by age (COLO/DPI/02/06[64] and COLO/DPI/02/05[64]), though this was not requested by EMA guidelines in adult cohorts.

Whilst none of the studies reported the specific diagnostic strategy called for in the EMA guidelines, none of the studies were thought to have included patients who did not have CF; diagnosis of cystic fibrosis was reported as "documented from a specialised CF unit" in two of the studies (COLO/DPI/02/06[64] and COLO/DPI/02/05[64]), whilst one study reported the diagnosis as "confirmed cystic fibrosis" (the EAGER trial[63]). The confirmed presence of a chronic *Pseudomonas aeruginosa* infection according to EMA guidelines was not reported in any trial. All three trials instead used less stringent criteria, which may have led to inclusion of patients with an intermittent infection. Study COLO/DPI/02/06[64] followed the American Thoracic Society guidelines to measure FEV_1% and so scored well for standardisation of method.The methods by which FEV_1% measurement were made

were not clear within either the EAGER trial[63] or trial COLO/DPI/02/05,[64] which may allow a margin for imprecision and/or inaccuracy in the data, and is a potential source of bias in an open label study.

According to the EMA guidelines for CF and for the purpose of this clinical effectiveness review, only one of the studies had an appropriately chosen primary endpoint, (COLO/DPI/02/06[64]) namely lung function described by FEV_1%. COLO/DPI/02/05[64] and the EAGER trial[63] used the incidence of adverse events as the primary endpoint. However, the EAGER trial was powered to detect effects in FEV_1%. COLO/DPI/02/06[64] and the EAGER trial[63] aimed to report outcomes at 24 weeks, which is just short of the ≥ 6 months follow up recommended by the EMA for studies of respiratory efficacy, and does not comply with the 1-year follow up recommended by the EMA for trials aiming to show slowing of rate of decline in respiratory function. Therefore, the studies are unlikely to provide useful data to indicate long-term outcomes. Only one of the studies supported the primary FEV_1 endpoint with a microbiological endpoint (EAGER[63]). Only the COLO/DPI/02/06[64] trial recorded and defined acute exacerbations whilst the EAGER trial referred to 'lung disorder', described as "generally reported by the investigator as pulmonary or cystic fibrosis exacerbation" and is therefore not a comprehensive definition of an acute exacerbation. All three studies had an active control group.

Study quality assessed using CONSORT checklist for non-inferiority studies[62].
Two of the three included studies adopted a non-inferiority design (EAGER[63] and COLO/DPI/02/06[64]). An appropriate rationale for this statistical design is not provided within the Novartis submission to NICE[58] but this is justified in the corresponding peer reviewed journal article.[63] The COLO/DPI/02/06[64] does provide justification for using a non-inferiority design. One study does not claim to be a non-inferiority trial COLO/DPI/02/05.[64]

With respect to the two non-inferiority studies (EAGER[63] and COLO/DPI/02/06[64]), neither explicitly state whether their eligibility criteria and subsequently their participants were similar to those in any trial(s) that established efficacy of the reference treatment and the settings and locations where the data were collected. Similarly neither of the inferiority trials provide precise details of whether the interventions intended for each group are identical (or very similar) to that in any trial(s) that established efficacy, and how and when they were actually administered. As such, it is not clear that these trials adequately assess the efficacy and safety of the novel treatment (dry powder formulation) as it is not clear whether the population is comparable to the trial which justified the use of the reference standard (nebulised formulation).

Although both non-inferiority studies (EAGER[63] and COLO/DPI/02/06[64]) have clearly defined primary and secondary outcomes, they do not state whether these outcomes are similar or identical to those which established efficacy in the reference treatment. Both studies do provide rationale for

sample sizes based on non-inferiority power calculations for FEV_1 data. Both studies provide results and confidence intervals for the analysis of FEV_1 data which was the primary outcome for COLO/DPI/02/06. [64] However the EAGER trial[63] used safety (in the form of adverse events) as the primary outcome and did not perform statistical analysis on these data.

5.3 Assessment of effectiveness

5.3.1 Lung function (FEV_1%)

The most commonly reported measure of lung function across the included studies was FEV_1%. Data were sought at 4, 20 and 24 weeks where available. Tobramycin was administered 28 days on and 28 days off, which results in a peak and trough in FEV_1% values.[63] This has the potential to bias results, and it would seem appropriate to consider results at both the peak and trough of the efficacy cycle. As such, both 20 and 24 week data are presented within this review.

The presentation of data varied across the studies (see data extraction tables in Appendix 4).

- The COLO/DPI/02/06[64] reported several analyses for FEV_1% data. These included
    - ITT population with last observation carried forward (LOCF) imputation;
    - ITT population with no imputation (completers);
    - PP population with LOCF imputation, and;
    - PP population with no imputation (completers).

  Tests specified *a priori* showed that the data were non-normal in distribution; an additional non-parametric analysis, and an analysis using logarithmic transformed data were also performed by the manufacturer to correct for this.[64] As such, 12 analyses were presented for these data. ANCOVA comparative data were reported, with adjustment for baseline FEV_1% and pooled centre.
- The EAGER trial[63] data were not transformed, nor was a non-parametric test performed, though no test of normality was apparently planned or performed either. No imputation was performed on the Novartis data, and only limited data were presented at 24 weeks. Some adjusted comparative data were presented, with adjustments for main effects treatment, baseline FEV_1% predicted and pooled centre.

Where data were not available in the manufacturers' submissions to NICE or within journal publications, the Assessment Group requested or calculated missing values. However, some values remained missing or unclear. Given the available evidence, a network meta-analysis was not possible (see Appendix 4) and as such, a narrative synthesis is presented for the results.

Whilst all trials reported ITT analyses, the EAGER trial[63] did not perform any imputation. In the COLO/DPI/02/06 trial,[64] an analysis of completers is presented (where only those for whom there are data at both baseline and the timepoint of analysis are analysed) and an analysis with LOCF is presented (which should include all patients at every time point, but appears to vary from timepoint to

timepoint, Table 12). The differences in exclusion of data in the "no-imputation", "LOCF" and "completers" analyses are likely to affect results, but it is unclear in which direction. The most usual direction of effect of attrition is to overestimate efficacy.[82-84] Attrition is most problematic in the EAGER trial[63] "no imputation" analysis, as demonstrated by the N numbers in Table 12. As such, results from the trials are not directly comparable. However, to allow some form of simple comparison to be made, data from the "no-imputation" (EAGER trial)[58,63] and "completers" (COLO/DPI/06)[64] analyses have been collated and synthesised in parts of this section. Note that the data used for (COLO/DPI/06)[64] is from the original analysis, not the transformed or non-parametric analysis. PP analyses are discussed where data are available. Further results are presented in the data extraction tables in Appendix 5.

Non-inferiority results

Both trials were non-inferiority trials, but it is not clear how comparable their definitions of non-inferiority are. Both the EAGER trial[63] and the COLO/DPI/06 trial conclude that tobramycin DPI and colistimethate sodium DPI (respectively) are non-inferior to nebulised tobramycin.

The EAGER trial[63] reports non-inferiority for tobramycin DPI at 20 weeks, supported by least squares mean difference relative change of 1.1% (SE 1.75), which has a lower limit of the one-sided 85% confidence interval within the predefined 6% margin for non-inferiority.[63] As noted previously, this analysis was performed with no imputation of data in the ITT population. A non-inferiority analysis was not presented for the 24-week data, where FEV_1% measurements are expected to be lower than at 20 weeks.

Trial COLO/DPI/02/06[64] reports non-inferiority at 24 weeks (lower bound of the confidence interval <3% for ITT and PP populations) for colistimethate sodium DPI under the non-parametric analysis, (median difference in change in FEV_1%, ITT, LOCF [redacted] (95% CI -2.16 [redacted]), ITT completers [redacted] (95% CI -1.61[redacted] PP LOCF [redacted] (95% CI -2.57 [redacted]), PP completers [redacted] (95% CI -2.14 to [redacted])), but not under the logarithmic analysis or original analysis (adjusted mean difference in change in FEV_1%, ITT, LOCF -1.16% (95% CI -3.15 to 0.84), ITT completers -0.43% (95% CI -2.59 to 1.72); PP LOCF -1.49 (95% CI -3.79 to 0.81), PP completers -0.99% (95% -3.48 to 1.51). The non-parametric analysis was defined *a priori*, and all analyses relate to the ITT analysis with LOCF. Similar results were reported for data without imputation and data at 20 weeks.

Mean FEV_1% over time

COLO/DPI/02/06[64] and EAGER[63] both had similar mean FEV_1% values at baseline, although the patients in the EAGER trial had slightly higher FEV_1% values, mean age and BMI. The COLO/DPI/02/05 trial[64] started with much higher baseline mean FEV_1% values. Mean FEV_1% varies

over time. The completers analysis presented in COLO/DPI/02/06[64] shows a slightly improved FEV_1% at 4 and 20 weeks in both treatment arms, with levels falling back to near baseline at 24 weeks (Table 12). The LOCF analysis is consistently more conservative than the completers analysis, both in terms of absolute FEV_1% values, and in terms of relative differences.

Table 12: Mean FEV_1% over time for COLO/DPI/02/06[64] (ITT, completers and LOCF) trial and EAGER[63] (ITT, no imputation) trial.

Trial name	Intervention	Baseline	4 weeks	20 weeks	24 weeks
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAGER[63]	TDPI no imputation	[redacted]	54.38 (SE 0.63, SD 10.39) n=268	55.97 (SE and n not reported)	NR*
	NT no imputation	[redacted]	54.70 (SE 0.54, SD 7.57) n=194	55.28 (SE and n not reported)	NR*

** These data were requested from the manufacturer by the Assessment Group, but were not provided.*

CDPI, colistimethate sodium dry powder for inhalation; LOCF, last observation carried forward; NT, nebulised tobramycin; TDPI, tobramycin dry powder for inhalation; RC, reviewer calculated; NR, not reported; SE, standard error; SD, standard deviation.

Within the EAGER trial,[63] FEV_1% values increased at 4 and 20 weeks, though there are no data at 24 weeks.

[redacted]

It is not possible to determine whether the changes seen in the colistimethate DPI arm are significantly different to the changes seen in the tobramycin DPI arm due to a lack of data at 24 weeks, different population analyses of results and uncertain comparability of patient characteristics at baseline.

Comparative data at 4 weeks

At 4 weeks, three sets of data were available. COLO/DPI/02/06[64] compared colistimethate sodium DPI to nebulised tobramycin, COLO/DPI/02/05[64] compared colistimethate sodium DPI to nebulised colistimethate sodium and the EAGER trial[63] compared tobramycin DPI to nebulised tobramycin (Table 13).

The difference in the unadjusted % mean change from baseline (Table 13) for colistimethate sodium DPI versus nebulised tobramycin was [redacted] (data calculated by reviewer), whilst for tobramycin DPI versus nebulised tobramycin this was [redacted] (data calculated by reviewer). For COLO/DPI/02/05,[64] the difference in the unadjusted mean change from baseline was [redacted]. In all cases, the intervention (DPI) appeared [redacted] than the comparator (nebulised). Significance statistics were not performed for these outcomes, hence it is not clear if this numerical difference is significant. PP data (not available for COLO/DPI/02/05[64]) showed a similar trend.

The smaller COLO/DPI/02/05[64] trial, which had much higher mean baseline FEV_1% values than the other trials and compared colistimethate sodium DPI to colistimethate sodium nebulised solution, reported simply that there were no significant changes in lung function in either treatment arm. The short duration of the trial, small number of participants and higher mean baseline FEV_1% values of this group mean that a meaningful comparison to the other trials cannot be made.

Comparative data at 20 and 24 weeks

Only two studies reported data at 20 and 24 weeks. The COLO/DPI/02/06 trial[64] compared colistimethate sodium DPI to nebulised tobramycin, and the EAGER trial[63] compared tobramycin DPI to nebulised tobramycin (Table 13).

A comparison of data within trials at both 20 and 24 weeks is preferred, as tobramycin is given in a cycle of 28 days on and 28 days off, forming peaks and troughs in efficacy. However, there are gaps in the comparative data, as shown in Table 13.

Table 13: Summary of comparative analyses for FEV_1% between intervention and comparator

Time	Study	No imputation Difference in % mean change from baseline between intervention and comparator (calculated by reviewer)	No imputation Adjusted difference	LOCF Adjusted difference (ANCOVA)
4 weeks	COLO/DPI/02/05[64] (CDPI vs NC)	[redacted]	[redacted]	[redacted]
	COLO/DPI/02/06[64] (CDPI vs NT)	[redacted]	[redacted]	[redacted]
	EAGER[63] (TDPI vs NT)	[redacted]	NR	NR
20 weeks	COLO/DPI/02/06[64] (CDPI vs NT)	[redacted]	NR	-1.40% (95% CI -3.43% to 0.63%) (LOCF analysis)
	EAGER[63] (TDPI vs NT)	[redacted]	[redacted]	NR
24 weeks	COLO/DPI/02/06[64] (CDPI vs NT)	[redacted]	-0.43% [redacted]	-1.16% (95% CI -3.15 to 0.84)
	EAGER[63] (TDPI vs NT)	[redacted]	NR	NR*

** These data were requested from the manufacturer by the Assessment Group, but were not provided.*

CDPI, colistimethate sodium dry powder for inhalation; LOCF, last observation carried forward; NT, nebulised tobramycin; TDPI, tobramycin dry powder for inhalation; RC, reviewer calculated; NR, not reported; SE, standard error; SD, standard deviation.

At 20 weeks, both trials provide adjusted data, but the data for COLO/DPI/02/06[64] are only available with a LOCF analysis. The adjusted difference in % mean FEV_1% (LOCF) from baseline to 20 weeks was -1.40% (95% CI -3.43 to 0.63) for colistimethate sodium DPI versus nebulised tobramycin and the adjusted absolute difference in mean FEV_1% (no imputation) from baseline to 20 weeks was 0.59 (SE 0.92) for tobramycin DPI versus nebulised DPI. [redacted] for tobramycin DPI compared to nebulised tobramycim, though this analysis used least mean squares. The unadjusted difference [redacted]. [redacted]

[redacted]

[redacted]

As discussed above, it is unclear exactly how comparable the baseline characteristics of the two groups are, and how comparable the completer and no-imputation analyses make the data, so between trial comparisons are difficult. It is also difficult to establish whether non-inferiority is maintained in the EAGER trial at 24 weeks, though it seems likely that it would be. In the COLO/DPI/02/06[64] trial, non-inferiority was demonstrated in the non-parametric analysis at [redacted] 24 weeks, but not in the original analysis or logarithmic analysis.

5.3.2 Microbiological outcomes (colony density and resistance)

The EMA recommend that microbiological data should support FEV_1% efficacy data.[1] The COLO/DPI/02/05[64] trial did not report any microbiological data, whilst COLO/DPI/02/06[64] reported resistance data (see Table 14) and EAGER[63] reported both resistance data and sputum density data (Tables 14 and 15).

As noted in Section 3.1.6, the BSAC breakpoints for resistance have changed since the trials were performed. COLO/DPI/02/06[64] reported both the new (4mg/L) and old (8mg/L) breakpoints for resistance, whilst only data for the old breakpoint was available for the EAGER trial. [redacted]COLO/DPI/02/06,[64] resistance (4mg/L or 8mg/L breakpoints) to colistimethate sodium remained very low (≤ 1.1%) throughout the 24 week trial in the colistimethate sodium DPI arm, whilst resistance to tobramycin was reported to not change substantially during the study, with values [redacted]. In the EAGER trial,[63] resistance (8mg/L breakpoint) to tobramycin started at around 20% (the baseline value was at the end of 28 days off treatment) and was lower at 24 weeks (also at the end of 28 days off treatment). Again, it is unclear if there was a trend of change in resistance over time, or merely fluctuations around the mean. The high levels of resistance at baseline [redacted] is not surprising as 100% of patients in the COLO/DPI/02/06[64] trial and more than 90% in the EAGER had received tobramycin before the trial, and are likely to have already developed

some level of resistance. As already discussed elsewhere, the significance of increasing resistance to tobramycin is unclear.

Table 14: Resistance (MIC breakpoints) for EAGER[63] and COLO/DPI/02/06[64] trials

	EAGER[63]					[redacted]				
	Tobramycin DPI N=308		Tobramycin nebulised N=209		Comparison	[redacted]				
	MIC$_{50}$ (mg/L)	MIC$_{90}$ (mg/L)	MIC$_{50}$ (mg/L)	MIC$_{90}$ (mg/L)		[redacted]				
Tobramycin Baseline	NR	NR	NR	NR		[redacted]				
Week 4	NR	NR	NR	NR		[redacted]				
Week 8	NR	NR	NR	NR		[redacted]				
Week 16	NR	NR	NR	NR		[redacted]				
Week 20	NR	NR	NR	NR		[redacted]				
Week 24	NR	NR	NR	NR		[redacted]				
Colistimethate sodium Baseline	NR	NR	NR	NR		[redacted]				
Week 4	NR	NR	NR	NR		[redacted]				
Week 8	NR	NR	NR	NR		[redacted]				
Week 16	NR	NR	NR	NR		[redacted]				
Week 20	NR	NR	NR	NR		[redacted]				
Week 24	NR	NR	NR	NR		[redacted]				

MIC50 Tobramycin, breakpoint 4mg/L	NR*	NR*	NR	NA	[redacted]	[redacted]
MIC50 Colistimethate sodium, breakpoint 4mg/L	NA	NA	NA	Throughout 24 weeks ≤ 1.1% Significance of change from baseline for whole group NR	[redacted]	[redacted]
MIC50 Tobramycin, breakpoint 8mg/L	Baseline: 22.1% resistant 24 weeks: 19.1% resistant	Baseline: 23.0% resistant 24 weeks: 14.9%	NR	NA	[redacted]	[redacted]
MIC50 Colistimethate sodium, breakpoint 8mg/L	NA	NA		[redacted]	NA	[redacted]
** These data were requested from the manufacturer by the Assessment Group, but were not provided.*						

Table 15 shows the results of the sputum density tests in the EAGER trial.[63] These data were not recorded in the COLO/DPI/02/06 trial.[64] Mean change from baseline log10 values show numerically though it is unclear greater reductions in sputum density are achieved with tobramycin DPI at 20 weeks in comparison to nebulised tobramycin. Results at 24 weeks are not reported. These values are in accordance with the slightly greater increase in FEV_1% seen for tobramycin DPI, but their statistical and clinical significance is not known.

Table 15: *Pseudomonas aeruginosa* sputum density outcome for EAGER[63] trial

	week 4	week 20				
	Mean CFB log10 CFU unspecified biotype	Mean CFB log10 CFU unspecified biotype	Mean log10 CFU dry biotype	Mean CFB log10 CFU dry biotype	Mean log10 CFU mucoid biotype	Mean CFB log10 CFU mucoid biotype
TDPI	-1.76 (SD 1.96)	-1.61 (SD 2.03)	5.17	-1.77	5.40	-1.60
NT	-1.32 (SD 2.03)	-0.77 (SD 1.78)	6.18	-0.73	6.30	-0.92

TCPI, tobramycin dry powder for inhalation; NT, nebulised tobramycin; CFB, change from baseline; CFU, colony forming units

5.3.3 Exacerbations

Data on protocol-defined acute exacerbations were not reported in a consistent way across the three included trials. COLO/DPI/02/06[64] reported time to event data for acute exacerbations. Despite the EMA research guidelines requesting this outcome, Novartis did not provide any acute exacerbation data, though amongst the adverse events reported by Konstan *et al*[63] lung disorder is defined as "generally reported by the investigator as pulmonary or cystic fibrosis exacerbation". This is regarded as a proxy for acute exacerbations for the purpose of this assessment, though is clearly not an entirely specific measure and it is unclear what other events may have also been included in this outcome. The EAGER trial[63] data were provided as the number of patients experiencing the event, rather than the number of events. Equally, for the time to event data provided by Forest for COLO/DPI/02/06[64] to be a useful outcome, it would have to be assumed that the time to the first event is directly related to the overall incidence of events. As one patient could theoretically experience more than one exacerbation through the duration of the trial (24 weeks), the Assessment Group requested data relating to the number of events from both manufacturers. Only Forest complied with the request, however the correct interpretation of these data was unclear. Neither manufacturer was able to provide data on the severity of exacerbations. Data relating to this outcome is presented in Table 16.

[redacted]), though it is unclear if the same trend would be observed for data relating to the number of events. [redacted] the mean duration of use of antibiotics to treat the exacerbation was slightly less at 13.6 days in the colistimethate sodium DPI arm versus 14.4 days in

the nebulised tobramycin arm.

[redacted]

Within the EAGER trial,[63] the number of patients experiencing lung disorders was greater in the tobramycin DPI arm (33.8%) than the nebulised tobramycin arm (30.1%). It is unclear if the same trend would be observed for data relating to the number of events. Mean duration of antipseudomonal antibiotic treatment was also slightly shorter in the tobramycin DPI arm than in the nebulised tobramycin arm (30.9 days versus 33.4 days). The number of patients receiving additional antipseudomonal treatments was higher in the tobramycin DPI arm.

[redacted]

The clinical advisors to the Assessment Group were unsure why this might be [redacted]

One potential explanation is that treatments are given as soon as an exacerbation is suspected, and stopped when tests do not confirm it. As the trial is open-label, performance bias (e.g. being more likely to treat a patient's symptoms as an exacerbation if they are in the DPI arm) and outcome assessment bias (the criteria for an acute exacerbation were subjective to some degree in the COLO/DPI/02/06 trial, [64] and to an unknown degree in the EAGER trial[63]) could affect results. These types of bias could work to increase or decrease the number of exacerbations and number of patients receiving additional antibiotics, and it is unclear to what extent and in what direction they may have affected the outcomes in question.

[redacted]

The influence of bias and the lack of consistency in the direction of effect makes the outcomes relating to acute exacerbations difficult to interpret with any certainty.

It is not possible to draw a comparative conclusion as to the relative efficacy between trials in terms of exacerbations, given the difference in the way they have been reported, and the uncertainty about the comparability of the patient data populations and characteristics.

Table 16: Acute exacerbations, hospitalisations and i.v. treatments across the 3 studies; proportion of patients experiencing events

	EAGER[63]		COLO/DPI/02/06[64]		COLO/DPI/02/05[64]	
	Tobramycin DPI N=308	Nebulised tobramycin N=209	Colistimethate sodium DPI N=183	Nebulised tobramycin N=191	Colistimethate sodium DPI N=16	Nebulised colistimethate sodium N=15
Number of patients experiencing at least one (protocol defined) acute exacerbation (N (%))	NR	NR	[redacted]	[redacted]	NR	NR
Number of patients experiencing at least one (non protocol defined) acute exacerbation (N (%))	NR	NR	[redacted]	[redacted]	NR	NR
Number of patients experiencing at least one (protocol or non protocol defined) acute exacerbation (N (%))*	NR	NR	69 (37.7%)	75 (39.3%)	NR	NR
Number of patients experiencing at least one episode of "Lung disorder" (*sic*)**	104 (33.8%)	63 (30.1%)	NA	NA	NA	NA
Time to	NR	NR	63.70 days	59.39 days	NR	NR

acute exacerbation (Mean no. days (SD))			[redacted]	[redacted]		
Number of patient with at least one hospitalisation***	75 (24.4%)	46 (22.0%)	NR	NR	NR	NR
Hospitalisation duration (Mean no. days (SD))	15.6 (SE 13.31)	15.3 (SE 10.23)	NR	NR	NR	NR
Number of patients using additional antipseudomonal treatments (N(%))	RC: 200 (64.9%)	RC:114 (54.5%)	92 (50.3%)	96 (50.3%)	NR	NR
Time to first additional antipseudomonal treatment (Mean no. days (SD))	NR	NR	55.28 (SD 43.2)	51.79 (SD 41.9)	NR	NR
Duration of use of additional antipseudomonal treatment (Mean no. days (SD))	30.9 (SD 23.34)	33.4 (SD 24.42)	13.6 (SD 5.4)	14.4 (SD 7.3)	NR	NR

NR, not reported; NA, not applicable; RC, reviwer calculated; SD, standard deviation; SE, standard error.

** data provided for overall number of acute exacerbations do not match the total numbers of protocol and non-protocol numbers provided in the rows above*

*** "Lung disorder" was not clearly defined, but described in Konstan et al[63] as "generally reported by the investigator as pulmonary or cystic fibrosis exacerbation".*

****due to respiratory events*

5.3.4 BMI

Table 17 shows the BMI measurements from the EAGER[63] and COLO/DPI/02/06 trials.[64] The EAGER trial[63] states that BMI is an outcome under investigation however the BMI data are not provided for any of the timepoints after baseline. The COLO/DPI/02/06 trial[64] reports BMI at every timepoint. The data presented in Table 17 are for the ITT population and demonstrate very little change in BMI from baseline. BMI data for the COLO/DPI/02/05[64] is not presented as it was not an outcome under investigation in that trial. It is unlikely that changes in BMI would be seen before 6 months, so the lack of change is unsurprising.

Table 17: Changes in BMI from baseline to 24 weeks between EAGER[63] and COLO/DPI/02/06[64] trials

	EAGER[63]		COLO/DPI/02/06[64]	
	Tobramycin DPI N=308	Nebulised tobramycin N=209	Colistimethate sodium DPI N=183	Nebulised tobramycin N=191
Baseline BMI (Mean (SD))	20.77 (5.81)	20.39 (3.45)	18.67 (3.39)	18.46 (3.58)
BMI at 24 weeks (Mean (SD))	NR	NR	18.70 (3.29)	18.66 (3.57)
Change from Baseline Week 24	NR	NR	0.08 (0.78)	0.17 (0.89)
BMI, body mass index; NR, not reported; SD, standard deviation.				

5.3.5 Health related quality of life

Table 18 presents the CFQ-R results for the health-related quality of life outcome. The two trials which investigated this outcome were COLO/DPI/02/06[64] and COLO/DPI/02/05.[64] For COLO/DPI/02/06[64] the data presented are the adjusted means in the numerous domains of the CFQ from baseline to week 24. Most of the scores tend to be in favour of the dry powder intervention although none of the differences are statistically significant. It is interesting to note that one of the few negative results is for the respiratory domain, though this does not reach significance. Although the COLO/DPI/02/05[64] trial did also use the CFQ throughout the trial, the data are not provided [redacted]

[redacted]

As already noted, this quality of life measure has not been validated and is not preference-based in line with the NICE Reference Case. It is therefore difficult to interpret the results in terms of impact on health-related quality of life and relative weight of the individual items in the measure.

One key argument put forward in favour of the DPI formulations is its ease of use. This may have many benefits, including increased patient satisfaction with treatment, reduced treatment burden, and increased compliance with the medication. The results in Table 18 demonstrate a non-significant trend in improvements in treatment burden for colistimethate sodium DPI compared to nebulised tobramycin. In addition, Treatment satisfaction Questionnaire for Medication (TSQM) reported in the EAGER trial[63] showed higher values in the tobramycin DPI arm (see Appendix 5 for data). It is worth noting that in both trials the comparator was administered using a PARI LC Plus jet nebuliser; this device requires approximately 15 minutes to administer the full dose of tobramycin. Nebulisers with quicker delivery time (around 5 minutes), such as the PARI eFlow jet nebuliser are now on the market and are in widespread use (personal communication: Dr Diana Bilton, Consultant Physician / Honorary Senior Lecturer, Department of Respiratory Medicine, Royal Brompton Hospital). However, these quicker nebulisers may still require time to maintain (cleaning) and assemble. With respect to the relative advantages and disadvantages, it remains unclear whether the reduced treatment burden and improved treatment satisfaction scores would reamain significant when compared to the newer, quicker nebulisers.

Table 18: Adjusted mean changes in CFQ-R quality of life from baseline to Week 24 for COLO/DPI/02/06[64] and COLO/DPI/02/05[64] trials (positive scores indicate an improvement in QoL).

	COLO/DPI/02/06[64]				COLO/DPI/02/05[64]	
CFQ-R domain	Colistimethate sodium DPI N=183	Nebulised tobramycin N=191	Adjusted difference	*P*-value	Colistimethate sodium DPI N=16	Nebulised olistimethate sodium N=15
Physical	0.26	–1.56	1.82	0.353	NR	NR
Vitality	0.86	–1.40	2.27	0.293	NR	NR
Emotion	2.23	0.47	1.75	0.244	NR	NR
Eating	0.48	0.66	–0.19	0.925	NR	NR
Treatment burden	5.62	2.75	2.87	0.091	NR	NR
Health perceptions	0.25	–2.71	2.96	0.159	NR	NR
Social	3.10	0.92	2.18	0.153	NR	NR
Body image	7.83	5.98	1.85	0.385	NR	NR
Role	0.65	1.87	–1.22	0.607	NR	NR
Weight	0.88	–1.93	2.81	0.461	NR	NR
Respiratory	2.99	3.51	–0.53	0.756	NR	NR
Digestion	5.06	2.89	3.22	0.077	NR	NR
NR, not reported.						

5.3.6 Adverse events

Table 19 shows the number of adverse events by severity across the 3 trials. The percentage of patients experiencing any adverse event in all three of the trials is high, although this is to be expected in a patient population with cystic fibrosis, who have a high level of baseline adverse events. Mild and

moderate adverse events appear similar between arms within trials. The EAGER trial[63] does not state how many events were severe, whilst both of the colistimethate sodium DPI trials report more severe events in the intervention (DPI) arm. Serious adverse events (which are internationally defined as adverse events that cause death, are life threatening, require hospitalisation/prolong hospitalisation or result in disability or birth defect[85]) appear to occur approximately equally, but slightly less frequently in the DPI treatments in both key trials. There appears to be a marked difference between the proportion of serious events reported in the EAGER trial[63] compared to the colistimethate sodium trials, even when comparing the nebulised tobramycin arms of EAGER[63] and COLO/DPI/02/06.[64] This difference would appear to be too large to be explained by heterogeneity in study characteristics and study populations. It would seem more likely that this is due to a difference in interpretation of the "serious" criteria between trials, rather than an indication that there is a true difference in number of events.

The number of patients withdrawing from the study due to adverse events was higher in the dry powder intervention groups across all the trials. As previously discussed, patients in both trials were largely experienced with nebulised tobramycin, and it is likely that this difference in drop out rates is at least in part due to selection bias of patients tolerant to nebulised tobramycin, and desensitisation to its adverse events through prior use.

Table 19: Proportion of patients experiencing adverse events

	EAGER[63]		COLO/DPI/02/06[64]		COLO/DPI/02/05[64]	
	Tobramycin DPI	Nebulised tobramycin	Colistimethate sodium DPI	Nebulised tobramycin	Colistimethate sodium DPI	Nebulised colistimethate sodium
Number of patients	N=308	N=209	N=187	N=193	N=16	N=15
Any adverse event	90.3%	84.2%	175 (93.6%)	172 (89.1%)	16 (100%)	9 (60%)
Mild or moderate AE	73.4%	68.5%	159 (85.0%)	165 (85.5%)	NR	NR
Severe (related) AE	NR	NR	73 (39.0%)	12 (6.2%)	7 (43.75)	1 (6.6%)
Serious AE	27.4%	29.2%	8 (4.3%)	12 (6.2%)	0 (0%)	0 (0%)
Study drug related AE	NR	NR	153 (81.8%)	90 (46.6%)	16 (100%)	9 (60%)
Patients withdrawn due to AE	40 (13.0%)	17 (8.1%)	22 (11.8%)	5 (2.6%)	2 (12.5%)	0 (0%)

Table 20 documents the most common adverse events (≥ 5% in any group) occurring in any of the three trials. The data presented relate to the number of patients who experienced adverse events. Data on the actual number of events was available for the COLO/DPI/02/06[64] and COLO/DPI/02/05[64] studies but is not presented here. The most common adverse event in all three trials is cough. The percentage of patients experiencing cough was higher in the COLO/DPI/02/06[64] and COLO/DPI/02/05[64] studies than in the EAGER trial,[63] though this may again represent a difference in the definition of cough used in the studies rather than an actual difference in incidence of cough, as

the difference persists when comparing the nebulised tobramycin arms of each trial. Cough was more common in the DPI intervention group for all trials. Cough is a known side effect of dry powder formulations and is thought to generally reduce over time, with improved technique, and may be controlled with use of bronchodilators to some extent, in some patients. Clinical advisors to the Assessment Group were interested to note that hemoptysis did not appear to increase to any great extent in the tobramycin DPI group compared to nebulised tobramycin, though there does appear to be a small increase in hemoptysis in the colistimethate sodium DPI group compared to nebulised tobramycin. It is unclear whether this difference is clinically or statistically significant.

Whilst no statistical comparisons have been made, other adverse events that appear to be worse in the DPI arm include [redacted] chest discomfort and dysphonia in the tobramycin DPI arm in the EAGER trial,[63] and throat irritation and dysgeusia in the colistimethate sodium DPI arm in the COLO/DPI/02/06 trial.[64] There are minor improvements in a number of other adverse events in the colistimethate sodium DPI arm (see Table 20).

Table 20: Most common adverse events (≥ 5% in any group) across the three studies; number of patients experiencing the event at least once

	EAGER[63]		COLO/DPI/02/06[64]		COLO/DPI/02/05[64]	
	Tobramycin DPI	Nebulised tobramycin	Colistimethate sodium DPI	Nebulised tobramycin	Colistimethate sodium DPI	Nebulised colistimethate sodium
Number of patients	N=308	N=209	N=187	N=193	N=16	N=15
Cough	149 (48.4%)	65 (31.1%)	168 (89.8%)	151 (78.2%)	13 (81.3%)	7 (46.7%)
Throat Irritation	[redacted]	[redacted]	141 (75.4%)	84 (43.5%)	13 (81.3%)	3 (20.0%)
Productive cough	56 (18.2%)	41 (19.6%)	38 (20.3%)	44 (22.8%)	2 (12.5%)	1 (6.7%)
Dyspnoea	48 (15.6%)	26 (12.4%)	49 (26.2%)	52 (26.9%)	3 (18.8%)	4 (26.7%)
Oropharyngeal pain	43 (14.0%)	21 (10.5%)	4 (2.1%)	1 (0.5%)	2 (12.5%)	2 (13.3%)
Rales	22 (7.1%)	13 (6.2%)	2 (1.1%)	5 (2.6%)	NR	NR
Rhinorrhea	22 (7.1%)	15 (7.2%)	1 (0.5%)	2 (1.0%)	NR	NR
Pulmonary function test decreased	21 (6.8%)	17 (8.1%)	0 (0%)	3 (1.6%)	NR	NR
Pyrexia	48 (15.6%)	26 (12.4%)	23 (12.3%)	19 (9.8%)	2 (12.5%)	1 (6.7%)
Dysgeusia	[redacted]	[redacted]	117 (62.6%)	53 (27.5%)	14 (87.5%)	3 (20.0%)
Respiratory disorders	21 (6.8%)	18 (8.6%)	53 (28.3%)	57 (29.5%)	16 (100%)	7 (46.7%)
Wheezing	21 (6.8%)	13 (6.2%)	31 (16.6%)	38 (19.7%)	7 (43.8%)	5 (33.3%)
Chest discomfort	20 (6.5%)	6 (2.9%)	26 (13.9%)	34 (17.6%)	4 (25%)	2 (13.3%)
Sinusitis	18 (5.8%)	15 (7.2%)	3 (1.6%)	2 (1.0%)	NR	NR
Pulmonary congestion	17 (5.5%)	9 (4.3%)	NR	NR	NR	NR
Dysphonia	42 (13.6%)	8 (3.8%)	22 (11.8%)	30 (15.5%)	NR	NR
Nasal congestion	25 (8.1%)	15 (7.2%)	2 (1.1%)	4 (2.1%)	NR	NR
Vomiting	19 (6.2%)	12 (5.7%)	6 (3.2%)	8 (4.1%)	2 (12.0%)	0 (0%)
Hemoptysis	40 (13.0%)	26 (12.4%)	20 (10.7%)	13 (6.7%)	NR	NR
Nausea	23 (7.5%)	20 (9.6%)	7 (3.7%)	9 (4.7%)	NR	NR
Headache	35 (11.4%)	25 (12.0%)	9 (4.8%)	16 (8.3%)	1 (6.3%)	2 (13.3%)
Fatigue	20 (6.5%)	10 (4.8%)	9 (4.8%)	8 (4.1%)	NR	NR
Serious Lung disorder	[redacted]	[redacted]	NR	NR	NR	NR
Chest pain	[redacted]	[redacted]	13 (7.0%)	16 (8.3%)	NR	NR
Crackles lung	NR	NR	13 (7.0%)	14 (7.3%)	NR	NR
Increased upper airway secretion	NR	NR	12 (6.4%)	13 (6.7%)	NR	NR
Pharyngitis	NR	NR	10 (5.3%)	14 (7.3%)	NR	NR
Rhonchi	**NR**	**NR**	**8 (4.3%)**	**10 (5.2%)**	**NR**	**NR**

5.3.7 Mortality

Three patients died in the tobramycin DPI group in the EAGER trial.[63] Two patients died in the tobramycin nebulised group in the COLO/DPI/02/06 trial.[64] None of the deaths are attributed to the study medication.

[redacted] For the COLO/DPI/02/06[64] trial there were two deaths (both in the nebulised tobramycin group), both of which were assessed as being unrelated to study medication, and were attributed to the underlying disease, though it is unclear if these deaths were also due to acute exacerbations. One clinical advisor to the Assessment Group noted that the number of deaths seemed high for the size of the cohorts and length of the studies, and may indicate that the selected population were not well defined for the purpose of the study. With the small number of events in all arms and the relatively short time-horizon of the trials, it is very difficult to draw firm conclusions regarding mortality.

Table 21: Mortality data

	EAGER[58]		COLO/DPI/02/06[64]		COLO/DPI/02/05[64]	
	Tobramycin DPI	Nebulised tobramycin	Colistimethate sodium DPI	Nebulised tobramycin	Colistimethate sodium DPI	Nebulised colistimethate sodium
Number patients	N=308	N=209	N=187	N=193	N=16	N=15
Mortality	3 (0.97%)	0 (0%)	0(0%)	2 (1.03%)	0 (0%)	0 (0%)

5.3.4 Compliance

Compliance with study medication was reported in both key trials, but it is not clear whether the methods and analyses provided are compatible between trials. In the COLO/DPI/02/06[64] trial, fewer patients were compliant with medication in the colistimethate sodium DPI arm than in the nebulised tobramycin arm (66.7% versus 70.7% respectively complied with >75% of doses). The EAGER trial[63] did not define how compliance was judged, but simply states it was "generally high" with >90% compliance in both arms. It is not clear if this data includes those who withdrew, but seems likely that it does not as the discontinuation rate was 26.7% in the tobramycin DPI arm and 18.2% in the nebulised tobramycin arm, so values for compliance would be expected to be lower if these patients were counted. In comparison, withdrawals in the COLO/DPI/02/06[64] were 17.2% in the colistimethate sodium DPI arm and 14.2% in the nebulised tobramycin arm, and it is unclear if these are counted in the compliance figures reported. Results for both DPI formulations do not appear to support the manufacturer's claim that the improved delivery time would result in better compliance.

5.4 Discussion

Three trials were included in the review of clinical effectiveness. Both colistimethate sodium DPI and tobramycin DPI were reported to be non-inferior to nebulised tobramycin in pivotal Phase III trials, for the outcome FEV_1%.[58,64] A small trial comparing colistimethate sodium DPI to nebulised colistimethate sodium in a younger, healthier cohort of patients showed no significant change in lung function in either arm, but was primarily a safety trial.[65]

The quality of the included studies was generally poor to moderate. None of the trials scored well on all risk of bias items, with blinding and non-adherence to the EMA research guidelines[1] being key problems. This could lead to selection bias and reporting bias for subjective outcomes such as adverse events, inaccuracies and imprecision in the results, and may limit the generalisability of the findings.

Specific criticisms of the data analysis for the EAGER trial[63] include using an ITT analysis without imputation, and not providing an analysis at both 20 and 24 weeks. Criticisms of the COLO/DPI/02/06[64] trial include the use of a non-parametric analysis to show non-inferiority, though this analysis was defined *a priori*.

It was not possible to draw any firm conclusions as to the relative efficacy of any intervention compared with any other intervention (except nebulised tobramycin) due to missing data, uncertain comparability of patient characteristics and incompatible data populations used when analysing the data. [redacted] tobramycin DPI [redacted] appeared to result in more people experiencing at least one exacerbation (as indicated by the surrogate outcome "lung disorders" in the EAGER trial) than nebulised tobramycin, and it is unclear if these results support non-inferiority of the intervention to nebulised tobramycin. Adverse events were mostly similar between arms within trials, except for cough which was higher in both DPI arms. More patients in DPI arms withdrew due to adverse events in both trials. Resistance of around 20% was reported for tobramycin arms across both key trials; a rate of $\leq$ 1.1% was reported for colistimethate sodium DPI. The statistical and clinical significance of exacerbation, resistance and adverse event data is not known.

This review has been conducted to a high standard including comprehensive search strategies with study selection, data extraction and quality assessment checked by a second reviewer. It is limited by the small number of trials available, and methodological weaknesses and incompatibilities within the trials. There are variations in the definition and measurement of the key outcomes, due to non-compliance with EMA research guidelines. No data which complies with the NICE Reference Case on quality of life was available from any of the trials.

A number of uncertainties remain, in particular:

- The comparability of the patients in the two pivotal trials
- The comparability of the definitions of non-inferiority between the two pivotal trials
- The impact on estimates of efficacy of presenting ITT analysis with no imputation (EAGER trial[63])
- The adequacy of short-term data in predicting long-term outcomes
- The significance of resistance to tobramycin in terms of long-term outcomes
- How many patients would not be able to tolerate the DPI formulations
- The long-term impact of these treatments on mortality
- The impact of DPI on HRQoL
- Whether the definitions of "acute exacerbation" used in the trials was generalisable to a wider population, given the lack of an international consensus.

In addition, whilst the key outcome measure, FEV_1%, is the standard measure in cystic fibrosis research, it is considered by some within the research community to be insensitive to small changes, especially in early disease. However, the EMA still recommend that FEV_1% should be the primary outcome measure, but should be considered in conjunction with microbial outcomes and "harder" outcomes such as acute exacerbations. In these trials, acute exacerbations or their surrogate [redacted], though it is unclear whether the studies were powered for this outcome, whether these results were clinically or statistically relevant, or whether six months is long enough to see an effect on exacerbations.

In summary, colistimethate sodium DPI and tobramycin DPI have both been reported to be non-inferior in terms of FEV_1% in appropriately powered Phase III non-inferiority trials at 20 or 24 weeks. However, it would appear that both DPI interventions [redacted] A significant number of patients in both trials dropped out from the intervention arms due to adverse events, and cough was reported more often in the DPI treatment groups compared to the nebulised groups. A comparison of colistimethate sodium DPI to tobramycin DPI was not possible due to data limitations and study heterogeneity. Both studies can be criticised for statistical analysis techniques and a lack of adherence to EMA research guidelines. The long-term efficacy of either intervention is unknown, and trials recording and powered for non-surrogate outcomes such as exacerbations and mortality over the longer term are required.

6. ASSESSMENT OF COST-EFFECTIVENESS

This section presents evidence concerning the cost-effectiveness of colistimethate sodium DPI and tobramycin DPI for the treatment of *Pseudomonas aeruginosa* in patients with CF. The chapter is set out as follows. Section 6.1 presents a review of published economic evaluations of colistimethate sodium and tobramycin. Section 6.2 presents a critical appraisal of submissions made to NICE by the manufacturers of colistimethate sodium DPI and tobramycin DPI. Section 6.3 presents a discussion of the methodological problems associated with the economic evaluation of treatments for CF. Section 6.4 presents the methods and results of a *de novo* economic analysis of these drugs from the perspective of the NHS. Section 6.5 presents a budget impact analysis for colistimethate sodium DPI and tobramycin DPI. Section 6.6 discusses the limitations of the economic analysis and draws conclusions regarding the expected cost-effectiveness of the dry powder treatments.

6.1 Systematic review of existing economic analyses

6.1.1 Cost-effectiveness review methods

Systematic literature searches were undertaken to identify published economic evaluations of colistimethate sodium and tobramycin for the treatment of CF. Details of the search strategies are reported in Section 5.1 and the search strategies for the cost-effectiveness review are presented in Appendix 2. Handsearching of sponsor submissions to NICE[58,68] was also undertaken in order to identify any further studies missed by the electronic searches. The studies included in the review were critically appraised using the Drummond *et al* checklist for economic evaluations.[86]

6.1.2 Results of the systematic review

Three published studies were identified by the systematic searches.[6,87,88] None of these three studies relates to either colistimethate sodium or tobramycin in DPI form. However these studies do provide some information concerning the costs and outcomes of the comparator therapies for this assessment and elucidate some of the key methodological problems surrounding the economic evaluation of treatments for CF. A critical appraisal of these studies is briefly detailed below.

Wolter *et al.* (1997) Home intravenous therapy in cystic fibrosis: a prospective randomized trial examining clinical, quality of life and costs aspects[87]

Wolter *et al.* conducted a cost-consequence analysis (CCA) of home intravenous (i.v.) antibiotic therapy in adult patients with an infective exacerbation of CF compared to hospital i.v. antibiotic therapy. The perspective of the study was not clearly stated, however the authors appear to include costs incurred by the hospital and costs incurred by patients and families. The main clinical outcome measures assessed within the study were lung function and health-related quality of life (HRQoL).

Seventeen adolescents and adults with CF attending two hospitals in Brisbane Australia were randomised between the groups (31 admissions: 13 home and 18 hospital). The median age of study subjects was 22 years (range 19-41 years), with no statistically significant difference between patient characteristics in the two group regarding age, sex, FEV_1 at admission, or type of i.v. received. Type of i.v. included peripheral, port-a-cath and central line.

Antibiotic treatment consisted of ceftazidime 2g 12-hourly, and tobramycin 4-6mg per kg daily as a single bolus. Treatment was conducted for a minimum of 10 days and was guided by clinical response. Patients also received twice daily physiotherapy plus 20 minutes of aerobic exercise. There were no statistically significant differences between the groups in terms of the duration of treatment or use of antibiotics. The median duration of treatment was 12 days (range 10-24 days) for the home group and 11 days (range 7-26 days) for the hospital group (p=0.2).

Clinical outcomes were presented in terms of HRQoL, FEV_1, FVC, weight gain (kg), 12 minute walking distance, sputum production over 12 hours, pulse oximetry, serum creatinine levels, aminoglycoside levels and audiology. HRQoL was measured using the Chronic Respiratory Disease Questionnaire (CRDQ)[89] which measures change in dyspnoea, fatigue, emotion and patients feeling of control over the disease and its consequences (referred to as "mastery"). In addition, non-validated quality of life questions were also administered to patients, based on a grade out of seven, to assess the degree of disruption to their family, personal life, sleeping and eating as a result of their illness. The timing of outcome measurement within the study is summarised in Table 22.

Table 22: Outcome measures and timing of assessment within Wolter *et al*[87]

Outcome measure	Time point assessed
Spirometry (FEV_1, FVC), pulse oximetry, 12 minute walking distance, sputum weight (production over hours), weight gain	Day 0, Day 10, Post-Rx
Serum creatinine	Day 0, Day 2, Day 7
Aminoglycoside levels	Day 2, Day 7
Audiology	Before and after therapy
Dyspnoea score, fatigue score, emotional score, mastery score	Day 0, Post-Rx
Family disruption, personal disruption, sleep disruption, eating disruption	Post-Rx
Toxicity and complications: death, short-term readmission, drug attributable events	Unknown

Day 0: admission; Day 10: Day ten of therapy; Post-Rx: approximately 10 days after cessation of i.v. therapy

Costs were valued in Australian dollars at 1992-1993 prices. Hospital costs were calculated using CF inpatient costs from the Prince Charles Hospital and from projected diagnostic-related group reimbursement figures. Home therapy costs were calculated based on hospital acquisition costs and consumption of resource. Staff costs spent on education and home visits were calculated from hourly wages. Travel costs were determined according to a standard cents-per-kilometre fee. Other patient

and family costs were determined by interview, however details are not given within the paper with respect to who undertook the interview. Costs were also compared in terms of mean total cost of therapy including the costs of home physiotherapy, home visits, training, equipment, drugs and bed occupancy.

Results are presented in terms of means and standard deviations; formal uncertainty analysis was not undertaken. Discounting was also not applied however this is reasonable given the short time horizon of the study. The headline results of the study are presented in Table 23.

Table 23: Headline results reported by Wolter *et al*[87]

		Home (number of admissions=18)	Hospital (number of admissions =13)	*p*-value
Clinical outcomes				
$FEV_{1,}$ % predicted value:	Day 0 Day 10 Day 21	39 (17) 45 (22) 43 (19)	44 (20) 50 (21) 51 (21)	0.27
FVC % predicted value:	Day 0 Day 10 Day 21	56 (19) 58 (21) 58 (22)	58 (17) 64 (19) 66 (19)	0.30
CRDQ quality of life dimensions				
Change in dyspnoea score		5.9 (5.5)	8.2 (5.4)	0.25
Change in fatigue score		3.6 (3.4)	6.8 (4.6)	0.04
Change in emotional score		4.4 (5.2)	8.6 (8.1)	0.11
Change in mastery score		2.6 (3.4)	5.5 (3.8)	0.03
Change in total score		16.5 (14.8)	29.5 (16.5)	0.03
Other quality of life dimensions				
Mean change in family disruption		6.2 (1.1)	4.5 (1.3)	0.001
Mean change in personal disruption		5.1 (1.0)	3.8 (1.3)	0.004
Mean change in sleep disruption		6.0 (1.3)	4.4 (1.6)	0.005
Change in eating disruption		6.6 (0.6)	5.9 (1.5)	0.07
Change in total disruption		23.9 (3.3)	18.3 (3.3)	<0.001
Cost outcomes (Australian dollars 1992/3)				
Cost per day for families		$15.08 ($13.48)	$23.77 ($17.77)	n/a
Crude mean hospital cost per episode		$2,476	$5,028	n/a

sd shown in parentheses

The authors conclude that home therapy is considerably less expensive for families than hospitalisation per day of hospitalisation ($15.08 versus $23.77). The crude estimated cost saving for managing exacerbations at home versus hospital was estimated to be $2,552. These estimates should be approached with some caution due to the small sample size within the study. It is also unclear whether these findings would hold in a UK setting.

Thornton *et al.* (2005) Clinical and economic choices in the treatment of respiratory infection in cystic fibrosis: Comparing hospital and home care[6]

Thornton *et al.* assessed the cost-effectiveness of home-based i.v. antibiotics for respiratory exacerbations in adults with CF (not limited to *Pseudomonas aeruginosa* lung infection) compared to hospital i.v. antibiotic therapy. The study was conducted from the perspective of a secondary care provider (NHS Trust). The study was a retrospective, observational, one-year pragmatic study analysed on an ITT basis. The primary clinical outcome was lung function measured in terms of FEV_1. One hundred and sixteen patients in the Manchester Adults CF Centre in the UK were recruited, 88.8% of whom had *Pseudomonas aeruginosa* lung infection. The authors report that there were no differences in patient characteristics or FEV_1 at the start of the study.

Treatment consisted of nebulised tobramycin, nebulised colistin, nebulised rhDNase, nebulised gentamicin, oral antibiotics, inhaled/nebulised corticosteroids, regular oral corticosteroids, and inhaled/nebulised bronchodilators or oral bronchodilators. Patients received treatment over the course of one year and their outcomes were analysed retrospectively. Patients were categorised as belonging to the 'home' or 'hospital' group if they received more than 60% of treatment at home or in hospital correspondingly. The remaining patients that received 40-60% of treatment at home or in hospital were categorised as belonging to the 'both' group. Of the 116 patients, 2 patients (1.7%) received nebulised tobramycin and 58 patients (50%) received nebulised colistin. During the study period patients in the 'home' group received a mean of 63 days (range 10-182 days) treatment in total, of which 52 days were at home and the remaining 11 days were in hospital. The 'hospital' group received a mean of 54 days (range 8-308 days) treatment in total, of which 45 days were in hospital and 9 days were at home. Patients in the 'both' group received a mean of 66 days (14-166 days) treatment, of which 40 days were at home and 26 days in hospital.

Health outcomes were presented in terms of FEV_1. The frequency of FEV_1 measurement was different between the two groups. FEV_1 for home-based patients was measured at the start and end of each course of i.v. antibiotics, whereas for hospital-based patients FEV_1 was measured at admission, twice weekly, and at discharge. Two baseline FEV_1 values were determined for each patient in the one-year baseline period before the one-year study period. The "best" FEV_1 was the highest FEV_1 value recorded during the baseline year, with the "average" FEV_1 value being the mean of all FEV_1 measurements during the baseline year. Treatment was defined as effective if lung function was maintained at the baseline "best" FEV_1 level i.e. percentage decline in FEV_1 was $\leq 0\%$. Given that it may be more reasonable to expect FEV_1 to decline over time, an additional analysis with a less stringent definition of effectiveness of percentage decline in $FEV_1 \leq 2\%$ was also performed. HRQoL was not measured or valued within the study.

Costs were valued in UK Sterling at 2002 prices. Unit costs were calculated from the NHS Trust, the CF Unit budget, the British National Formulary (BNF) and the hospital supplied catalogue. Resource

use and costs were estimated for i.v. antibiotics, disposable equipment, home kits, sputum microbiology and sensitivity and blood drug level assays. The time spent with each patient was estimated using a time sheet completed by each staff member attending the patient. Staff costs were obtained from the CF Unit budget. Clinical records were used to determine the number of days patients spent in hospital relating to i.v. antibiotic treatment. Fixed costs for the ward and outpatient clinic were calculated from the CF Unit budget; these were used to estimate a fixed cost per hour related to an inpatient stay or clinic visit. A standard time per home visit was determined by interviewing staff. Travel time from the clinic to each patient's home was estimated using data from the Automobile Association. The cost of travel for each home visit was calculated using a standard mileage allowance obtained from the hospital payroll department. Uncertainty analysis was conducted using non-parametric bootstrapping. Discounting was not applied to either the health outcomes or costs, presumably due to the short time horizon for the analysis. The headline results of the study are reported in Table 24.

Table 24: Headline results reported by Thornton *et al*[6]

	Hospital (n=51)	Both (n=18)	Home (n=47)	*p*-value
FEV_1 baseline values				
Mean (sd) FEV_1, % pred. "best"	59.3 (22.1)	60.6 (19.1)	64.7 (22.4)	-
Mean (sd) FEV_1, % pred. "average"	49.3 (18.6)	50.4 (16.0)	54.8 (19.0)	-
Effectiveness and costs at end of 1-year				
Number (%) patients with decline in $FEV_1 \leq 0\%$ over study period	30 (58.8%)	9 (50.0%)	20 (42.6%)	-
Number (%) patients with decline in $FEV_1 \leq 2\%$ over study period	32 (62.7%)	10 (55.6%)	20 (42.6%)	0.045
Mean cost per patient per year	£22,609 (£17,648, £27,569)	£19,927 (£13,433, £26,421)	£13,528 (£9,989, £17,068)	
Incremental cost-effectiveness (2002 UK pounds sterling)				
ICER ($FEV_1 \leq 0\%$)	*vs both* £10,923	*vs home* £71,710	-	-
ICER ($FEV_1 \leq 2\%$)	*vs both* £12,878	*vs home* £39,122	-	-

sd shown in parentheses

The authors reported that hospital-based treatment was more effective in terms of FEV_1 but also more expensive compared to home-based treatment. The authors report that there was a decline in baseline average FEV_1 in home-based patients whereas there was an improvement for hospital-based patients (Tukey's HSD mean difference 10.1%, 95% CI 2.9 to 17.2, p=0.003). The decline in FEV_1 over the study period was significantly different using a criterion of decline in $FEV_1 \leq$ 2% (p=0.045) however it was not statistically significant using $FEV_1 \leq$ 0% (p-value not reported). Analysis of patients lung function on a course-by-course basis suggests that hospital-based patients had statistically significantly more courses of treatment in which lung function was maintained at baseline "average" ($FEV_1 \leq$ 0%) compared to home-based patients (17.4% compared to 9.0%, p=0.001). For each course

of treatment the improvement in FEV_1 from the baseline "best" was also statistically significantly higher for hospital-based patients compared to home-based (mean difference 4.6%, 95% CI 1.8 to 7.4, p=0.001). The cost of administering i.v. antibiotics at hospital was significantly higher than home-based therapy (mean difference £9,005, 95% CI £3,507 to £14,700, p <0.001).

Incremental cost-effectiveness ratios (ICERs) were calculated separately using the two benefit criteria of decline in $FEV_1 \leq 0\%$ and $FEV_1 \leq 2\%$. Cost-effectiveness planes and cost-effectiveness acceptability curves (CEAC) were also presented. The authors report that hospital-based care may be cost-effective with a 95% probability at a willingness to pay of £262,500 for one extra patient with a decline in $FEV_1 \leq 2\%$. However using a stricter definition of lung function (decline in $FEV_1 \leq 0\%$) the probability that hospital-based care is cost-effective at a willingness to pay of £10 million per patient is below 0.05.

Iles *et al.* (2003) Economic evaluation of tobramycin nebuliser solution in cystic fibrosis[88]

Iles *et al*[88] report the methods and results of a cost-consequence analysis of inhaled tobramycin nebuliser solution (TNS) in children and adults with CF compared to usual therapy. Usual therapy is referred to as actual clinical practice in the UK, however no further details are provided within the paper. The study was conducted from the perspective of the NHS, with other interventions and medications taken on and off the study treatment being recorded. Lung function and body weight were the main dimensions of clinical outcome assessed. Seventy one patients with *Pseudomonas aeruginosa* lung infection were studied; 41 patients received TNS, of which 30 were matched with a paired control on usual therapy. The time horizon for the evaluation was 24 months. Outcomes and costs were not synthesised into an incremental cost-effectiveness ratio.

Treatment in the TNS group consisted of 300mg/5 ml TNS twice daily for 28 days followed by 28 days without treatment. Treatment was conducted for 12 months, with patients monitored for 12 months prior to therapy. Patients in the TNS group were matched at the start of treatment to patients who had not had TNS therapy (the control group). Matching was conducted according to age (within ±6 months), gender, lung function (within ±20% FEV_1% predicted) and chronic infection with *Pseudomonas aeruginosa*. The authors state that the TNS group and control group were "well matched" in terms of age, gender and pre-treatment FEV_1.

Clinical outcomes were presented in terms of FEV_1 and body weight expressed in the form of the net effect during the 1-year prior to therapy and 1-year following therapy. Impacts upon HRQoL were neither measured nor valued. Resource use recorded within the study included days in hospital, length of i.v. infusions, clinics attendances, outpatient visits, i.v. courses, ward admissions and intensive care unit (ICU) admissions. The authors state that illness that occurred during or in between therapy

(referred to as intercurrent illness), and surgical procedures were also recorded however these are not reported within the paper.

Costs were valued in UK Sterling at 2001 prices. Unit costs of ward and intensive care unit stays were ascertained using routinely available NHS Reference Cost data. The mean unit cost of a hospitalisation day (for general medical paediatric and adult beds) and an ICU day was reported. The authors note that the mean cost of a hospitalisation day used in the analysis may be an underestimate of the true cost of ward care for CF patients because the estimate does not specifically relate to this patient population. The number of days in hospital was recorded as the authors state that these are expensive and may be expected to degrade HRQoL and reduce patient's educational possibilities or capacity for wage earning (although these outcome and resource impacts were not assessed within the study). No formal uncertainty analysis was undertaken and the results were not discounted.

Twenty nine (71%) patients in the tobramycin group used inhaled antibiotics prior to therapy compared to 16 (53%) patients in the control group. In addition, 20 (49%) patients in the tobramycin group received inhaled colistin during the alternating months off tobramycin. There were also imbalances between the tobramycin group and the control group in terms of the number of days of hospitalisation for the year before therapy (32.1 days compared to 27.0 days respectively).

Table 25: Headline results for case-matched pairs reported by Iles *et al*[88]

Matched pairs		Year Pre	Year Post	Change
FEV_1% predicted: (n=30)	Tobramycin	56.3	54.9	-1.36
	Control	57.4	55.8	-1.63
Weight s.d. score: (n=27)	Tobramycin	-1.16	-1.05	0.12
	Control	-1.27	-1.24	0.03
Days in hospital: (n=30)	Tobramycin	32.1	21.6	-10.5
	Control	27.0	14.1	-12.9
Length of i.v.s (days): (n=30)	Tobramycin	57.6	33.5	-24.1
	Control	33.6	32.9	-0.8
Number clinics: (n=30)	Tobramycin	10.8	8.1	-2.66
	Control	9.7	8.5	-1.20
Number OP visits: (n=30)	Tobramycin	0.9	0.7	-0.23
	Control	0.2	0.4	0.19
Number i.v. courses: (n=30)	Tobramycin	3.6	2.3	-1.27
	Control	2.3	2.3	0.00
Number ward admissions: (n=30)	Tobramycin	2.9	2.0	-0.94
	Control	2.1	1.5	-0.59
Number ICU admissions: (n=30)	Tobramycin	0.2	0.2	0.07
	Control	0.1	0.1	-0.01

Mean FEV_1 % predicted decreased less in the study group (-1.36) compared to the control group (-1.63) however the authors do not state whether the difference was statistically significant. The increase in weight standard deviations was marginally greater in the treatment group (0.12) compared to the control group (0.03) however this was also not statistically significant (*p*-value not reported). The mean total number of days of hospitalisation decreased from 32.1 days to 21.6 days in the tobramycin group (a reduction of 10.5 days), however there was a greater reduction of 12.9 days in the control group which decreased from 27.0 to 14.1 days. The authors state that the figure before treatment in the control group was considerably increased by an outlier; a patient who was admitted as an inpatient due to pulmonary exacerbation before the period that corresponded to tobramycin treatment of his matched pair. This increase in the mean total number of hospitalisation days in only the control group prior to treatment may therefore have contributed to the greater reduction in hospitalisation days in the control group compared to the tobramycin group. There was a statistically significant reduction in the length of i.v. treatment days in the tobramycin group compared to the control group of -24.1 days compared to -0.8 days ($p<0.001$). The authors also report that in both the tobramycin and control groups there was a reduction in the number of hospital attendances compared to the year prior to therapy. The magnitude of the reduction was however slightly greater in the control group; the authors attribute this to the inclusion of an outlier in the control group. There was a statistically significant reduction in the length of i.v. treatment days in the tobramycin group compared to the control group ($p<0.001$). The authors report that the mean costs within the tobramycin treated subgroup (41 patients) increased by £6,292 over the study period; the majority of

this difference was driven by the higher acquisition cost of tobramycin. The results of this study should however be interpreted with caution due to the case-matching design and the imbalances between the treatment groups.

6.1.3 Summary of published economic analyses

The review of the three published economic analyses presented above highlights the lack of relevant economic evidence relating to the cost-effectiveness of tobramycin and colistimethate sodium, in either nebulised or dry powder form, for the treatment of *Pseudomonas aeruginosa* in patients with CF. Only one of the three studies is a cost-effectiveness analysis[6] and even in this case, the adopted measure of clinical benefit is difficult to interpret in a policy context. None of the three studies met the NICE Reference Case due to their short time horizons. None of the included studies reported final patient outcomes in terms of life years gained or quality adjusted life years (QALYs) gained.

6.2 Review of manufacturers' submissions

This section presents a detailed exposition and critical appraisal of the economic evidence submitted by the manufacturers of colistimethate sodium DPI and tobramycin DPI.[58,64]

6.2.1 The Novartis submission (tobramycin DPI)[58]

Novartis submitted evidence to NICE relating to the clinical effectiveness of tobramycin DPI for the treatment of *Pseudomonas aeruginosa* lung infection in patients with CF. The Novartis submission presents the details of a network meta-analysis, a discussion of the difficulties of undertaking economic analyses of treatments for CF, and a brief discussion of three previously published economic analyses of CF treatments.[6,88,90] The submission makes particular note that these three economic analyses have deviated considerably from NICE's Reference Case[91] with respect to the primary health economic outcome measure adopted, which in each case relates to short-term FEV_1 improvements rather than QALYs gained. The Novartis submission does not include any form of *de novo* economic evaluation. Whilst the submission states that a cost-utility analysis was explored, but this was not pursued due to data limitations (including the absence of sufficient public domain information relating to the efficacy of colistimethate sodium DPI), a failure to demonstrate statistical significance within the network meta-analysis, and the presence of considerable heterogeneity in study design across the trials included in the network. In addition, at the time of writing their submission, Novartis had not proposed a list price, or potential range of list prices, for tobramycin DPI. The submission therefore does not present any economic evidence for tobramycin DPI.

6.2.2 The Forest submission (colistimethate sodium DPI)

The Forest submission[64] reports the methods and results of five clinical studies of colistimethate sodium DPI and an economic analysis of colistimethate sodium DPI versus nebulised tobramycin using data from the Phase III COLO/DPI/02/06 trial.

The review of the Forest economic model undertaken by the Assessment Group is divided into three parts: (i) a descriptive exposition of the model's mathematical structure and the evidence sources used to inform its parameters; (ii) a critical appraisal of the Forest model including a summary of adherence to, and deviations from, the NICE Reference Case,[91] and; (iii) a re-analysis of the Forest model using assumptions deemed more appropriate by the Assessment Group. This critical review is based upon four main evidence sources which were made available to the Assessment Group by Forest:

(1) A partially executable cost-effectiveness model developed using Microsoft Excel® and Visual Basic for Applications (VBA);
(2) A written description of the methods and results of the economic analysis presented within the Forest submission to NICE;[64]
(3) An accompanying mapping report detailing methods to estimate health utilities using data from the COLO/DPI/02/06 trial.[92]
(4) A detailed spreadsheet showing the translation of FEV_1 to expected QALY gains (note: this was not included within the original Forest submission but was later provided by Forest as part of the clarification process for the appraisal).

In addition, further clarification regarding the methods of the analysis was sought from Forest by the Assessment Group over the course of the technology appraisal.

Exposition of the Forest model

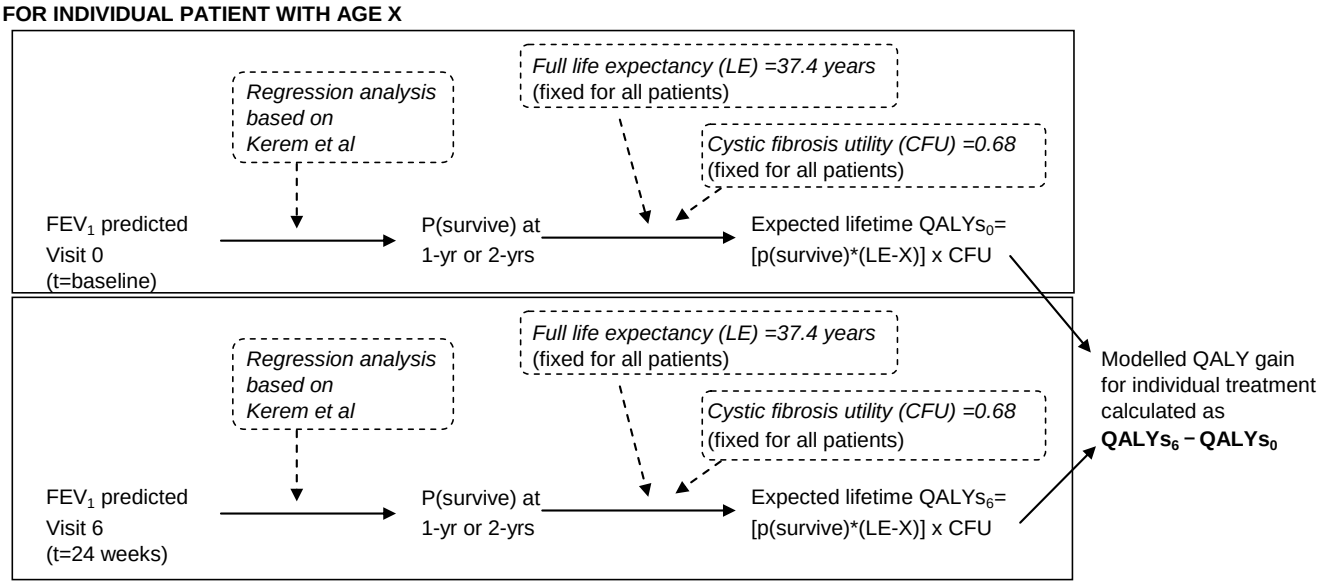
The Forest submission presents a model-based cost-utility analysis of colistimethate sodium DPI versus nebulised tobramycin from the perspective of the UK NHS. The model time horizon is short, but is unclear and inconsistent between health outcomes and costs. The primary economic outcome is presented in terms of incremental net monetary benefit, assuming a willingness to pay threshold of £30,000 per QALY gained. The form of the model would be most accurately described as a cohort-based decision analysis.

The economic analysis includes an estimate of incremental QALY gains accrued over a lifetime horizon, and the short-term costs associated with antibiotic drug acquisition and the management of

exacerbations in each treatment group. The economic analysis draws on seven evidence sources: (1) patient-level data from the COLO/DPI/02/06 trial,[64] (2) patient-level data from a study in which individuals completed both the child-friendly EQ-5D-Y and CF Questionnaire (CFQ-R),[93] (3) a mapping study used to map from the CFQ-R instrument to the EQ-5D-Y,[92] (4) observational data relating to an assumed relationship between 1-year and 2-year mortality risk and FEV_1% predicted,[40] (5) a fixed estimate of life expectancy from the CF Foundation,[94] (6) 2009-2010 NHS Reference Costs,[95] and (7) the British National Formulary number 61 (BNF 61).[96]

The general derivation of estimated QALYs for patients receiving either colistimethate sodium DPI or nebulised tobramycin within the Forest model is summarised in Figure 8. This approach is based on three mapped relationships: (1) the translation of FEV_1% predicted to the probability of mortality at 1- or 2-years, (2) the estimation of remaining life expectancy given the individual patient's age, and (3) the translation of the CFQ-R to the EQ-5D-Y.

Figure 8: QALY derivation within the Forest model



Where LE = life expectancy; CFU = CF utility; x = patient age

Predicted mortality differences between colistimethate sodium DPI and nebulised tobramycin were estimated by deriving regression equations for mortality at 1-year and 2-years using reported data on FEV_1% predicted and death from a retrospective analysis of the risk of mortality by FEV_1, FVC, PaO2, PaCO2, sex, weight and height.[40] Forest fitted polynomial regression equations to the Kerem *et al* data for 1- or 2-years by FEV_1 group. The derived mortality risk equations are as follows:

1-yr mortality risk = [redacted] [i]

2-yr mortality risk = [redacted] [ii]

All patients in the analysis are assumed to have a fixed survival duration of 37.4 years based on an estimate from the CF Foundation. Remaining expected life years for each individual patient were calculated as the patient's remaining life expectancy (maximum survival – current patient age) multiplied by the probability of surviving beyond 1- or 2-years based on the regression equation.

Preference-based health utilities were not collected within the COLO/DPI/02/06 trial. Forest undertook a mapping exercise to cross-walk from the CFQ-R to the EQ-5D-Y using patient data from a German study reported by Eidt-Koch *et al*.[93] This mapping exercise produced a single utility value for CF patients with chronic *Pseudomonas aeruginosa* lung infection within the COLO/DPI/02/06 trial. The calculations used to estimate the total QALYs gained are not entirely clear from the Forest submission but appear to adopt the following general logic:

(1) The mortality risk equation based on Kerem *et al* was applied to the individual patient's FEV_1% predicted score at baseline within COLO/DPI/02/06 (Visit 0).
(2) The individual patient's remaining life expectancy was calculated as the difference between a fixed life expectancy of 37.4 years and the patient's current age.
(3) Expected QALYs before treatment were calculated as the probability of surviving at 1-year or 2-years multiplied by the patient's remaining life expectancy multiplied by a fixed utility score for patients with CF.
(4) The Kerem *et al* mortality risk equation was applied to the individual patient's FEV_1% predicted score at 24-weeks (Visit 6).
(5) The individual patient's remaining life expectancy was calculated as the difference between a fixed life expectancy of 37.4 years and the patient's current age.
(6) Expected QALYs after treatment were calculated as the probability of surviving at 1-year or 2-years multiplied by the patient's remaining life expectancy multiplied by a fixed utility score for patients with CF.
(7) The mean QALY change for patients receiving a given treatment was calculated as the difference between mean predicted QALYs before treatment and mean predicted QALYs after 24-weeks of treatment (i.e. the difference between Step #6 and Step #3).
(8) Steps #1 to #7 were undertaken separately for colistimethate sodium DPI and nebulised tobramycin. Incremental QALYs between the colistimethate sodium DPI and the nebulised tobramycin groups were calculated as the difference in mean QALY change within each treatment group.

Remaining survival was discounted at a rate of 3.5%. The FEV_1→QALY analysis excludes all patients already aged over 37.4 years and those for whom FEV_1% predicted estimates were not available at both Visit 0 and Visit 6 within COLO/DPI/02/06.[64]

Acquisition costs for nebulised tobramycin were taken from the BNF.[96] The model assumes a cost per dose of £21.20. The Forest submission states that the annual cost of tobramycin is £7,738, which corresponds to a regimen in which two doses of nebulised tobramycin are used each day, and each 28-day treatment period is followed by 28 days without nebulised tobramycin (see Forest Submission,[64] Table 8).

Acquisition costs for colistimethate sodium DPI are not yet listed within the BNF. The Forest submission states that if colistimethate sodium DPI was priced at parity with nebulised tobramycin it would cost £7,738.00 per year (Forest submission, page 32).[64] The model however, includes a parameter called "Colobreathe price" which has a value of £21.20 per dose, which if used twice daily on a continuous basis, as per the COLO/DPI/02/06 trial,[68] would imply an annual cost of £15,476.00 (2 x £21.20 x 365). The Forest submission later states that the unit cost for colistimethate sodium DPI is [redacted] per dose (Forest submission, page 33);[64] if used continuously, this would imply an annual treatment cost of [redacted]. Forest [redacted]. Towards the end of the appraisal process, Forest stated [redacted]. The range of prices for colistimethate sodium DPI are summarised in Table 26. Importantly, the costs of antibiotic treatment are not actually included in Forest's calculations of incremental net benefit. [redacted]

Table 26: Price scenarios for colistimethate sodium DPI

No.	Price statement	Annual cost	Cost per dose	Source
1	[redacted]	£6,648.21†	£9.11	[redacted]
2	[redacted]	£7,738.00	£10.60†	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	£14,339.29	£19.64	[redacted]

5	[redacted]	£15,476.00†	£21.20	[redacted]
6	[redacted]	£28,681.70†	£[redacted]	[redacted]

† Implied price per year/dose

Rates of CF exacerbations were estimated by calculating the mean time to exacerbation in each treatment group and converting this to the mean number of exacerbations within a 1-year period, thereby assuming a constant exacerbation rate. For colistimethate sodium DPI, the mean time to first exacerbation was estimated to be 63.6 days; the mean number of exacerbations within one year was then calculated as 365/63.6 = 5.74 exacerbations. For nebulised tobramycin, the mean time to first exacerbation was estimated to be 59.4 days; the corresponding mean number of exacerbations within one year was calculated as 365/59.4 = 6.14 exacerbations. Each exacerbation was assumed to cost £2,587 based on NHS Reference Cost tariffs for the management of asthma with major co-morbidities and complications without intubation.

All parameter values used in the Forest model are summarised in Table 27.

Table 27: Parameter values used in the Forest model

Model parameter	Value	Source
Health outcomes / treatment effectiveness		
Health utility for CF	0.68	Jointly derived using data from the CF Foundation, 2011[94] Rowen *et al*[92] Kerem *et al*[40] and the COLO/DPI/ 02/06 trial.[64]
QALYs gained – Colistimethate sodium DPI - 1yr mortality model	[redacted]	
QALYs gained – Colistimethate sodium DPI - 2yr mortality model	[redacted]	
QALYs gained – Nebulised tobramycin 1yr - 1yr mortality model	[redacted]	
QALYs gained – Nebulised tobramycin 2yr - mortality model	[redacted]	
Time to exacerbation – Colistimethate sodium DPI	63.6	COLO/DPI/ 02/06[64]
Time to exacerbation – Nebulised tobramycin	59.4	
Resource costs		
Cost of managing an exacerbation	£2,587.00	NHS Reference Costs 2009-10[95]
Assumed willingness to pay threshold (λ)	£30,000	Forest submission[64]

The incremental net benefit for colistimethate sodium DPI versus nebulised tobramycin is simply calculated as:

(QALYs Coli – QALYs Tobi x λ) – (Costs Coli exacerbations–Cost Tobi exacerbations) [iii]

Where: λ = assumed willingness to pay threshold; Coli = colistimethate sodium, Tobi neb = nebulised tobramycin

Health economic results reported within the Forest submission

The base case results from the Forest economic analysis are summarised in Tables 28 and 29.

Table 28: Base case results of the Forest model (assuming 1-year mortality risk)

	Colistimethate sodium DPI	Nebulised tobramycin	Incremental
Health outcomes			
QALY gained	[redacted]	[redacted]	[redacted]
Costs			
Costs of drug acquisition†	£7,738.00	£7,738.00	£0
Costs of managing exacerbations	£14,856.95	£15,907.44	£1,050.49
Total cost	£22,584.78	£23,634.59	£1,050.49
Cost-effectiveness outcomes			
Net benefit (assuming λ=£20,000 / QALY)	[redacted]	[redacted]	[redacted]
Net benefit (assuming λ=£30,000 / QALY)	[redacted]	[redacted]	[redacted]
Incremental cost-effectiveness ratio	Colistimethate sodium DPI dominates		

† Note this is implied but not actually included in the model calculations

Table 29: Base case results of the Forest model (assuming 2-year mortality risk)

	Colistimethate sodium DPI	Nebulised tobramycin	Incremental
Health outcomes			
QALY gained	[redacted]	[redacted]	[redacted]
Costs			
Costs of drug acquisition†	£7,738.00	£7,738.00	£0
Costs of managing exacerbations	£14,856.95	£15,907.44	£1,050.49
Total cost	£22,584.78	£23,634.59	£1,050.49
Cost-effectiveness outcomes			
Net benefit (assuming λ=£20,000 / QALY)	[redacted]	[redacted]	[redacted]
Net benefit (assuming λ=£30,000 / QALY)	[redacted]	[redacted]	[redacted]
Incremental cost-effectiveness ratio	Colistimethate sodium DPI dominates		

† Note this is implied but not actually included in the model calculations

Irrespective of whether the 1-year or 2-year mortality risk model is assumed, the Forest economic analysis suggests that colistimethate sodium DPI dominates nebulised tobramycin. The Forest submission also notes the following:

"[The] Net benefit approach is very often used in cost-effectiveness analysis of health technologies. If price for the new technology (Colobreathe®) were at parity to TOBI® at £7,738 per annum, Colobreathe® would show a net benefit of £2,280.49 per patient per year. This does not reflect the additional benefits compared to TOBI® which have not been modelled:

- *The more favourable performance of Colobreathe® with respect to antimicrobial sensitivity of respiratory tract isolates of P. aeruginosa. This will have impact both on costs and patient quality of life.*
- *The costs of devices and consumables required for nebulisation*
- *Carer time in relation to nebulisation by a predominantly young patient population*
- *The benefit of the patient experience (ease of use) that is not adequately captured by the quality of life instrument.*

Taking into account these additional benefits, the proposed price for Colobreathe® is [redacted]'',64

Critical review of the Forest model

This section presents a detailed critical appraisal of the Forest model. This critical appraisal should be interpreted in light of the limitations of the available evidence base surrounding the effectiveness of colistimethate sodium DPI as compared against other antibiotics for the treatment of *Pseudomonas aeruginosa* lung infection as well as the context of care within which these treatments are used. Most patients with chronic *Pseudomonas aeruginosa* will receive antibiotics for the rest of their lives. However, there is no long-term evidence to demonstrate the efficacy of colistimethate sodium DPI or tobramycin DPI beyond a maximum 24-week trial follow-up period (see Chapter 5), and the short-term trial evidence that is available does not include the direct measurement of HRQoL using a preference-based instrument (e.g. the Euroqol-5D). There is also only very limited evidence relating to survival benefits for either colistimethate sodium DPI or tobramycin DPI. The implications of these problems are discussed further in Section 6.3. The use of modelling as a means of translating from intermediate endpoints to final outcomes, and/or for projecting beyond the termination of a trial, is not a substitute for empirical evidence and should thus be interpreted with an appropriate degree of caution. Given these limitations in the available evidence, the appropriate handling of uncertainty should therefore be considered key.

Despite the limitations of the evidence base, the Forest model is subject to a number of methodological problems which are likely to produce considerable bias in the Forest's results. These concerns, limitations and biases are summarised in Box 1; specific issues are then discussed in more detail below.

Box 1: Summary of key problems within the Forest model

1. Multiple deviations from the NICE Reference Case
2. Conceptually inconsistent time horizon for costs and health outcomes
3. Assumption of intermittent treatment using colistimethate sodium DPI
4. Limitations of the CFQ-R→EQ-5D-Y mapping exercise
5. Questionable validity of methods for estimating mortality benefits
6. Incremental net benefit estimates may not reflect the price of colistimethate sodium DPI
7. Potential biases in modelling of exacerbation rates
8. Omission of relevant costs and health impacts
9. Incorrect application of discounting formula applied to future health gains
10. Limited justification of modelling methods and identification, selection and use of evidence

Multiple deviations from the NICE Reference Case

Table 30 shows the extent to which the Forest model adheres to NICE's Reference Case. The perspective of the economic analysis, namely that of the NHS, is appropriate. The use of discounting is however partial. No discounting is undertaken for costs due to the short time horizon considered. Future QALY gains were discounted. The justification for presenting economic results in terms of incremental net benefit rather than the incremental cost per QALY gained is unclear. Further, the Forest model is entirely deterministic and the submission report does not include any probabilistic sensitivity analysis (PSA). No justification is given regarding this exclusion. Simple sensitivity analysis is presented but this is limited to examining the differential impact of using 1-year or 2-year mortality predictions.

Table 30: Adherence to the NICE Reference Case

Element of economic analysis	Reference case	Comments
Defining the decision problem	The scope developed by the Institute	The submission report does not include a description of the scope of the decision problem to be addressed. The scope of the Forest economic analysis is narrower than the scope of the appraisal.[60] Only colistimethate sodium DPI is included as an intervention.
Comparator	Therapies routinely used in the NHS, including technologies regarded as current best practice	Nebulised tobramycin is the sole treatment comparator considered within the analysis. The relative cost-effectiveness of colistimethate sodium DPI versus nebulised colistimethate sodium or combination (cyclical switching) strategies is not considered.
Perspective on costs	NHS and PSS	An NHS perspective was adopted. Only exacerbation costs over a 1-year period are included within the incremental net benefit calculation.
Perspective on outcomes	All health effects on individuals	Health benefits for NHS patients are included. Short-term FEV_1 changes are translated into QALY gains accruing over the patient's estimated remaining lifetime.
Type of economic evaluation	Cost-effectiveness analysis	The economic analysis takes the form of a cost-effectiveness analysis. Economic outcomes are expressed in terms of incremental net monetary benefit rather than the incremental cost per QALY gained.
Synthesis of evidence on outcomes	Based on a systematic review	The economic analysis is based on one RCT (COLO/DPI/02/06) and other indirect evidence.[40,64,92,94]
Measure of health effects	QALYs	Health outcomes are valued in terms of QALYs gained.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	Health utilities were derived from a mapping study to translate the CFQ-R to the child-friendly EQ-5D-Y.[92] Preferences were valued using the adult EQ-5D tariff. Carer QALYs and process utility associated with more convenient treatment are discussed but not included in the analysis.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	
Discount rate	An annual rate of 3.5% on both costs and health effects	Costs were not discounted. Future QALY gains were discounted although the discount rate applied is incorrect.
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to the modelled QALY gains.

Conceptually inconsistent time horizon for costs and health outcomes

As noted above, there currently exists no evidence relating to the long-term costs or health outcomes associated with colistimethate sodium DPI or nebulised tobramycin for the treatment of *Pseudomonas aeruginosa* lung infection in patients with CF. The Forest submission does not state the intended time horizon for their economic analysis. However, it is evident from the model exposition presented above that the adopted time horizon is inconsistent in terms of the time period considered for costs and that considered for health outcomes. The model uses changes in FEV_1% predicted measured from baseline to 24 weeks within the COLO/DPI/02/06 trial and 'extrapolates' the impact of this shift in FEV_1 to lifetime QALY benefits. The economic model therefore reflects the predicted long-term mortality benefits associated with 24-weeks of treatment only. In direct contradiction to this, exacerbation costs are arbitrarily modelled over a 1-year period, without any consideration of longer-term costs. As acquisition costs are excluded entirely from the incremental net benefit calculation, there is an implication underlying the economic analysis that treatment in the intervention and control groups is the same after the first 24-weeks. Given this mismatch between the time horizon for costs and outcomes, it is conceptually unclear how the time horizon for incremental net benefit should be interpreted. The Forest submission provides no discussion or justification of this issue.

Assumption of intermittent treatment using colistimethate sodium DPI

There is a significant bias with respect to the options assessed within the Forest model. As the model includes equal cost per dose parameters for colistimethate sodium DPI and nebulised tobramycin, the model appears to assume that colistimethate sodium DPI is used according to the same treatment schedule as nebulised tobramycin, that is, each 28-day treatment period is followed by a 28-day period without treatment. This reflects the licensed indication for nebulised tobramycin, but does not reflect either the protocol or practice of the COLO/DPI/02/06 trial or the licensed indication for colistimethate sodium DPI. Within the COLO/DPI/02/06 trial, patients allocated to the colistimethate sodium DPI group received treatment on a continuous basis.[68] The consequence of assuming a "cycle-on cycle-off" regimen is that the modelled treatment benefits reflect those associated with the continuous use of colistimethate sodium DPI at only half the cost of generating these benefits. Unless colistimethate sodium DPI is priced at parity with the annual cost of nebulised tobramycin, this is inappropriate and produces a substantial bias in favour of colistimethate sodium DPI.

Limitations of the CFQ-R→EQ-5D-Y mapping exercise

The COLO/DPI/02/06 trial[64] did not include the collection of data on HRQoL using a preference-based instrument. As a consequence, no data were available from the clinical trial to produce direct estimates of QALYs gained for colistimethate sodium DPI or nebulised tobramycin. The COLO/DPI/02/06 trial did however include the use of a disease-specific measure: the CFQ-R. In order to estimate health utilities associated with colistimethate sodium DPI and nebulised tobramycin, Forest undertook a mapping exercise using patient-level data from a published supplementary study in CF patients.[93] The mapping exercise relates to two distinct patient cohorts: (1) an "estimation dataset" – Eidt-Koch *et al*[93] and (2) an "application dataset" – the COLO/DPI/02/06 trial.[64] Collection of data for the estimation dataset[93] was undertaken in 2006 across four CF centres in Germany. Within this study, a cohort of 96 patients with CF completed both the German version[97] of the CF Questionnaire[46,50] and the EQ-5D-Y.[98] Patients included in this study were generally of young age (mean = approximately 13 years, range 8-17 years) and mean FEV_1% predicted was generally high both in the children and adolescent groups (93.6% and 90.7% respectively). Patient-level data from the estimation dataset were used to produce a series of regression equations to "cross-walk" from the CFQ to the EQ-5D-Y. The selected regression equation was then applied to patient-level data from the COLO/DPI/02/06 trial in which quality of life data was collected only using the CFQ-R instrument. Details relating to the estimation of alternative mapping functions in the child and adolescent populations were made available by Forest as a technical appendix to the main submission.[92]

There are a number of problems associated with the mapping exercise and its use within the colistimethate sodium DPI model; these are detailed below.

(1) Comparability of populations within the estimation dataset and the estimation dataset

The NICE Decision Support Unit (DSU) Technical Support Document on the use of mapping in health technology appraisals states the following:

"The characteristics of the estimation sample should be similar to the target sample for the mapping analysis, and should contain all variables from the target sample or included in the economic model that are thought to impact on EQ-5D scores. Under some circumstances, it may be appropriate for the estimation sample to include a broader range of people, providing that the target sample is sufficiently represented."[99]

The comparability of the estimation dataset[93] and the application dataset (COLO/DPI/02/06) appears to be subject to certain potentially important heterogeneities in terms of basic demographic and clinical variables. A crude comparison of patient characteristics within the Eidt-Koch *et al* cohort and the baseline characteristics of patients recruited to COLO/DPI/02/06 is presented in Table 31. In particular, Only 65 patients (67.7%) included in Eidt-Koch *et al*[93] had a bacterial colonization of the lung, although it is unclear what proportion of these patients had chronic *Pseudonomas aeruginosa* or an alternative type of bacterial infection. In addition, there are noticeable differences in terms of patient age and baseline FEV_1 lung function.

Table 31: Comparison of demographic and clinical variables in the estimation and application datasets

Variable	Estimation dataset (Eidt-Koch et al[93])		COLO/DPI/02/06 at baseline[64]
	Children (8-13 years)	Adolescents (14-17 years)	ITT population (6-56 years)
Sex (male)	43.6% (n=24)	58.5% (n=24)	54.5% (n=374)
Age (mean/sd)	10.8/1.7	15.9/1.80	21.1/9.49. 58.8% patients were aged>18years
% vital capacity (mean/sd)	92.5%/11.9% (n=47)	97.2%/13.1% (n=34)	Not reported
$\%FEV_1$ (mean/sd)	93.6%/15.2% (n=47)	90.7%/20.3% (n=34)	Precise values not reported. FEV_1 range 25%-75% predicted required for eligibility.
$\%MEF_{25}$ (mean/sd)	68.4%/41.7% (n=47)	58.9%/37.5% (n=34)	Not reported
Bacterial colonisation of the lung	63.6% (n=35)	73.2% (n=30)	100% infected with chronic *Pseudomonas aeruginosa*
Pneumothorax	1.8% (n=1)	0% (n=0)	Not reported
Allergic bronchopulmonary aspergillosis (ABPA)	3.6% (n=2)	12.2% (n=5)	Exclusion criteria within trial
Pancreatic insufficiency	80.0% (n=44)	78.1% (n=32)	Not reported
Hepatobiliary complications	23.6 (n=13)	26.8 (n=11)	33.3% in the colistimethate sodium DPI group, 40.3% in the nebulised tobramycin group
Distal intestinal obstruction	7.3% (n=4)	0% (n=0)	Not reported
Diabetes mellitus	0% (n=0)	7.3% (n=3)	Not reported
Nasal polyp	10.9% (n=6)	17.1% (n=7)	Not reported
Isolation obligation for patient	1.8% (n=1)	9.8% (n=4)	Not reported

(2) Limited sample size within the estimation dataset

The Eidt-Koch *et al* study recruited only a small number of patients (n=96). Of these, 93 patients completed both the CFQ and the EQ-5D-Y,[93] and 93 patients were included in the mapping exercise.[92]

Inevitably, this leads to considerable uncertainty surrounding the use of the mapping function, none of which is addressed in the health economic analysis.

(3) Range of state space captured within the estimation dataset

The Eidt-Koch *et al* publication states that 44.6% patients had no problems on any of the dimensions of the EQ-5D-Y.[93] In other words, nearly half of the estimation dataset cohort reported an EQ-5D-Y profile of (1,1,1,1,1) which represents a notional state of "perfect health" (health utility=1.0). This can be a common problem in utility mapping exercises, but is further compounded here by the small sample size of the estimation dataset. At the lower ends of the scale, Eidt-Koch *et al* report that only *"one or two patients reported extreme problems (level 3)"*[93] on at least one of the dimensions of the EQ-5D-Y. As a consequence, the limited coverage of the EQ-5D state space within the estimation dataset may call to question the validity of applying the mapping function to a cohort of patients with a generally higher level of disease activity.

(4) Valuation of the EQ-5D-Y

Eidt-Koch *et al* used the child-friendly EQ-5D-Y (see Wille *et al*[98]). Within the mapping exercise, responses were valued using the UK adult EQ-5D tariff reported by Kind *et al*[100] in which the lowest age of respondents was 18 years. A valuation tariff for children below this age does not currently exist.

(5) Ambiguity regarding the selection and justification of the statistical mapping function

The Forest submission[64] presents 12 mapping functions including Ordinary Least Squares, TOBIT regressions and Censored Last Absolute Deviations (CLAD) forms. Seven alternative regression models are presented for children (aged 8-13) and five alternative regression models are presented for adolescents and adults (age 14-17). The Forest submission states *"The preferred model was chosen using root mean squared error, mean squared error and mean absolute error."* These selection criteria are appropriate.[99] However, neither the submission report nor the accompanying appendices state which mapping function was actually selected for use in the health economic model analysis. Further, whilst the Forest submission claims favourable benefits in terms of improved ease of use and improved sensitivity for colistimethate sodium DPI, the use of a single health utility score within the model indicates that such potential benefits are not captured in the economic model.

Questionable validity of methods for estimating mortality benefits

Whilst mortality was recorded within the COLO/DPI/02/06 trial as a safety endpoint, the study was not powered to demonstrate a treatment benefit in terms of survival. Within the COLO/DPI/02/06 trial, two patients died during the study follow-up period, both of whom were allocated to the nebulised tobramycin group (see Table 21). Both of these deaths were reported to be unrelated to the study drug and were instead attributed to the underlying disease. Within the economic analysis,

modelled differences in survival are captured by deriving and applying regression equations describing a potential relationship between FEV_1 predicted and mortality at 1-year and 2-years from a retrospective analysis of the risk of mortality by FEV_1, PaO2, FVC, weight and height[40] to patient-level changes in FEV_1 observed within the COLO/DPI/02/06 trial. This change in predicted survival is then weighted by a single utility score, discounted, and compared incrementally between treatments. There are a number of problems with this approach, as detailed below.

Assumption of a single fixed life expectancy

The Forest analysis assumes that all patients have a fixed maximum life expectancy of 37.4 years. In reality, the trial cohort would be expected to follow a survival distribution. Furthermore, the potential QALY gains of individuals with an age greater than 37.4 years within COLO/DPI/02/06 were excluded from the analysis (n excluded=32). The impact of this bias on the cost-effectiveness of colistimethate sodium DPI is unclear.

Validity of the relationship between FEV_1% predicted and mortality

The long-term mortality benefits included in the model are based on data presented within two figures reported by Kerem *et al*.[40] The Forest submission itself notes that this assumed relationship is only "*a suggestion.*"[64] As the model applies a common health utility score for all patients irrespective of treatment group, this predicted survival benefit drives the entire QALY gain attributed to colistimethate sodium DPI. However, scrutiny of the Kerem *et al* publication indicates that increased mortality risk was also associated with decreasing PaO2, increasing PaCO2, increasing weight-for-height, and increasing age. Further, a multivariate regression presented within Kerem *et al* indicates that all variables except sex were statistically significant at the 5% level. It is therefore reasonable to suggest that the potential for confounding within the proposed FEV_1→mortality relationship is substantial. The validity of using FEV_1 as a single independent surrogate for mortality is not explored, justified or discussed within the submission.

Questionable value of the regression equation

Whilst Kerem *et al* clearly report categorical data, Forest fitted their 1-year and 2-year regression equations to the mid-point of each FEV_1 category (see Figures 9 and 10, refitted by the Assessment Group), thereby inappropriately treating categorical data as if they were continuous. It is unclear why Forest needed to apply a regression equation (which in itself is an approximation) as it should have been possible to directly apply the Kerem *et al* mortality probabilities to the categorical FEV_1 bands from COLO/DPI/02/06. The value of the regression equation is thus unclear and is not justified within the submission.

It should also be noted that the FEV_1% mean change from baseline value reported in COLO/DPI/02/06 did not show that colistimethate sodium DPI was superior to nebulised tobramycin.

A crude analysis of the raw trial data indicates undertaken by the Assessment Group indicates that the mean FEV_1 change is actually more favourable for nebulised tobramycin than colistimethate sodium DPI. It therefore appears counter-intuitive that a less favourable FEV_1 improvement may lead to a more favourable estimate of QALY gain for colistimethate sodium DPI versus nebulised tobramycin.

Figure 9: Fitted mortality probabilities predicted at 1-years by FEV_1 category

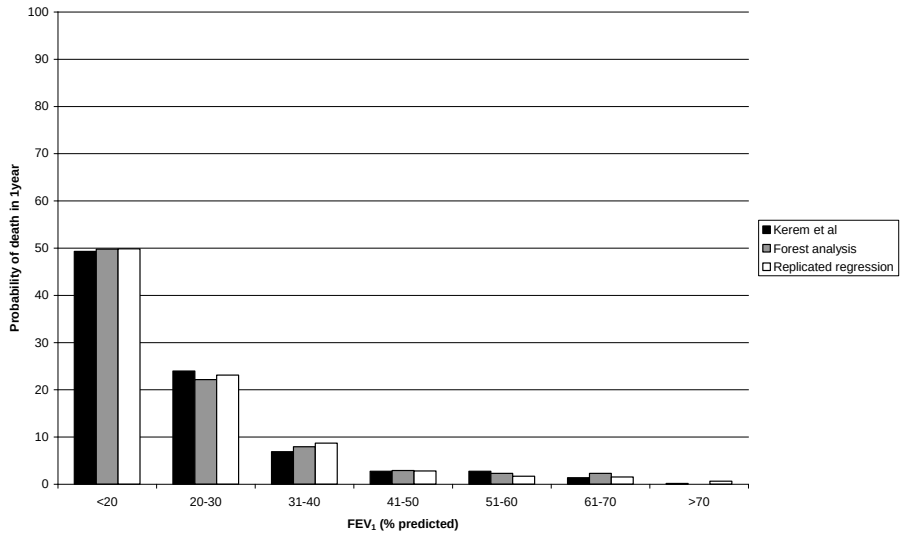
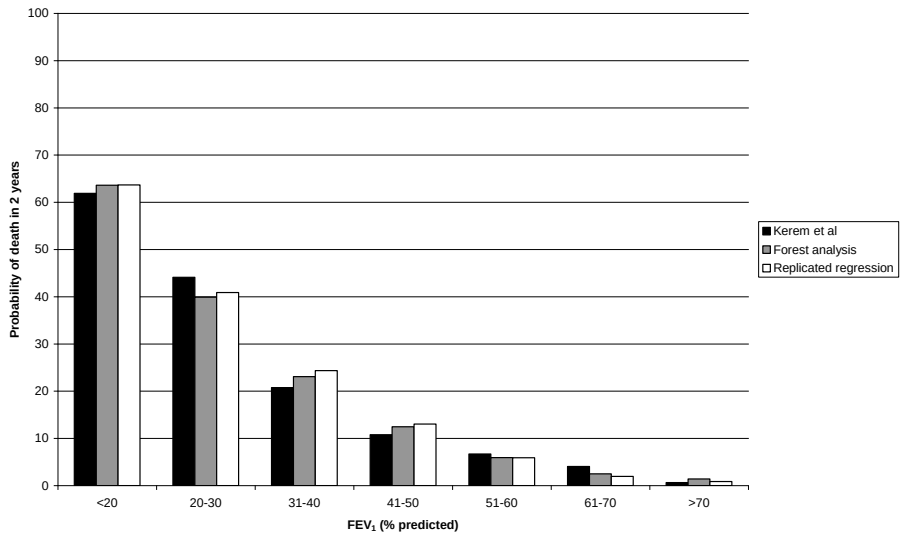


Figure 10: Fitted mortality probabilities predicted at 2-years by FEV_1 category



Incremental net benefit estimates do not reflect the price of colistimethate sodium DPI

On page 32 of the Forest submission, there is a suggestion that colistimethate sodium DPI will be priced at parity with nebulised tobramycin on an annual basis (£7,738).[64] However, the economic model includes a parameter which indicates that the unit cost per dose of colistimethate sodium DPI is £21.20, which indicates price parity with tobramycin on a per-dose basis. As nebulised tobramycin is used on a "cycle-on cycle-off" basis, but colistimethate sodium DPI is not, the actual cost of colistimethate sodium priced on this basis would be double that of nebulised tobramycin over a one year period. The submission later states that as the model does not capture other benefits of colistimethate sodium DPI (more favourable performance regarding antimicrobial resistance, reduced costs of devices and consumables, reductions in carer time and ease of use), a per-dose price of £[redacted] isused. This would obviously lead to a higher incremental cost for colistimethate sodium DPI versus nebulised tobramycin. Crucially, the positive incremental net benefits claimed within the submission do not therefore reflect either the appropriate dosage regimen or the actual suggested price of colistimethate sodium DPI; the results presented by Forest therefore only reflect the scenario in which colistimethate sodium DPI is priced at parity with tobramycin on an annual basis. This is the lowest price suggested by Forest (£10.60 per dose). As noted above, Forest later used a cost of [redacted] of colistimethate sodium DPI (see Table 26).

Potential biases in modelling exacerbation rates

The Forest model uses data on time to exacerbation for colistimethate sodium DPI and nebulised tobramycin from COLO/DPI/02/06 to estimate the mean number of expected exacerbations over a 1-year period assuming a constant rate in each group. As the acquisition costs of the intervention and the comparator are not included in the incremental net benefit calculation, all predicted cost savings are driven by this element of the model. In order to produce these time-to-event estimates, Forest must have used data on the observed number of exacerbations in each group together with the time at which they occurred. Therefore, the analysis takes the observed number and timing of exacerbations, converts these into time-to-event estimates, and then converts them back to the estimated number of exacerbations over a one year period. No justification of this approach is provided within the Forest submission. It would have been more appropriate simply to use annualised exacerbation rates (taking into account censored observations) using the COLO/DPI/02/06 trial data, and a relative risk to reflect the differences between treatment groups.

Omission of relevant costs and health impacts

The systematic review of clinical effectiveness (see Chapter 5) reported that across many adverse events, incidence was higher for colistimethate sodium DPI than nebulised tobramycin. Many of these adverse events may be self-limiting and transient in nature, and the costs of managing them may be minimal. However, the Forest model does not include any consideration of these costs or potential impacts on HRQoL and the submission report does not discuss or justify their exclusion.

Incorrect discounting formulae applied to future health benefits

Whilst the Forest analysis includes discounting of future health benefits, the discounting formulae have been applied incorrectly. Within the Forest $FEV_1 \rightarrow QALY$ analysis, the discount weight is calculated using the following formula for each additional year of survival:

Discounted utility in a given year = UtilityValue . exp(-DiscountRate . year) [iv]

If this method is used to calculate discount weights, the discount rate *r* should be converted to (log[1+*r*]). This error produces only a minor bias in the results.

Limited justification of modelling methods and identification, selection and use of evidence

The Forest submission presents very little justification for the modelling approach adopted. The methods used to identify, select or use particular sources of evidence (e.g. Kerem *et al*[40]) are not discussed within the Forest submission.

Re-analysis of the Forest model by the Assessment Group

This section presents some simple re-analyses of the Forest model to demonstrate the impact of some of the biases detailed above. These analyses are presented as detailed in Table 32 for both the 1-year and 2-year mortality models.

Table 32: Re-analysis of the Forest model

Revised scenario	Description of model amendment		
Forest base case	Lifetime benefits of 24 weeks treatment	No drug acquisition costs included	1-year horizon for exacerbations
Scenario 1		Colistimethate sodium DPI priced at £9.11 per dose†	24 week horizon for exacerbations
Scenario 2		Colistimethate sodium DPI priced at £10.60 per dose†	
Scenario 3		Colistimethate sodium DPI priced at [redacted] per dose†	
Scenario 4		Colistimethate sodium DPI priced at £19.64 per dose†	
Scenario 5		Colistimethate sodium DPI priced at £21.20 per dose†	
Scenario 6		Colistimethate sodium DPI priced at £[redacted] per dose†	

†24 weeks treatment (365 treatment days/year)

The results of these alternative analyses are presented in Table 33. It should be noted that this reanalysis does not fully resolve the problems regarding the model time horizon, the health impact of adverse events, or the considerable uncertainty surrounding the estimation of QALY benefits for colistimethate sodium DPI. The results of the analysis suggest that the price of colistimethate sodium DPI and the time horizon for costs are highly sensitive within the analysis. The re-analysis suggests that if colistimethate sodium DPI is priced lower than nebulised tobramycin per annum, it may dominate due to modelled cost savings associated with avoided exacerbations and the estimated incremental QALY gains. For the range of higher prices per dose administered, the incremental cost-effectiveness of colistimethate sodium DPI versus nebulised tobramycin is in the range £42,872 to £485,550 per QALY gained depending on assumptions regarding time horizon, mortality estimates and drug acquisition costs.

Table 33: Results of revised analysis using the Forest model

Revised scenario	Incremental results for colistimethate sodium DPI versus nebulised tobramycin		
	Incremental QALYs gained	Incremental costs	Incremental cost per QALY gained
1-year mortality prediction model results			
Forest base case[64]	[redacted]	-£1,050.49	**Dominating**
Scenario 1 (£9.11/dose)	[redacted]	-£987.20	**Dominating**
Scenario 2 (£10.60/dose)	[redacted]	-£484.84	**Dominating**
Scenario 3 [redacted]	[redacted]	£1,329.05	**£42,872.44**
Scenario 4 (£19.64/dose)	[redacted]	£2,563.03	**£82,678.35**
Scenario 5 (£21.20/dose)	[redacted]	£3,088.99	**£99,644.80**
Scenario 6 (£[redacted])	[redacted]	£9,188.10	**£296,390.38**
2-year mortality prediction model results			
Forest base case[64]	[redacted]	-£1,050.49	**Dominating**
Scenario 1 (£9.11/dose)	[redacted]	-£2,138.94	**Dominating**
Scenario 2 (£10.60/dose)	[redacted]	-£1,050.49	**Dominating**
Scenario 3 [redacted]	[redacted]	£2,879.60	**£70,234.12**
Scenario 4 (£19.64/dose)	[redacted]	£5,553.23	**£135,444.61**
Scenario 5 (£21.20/dose)	[redacted]	£6,692.81	**£163,239.24**
Scenario 6 (£[redacted]/dose)	[redacted]	£19,907.55	**£485,550.09**

6.2.3 Discussion of available economic evidence

There is clearly considerable uncertainty surrounding the cost-effectiveness of alternative antibiotics for the treatment of *Pseudomonas aeruginosa* in patients with CF. The review of published economic evaluations did not identify any directly relevant studies which report on the cost-effectiveness of colistimethate sodium DPI or tobramycin DPI compared to current standard treatments.

The Novartis submission did not report any economic results for tobramycin DPI within their submission.

Forest did present a simple economic analysis, however this is subject to a number of methodological weaknesses, as detailed above. The majority of these weaknesses cannot be easily rectified given Forest's adopted model structure. One of the most significant problems within the Forest model relates to the direct contradiction between the lifetime context of care and the apparently short time horizon adopted. As a consequence it is unclear how the results of the net benefit analysis should be interpreted. There is no obvious reason why colistimethate sodium DPI would be stopped after 24 weeks, yet Forest's economic analysis appears to imply the use of a "stopping rule" at this point. This reflects the limitations of the trial evidence and the methods for estimating QALYs rather than what would be considered reasonable clinical practice. The disparity between the time horizon for clinical benefit, the cost of managing exacerbations and drug costs mean that it is impossible to interpret Forest's economic analysis in a meaningful way. Further, the methods for translating a lower level of FEV_1 benefit for colistimethate sodium DPI into a greater number of QALYs than nebulised tobramycin remains counter-intuitive. Given Forest's model structure, if the selected price of colistimethate sodium DPI is priced higher than nebulised tobramycin, the cost per QALY gained for colistimethate sodium DPI versus nebulised tobramycin is expected to be in the range £42,872 to £485,550.

The next section discusses the difficulties in undertaking a robust economic evaluation of colistimethate sodium DPI and tobramycin DPI in order to justify the modelling approach adopted by the Assessment Group and to highlight the uncertainties surrounding the results of the *de novo* analysis.

6.3 Methodological issues surrounding the economic evaluation of CF treatments

Undertaking a robust economic evaluation of alternative treatments for chronic *Pseudomonas aeruginosa* in patients with CF represents a considerable challenge. There are a number of methodological issues which make such an evaluation difficult and, in turn, this leads to considerable uncertainty in the cost-effectiveness of colistimethate sodium DPI and tobramycin DPI. The most prominent of these are: (i) the absence of any direct comparative evidence of the impact of either colistimethate sodium DPI or tobramycin DPI upon HRQoL; (ii) the use of a short time horizon within the pivotal trials of colistimethate sodium DPI and tobramycin DPI; (iii) the questionable validity of relationships between the available intermediate endpoints and final outcomes, and; (iv) the limited availability of evidence on clinical outcome measures for all treatments relevant to the decision problem. These issues and their implications for the health economic analysis are briefly discussed below.

6.3.1 Absence of any direct evidence of the impact of treatment upon HRQoL

Within the pivotal trials of colistimethate sodium and tobramycin DPI, HRQoL was not directly assessed using a preference-based health utility instrument. As such, it is not possible to directly estimate health utilities for each competing treatment option from these sources. Whilst Forest reported a mapping exercise to translate the CFQ-R to the EQ-5D,[92] the resulting estimates of health utility were not differentiated by treatment; instead a common mean value was applied to both treatments. If it is plausible that DPI treatment influences quality of life, the only means of quantifying this is by assuming some relationship between other clinical endpoints measured within the clinical trials and their impact upon HRQoL.

6.3.2 The use of a short time horizon within the pivotal trials of colistimethate sodium DPI and tobramycin DPI

Research recommendations from the EMA CHMP state that for interventions which are intended to slow or stop pulmonary disease progression, a 12-month FEV_1 endpoint should be used.[1] Whilst this 12-month endpoint would represent only the impact of treatment within a limited proportion of a patient's lifetime, neither pivotal trial of colistimethate sodium DPI or tobramycin DPI met this criterion, as both trials were less than 6-months in duration. The adoption of such short study durations has three negative consequences: (1) the trial durations are insufficient to assess any treatment benefits in terms of potential mortality reduction; (2) uncertainties surrounding the relevance of intermediate outcome measures such as FEV_1% predicted and final endpoints such as mortality are inflated by the absence of long-term evidence, and; (3) evidence surrounding long-term adverse events and treatment compliance is absent.

Owing to the short study durations adopted within the EAGER trial and the COLO/DPI/02/06 trial, mortality estimates are subject to very high levels of censoring (approximately 99% in each trial). Within the COL/DPI/02/06 trial, no patients died in the colistimethate sodium DPI arm whilst two patients died within the tobramycin arm.[68] Within the EAGER trial,[63] three patients died in the tobramycin DPI arm whereas no patients died within the nebulised tobramycin arm. These event numbers are insufficient for comparative survival extrapolation over a lifetime horizon.

6.3.3 Validity of relationships between intermediate and final endpoints

As a consequence of the absence of direct comparative evidence of HRQoL impacts and the limited evidence of survival benefits, the economic analysis of treatments for *Pseudomonas aeruginosa* requires some proposition and quantification of relationships between other clinical endpoints which may impact upon HRQoL and/or survival. In order for an intermediate endpoint to be useful, it must represent an endpoint that can substitute for and be predictive of a final patient relevant clinical

outcome.[101] Judgments about the credibility and validity of such relationships may be made on the basis of a range of evidence and may be interpreted within a hierarchy, as suggested by Taylor and Elston[101] (see Table 34).

Table 34: Framework for the validation of surrogate outcomes (from Taylor and Elston[101])

Hierarchical level	Evidence requirement	Source of evidence
Level 1	Biological plausibility of relationship between surrogate outcome and final patient-related outcome	Pathophysiological studies and understanding of disease process
Level 2	Consistent association between surrogate outcome and final patient-related outcome	Epidemiological (observational) studies demonstrating an association between the surrogate outcome and final patient-related outcome
Level 3	Treatment effects on the surrogate correspond to effects on the patient-related outcome	Clinical trials showing that change in surrogate outcome with treatment is associated with a commensurate change in the final patient-related outcome
To fulfil the evidence requirement for level 2 or level 3 necessitates the fulfilment of the requirements of the previous levels *Based on ICH-9 guidelines[102] and the US NIH Biomarkers Definitions Working Group[103]*		

Potential intermediate outcome measures include one or more of the following: FEV_1% predicted, exacerbation rates and the incidence and duration of other adverse events.[1] The plausibility and methodological problems of using these relationships to estimate the QALY gains associated with DPI treatment are considered below.

6.3.3.1 Relationship between FEV_1% predicted and HRQoL

Systematic searches were undertaken by the Assessment Group to identify any studies which attempted to quantify the relationship between FEV_1% predicted and HRQoL in patients with CF (see Appendix 7). Searches were undertaken across Medline, Medline in Process, Embase, BIOSIS, Citation Indexes and Cochrane Library. The searches identified just 12 studies of which only one was relevant to CF.[104] Additional studies were identified by searching for evidence relating to specific symptoms associated with CF and its treatment (see Appendix 6), undertaking *ad hoc* searches and by handsearching the manufacturers' submissions. Four studies were identified which explored the potential relationship between health utility and a range of levels of FEV_1% predicted.[104-107] Three of these studies were undertaken in patients with CF,[104,106,107] whilst the fourth was undertaken in patients with chronic obstructive pulmonary disease (COPD).[105]

Johnson *et al*[104] report a prospective observational study assessing the relationship between a number of clinical variables including FEV_1, age, gender, BMI, and hospital admission, with SF-36 and EQ-

5D quality of life in patients with CF. Fifty nine patients were assessed at baseline and HRQoL was reassessed 1-year later by postal questionnaire. The observed mean change in EQ-5D index after 1-year was reported to be 0.0 (95% c.i. -0.069 to 0.069). The authors also reported the use of a multivariate ordinary least squares (OLS) regression model to examine associations between the clinical variables and EQ-5D index scores. The results of this analysis suggested a statistically significant association between FEV_1 and EQ-5D utility, however the β coefficient for EQ-5D from the regression was reported to be 0.000 (standard error = 0.001) which indicates that this relationship is unlikely to be clinically meaningful.

Bradley *et al*[107] report a health utility study in patients aged 16 years and older diagnosed with CF *Pseudomonas aeruginosa* infections who were taking nebulised or oral antibiotics. Study subjects were recruited from specialist clinics across the UK. The results of this analysis were available as a conference poster[107] and additional analyses were presented within the Novartis submission.[58] Patients included in the study performed spirometry tests for FEV_1 and completed the CFQ-R and the EQ-5D questionnaire. Mean EQ-5D utility across three FEV_1 strata (70-99%, 40-79% and <40%) was presented within the Novartis submission.[58] In addition, this study reports utility decrements associated with minor exacerbations and major exacerbations. EQ-5D values reported within this study are summarised in Table 35. It is worth noting that the mean EQ-5D score for FEV_1<40% reported by Bradley *et al*[107] is higher than the mean cohort value produced by Forest's mapping exercise.[92]

Table 35: Health utility estimates reported by Bradley *et al* (from Novartis submission[58]†

FEV_1 stratum / exacerbation severity	Mean EQ-5D (Standard deviation)
>70% predicted	0.864 (0.165)
40-79% predicted	0.81 (0.216)
<40% predicted	0.641 (0.319)
Major exacerbation	0.174 decrement (0.341)
Minor exacerbation	0.015 decrement (0.048)

†*standard deviations shown in parentheses*

Yi *et al*[106] reported a health utility study in adolescents with CF in order to assess how health status and clinical variables influence their health values. Sixty five adolescents between the ages of 12 and 18 years completed Child Health Questionnaire (CHQ), the Health Utilities Index Mark 2 (HUI-2) questionnaire in addition to valuing their own current health state using time trade off (TTO), standard gamble (SG) and visual analogue scale (VAS) elicitation methods. HRQoL estimates were presented according to four strata of FEV_1 function (>79%, 60-79%, 40-59% and <40%). The results for TTO, SG and HUI-2 suggested only very small differences in health utility between the three strata of FEV_1>40%. Across these higher FEV_1 strata there was no consistent relationship between worsening

lung function and health utility for TTO, SG or HUI-2. In contrast, the VAS scores, which do not involve any form of trade-off between health states, did suggest a consistent decline in health utility with decreasing FEV_1. For all instruments, the <40% strata was associated with a lower level of HRQoL than other FEV_1 states; this difference was most pronounced for the VAS but considerably less so for the preference-based methods. Health utility values estimated within this study are summarised in Table 36.

Table 36: Health utility estimates reported by Yi *et al*[106]†

FEV_1 stratum	VAS	TTO	SG	HUI-2
>79% predicted	0.85 (0.14)	0.96 (0.08)	0.92 (0.16)	0.82 (0.15)
60-79% predicted	0.79 (0.12)	0.97 (0.06)	0.96 (0.08)	0.85 (0.15)
40-59% predicted	0.71 (0.12)	0.98 (0.03)	0.96 (0.04)	0.83 (0.19)
<40% predicted	0.47 (0.22)	0.91 (0.09)	0.80 (0.21)	0.80 (0.16)

†*standard deviations shown in parentheses*

Stahl *et al*[105] undertook a study to assess the relationship between disease severity and HRQoL in patients with COPD. One hundred and sixty eight patients completed the SF-36, the St George's Respiratory Questionnaire and the EQ-5D. EQ-5D results were stratified according to FEV_1 level. This study suggests that EQ-5D utility declines with worsening lung function. Health utility values estimated within this study are summarised in Table 37.

Table 37: Health utility estimates reported by Stahl *et al*[105]†

FEV_1 stratum	EQ-5D (GOLD criteria)	EQ-5D (BTS criteria)
>79% predicted	0.84 (0.15)	0.84 (0.15)
60-79% predicted	0.73 (0.23)	0.74 (0.21)
40-59% predicted	0.74 (0.25)	0.72 (0.28)
<40% predicted	0.52 (0.26)	0.63 (0.25)

†*standard deviations shown in parentheses*

In summary, only one study identified attempted to examine whether a statistical association exists between FEV_1 and EQ-5D utility.[104] This 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 FEV_1, at least within the range of scores assessed within Johnson *et al*, does not represent a good discriminatory indicator of HRQoL. The remaining three studies[105-107] are inconsistent with respect to whether a relationship exists between FEV_1 and HRQoL. The results of two of these studies[105,107] appear to support the hypothesis that HRQoL is markedly lower for FEV_1<40%, however this appears to be influenced considerably by the method of preference elicitation.[106] The only EQ-5D study undertaken using CF patients[107] does not suggest a clear distinction in health status for FEV_1>40%.

Using the taxonomy presented by Taylor and Elston,[101] it is reasonable to argue that there is at best Level 1 evidence to support the hypothesis that FEV_1 represents a useful surrogate for HRQoL.

Whilst the evidence does not support a consistent decline in HRQoL with decreasing FEV_1, there is consistent evidence to support the theory that HRQoL is lower for lower FEV_1 strata (<40%).

6.3.3.2 Relationship between FEV_1% predicted and survival

Systematic searches were also undertaken to identify any studies which reported the use of statistical models through which to translate FEV_1 to survival/mortality in patients with CF. Searches were undertaken in Medline, Medline In-Process and Embase in January 2012. The search strategy is shown in Appendix 7.

A total of 625 citations were identified by the searches, of which 21 studies were examined in further detail. Of these, fourteen studies presented regression analyses which included either absolute FEV_1 levels or decline in FEV_1 as an independent variable and either survival or mortality as a dependent variable. The findings of these included studies are summarised in Table 38.

Of the fourteen studies identified by the searches, all considered a large number of other clinical variables alongside FEV_1. Most of the studies adopted a Cox proportional hazards model approach, although some used logistic regression or other statistical analyses. Few studies justified why particular covariates had been included in the regression analyses, although in a minority of cases a stepwise approach was employed to identify those covariates which significantly predicted survival for inclusion in the model. Some authors commented that predicting survival on the basis of FEV_1 alone remains controversial.[108] Within all of these studies, other clinical variables were also found to be statistically significant predictors of survival. Several studies suggested that the rate of decline in FEV_1, rather than absolute FEV_1, is likely to be a better predictor of survival, however the regression analyses were not consistent in this finding. It should be noted that decline in FEV_1 is also problematic due to the fluctuating nature of FEV_1 measurements. Irrespective of how lung function was characterised within individual studies, there was a broadly consistent finding across the studies that other clinical variables are also important in predicting survival in CF patients. In some analyses,[108,109] FEV_1 was not actually a statistically significant predictor of survival at all.

Table 38: Summary of studies presenting regression models between FEV_1 and mortality in CF

Study	Study type	Population	Model form (description of FEV_1 covariate)	Summary of study findings
Simmonds *et al* 2010[110]	Case control (78 cases, 152 controls)	Cases (long-term survivors) were patients with complete records who had reached 40 years of age without transplantation by December 31, 2004. Controls were selected from all patients with complete records who had died before 30 years of age or required transplantation at 30 years of age by December 31, 2004.	Probability-weighted logistic regression to predict survival up to 40 years (absolute FEV_1).	A number of factors resulted in increased probabilities of survival including BMI, FEV_1, FVC at transfer to the adult clinic and exclusive use of oral antibiotics. Factors resulting in decreased probabilities of survival included *Pseudomonas aeruginosa* acquisition, or pneumothorax before transfer to the adult clinic and referral from a paediatric clinic in a deprived area.
Ketchell *et al* 2009[108]	Retrospective case review (121 patients)	All adult patients with end-stage CF who died whilst on the Royal Brompton and Harefield Hospital lung transplant waiting list between July 1988 and June 2004.	Cox proportional hazards model (absolute FEV_1)	Significant association found between survival and FVC (p=0.027), but not FEV_1 (p=0.08) or any other parameter in patients performing the 6 minute walk test.
Courtney *et al* 2007[111]	Longitudinal analysis (183 patients)	Adult patients from Belfast and Cork were studied from 1995 to 2005. The patients studied were age 17 years or older in 2000.	Cox proportional hazards model (absolute FEV_1)	The patients who died during the study period had a significantly lower mean (sd) FEV_1% predicted in 1995 when compared to those who remained alive, 41.5 (15.2)% compared to 69.8 (23.2)%, respectively, p<0.001.
Elaffi *et al* 2004[109]	Retrospective case review (92 patients)	All patients admitted with severe pulmonary exacerbations to Pulmonary Department or ICU between January 1, 1997, and June 30, 2001,	Cox proportional hazards model (absolute FEV_1 and slope of FEV_1 decline).	Clinical characteristics before admission found to influence 1-year mortality were prior colonization with *B. cepacia* and a rapid decline in FEV_1 (FEV_1 was significant only in the univariate analysis). Absolute FEV_1 values were not significantly associated with probability of death.
Schlucter *et*	Model	Population-based sample of	Random effects linear	Separate results are presented by age group. The relationship

Study	Study type	Population	Model form (description of FEV_1 covariate)	Summary of study findings
al 2002[112]	development study with validation against registry data (188 patients)	188 patients with the delta-F homozygous genotype for CF born after 1 January 1965, followed at the CF Center at Rainbow Babies and Children's Hospital, Cleveland, Ohio.	model for FEV_1 and Gaussian model for age at death. Parameters estimated using Maximum Likelihood Estimation (MLE) methods (absolute FEV_1 and slope of FEV_1 decline).	between FEV_1 and age at death appears to be non-linear.
Augarten *et al* 2001[113]	Retrospective case review (40 patients)	Patients with FEV_1 % predicted <30% and were followed-up for at least 3 years between 1985 and 1997	Kaplan Meier product method with log rank test between strata (FEV_1 decline).	Rate of change in FEV_1 values found to be good predictor of survival. Patients whose slope was above the median (–2.33) were found to have a significantly superior prognosis when compared to patients with a slope below the median (p=0.04).
Milla *et al* 1998[114]	Retrospective case review (61 patients)	Patients who consistently had an FEV <30%	Cox proportional hazards model (rate of change in FEV_1).	Of the covariates included in the Cox model, only the rate of decline in FEV_1 was reported to be a significant predictor of death (p=0.0001).
Hayllar *et al* 1997[115]	Prospective case analysis with split sample validation (403 patients)	All patients with CF seen in the Royal Brompton Hospital between 1969 and 1987.	Cox proportional hazards model (absolute FEV_1)	Percentage predicted FEV, percentage predicted FVC, height, white blood cell count, hepatomegaly, serum concentrations of albumin, alkaline phosphatase reported to be significantly associated with survival (p<0.001).
Kerem *et al* 1992[40]	Cohort study (673 patients)	Patients with CF followed up at the Toronto Hospital for Sick Children between 1977 and 1989.	Cox proportional hazards model (absolute FEV_1)	All clinical covariates (FEV_1, FVC, PaO_2, $PaCO_2$ and weight for height) except age were significantly associated with 1-year and 2-year mortality rates.
Liou *et al* 2001[42]	Retrospective analysis of registry data (11,630 patients)	CF patients within the US CF Foundation Patient Registry who were alive on January 1, 1993, and for whom follow-up data were available through December 31, 1997, were	Cox proportional hazards model (absolute FEV_1 and rate of decline in FEV_1)	FEV_1 slope was not statistically significant and was therefore excluded from the predictive model. Absolute FEV_1 was significant and was included in the final model. The best multiple logistic regression model included nine variables with one interaction (age, gender, FEV_1, weight for age score, pancreatic sufficiency, diabetes mellitus, *Staphylococcus aureus*, *Burkerholderia cepacia*, number of acute exacerbations, and number of acute exacerbations *x*

Study	Study type	Population	Model form (description of FEV_1 covariate)	Summary of study findings
		included in the study.		*Burkerholderia cepacia*).
Aurora *et al* 2000[116]	Retrospective case review (181 patients)	Subjects consisted of children with severe CF lung disease referred for transplantation assessment between 1988 and 1998.	Cox proportional hazards model (absolute FEV_1)	Univariate Cox model suggests that SaO_2 min, FEV_1, FVC, distance, AAHR, albumin levels, number of courses of IV antibiotics administered, and blood haemoglobin concentrations were significantly associated with survival.
Mayer-Hamblett *et al* 2002[117]	Analysis of registry data (14,572 patients)	Patients in the Cystic Fibrosis Foundation National Patient Registry who were 6 years of age or older in 1996	Multiple logistic regression (absolute and slope of decline considered)	Significant predictors of mortality in the univariate analyses included number of hospitalisations for acute exacerbations, number of courses of home intravenous antibiotics, respiratory colonisation with *B. cepacia*, FEV_1% predicted, height percentile and age. Multiple logistic regression, each liter increase in FEV_1 significantly decreased the odds of dying within 2 years by 9%.
Belkin *et al* 2005[118]	Retrospective cohort study (343 patients)	Adult and paediatric patients with CF listed for lung, heart-lung or heart-lung-liver transplant at the University of Pennsylvania Medical Centre	Cox regression (yearly rate of decline in FEV_1)	Univariate analyses suggest that FEV_1<30% was associated with a higher risk of death ($p<0.01$). Other significant variables included decrease in FEV_1 and FVC, hypercapnia, rise in $PaCO_2$, place of referral, and time of listing. Multivariate analyses suggested a significant interaction between FEV_1 and $PaCO_2$.
Henry *et al* 1992[18]	Cohort study (81 patients)	Children with CF who coughed up sputum daily	Cox proportional hazards model (absolute FEV_1)	Stepwise survival analysis suggested that FEV_1 and younger age were significantly associated with poorer survival ($p<0.05$)

Of the identified studies, only one reported summary data on survival stratified by FEV_1 group (albeit in an unadjusted manner[40]). However, the prognostic value of this study has been criticised elsewhere. In particular, George *et al*,[119] highlights that a number of clinical developments in the management of CF over the past 20 years may make the findings of the Kerem *et al* study unreliable. These factors include the drive towards intensive nutritional management in CF, the development of new treatments, the increased use of non-invasive ventilation in those with respiratory failure and the push towards multidisciplinary care.[119] Other commentators were further critical of using absolute FEV_1 levels due to measurement error and fluctuations in FEV_1 values over time.

On the basis of this review, it is reasonable to suggest that there exists Level 1/2 evidence to support the hypothesis that a change in FEV_1 directly leads to a change in mortality, and therefore FEV_1 alone is unlikely to represent a valid *independent* surrogate for patient survival. As such, the assumption of a direct linear relationship between FEV_1 alone and mortality risk, without adjustment for other confounding factors, as assumed within the Forest analysis, should be approached with considerable caution.

6.3.3.3 Relationship between exacerbation rates and other incidence of adverse events and HRQoL/survival

It is clinically plausible that the incidence of pulmonary exacerbation and other adverse events could have meaningful impacts upon HRQoL. If HRQoL had been assessed directly within the trials, one may expect such effects to be directly captured. However, without the use of preference-based measures such as the EQ-5D, the inclusion of such effects becomes reliant on (a) the availability of external valuation studies which assess the impact of <u>all</u> potential adverse events and (b) the adequate reporting of the number of adverse events experienced within clinical study publications and reports. It should also be noted that many adverse events associated with CF and its treatment do not occur in isolation but instead may manifest simultaneously. Ignoring this potential overlap would likely skew the results of an economic analysis and may lead to overestimating the benefits associated with those technologies with more favourable adverse event profiles.

Systematic searches were undertaken to identify studies which report EQ-5D utility estimates with and without specific adverse events associated with a range of adverse events associated with CF treatments (see Table 39). Searches were undertaken across Medline, Medline in Process, EMBASE, BIOSIS, Citation Indexes and the Cochrane Library. The search strategy is shown in Appendix 6.

Table 39: Symptoms included in the EQ-5D search

Respiratory	Nasal/Mouth/Throat	Other
Cough Lung disorder/exacerbation [redacted] Dyspnoea [redacted] Haemoptysis [redacted] Rales/respiratory noises Respiratory tract infection Wheezing Chest discomfort [redacted] Pulmonary function test decreased Pulmonary congestion/blockage	Oropharyngeal pain (mouth and pharynx pain) Other pain [redacted] Dysphonia Nasal congestion/obstruction Rhinorrhea/runny nose Sinusitis [redacted]	Pyrexia/fever Hyperthermia [redacted] Headache Fatigue Nausea Vomiting [redacted]

A total of 325 studies were identified by the searches. One additional study was identified by handsearching the Novartis submission.[58] However, of these only five studies[107,120-123] reported sufficient information through which to directly estimate a utility decrement for specific symptoms (note this figure excludes those studies detailed above which consider report EQ-5D values by FEV_1 level as discussed above). Undertaking an economic evaluation which attempts to quantify the HRQoL impact of a selection of adverse events but ignores others would inevitably result in bias, however the direction of such bias would be unclear. Given the current availability of evidence relating adverse events to EQ-5D utility, this approach should be avoided.

6.3.4 Limited availability of evidence on clinical outcome measures all relevant treatments

A comprehensive economic analysis of CF treatments would synthesise all relevant evidence on treatment effects within a meta-analytic framework.[99] However, from the perspective of health economic evaluation, this type of evidence synthesis would only be useful if a plausible and quantifiable relationship exists between FEV_1, or other intermediate clinical endpoints, and HRQoL and/or survival. The majority of clinical trials of colistimethate sodium and tobramycin (in either dry powder or nebulised form) report mean change in FEV_1 within the trial cohorts, and very few report FEV_1 outcomes beyond 4 weeks. Given the concerns regarding the validity of the relationships between FEV_1 and mortality and HRQoL outlined above, this would *not* be useful as it would require that the translated relationship has interval properties (e.g. *x*% change in FEV_1 leads to *y*% change in HRQoL). Further, the systematic reviews presented above suggest that this type of relationship is unlikely to hold; the value of a network meta-analysis based on summary data is therefore questionable in this context.

6.4 *De novo* independent economic analysis

This section presents the methods and results of the *de novo* economic analysis undertaken by the Assessment Group.

6.4.1 Scope of the economic analysis

A number of potential options are relevant to the economic analysis of antibiotic treatments for *Pseudomonas aeruginosa*. These include:

(1) Colistimethate sodium DPI (Colobreathe®)

(2) Tobramycin DPI (TOBIPodhaler®)

(3) Colistimethate sodium nebulised (Promixin® or Colistin®)

(4) Tobramycin nebulised (Bramitob® or TOBI®)

(5) Aztreonam (Cayston®)

Some patients may switch between tobramycin and colistimethate sodium at some point in their lives. This may be happen due to apparent treatment failure on the current drug, or may be part of a planned treatment regimen whereby colistimethate sodium and tobramycin are alternated every 28-days.

The Assessment Group developed a *de novo* health economic model to assess the cost-effectiveness of two competing treatment options (1) colistimethate sodium DPI versus (2) nebulised tobramycin for the treatment of chronic *Pseudomonas aeruginosa* in patients with CF. A number of potentially relevant interventions and comparators were therefore excluded from the analysis (see Table 40). In addition, a crude threshold analysis is presented to compare tobramycin DPI versus nebulised tobramycin.

Table 40: Reasons for inclusion/exclusion of treatments

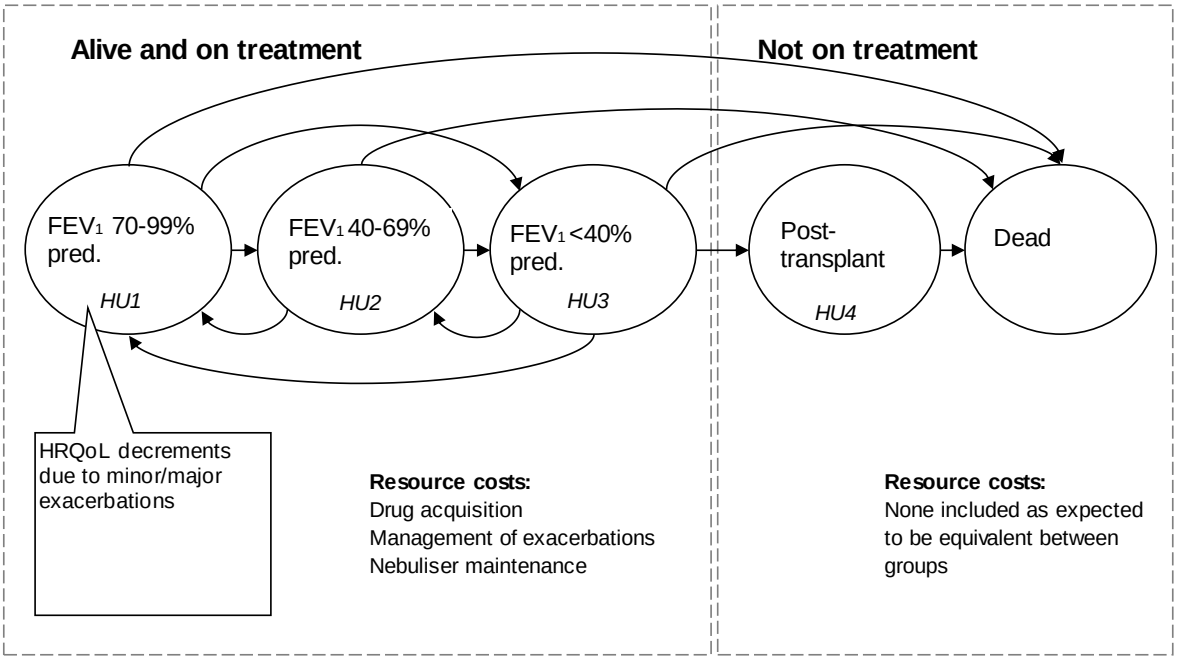
Treatment option	Reasons for inclusion/exclusion
Options included in the economic analysis	
Colistimethate sodium DPI	Patient-level data on FEV_1 from COL/DPI/02/06 available (data held on file)
Tobramycin nebulised	
Options excluded from the economic analysis	
Tobramycin DPI	Patient-level FEV_1 data were not available, the price of tobramycin DPI was not determined or suggested until February 2012. The implied incremental QALY requirement given the drug's incremental cost is considered as part of a threshold analysis.
Colistimethate sodium nebulised	No relevant studies included in the evidence network, patient-level data not available.
Aztreonam	Predominantly used third-line and not currently recommended for use in published UK consensus guidelines.[4]
Treatment sequences (switching)	Lack of evidence of clinical efficacy and safety.

6.4.2 Model structure

The model estimates the expected costs and QALY gains associated with colistimethate sodium DPI versus nebulised tobramycin. The analysis adopts an NHS perspective over a lifetime horizon. The primary economic outcome measure for the analysis is the incremental cost per QALY gained. All costs and health outcomes within the model were discounted using the standard approach at a rate of 3.5%. Costs were valued at 2011 prices.

The model takes the form of a state transition model to estimate transitions between three FEV_1 strata ([1] FEV_1 70-99% [2] FEV_1 40-69% and [3] FEV_1 <40%). 24-week transition probabilities are estimated based on those observed within COL/DPI/02/06. Different levels of HRQoL are assumed for each health state. Treatment duration, which is assumed to be directly related to survival duration, is assumed to be exactly equivalent between the competing treatment options. During each cycle, patients may remain in their current FEV_1 state, transit to an improved or worsened FEV_1 state or die. Patients with FEV_1<40% may undergo lung transplantation and do not subsequently receive further treatment with colistimethate sodium DPI or tobramycin; other treatments received by these patients are assumed to be identical irrespective of previous antibiotic treatments received. Additional HRQoL decrements are applied for minor and major exacerbations based on treatment-specific rates and data relating to the mean time receiving i.v. antibiotics. Total QALYs are calculated as the total sojourn time in each health state weighted by the respective utility for that health state, less any QALY losses resulting from exacerbations. Costs within each treatment group include drug acquisition costs and the costs of managing exacerbations (either in hospital or at home). Potential cost savings associated with reduced maintenance of nebulisers are also included in the economic analysis. Costs associated with follow-up and concomitant medications are assumed to be related only to treatment time and are therefore assumed to be equivalent between treatment groups. A conceptual form of the implemented health economic model is presented in Figure 11.

Figure 11: Conceptual form of the implemented economic model



Given the considerable uncertainty surrounding the extrapolation of the 24-week efficacy data to a lifetime horizon, two separate analyses are presented:

(1) A Reference Case analysis based on FEV_1 extrapolation over a lifetime horizon;

(2) A "within-trial" analysis which does not include any extrapolation.

Separate analyses are presented for each of the six prices presented in Table 26.

6.4.3 Evidence used to inform the model parameters

The sources of evidence used to inform the model parameters are detailed below. For the most part, the model parameters have been informed directly using data from the COLO/DPI/02/06 trial; these have been augmented using other data from external sources. A summary of model parameter values and distributions used in the base case analysis is presented in Table 41.

Table 41: Model parameters

Parameter description	Distribution	Param1	Param 2	Mean	Source
Management variables					
Initial cohort age	N/a	-	-	21	COLO/DPI/02/06[64]
Discount rate – QALYs	N/a	-	-	0.035	NICE Methods Guide[91]
Discount rate - costs	N/a	-	-	0.035	
Survival parameters					
Weibull log lambda	Multivariate normal	-12.33	Var log λ=0.004, var γ=0.0041, covar=0.003	-12.33	Based on Dodge *et al*[21]
Weibull gamma		3.34		3.34	
Transplant parameters					
Prob transplant during 24-wks	Beta	7.89	858.17	0.0092	CF Registry 2010[7]
Initial distribution of patients					
FEV60-79%	Dirichlet	[redacted]	[redacted]	0.09	COLO/DPI/02/06 (pooled arms)
FEV40-59%	Dirichlet	[redacted]	[redacted]	0.65	
FEV<40%	Dirichlet	[redacted]	[redacted]	0.26	
Transition probabilities between FEV_1 strata					
FEV70-99%→FEV70-99% (Coli)	Dirichlet	[redacted]	[redacted]	0.63	COLO/DPI/02/06 (individual treatment arms)
FEV70-99%→FEV40-69% (Coli)	Dirichlet	[redacted]	[redacted]	0.32	
FEV70-99%→FEV<40% (Coli)	Dirichlet	[redacted]	[redacted]	0.05	
FEV40-69%→FEV70-99% (Coli)	Dirichlet	[redacted]	[redacted]	0.14	
FEV40-69%→FEV40-69% (Coli)	Dirichlet	[redacted]	[redacted]	0.71	
FEV40-69%→FEV<40% (Coli)	Dirichlet	[redacted]	[redacted]	0.15	
FEV<40%→FEV70-99% (Coli)	Dirichlet	[redacted]	[redacted]	0.02	
FEV<40%→FEV40-69% (Coli)	Dirichlet	[redacted]	[redacted]	0.17	
FEV<40%→FEV<40% (Coli)	Dirichlet	[redacted]	[redacted]	0.81	
FEV70-99%→FEV70-99% (Tobi)	Dirichlet	[redacted]	[redacted]	0.75	
FEV70-99%→FEV40-69% (Tobi)	Dirichlet	[redacted]	[redacted]	0.20	
FEV70-99%→FEV<40% (Tobi)	Dirichlet	[redacted]	[redacted]	0.05	
FEV40-69%→FEV70-99% (Tobi)	Dirichlet	[redacted]	[redacted]	0.15	
FEV40-69%→FEV40-69% (Tobi)	Dirichlet	[redacted]	[redacted]	0.75	
FEV40-69%→FEV<40% (Tobi)	Dirichlet	[redacted]	[redacted]	0.10	
FEV<40%→FEV70-99% (Tobi)	Dirichlet	[redacted]	[redacted]	0.02	
FEV<40%→FEV40-69% (Tobi)	Dirichlet	[redacted]	[redacted]	0.13	
FEV<40%→FEV<40% (Tobi)	Dirichlet	[redacted]	[redacted]	0.85	
Exacerbation rates					
Prob exacerbation (Tobi)	Beta	[redacted]	[redacted]	0.39	COLO/DPI/02/06 (CSR)[67]
Prob exacerbation (Coli)	Lognormal	[redacted]	[redacted]	0.38	
HRQoL parameters					
Disutility major exacerbation	Beta	0.17	0.08	0.1740	Bradley *et al*[107] / Novartis submission[58]
Disutility minor exacerbation	Beta	0.02	0.01	0.0150	
Utility >70% predicted	Beta	0.86	0.03	0.8640	
Utility 40-69% predicted	Beta	0.81	0.04	0.8100	
Utility <40% predicted	Beta	0.64	0.06	0.6400	
Prob. exacerbations is major	Beta	[redacted]	[redacted]	0.66	COLO/DPI/02/06 (CSR)[67]
Duration exacerbations (Coli)	Beta	[redacted]	[redacted]	0.0372	
Duration exacerbations (Tobi)	Beta	[redacted]	[redacted]	0.0394	
Utility post-transplant	Beta	[redacted]	[redacted]	0.8300	Anyanwu *et al*[124]
Cost parameters					
Cost per dose (Coli)	See Table 26 (price range = £9.11 to £[redacted])				Forest submission[64]
Cost per dose (Tobi)	n/a	£21.20	n/a	£21.20	BNF 62[59]
Cost minor exacerbation	Normal	£427.69	£10.98	£412.74	NHS Reference Costs 2010-2011[125]
Cost major exacerbation	Normal	£1,500.14	£33.06	£1,500.14	
Marginal nebuliser savings	Normal	£200.00	£10.00	£200.00	Personal communication†

† Diana Bilton, Consultant Physician / Honorary Senior Lecturer, Department of Respiratory Medicine, Royal Brompton Hospital; Mal Apter, UK and Ireland Sales and Marketing Manager, PARI EU

Patient survival

Mean survival for patients with cystic fibrosis was estimated using data reported by Dodge *et al*.[21] This study reported survival data up to the end of 2003 for all subjects with CF born in the UK in the period 1968-1992 collated via active enquiry of CF clinics and other hospital consultants. Survival curves are reported within this paper separately for males and females (see Figure 2). Data are not available on the number of patients at risk over time.

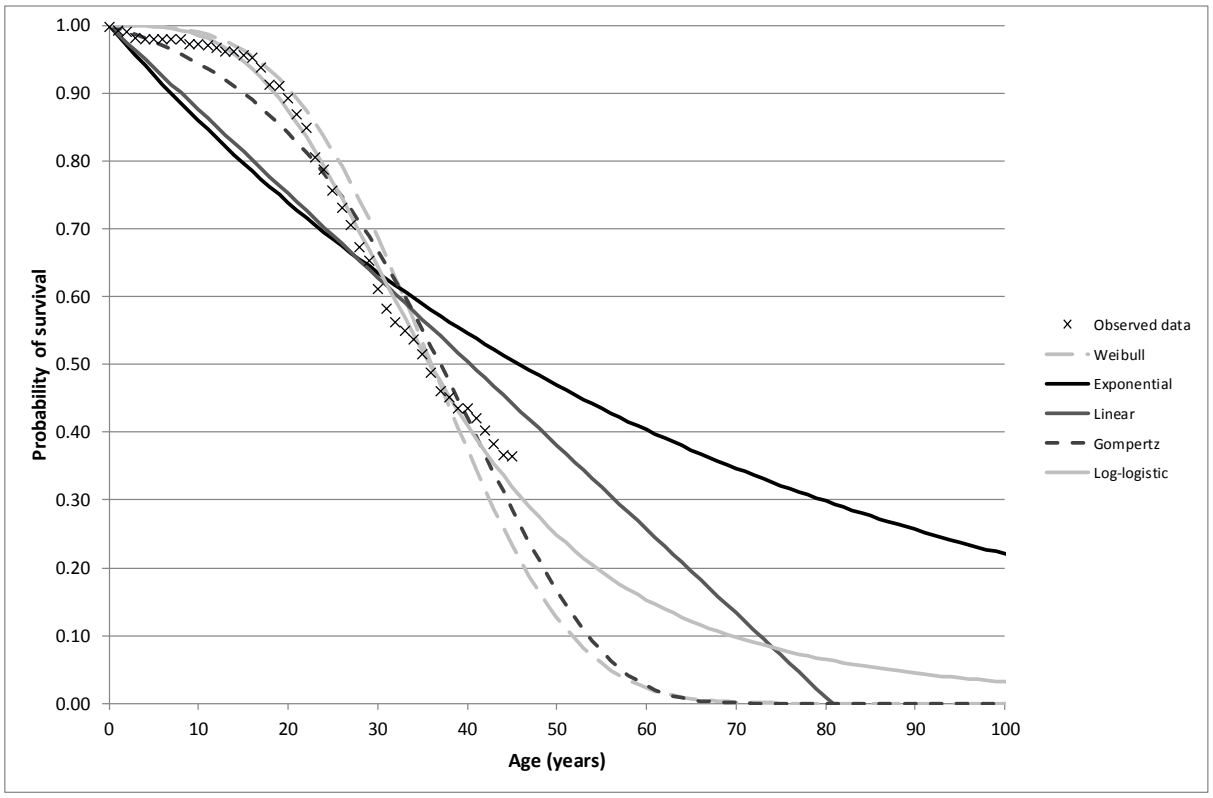
Engauge® digitising software (http://digitizer.sourceforge.net/) was used to replicate the published survival data from the graphs assuming a 50:50 split between males and females. Parametric survival curves were fitted to these data in order to estimate the mean durations of survival within the cohorts. Exponential, Weibull, linear, Gompertz and log-logistic curves were fitted to the empirical survival curve data. Each of these curves result in different distributions of survival. Information regarding the number of patients at risk and the number of events was not available from Dodge *et al* hence curves were fitted using Solver add-in within Microsoft Excel. Each curve was inspected visually with respect to how well the distribution fitted the observed data. The plausibility of the unobserved portion of each curve was considered by comparing the median survival of the fitted curve against the predicted median survival from the 2010 registry report (see Table 42).

Table 42: Median predicted survival from the CF Registry[7]

Year	2007	2008	2009	2010
Median predicted survival in years (95% CI)	35.2 (31.0, 42.6)	38.8 (34.2, 47.3)	34.4 (30.7, 37.0)	41.4 (36.8, 46.7)

Figure 12 presents the actual and predicted survival using a range of different curves. The Weibull and log-logistic models appear to provide the best fit to the data. Both of these curves provide a reasonable fit to the median survival as well as the overall distribution. However, the tail of the log-logistic distribution appears to overestimate survival during the later decades of life. Therefore, the Weibull curve was used in the base case economic analysis.

Figure 12: Long-term survival estimated from Dodge *et al*[21]



Uncertainty surrounding the two parameters of the Weibull survivor function was modelled using a multivariate normal distribution. As patient-level data were not available, the variance and covariance of the parameters was assumed rather than estimated. These were fitted against the maximum and minimum median predicted survival data from the CF Registry reports for the years 2007-2010.

FEV_1 transition probabilities

Transition probabilities between the health states were estimated directly using patient-level FEV_1 data from Visit 0 and Visit 6 within the COL/DPI/02/06 trial (the same data used by Forest to estimate mortality gains, see Section 6.2.2.2). A summary of the number of number of transitions from and to each FEV_1 stratum is presented in Tables 43 and 44.

Table 43: FEV_1 transitions at 24-weeks in the colistimethate sodium DPI group

	FEV_1 70-99%	FEV_1 40-69%	FEV_1 <40%	Total
FEV_1 70-99%	[redacted]	[redacted]	[redacted]	[redacted]
FEV_1 40-69%	[redacted]	[redacted]	[redacted]	[redacted]
FEV_1 <40%	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Table 44: FEV_1 transitions at 24-weeks in the tobramycin nebulised group

	FEV_1 70-99%	FEV_1 40-69%	FEV_1 <40%	Total
FEV_1 70-99%	[redacted]	[redacted]	[redacted]	[redacted]
FEV_1 40-69%	[redacted]	[redacted]	[redacted]	[redacted]
FEV_1 <40%	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Uncertainty surrounding these transition probabilities was characterised using Dirichlet distributions with minimally informative priors using the methods reported by Briggs *et al*.[126]

Initial FEV_1 distribution

As there are some slight imbalances in the baseline distribution of FEV_1 across the two treatment groups, the initial distribution of patients across the three FEV_1 strata within the model uses pooled estimates from both treatment groups (FEV_1 70-99%=33, FEV_1 40-69%=235, FEV_1 <40%=94). Uncertainty surrounding the initial distribution of patients is again characterised using a Dirichlet distribution with minimally informative priors.[126]

Exacerbation probabilities

Exacerbations were reported within the clinical study report for COL/DPI/02/06 as either protocol-defined or non-protocol-defined. The overall number of exacerbations (the sum of protocol-defined and non-protocol-defined exacerbations) was used to estimate the baseline risk of exacerbation for tobramycin nebulised group (75/191=0.39). The exacerbation rate in the colistimethate sodium DPI group was estimated to be [redacted].[67] As the CSR reports the number of patients with documented exacerbations, the assumption underlying these calculations is that only one exacerbation occurred per patient. It should be noted that including "overall" exacerbations rather than the protocol-defined values favours colistimethate sodium DPI. Uncertainty surrounding exacerbation probabilities was characterised using independent beta distributions.

Probability of undergoing lung transplantation

There is limited information concerning the lifetime probability that an individual with cystic fibrosis will undergo lung transplantation. The probability that a patient with FEV_1 <40% undergoes lung transplant during each cycle was estimated crudely based on data from the UK CF Registry and data from the US Cystic Fibrosis Foundation (http://www.cff.org/treatments/LungTransplantation/). The model assumes that the lifetime probability of undergoing lung transplantation is approximately 3%. The probability of undergoing transplantation within each model cycle was assumed to be stable over time and independent of patient age. Following transplantation, patients are assumed to no longer

require the use of antipseudomonal drugs. Uncertainty surrounding this probability was modelled using a beta distribution.

Health-related quality of life

The base case scenario uses the utilities for FEV_1 strata and disutilities for exacerbations reported by Bradley *et al,*[107] as shown in Table 35. The impact of minor/major exacerbations on HRQoL were modelled by applying a disutility based on the event rates reported within the COLO/DPI/02/06 Clinical Study Report[67] and minor/major utility decrements reported by Bradley *et al.*[107] Uncertainty surrounding these parameters was characterised using beta distributions. The duration of minor/major exacerbations was not available directly but was instead estimated by taking the mean duration of time on additional i.v. antibiotics as a proxy;[67] a slightly longer duration was assumed for the tobramycin group based on these data ([redacted][67]

For those patients who undergo lung transplantation, a health utility score of 0.83 was assumed until death;[124] further utility decrements relating to exacerbations are not applied to these patients. Uncertainty surrounding this utility score was characterised using a beta distribution.

Resources and costs

The model includes only the acquisition costs associated with colistimethate sodium DPI and nebulised tobramycin as well as the costs associated with managing exacerbations. The range of potential prices of colistimethate sodium DPI was sourced from the Forest submission to NICE[64] and from further correspondence with Forest. A price range of £9.11 to £[redacted] per dose was assumed over six pricing scenarios (see Table 26). Colistimethate sodium DPI was assumed to be used twice every day.

The acquisition cost of nebulised tobramycin was derived from BNF 62.[59] At the time of writing, the cost of 56 5-mL (300-mg) units costed £1187.20. Assuming a treatment regimen in which tobramycin is used for 28 days and then not used for the next 28 days, this corresponds to a price per dose of £21.20.

The model assumes that minor exacerbations incur less cost than major exacerbations, and that the latter require hospitalisation. The 2010-2011 NHS Reference Costs do not report costs specific to CF exacerbations. Instead, the costs of asthma complications were taken as a proxy. The reference cost for asthma with major complications without intubation (DZ15D, long stay) was assumed to reflect the cost of major exacerbations due to CF (mean=£1,500). The cost of asthma complications without intubation (DZ15E, short stay) was assumed to reflect the cost of minor exacerbations (mean=£403). Uncertainty surrounding the costs of exacerbations was characterised using normal distributions.

Costs associated with other treatments and hospital appointments for CF are assumed to be identical between the treatment groups.

The use of nebulisers for the delivery of antibiotic treatments is associated with fixed costs related to equipment purchase and ongoing costs associated with maintenance and replacement parts (e.g. aerosol heads and filters). Maintenance costs may be dependent on the number of drugs being nebulised. Some nebuliser devices are funded separately, whilst others are intended to be used for the administration of specific drugs, for example the I-neb AAD device is provided specifically for use with Promixin (although can be programmed to operate with certain other drugs) and its purchase price and maintenance costs are both covered by Profile Pharma. Purchasing arrangements for these devices in the UK are complex. Some nebulisers funded directly by NHS Trusts, whilst others may be funded by third-party donations from charitable organisations or pharmaceutical companies. Some nebuliser devices are currently privately funded by NHS patients. There is limited information available within the public domain with respect to the proportion of devices funded by the NHS and the uptake of specific devices or the true costs borne by the NHS. It appears likely that arrangements for funding for nebuliser purchasing and maintenance are also subject to geographical variability.

The potential implications of introducing DPIs on the costs of purchasing and maintaining nebulisers borne by the NHS are not straightforward. For some patient subgroups, the introduction of DPIs could lead to a reduction in the costs of nebulisers - whilst some patients with *Pseudomonas aeruginosa* may still require nebulisers, a shift to DPIs may lead to a reduction in the costs of nebuliser maintenance. This may or may not also result in some switching behaviour within Trusts to lower cost devices. For those patients who do not require nebulised bronchodilators or mucolytics, nebulisers may not be required at all, thereby leading to savings both on purchase costs and maintenance costs. However, the introduction of DPIs could also lead to some additional costs – for example replacing Promixin with colistimethate sodium DPI in patients that still require a nebuliser for the administration of other drugs would mean that a nebuliser device would have to be funded for the administration of bronchodilators and/or mucolytics where previously the costs were funded by other parties.

Given the uncertainty both with respect to the current costs of nebulisers and the implications of switching to DPIs, the base case health economic analysis includes a crude estimate of the maintenance costs of nebuliser maintenance. This is assumed to be £200 per year and covers the replacement of aerosol heads and filters; this estimate is based expert opinion (personal communication: Dr Diana Bilton, Consultant Physician / Honorary Senior Lecturer, Department of Respiratory Medicine, Royal Brompton Hospital) and information provided by PARI EU. A standard

error of £10 is assumed. It is likely that this represents an over-estimate of the actual cost savings and therefore favours colistimethate sodium DPI.

6.4.4 Key assumptions within the de novo economic analysis

The model makes the following key assumptions

(1) FEV_1 measurements are stable and not subject to measurement error
(2) HRQoL is assumed to differ by FEV_1 strata
(3) Transitions between FEV_1 strata are assumed to be independent of patient's previous transitions
(4) Colistimethate sodium DPI has no additional benefit over nebulised tobramycin in terms of patient survival
(5) The costs of follow-up and concomitant medication are equivalent between colistimethate sodium DPI and tobramycin nebulised

6.4.5 Uncertainty analysis

The model is fully probabilistic. Monte Carlo sampling was used to propagate uncertainty through the model in order to produce distributions of expected costs and outcomes for each treatment option. The model was run over 5,000 Monte Carlo samples. The results of the probabilistic sensitivity analysis are presented in terms of incremental cost-effectiveness planes and cost-effectiveness acceptability curves. Simple sensitivity analyses were undertaken to examine the impact of parameter uncertainty and structural uncertainty on the model results. The following analyses were explored:

- Scenario 1: The analysis was run using point estimates of parameters rather than the probabilistic means.
- Scenarios 2-6: Secondary analyses are presented using alternative FEV_1 utility estimates reported by Yi *et al*[106] and Stahl *et al.*[105] It should be noted that these studies report health utility using different categories of FEV_1 bands (FEV_1 >79%, FEV_1 60-79%, FEV_1 40-59% and FEV_1 <40%). As such, it was necessary to redefine the structure of the model and re-estimate the transition probabilities between four instead of three states. The general logic of the model however remains the same as the base case analysis.
- Scenario 7: FEV_1 transition probabilities for the nebulised tobramycin group were set equal to those for the colistimethate sodium DPI group.
- Scenario 8: The HRQoL decrement associated with minor and major exacerbations was doubled.
- Scenario 9: The cost of hospitalisation for major exacerbations was doubled.

6.4.6 Model validation and verification methods

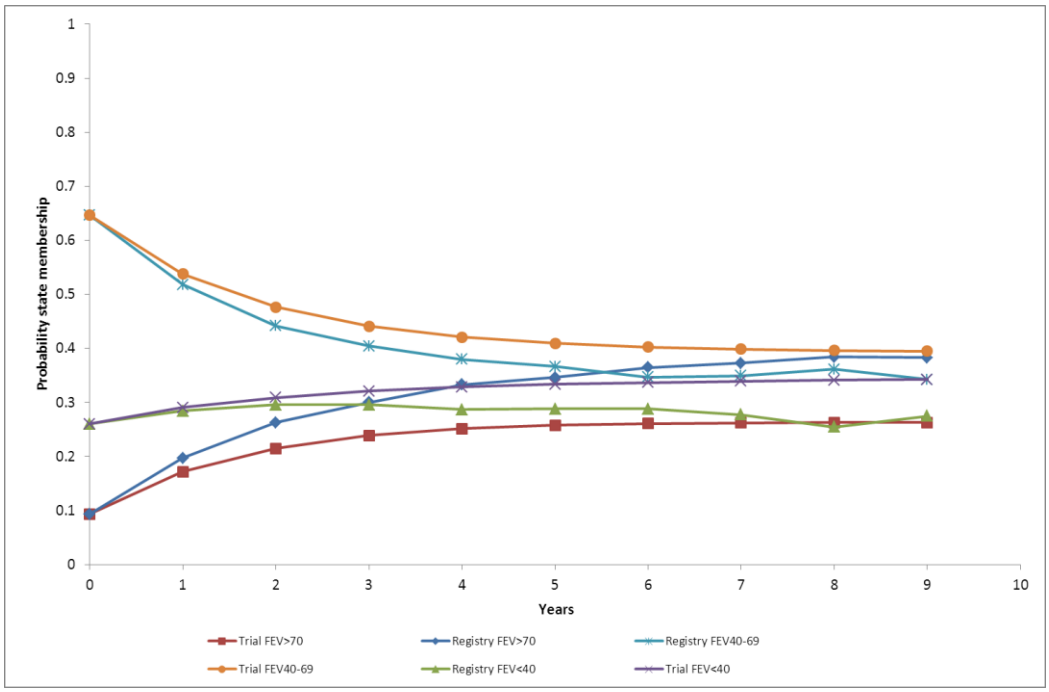
A number of measures were taken to ensure that the Assessment Group model was credible and not subject to computational errors. Firstly, the methods and results of the health economic model were peer reviewed by three clinical advisors to the project (see Acknowledgements). The executable model and its underlying logic were checked by the model authors and a third modeller who was not involved in its development. The expectations of each model parameter were compared against their deterministic counterpart. All model input parameters were double-checked against the sources from which they were derived. The plausibility of the model results were considered against the model developers' expectations of those results prior to model development.

In addition to the above activities, a validation exercise was undertaken to examine the plausibility of the extrapolated Markov trace based on the COLO/DPI/02/06 trial by deriving equivalent transition matrices using longitudinal panel data from the CF Registry for the period 1997-2008. Transition matrices were generated as follows:

- The first FEV_1 measurement each calendar year was taken as each patient's observation for year *t*
- As patients entered the registry during different calendar years, the first observation for each patient was transposed to a common starting year
- Missing data between observations were imputed according to a last observation carried forward rule (final observations were not imputed)
- FEV_1 scores were mapped to three FEV_1 bands (FEV_1>70%, $FEV_1$40-69%, FEV_1<40%)
- Transition matrices for year *t* were calculated based on the number of patients transiting between each state between years *t* and year *t*+1.

These transition matrices were then applied to the initial distribution of patients in the model and the resulting Markov trace was compared against the Markov trace for the tobramycin group. The results of this analysis are shown in Figure 13.

Figure 13: Comparison of registry-derived and trial-derived Markov trace



This analysis shows that the registry-derived transition matrices suggest a similar shape in the Markov trace as those derived from the COLO/DPI/02/06 trial. There are clearly some differences between the traces generated using the registry data and the trial, however the FEV_1<40% state population, which has the greatest impact on HRQoL, appears fairly similar between the two sources. Some of this discrepancy may be caused by differences between the registry and the trial in terms of patient characteristics, for example the registry cohort does not exclusively include those patients with *Pseudomonas aeruginosa*. This analysis lends some weight to the credibility of the trial extrapolation.

6.4.7 Simplifications and exclusions from the economic analysis

Potential process utilities due to increased convenience and faster treatment delivery

One of the appealing aspects of using the DPIs is the increased convenience afforded by reduced treatment time and increased portability in the administration as compared against nebulised antibiotics. It is plausible that this represents a "process utility" which is not captured in the health economic analysis presented here. However, neither the Novartis submission[58] nor the Forest submission[64] reported any empirical preference-based evidence of the impact of this potential benefit on HRQoL. It should be also noted that that this impact would be lessened by the use of newer faster delivery nebuliser devices such as the eFlow® Rapid Nebuliser (PARI) and the I-neb AAD System (Philips Respironics).

Exclusion of disutilities due to adverse events

The model does not include utility adjustments to account for the incidence of adverse events. Whilst the incidence of cough, productive cough and dysgeusia were markedly higher for colistimethate sodium DPI than nebulised tobramycin, some adverse events were less common for colistimethate

sodium DPI. As a consequence, it is unclear whether the inclusion of health utility decrements associated with the incidence of adverse events would improve or worsen the economic case for colistimethate sodium DPI. Whilst Forest kindly provided detailed adverse event data for each treatment group at each visit, the considerable gaps in the available EQ-5D evidence (see Section 6.3) relating to the disutility of these events precluded the inclusion of these effects within the model.

It should also be noted that the model does not include the potential impact of resistance to tobramycin. This exclusion is reasonable as it is unclear how this phenomenon would manifest in terms of reduced treatment effect.

Limitations in methods for modelling treatment benefits

The model extrapolates treatment effects in terms of shifts between different health states, each of which is associated with different EQ-5D scores. The definition of health states within the model is "blunt" in that only three FEV_1 strata are defined and there appears to be little difference in health utility for FEV_1 states > 40%. Whilst it could be argued that the EQ-5D is not particularly sensitive in the valuation of health for patients with cystic fibrosis, the study reported by Yi *et al* suggests that other preference-based health utility instruments result in a similar relationship between FEV_1 and HRQoL. On the basis of the weaknesses in the evidence associated with the potential relationship between FEV_1 and mortality (see Section 6.3), this relationship was not considered within the Assessment Group model.

6.4.8 Health economic results

6.4.8.1 Headline cost-effectiveness results

The base case probabilistic model results are presented in Table 45. The impact of constraining the time horizon to 24 weeks (the duration of the COLO/DPI/02/06 trial) is shown in Table 46.

Table 45: Reference Case model (probabilistic)

Colistimethate sodium DPI price	QALYs			Costs			ICER
	Coli DPI	Tobi neb	Inc.	Coli DPI	Tobi neb	Inc.	
£9.11	9.48	9.61	-0.13	£93,915.58	£110,518.68	-£16,603.10	**£126,259**
£10.60	9.48	9.61	-0.13	£107,390.59	£110,518.68	-£3,128.08	**£23,788**
[redacted]	9.48	9.61	-0.13	£156,045.35	£110,518.68	£45,526.67	**Dominated**
£19.64	9.48	9.61	-0.13	£189,145.05	£110,518.68	£78,626.38	**Dominated**
£21.20	9.48	9.61	-0.13	£203,253.12	£110,518.68	£92,734.45	**Dominated**
£[redacted]	9.48	9.61	-0.13	£366,852.48	£110,518.68	£256,333.80	**Dominated**

The results presented in Table 45 suggest that colistimethate sodium DPI is expected to result in a loss of around 0.13 QALYs over the patient's lifetime compared against nebulised tobramycin. If colistimethate sodium DPI is priced at one of the prices which is higher than that of nebulised

tobramycin, it is also expected to have a positive incremental cost compared to nebulised tobramycin. As a consequence, colistimethate sodium DPI is expected to be dominated for these pricing scenarios. If priced at £9.11 per dose or £10.60 per dose, colistimethate sodium DPI is expected to be less expensive and less effective than nebulised tobramycin. The resulting ICERs are around £126,000 and £24,000 per QALY gained. It should be noted that the positive ICER in this instance reflects a QALY loss and cost savings for colistimethate sodium DPI compared to nebulised tobramycin (therefore colistimethate sodium DPI lies in the South-West quadrant of the cost-effectiveness plane).

Table 46: Short-term "within-trial" model (probabilistic)

Colistimethate sodium DPI price	QALYs			Costs			ICER
	Coli DPI	Tobi neb	Inc.	Coli DPI	Tobi neb	Inc.	
£9.11	0.35	0.35	-0.00	£3,469.00	£4,075.35	-£606.35	**£276,814**
£10.60	0.35	0.35	-0.00	£3,966.71	£4,075.35	-£108.64	**£49,596**
£[redacted]	0.35	0.35	-0.00	£5,763.82	£4,075.35	£1,688.48	**Dominated**
£19.64	0.35	0.35	-0.00	£6,986.40	£4,075.35	£2,911.05	**Dominated**
£21.20	0.35	0.35	-0.00	£7,507.49	£4,075.35	£3,432.15	**Dominated**
£[redacted]	0.35	0.35	-0.00	£13,550.21	£4,075.35	£9,474.86	**Dominated**

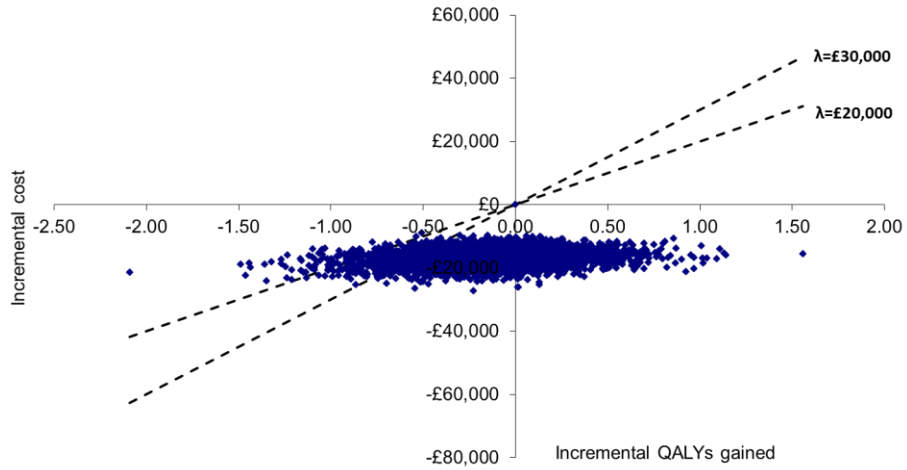
The results of the short-term "within-trial" analysis suggest that colistimethate sodium DPI is expected to result in a small decrease in QALYs compared against nebulised tobramycin (0.002 QALYs lost). If colistimethate sodium DPI is priced at one of the prices which is higher than that of nebulised tobramycin, it is also expected to have a positive incremental cost than nebulised tobramycin and is thus dominated. If priced at £9.11 per dose or £10.60 per dose, colistimethate sodium DPI is expected to be less expensive than nebulised tobramycin (ICER=£277,000 and £50,000 per QALY gained respectively). Again, the positive ICER reflects a QALY loss and cost savings for colistimethate sodium DPI compared to nebulised tobramycin.

6.4.8.2 Uncertainty analysis

Results of the long-term Reference Case economic analysis

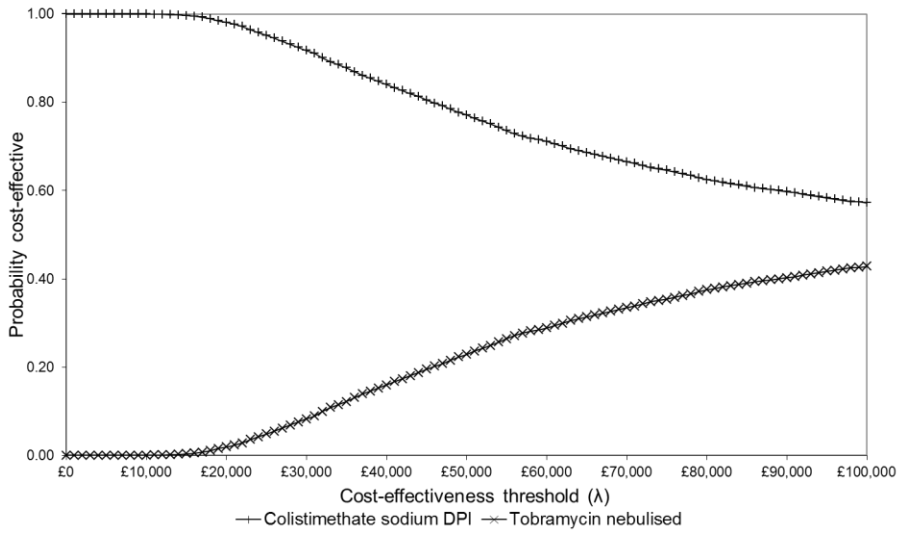
Figures 14 to 25 present cost-effectiveness planes and CEACs for the long-term Reference Case model over the range of pricing scenarios for colistimethate sodium DPI.

Figure 14: Reference Case model – cost-effectiveness plane (price per dose=£9.11)



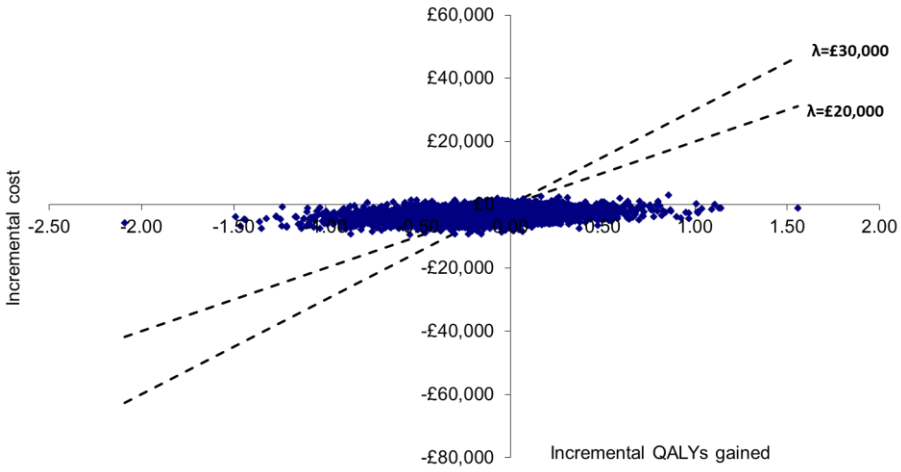
Assuming a price per dose of £9.11, the long-term model suggests that the probability that colistimethate sodium DPI produces a positive QALY gain and has an incremental cost-effectiveness ratio that is better than £20,000 per QALY gained is around 0.32. The probability that colistimethate sodium DPI produces a positive QALY gain and has an incremental cost-effectiveness ratio that is better than £30,000 per QALY gained is also approximately 0.32. The probability that colistimethate sodium DPI is dominated by nebulised tobramycin is alsapproximately zero.

Figure 15: Reference Case model – cost-effectiveness acceptability curve (price per dose=£9.11)



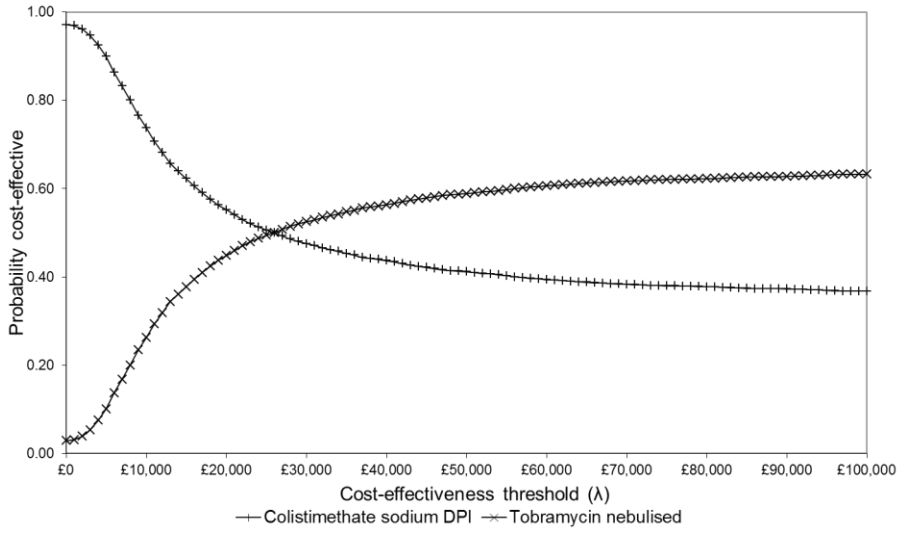
Assuming a willingness to pay threshold of £20,000 per QALY gained and a price per dose of £9.11, the probability that colistimethate sodium DPI is optimal is approximately 0.98. At a willingness to pay threshold of £30,000 per QALY gained, the probability that colistimethate sodium DPI is optimal is approximately 0.92.

Figure 16: Reference Case model – cost-effectiveness plane (price per dose=£10.60)



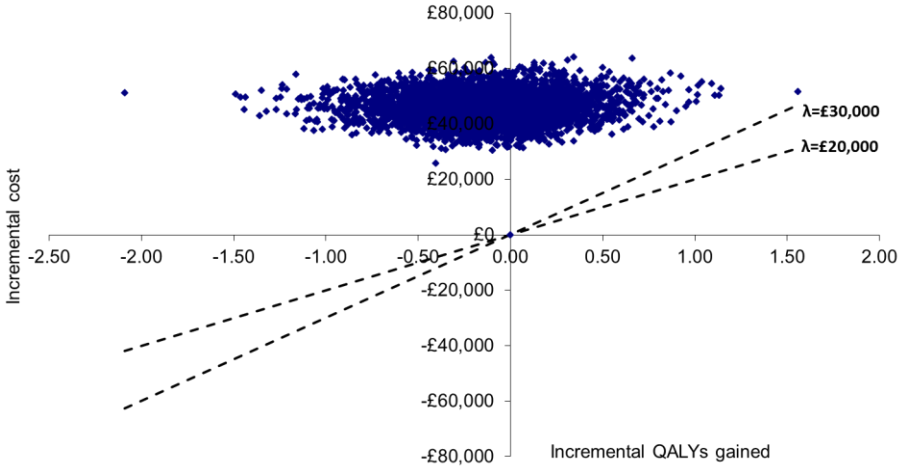
Assuming a price per dose of £10.60, the long-term model suggests that the probability that colistimethate sodium DPI produces a positive QALY gain and has an incremental cost-effectiveness ratio that is better than £20,000 per QALY gained is around 0.32. The probability that colistimethate sodium DPI produces a positive QALY gain and has an incremental cost-effectiveness ratio that is better than £30,000 per QALY gained is also approximately 0.32. The probability that colistimethate sodium DPI is dominated by nebulised tobramycin is alsapproximately 0.01.

Figure 17: Reference Case model – cost-effectiveness acceptability curve (price per dose=£10.60)



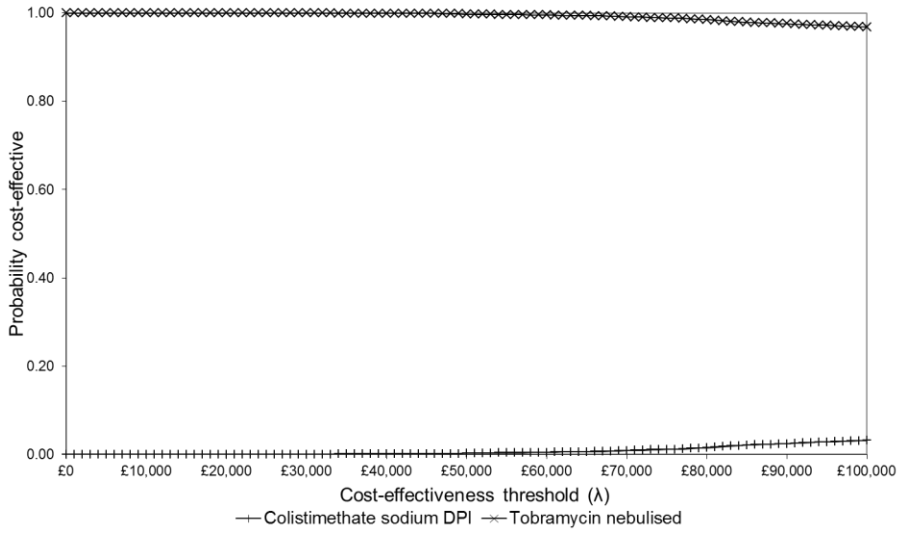
Assuming a willingness to pay threshold of £20,000 per QALY gained and a price per dose of £10.60, the probability that colistimethate sodium DPI is optimal is approximately 0.55. At a willingness to pay threshold of £30,000 per QALY gained, the probability that colistimethate sodium DPI is optimal is approximately 0.48.

Figure 18: Reference Case model – cost-effectiveness plane (price per dose=[redacted])



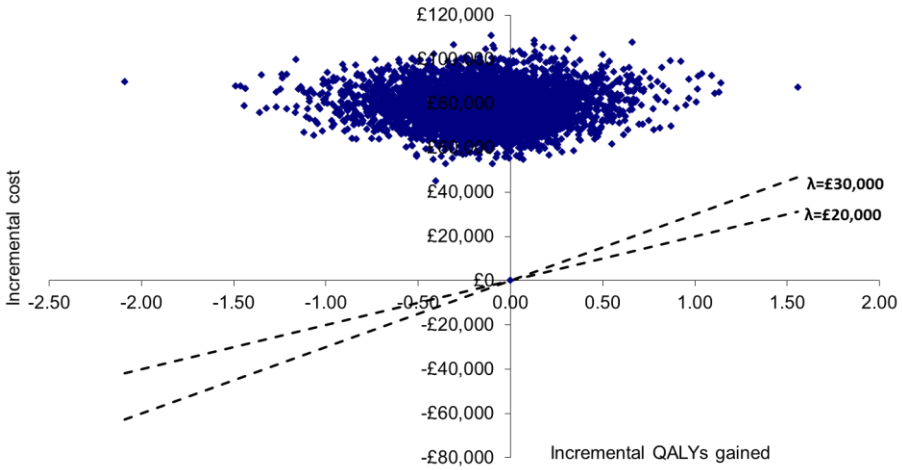
Assuming a price per dose of [redacted], the long-term model suggests that the probability that colistimethate sodium DPI produces a positive QALY gain and has an incremental cost-effectiveness ratio that is better than £30,000 per QALY gained is zero. The probability that colistimethate sodium DPI is dominated is approximately 0.68.

Figure 19: Reference Case model – cost-effectiveness acceptability curve (price per dose=[redacted])



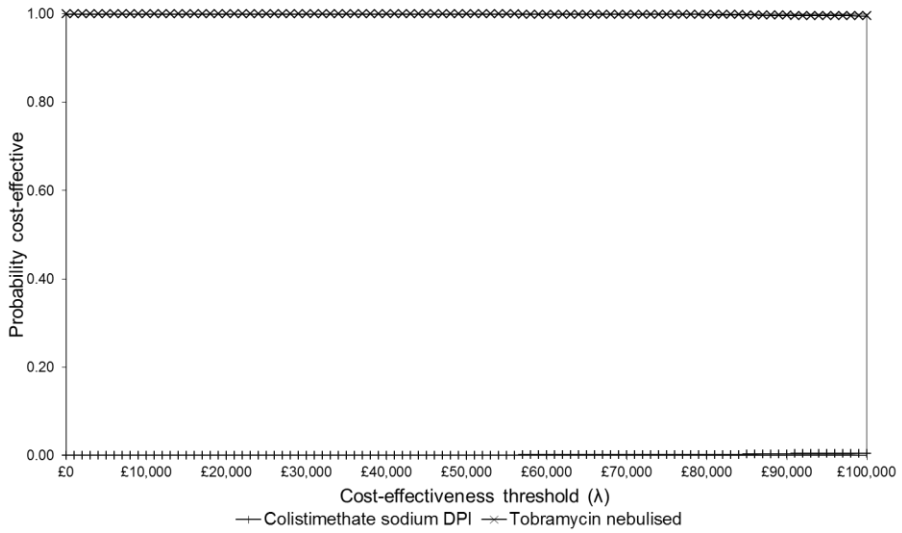
Assuming a willingness to pay threshold of £20,000 per QALY gained and a price per dose of [redacted], the probability that colistimethate sodium DPI is optimal is zero. At a willingness to pay threshold of £30,000 per QALY gained, the probability that colistimethate sodium DPI is optimal is also zero.

Figure 20: Reference Case model – cost-effectiveness plane (price per dose=£19.64)



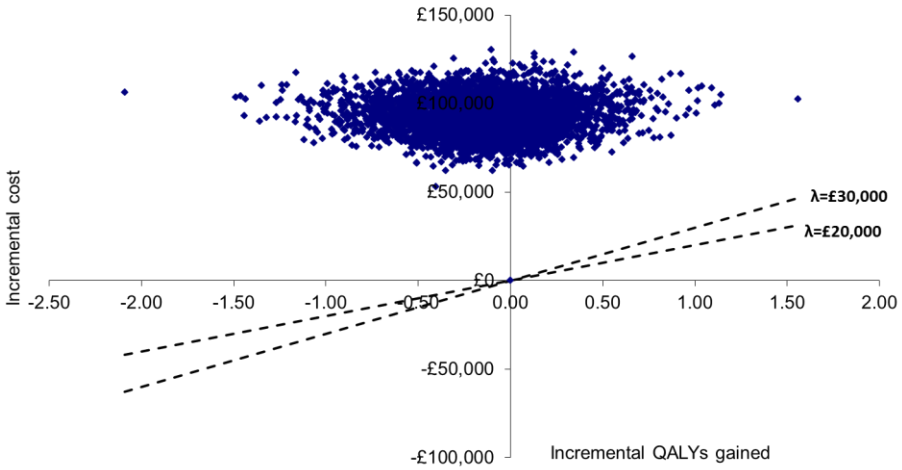
Assuming a price per dose of £19.64, the long-term model suggests that the probability that colistimethate sodium DPI produces a positive QALY gain and has an incremental cost-effectiveness ratio that is better than £30,000 per QALY gained is zero. The probability that colistimethate sodium DPI is dominated is approximately 0.68.

Figure 21: Reference Case model – cost-effectiveness acceptability curve (price per dose=£19.64)



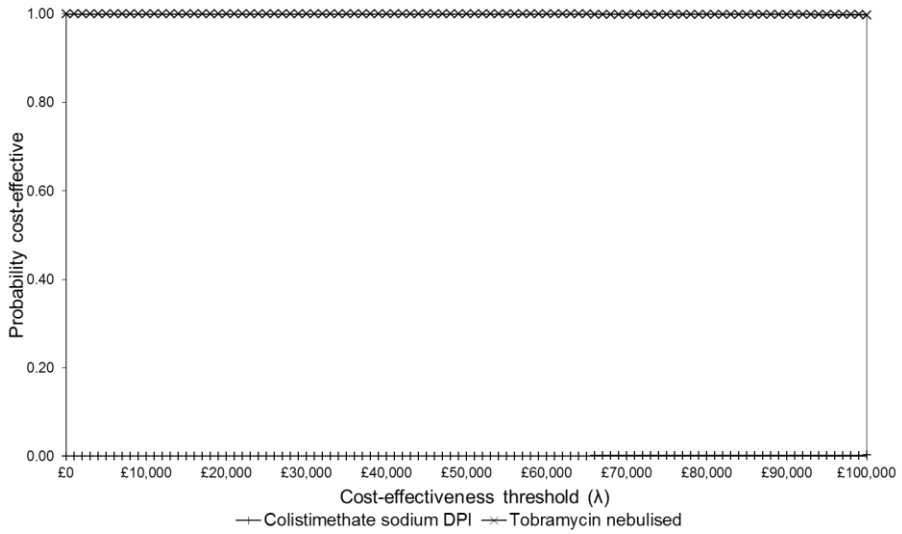
Assuming a willingness to pay threshold of £20,000 per QALY gained and a price per dose of £19.64, the probability that colistimethate sodium DPI is optimal is zero. At a willingness to pay threshold of £30,000 per QALY gained, the probability that colistimethate sodium DPI is optimal is also zero.

Figure 22: Reference Case model – cost-effectiveness plane (price per dose=£21.20)



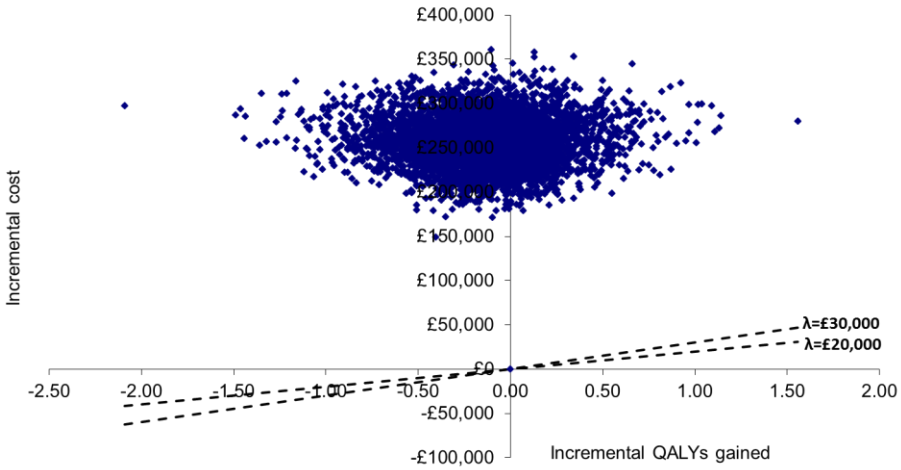
Assuming a price per dose of £21.20, the long-term model suggests that the probability that colistimethate sodium DPI produces a positive QALY gain and has an incremental cost-effectiveness ratio that is better than £30,000 per QALY gained is zero. The probability that colistimethate sodium DPI is dominated is approximately 0.68.

Figure 23: Reference Case model – cost-effectiveness acceptability curve (price per dose=£21.20)



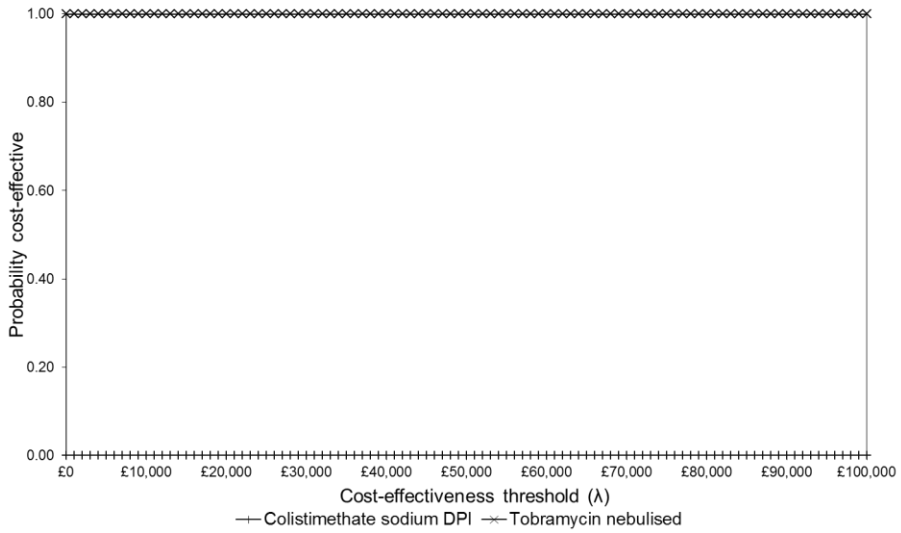
Assuming a willingness to pay threshold of £30,000 per QALY gained and a price per dose of £21.20, the probability that colistimethate sodium DPI is optimal is zero.

Figure 24: Reference Case model – cost-effectiveness plane (price per dose=£[redacted])



Assuming a price per dose of £[redacted], the long-term model suggests that the probability that colistimethate sodium DPI produces a positive QALY gain and has an incremental cost-effectiveness ratio that is better than £30,000 per QALY gained is zero. The probability that colistimethate sodium DPI is dominated is approximately 0.68.

Figure 25: Reference Case model – cost-effectiveness acceptability curve (price per dose=£[redacted])

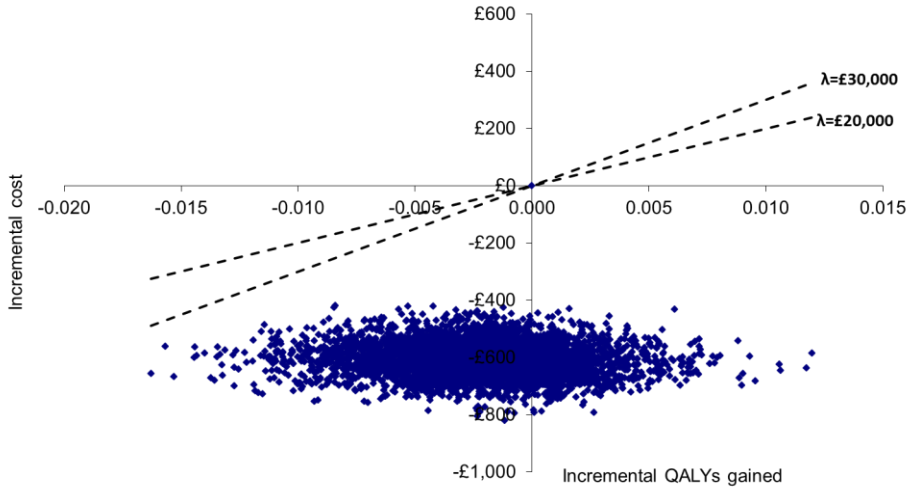


Assuming a willingness to pay threshold of £30,000 per QALY gained and a price per dose of [redacted], the probability that colistimethate sodium DPI is optimal is zero.

Results of the short-term "within-trial" economic analysis (excluding any extrapolation)

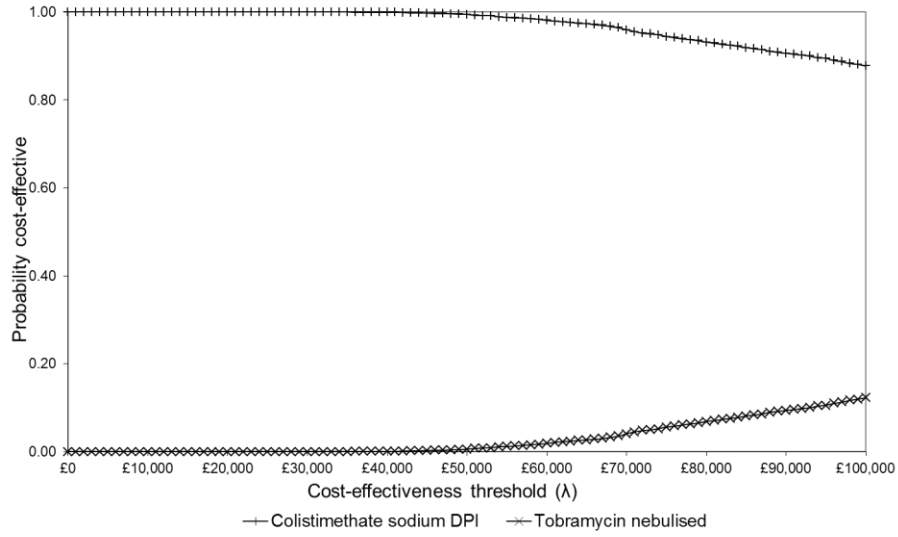
Figures 26 to 37 present cost-effectiveness planes and CEACs for the short-term model over the six pricing scenarios for colistimethate sodium DPI.

Figure 26: Short-term model – cost-effectiveness plane (price per dose=£9.11)



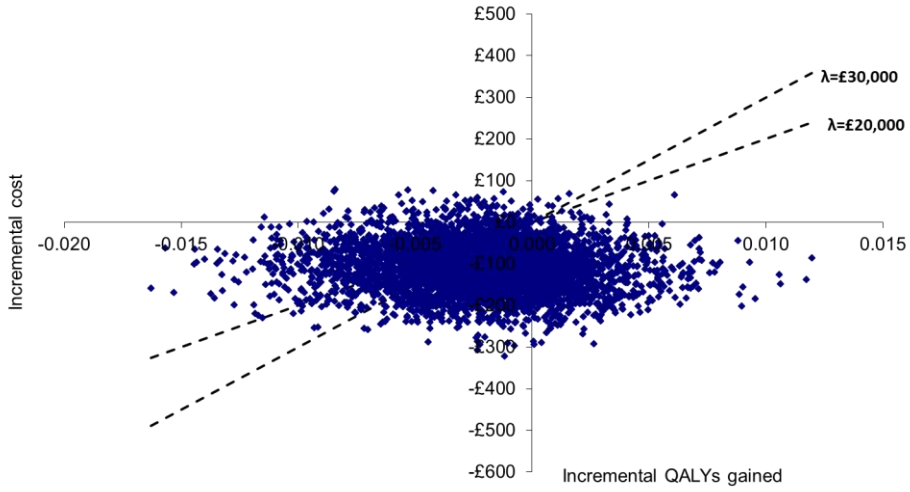
Assuming a price per dose of £9.11, the short-term model suggests that the probability that colistimethate sodium DPI produces a positive QALY gain and has an incremental cost-effectiveness ratio that is better than £20,000 per QALY gained is around 0.23. The probability that colistimethate sodium DPI produces a positive QALY gain and has an incremental cost-effectiveness ratio that is better than £30,000 per QALY gained is also approximately 0.23. The probability that colistimethate sodium DPI is dominated is approximately zero.

Figure 27: Short-term model – cost-effectiveness acceptability curve (price per dose=£9.11)



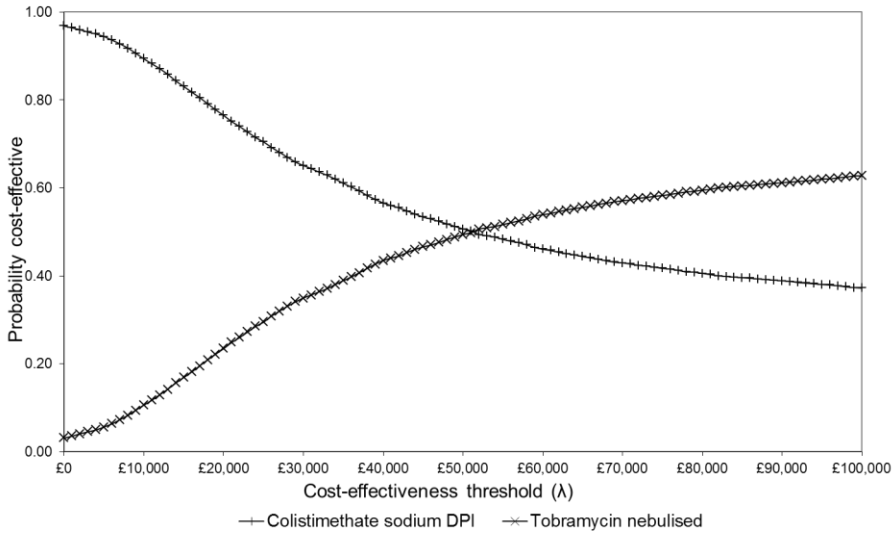
Assuming a willingness to pay threshold of £20,000 per QALY gained and a price per dose of £9.11, the probability that colistimethate sodium DPI is optimal within the short-term model is approximately 1.0. At a willingness to pay threshold of £30,000 per QALY gained, the probability that colistimethate sodium DPI is optimal is also approximately 1.0.

Figure 28: Short-term model – cost-effectiveness plane (price per dose=£10.60)



Assuming a price per dose of £10.60, the short-term model suggests that the probability that colistimethate sodium DPI produces a positive QALY gain and has an incremental cost-effectiveness ratio that is better than £20,000 per QALY gained is around 0.23. The probability that colistimethate sodium DPI produces a positive QALY gain and has an incremental cost-effectiveness ratio that is better than £30,000 per QALY gained is also approximately 0.23. The probability that colistimethate sodium DPI is dominated is approximately 0.03.

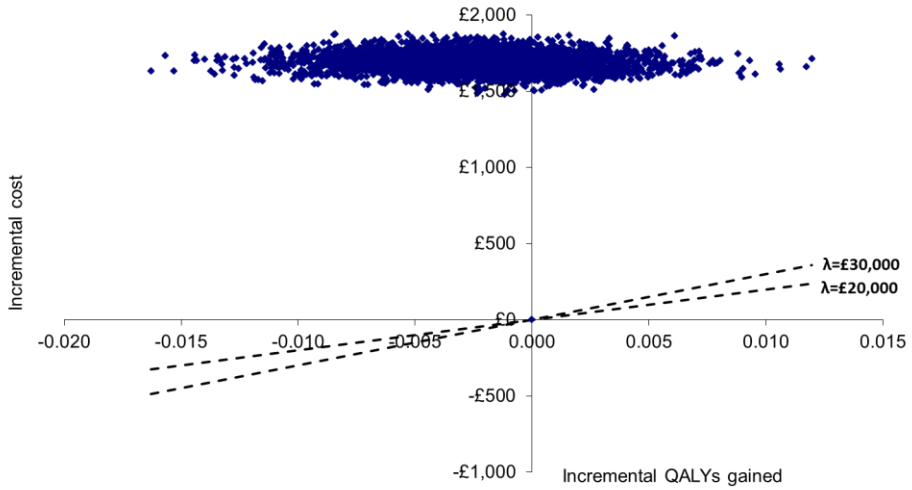
Figure 29: Short-term model – cost-effectiveness acceptability curve (price per dose=£10.60)



Assuming a willingness to pay threshold of £20,000 per QALY gained and a price per dose of £10.60, the probability that colistimethate sodium DPI is optimal within the short-term model is

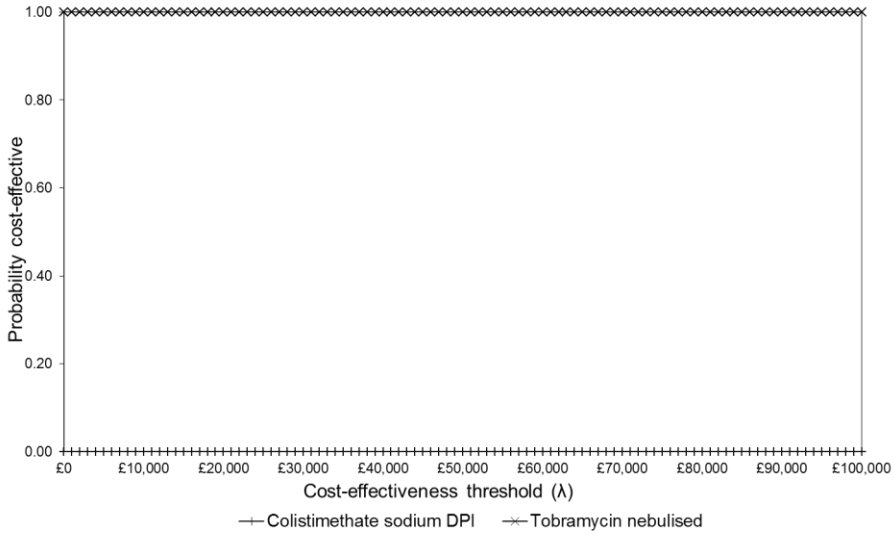
approximately 0.77. At a willingness to pay threshold of £30,000 per QALY gained, the probability that colistimethate sodium DPI is optimal is approximately 0.65.

Figure 30: Short-term model – cost-effectiveness plane (price per dose=[redacted])



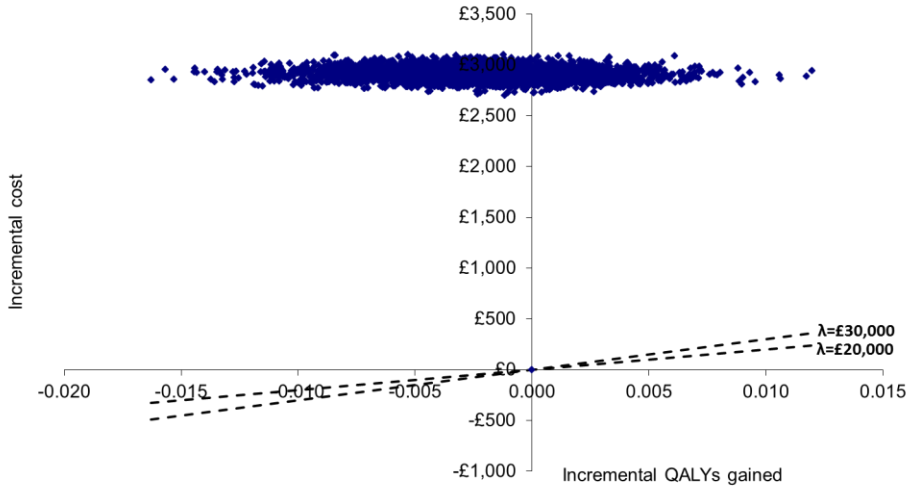
Assuming a price per dose of [redacted], the short-term model suggests that the probability that colistimethate sodium DPI produces a positive QALY gain and has an incremental cost-effectiveness ratio that is better than £30,000 per QALY gained is zero. The probability that colistimethate sodium DPI is dominated is approximately 0.77.

Figure 31: Short-term model – cost-effectiveness acceptability curve (price per dose=[redacted])



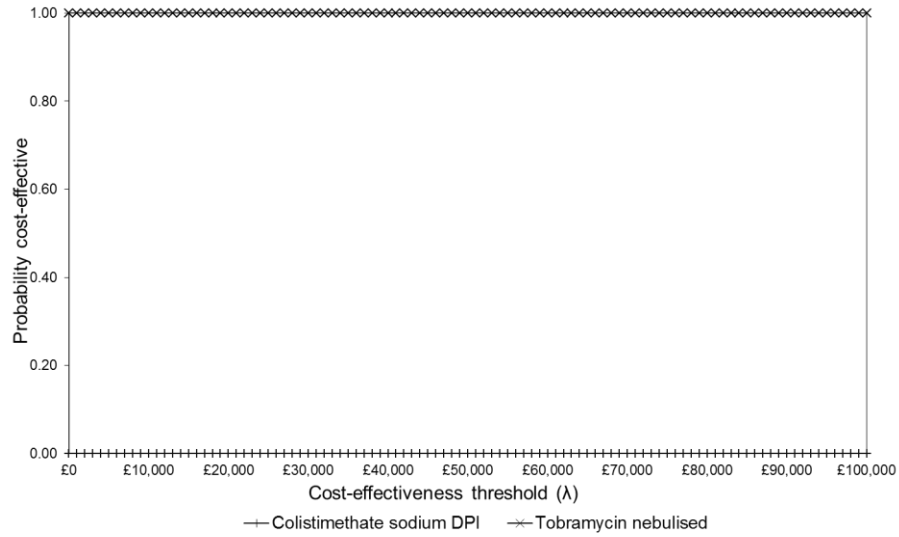
Assuming a willingness to pay threshold of £30,000 per QALY gained and a price per dose of [redacted], the probability that colistimethate sodium DPI is optimal within the short-term model is zero.

Figure 32: Short-term model – cost-effectiveness plane (price per dose=£19.64)



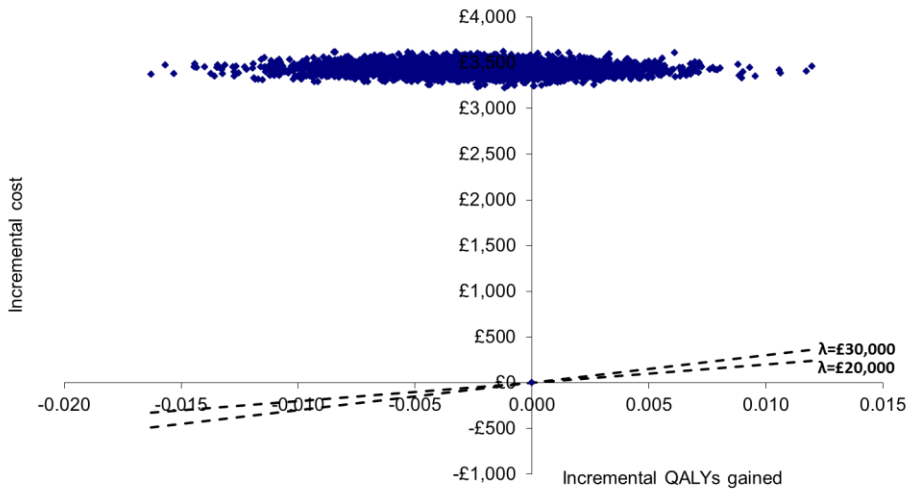
Assuming a price per dose of £19.64, the short-term model suggests that the probability that colistimethate sodium DPI produces a positive QALY gain and has an incremental cost-effectiveness ratio that is better than £30,000 per QALY gained is zero. The probability that colistimethate sodium DPI is dominated is approximately 0.77.

Figure 33: Short-term model – cost-effectiveness acceptability curve (price per dose=£19.64)



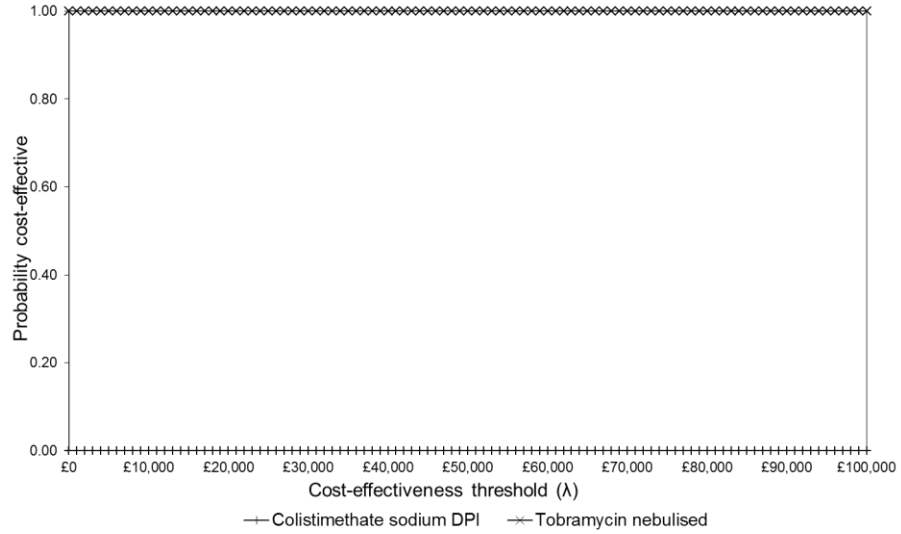
Assuming a willingness to pay threshold of £30,000 per QALY gained and a price per dose of £19.64, the probability that colistimethate sodium DPI is optimal within the short-term model is zero.

Figure 34: Short-term model – cost-effectiveness plane (price per dose=£21.20)



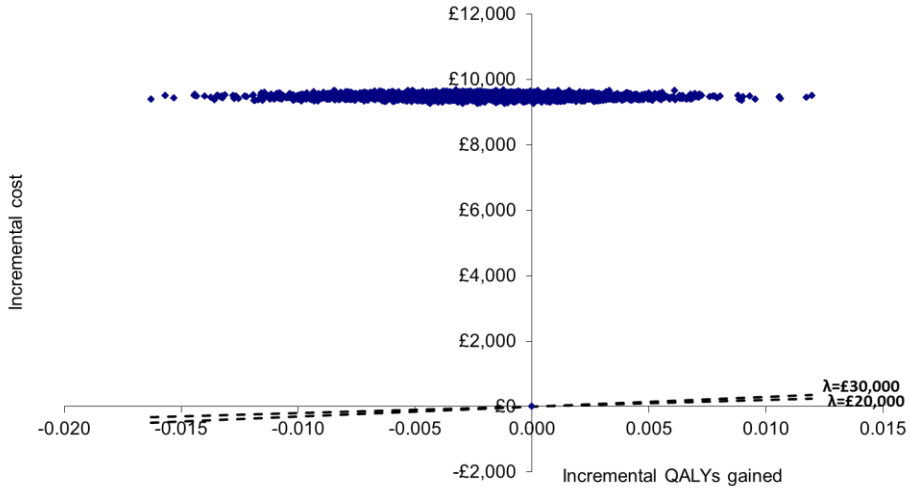
Assuming a price per dose of £21.20, the short-term model suggests that the probability that colistimethate sodium DPI produces a positive QALY gain and has an incremental cost-effectiveness ratio that is better than £30,000 per QALY gained is zero. The probability that colistimethate sodium DPI is dominated is approximately 0.77.

Figure 35: Short-term model – cost-effectiveness acceptability curve (price per dose=£21.20)



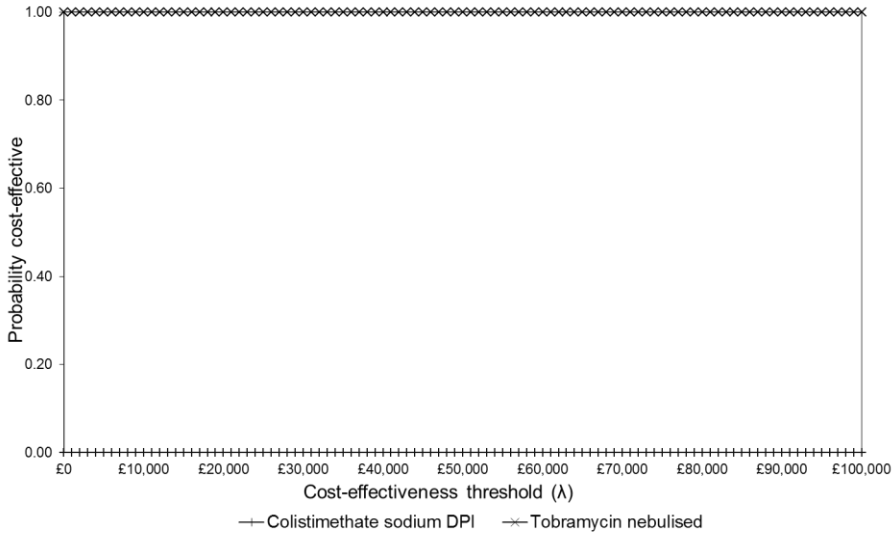
Assuming a willingness to pay threshold of £30,000 per QALY gained and a price per dose of £21.20, the probability that colistimethate sodium DPI is optimal within the short-term model is zero.

Figure 36: Short-term model – cost-effectiveness plane (price per dose=£[redacted])



Assuming a price per dose of £[redacted], the short-term model suggests that the probability that colistimethate sodium DPI produces a positive QALY gain and has an incremental cost-effectiveness ratio that is better than £30,000 per QALY gained is zero. The probability that colistimethate sodium DPI is dominated is approximately 0.77.

Figure 37: Short-term model – cost-effectiveness acceptability curve (price per dose=£[redacted])



Assuming a willingness to pay threshold of £30,000 per QALY gained and a price per dose of £[redacted], the probability that colistimethate sodium DPI is optimal within the short-term model is approximately zero.

The results of the probabilistic sensitivity analysis highlight an important aspect of the model: whilst there is clearly considerable uncertainty surrounding the extrapolation of the COLO/DPI/02/06 trial data, this element of the model has virtually no bearing on the economic conclusions of the model, as colistimethate sodium DPI remains dominated when the price is set at one of the higher prices than that of nebulised tobramycin.

Simple (deterministic) sensitivity analysis

Table 47 presents the results of the simple sensitivity analysis; this is presented only for the long-term model. It should be noted that this analysis is deterministic and uses the point estimates of each parameter rather than the expectation of the mean (although the transition probabilities also include the weak priors to allow for comparison against the probabilistic results).

The results of the deterministic sensitivity analysis presented in Table 47 show that the results are particularly sensitive to the choice of utility values used within the model. Where colistimethate sodium DPI produces a positive QALY gain, this is very small and results in ICER ranging from dominating to in excess of £121million per QALY gained.

Table 47: Simple sensitivity analysis (long-term model)

Colistimethate sodium DPI price	QALYs			Costs			ICER
	Coli DPI	Tobi neb	Inc.	Coli DPI	Tobi neb	Inc.	
1. Deterministic point estimates for parameters							
£9.11	9.46	9.57	-0.12	£93,720.31	£110,278.31	-£16,558.00	**£143,325**
£10.60	9.46	9.57	-0.12	£107,166.44	£110,278.31	-£3,111.87	**£26,936.14**
[redacted]	9.46	9.57	-0.12	£155,716.90	£110,278.31	£45,438.59	**Dominated**
£19.64	9.46	9.57	-0.12	£188,745.65	£110,278.31	£78,467.34	**Dominated**
£21.20	9.46	9.57	-0.12	£202,823.48	£110,278.31	£92,545.17	**Dominated**
£[redacted]	9.46	9.57	-0.12	£366,072.13	£110,278.31	£255,793.82	**Dominated**
2. Time trade off utility values from Yi et al[106]							
£9.11	11.83	11.83	0.00	£93,651.08	£110,086.92	-£16,435.84	**Dominating**
£10.60	11.83	11.83	0.00	£107,087.28	£110,086.92	-£2,999.64	**Dominating**
[redacted]	11.83	11.83	0.00	£155,601.87	£110,086.92	£45,514.96	**£21,699,661**
£19.64	11.83	11.83	0.00	£188,606.22	£110,086.92	£78,519.31	**£37,434,780**
£21.20	11.83	11.83	0.00	£202,673.65	£110,086.92	£92,586.74	**£44,141,552**
£[redacted]	11.83	11.83	0.00	£365,801.72	£110,086.92	£255,714.80	**£121,914,312**
3. Standard gamble utility values from Yi et al[106]							
£9.11	11.15	11.15	0.00	£93,651.08	£110,086.92	-£16,435.84	**Dominating**
£10.60	11.15	11.15	0.00	£107,087.28	£110,086.92	-£2,999.64	**Dominating**
[redacted]	11.15	11.15	0.00	£155,601.87	£110,086.92	£45,514.96	**£13,458,617**
£19.64	11.15	11.15	0.00	£188,606.22	£110,086.92	£78,519.31	**£23,217,891**
£21.20	11.15	11.15	0.00	£202,673.65	£110,086.92	£92,586.74	**£27,377,581**
£[redacted]	11.15	11.15	0.00	£365,801.72	£110,086.92	£255,714.80	**£75,613,992**
4. HUI-2 utility values from Yi et al[106]							
£9.11	10.25	10.24	0.01	£93,651.08	£110,086.92	-£16,435.84	**Dominating**
£10.60	10.25	10.24	0.01	£107,087.28	£110,086.92	-£2,999.64	**Dominating**
[redacted]	10.25	10.24	0.01	£155,601.87	£110,086.92	£45,514.96	**£4,030,094**
£19.64	10.25	10.24	0.01	£188,606.22	£110,086.92	£78,519.31	**£6,952,444**
£21.20	10.25	10.24	0.01	£202,673.65	£110,086.92	£92,586.74	**£8,198,036**
£[redacted]	10.25	10.24	0.01	£365,801.72	£110,086.92	£255,714.80	**£22,642,110**
5. EQ-5D values from Stahl et al[105] (GOLD criteria)							
£9.11	8.28	8.36	-0.08	£93,651.08	£110,086.92	-£16,435.84	**£213,185**
£10.60	8.28	8.36	-0.08	£107,087.28	£110,086.92	-£2,999.64	**£38,907**
[redacted]	8.28	8.36	-0.08	£155,601.87	£110,086.92	£45,514.96	**Dominated**
£19.64	8.28	8.36	-0.08	£188,606.22	£110,086.92	£78,519.31	**Dominated**
£21.20	8.28	8.36	-0.08	£202,673.65	£110,086.92	£92,586.74	**Dominated**
£[redacted]	8.28	8.36	-0.08	£365,801.72	£110,086.92	£255,714.80	**Dominated**
6. EQ-5D values from Stahl et al[105] (BTS criteria)							
£9.11	8.74	8.81	-0.06	£93,651.08	£110,086.92	-£16,435.84	**£264,903**
£10.60	8.74	8.81	-0.06	£107,087.28	£110,086.92	-£2,999.64	**£48,346**
[redacted]	8.74	8.81	-0.06	£155,601.87	£110,086.92	£45,514.96	**Dominated**
£19.64	8.74	8.81	-0.06	£188,606.22	£110,086.92	£78,519.31	**Dominated**
£21.20	8.74	8.81	-0.06	£202,673.65	£110,086.92	£92,586.74	**Dominated**
£[redacted]	8.74	8.81	-0.06	£365,801.72	£110,086.92	£255,714.80	**Dominated**
7. Transition probabilities for nebulised tobramycin set equal to those for colistimethate sodium DPI							
£9.11	9.46	9.46	0.00	£93,724.58	£110,118.99	-£16,394.41	**Dominating**
£10.60	9.46	9.46	0.00	£107,171.33	£110,118.99	-£2,947.67	**Dominating**
[redacted]	9.46	9.46	0.00	£155,724.00	£110,118.99	£45,605.00	**£9,793,372**
£19.64	9.46	9.46	0.00	£188,754.25	£110,118.99	£78,635.26	**£16,886,400**
£21.20	9.46	9.46	0.00	£202,832.72	£110,118.99	£92,713.73	**£19,909,658**
£[redacted]	9.46	9.46	0.00	£366,088.82	£110,118.99	£255,969.82	**£54,967,822**

Colistimethate sodium DPI price	QALYs			Costs			ICER
	Coli DPI	Tobi neb	Inc.	Coli DPI	Tobi neb	Inc.	
8. Utility decrement for exacerbations doubled							
£9.11	9.41	9.52	-0.11	£93,720.31	£110,278.31	-£16,558.00	**£149,445**
£10.60	9.41	9.52	-0.11	£107,166.44	£110,278.31	-£3,111.87	**£28,086**
[redacted]	9.41	9.52	-0.11	£155,716.90	£110,278.31	£45,438.59	**Dominated**
£19.64	9.41	9.52	-0.11	£188,745.65	£110,278.31	£78,467.34	**Dominated**
£21.20	9.41	9.52	-0.11	£202,823.48	£110,278.31	£92,545.17	**Dominated**
£[redacted]	9.41	9.52	-0.11	£366,072.13	£110,278.31	£255,793.82	**Dominated**
9. Cost of hospitalisation doubled							
£9.11	9.46	9.57	-0.12	£103,782.02	£120,772.51	-£16,990.49	**£147,069**
£10.60	9.46	9.57	-0.12	£117,228.15	£120,772.51	-£3,544.36	**£30,680**
[redacted]	9.46	9.57	-0.12	£165,778.61	£120,772.51	£45,006.10	**Dominated**
£19.64	9.46	9.57	-0.12	£198,807.36	£120,772.51	£78,034.85	**Dominated**
£21.20	9.46	9.57	-0.12	£212,885.19	£120,772.51	£92,112.68	**Dominated**
£[redacted]	9.46	9.57	-0.12	£376,133.84	£120,772.51	£255,361.33	**Dominated**

Commentary on the cost-effectiveness of tobramycin DPI

The *de novo* Assessment Group model explicitly excludes tobramycin DPI. This decision was taken by the Assessment Group, and NICE were informed of this in December 2011. This exclusion reflects the absence of suitable FEV_1 data for tobramycin DPI and the absence of a health economic model within the Novartis submission to NICE.[58] Despite the absence of a model, it is possible to crudely postulate the likely incremental cost-effectiveness of tobramycin DPI versus nebulised tobramycin on the basis of the following observations regarding the available evidence base.

- There is no empirical evidence that tobramycin DPI provides an improved or equivalent level of HRQoL as nebulised tobramycin.
- Within the EAGER trial, study follow-up was insufficient to assess any potential benefit in survival duration for tobramycin DPI. Three deaths occurred, all of which were in the tobramycin DPI group.[63]
- There appears to be a small incremental FEV_1% predicted associated with tobramycin DPI (see Table 12). However, as noted in Section 6.3, assumptions of a simple independent relationship between FEV_1% predicted and mortality should be interpreted with caution.
- Whilst Novartis did not provide data on exacerbations requested by the Assessment Group, results reported by Konstan *et al*[63] suggest that the incidence of lung disorder, which remains the best available proxy for exacerbation incidence, was higher in the tobramycin DPI group (relative risk = 1.12). It is likely that the cost of managing exacerbations would therefore be higher for tobramycin DPI than nebulised tobramycin. This would also likely result in a small QALY loss.
- The EAGER trial suggests a less favourable profile for tobramycin DPI across almost all of the common adverse events (especially cough and dysphonia) as compared against nebulised tobramycin.[63]

- The incremental drug cost per 28-day treatment cycle for tobramycin DPI is £602.80 higher than that for nebulised tobramycin. Based on the treatment time within the Assessment Group model, this would result in a discounted lifetime drug and nebuliser cost of around £144,442 per patient. Compared against nebulised tobramycin, the discounted lifetime incremental drug cost of tobramycin DPI is around £46,168 per patient. This explicitly excludes any cost disadvantage associated with the apparently higher exacerbation rate for tobramycin DPI.

Given the incremental cost of tobramycin DPI, in order to achieve a cost-utility ratio of £30,000 per QALY gained, tobramycin DPI would have to produce 1.54 additional discounted QALYs compared to nebulised tobramycin. In order to achieve a cost per QALY ratio of £20,000, tobramycin DPI would have to produce 2.31 additional discounted QALYs compared to nebulised tobramycin. Given the nebulised tobramycin transition matrix from COLO/DPI/02/06 for the comparator, the assumed treatment starting age (21 years) and the use of EQ-5D values for alternative FEV_1 bands,[58,107] neither of these incremental QALY thresholds is actually possible within the Assessment Group model.

As noted above, there may be a process-related utility benefit associated with tobramycin DPI due to treatment convenience which has not been considered within the above analysis. However, the trial investigators did not collect any information relating to HRQoL and therefore the plausibility of such an argument cannot be demonstrated empirically.

6.5 Budget impact analysis

Table 48 presents a simple budget impact analysis for colistimethate sodium DPI over the five prices ulitised. This analysis assumes that colistimethate sodium DPI and tobramycin DPI would replace only nebulised tobramycin, as this reflects the limitations of the scope of the economic analysis undertaken.

Table 48 Budget impact analysis

Parameter	Value	Population value	Budget impact	Source
Number cystic fibrosis patients with chronic *Pseudomonas aeruginosa*	*2,806*			CF Registry report 2010[7]
Proportion patients receiving tobramycin	*0.24*			
Estimated patients per year eligible for treatment	*673*			
Probability exacerbation/year (tobi)	[redacted]			COLO/DPI/02/06[67]
Probability exacerbation/year (coli)	[redacted]			
Probability exacerbation is major	[redacted]			
Cost minor exacerbation	£427.69			NHS Reference Costs 2010-11[125]
Cost major exacerbation	£1,500.14			
Mean cost exacerbation	£1,135.51			
Marginal cost of nebuliser maintenance	£200.00			Personal communication†
Nebulised tobramycin - drug, nebuliser and exacerbation costs / year	£8,898	£5,991,936		
Cost colistimethate sodium DPI / year (plus exacerbation costs) Price=£9.11	£7,585	£5,108,179	**-£883,757**	
Cost colistimethate sodium DPI / year (plus exacerbation costs) Price=£10.60	£8,673	£5,840,680	**-£151,256**	
Cost colistimethate sodium DPI / year (plus exacerbation costs) Price=[redacted]	£12,600	£8,485,548	**£2,493,612**	
Cost colistimethate sodium DPI / year (plus exacerbation costs) Price=£19.64	£15,272	£10,284,845	**£4,292,909**	
Cost colistimethate sodium DPI / year (plus exacerbation costs) Price=£19.64	£16,411	£11,051,758	**£5,059,822**	
Cost colistimethate sodium DPI / year (plus exacerbation costs) Price=£21.20	£29,617	£19,945,005	**£13,953,069**	
Cost tobramycin DPI / year (plus exacerbation costs)	£12,742	£8,580,710	**£2,588,774**	

†*Dr Diana Bilton, Consultant Physician / Honorary Senior Lecturer, Department of Respiratory Medicine, Royal Brompton Hospital*

The estimated budget impact of colistimethate sodium DPI is negative (cost saving) if the price of colistimethate sodium DPI is set at £9.11 per dose or £10.60 per dose. At the top end of the price range, the estimated cost to the NHS is around £14 million per year. Tobramycin DPI is expected to have an annual budget impact of around £2.6 million.

6.6 Discussion

6.6.1 Summary of available evidence

There is a dearth of economic evidence relating to the cost-effectiveness of colistimethate sodium DPI and tobramycin DPI for the treatment of *Pseudomonas aeruginosa* in patients with CF. The literature review did not identify any published economic analyses of colistimethate sodium DPI or tobramycin DPI. Novartis did not submit any economic evidence relating to the cost-effectiveness of tobramycin DPI. Forest did submit an economic model to assess colistimethate sodium DPI versus nebulised tobramycin, which suggests that colistimethate sodium DPI is expected to dominate nebulised tobramycin. However, this was subject to a number of methodological problems and biases which are likely to produce overly favourable estimates of cost-effectiveness. The basis of this model assumes that an absolute FEV_1 measurement is directly associated with survival duration. A review of the literature suggests that the validity of this relationship is dubious and is likely to be subject to considerable confounding. A re-analysis of the Forest model using more plausible assumptions suggests that the cost-effectiveness of colistimethate sodium DPI versus nebulised tobramycin is expected to range from dominating to £485,550 per QALY gained, depending on the price of the intervention.

6.6.2 Summary of the economic analysis undertaken by the Assessment Group

The Assessment Group developed a *de novo* health economic model based on patient-level data from the COLO/DPI/02/06 trial augmented using external sources. This model extrapolates 24-week FEV_1 to a lifetime horizon. Whilst this extrapolation is clearly subject to considerable uncertainty, the conclusions of the analysis appear robust as the short-term 24-week analysis of the COLO/DPI/02/06 trial produces consistent results to the lifetime model. An analysis of longitudinal patient-level data from the CF Registry suggests that the probabilities of transition between FEV_1 are relatively stable over time, which lends some weight to the credibility of the trial extrapolation.

The results of this analysis suggest that colistimethate sodium DPI is expected to produce fewer QALYs than nebulised tobramycin, both in the short-term and over a lifetime horizon. If the price of colistimethate sodium DPI is set at one of the prices which is higher than that of nebulised tobramycin, it is expected to be more expensive and hence dominated by nebulised tobramycin. If the price of colistimethate sodium DPI is set at £9.11, the incremental cost-effectiveness of nebulised tobramycin versus colistimethate sodium DPI is expected to be in the range £126,000 to £277,000 per QALY gained. If the price of colistimethate sodium DPI is set at £10.60, the incremental cost-effectiveness of nebulised tobramycin versus colistimethate sodium DPI is expected to be in the range £24,000 to £50,000 per QALY gained.

Insufficient data were available to produce a full economic evaluation of tobramycin DPI versus any comparator. Instead, a crude threshold analysis is presented to estimate the necessary QALY gain that tobramycin DPI would need to produce given its incremental lifetime cost. The model structure suggests that given its acquisition cost, it is not possible for tobramycin to have a cost-effectiveness ratio that is better than £30,000 per QALY gained.

7. ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

The introduction of colistimethate sodium DPI and tobramycin DPI would have a number of other implications for the NHS.

7.1 Treatment adherence and convenience

As noted in Chapter 5, one of the key potential benefits of dry powder formulations of these therapies is the reduced burden in treatment administration. However, it is unclear whether this would necessarily lead to improved treatment compliance, as a number of patients may not adhere to treatment due to increased side effects (e.g. cough). In principle, the technology could be used in a variety of settings, including home, hospital, work, or at school. It should also be noted that for many patients, the development of newer nebuliser devices which enable faster treatment administration will have already reduced the treatment time as compared against traditional nebulisers. It could be argued that the availability of dry powder treatment would increase the burden of treatment as most patients with *Pseudomonas aeruginosa* require nebulisers for other treatments, therefore a further inhaler device would involve adding to the equipment needed to treat patients. Research in this area is planned but has not yet commenced.

7.2 Training/impact on primary care

The introduction of colistimethate sodium DPI and tobramycin DPI may have implications for NHS staff training. There may be a need to monitor patients closely when they are initially placed on dry powder formulations due to the increase in some adverse events. Support for the patient will be needed from doctors, specialist nurses and physiotherapists. Most staff are however likely to already be familiar with dry powder technology formulations for other drugs such as bronchodilators.

7.3 Age of patients / appropriateness of use for children

Young children may struggle to use the dry powder technology. This is however most likely already dealt with by the licensing conditions of the dry powder technologies.

7.4 Reduced risk of contamination

Dry powder inhalers are disposable which reduces the risk of contamination and further infection. Previous nebulisers are prone to this kind of contamination unless regular maintenance is performed, thereby increasing the burden of treatment to the patient and family. Compliance with keeping these devices clean is poor. Cross contamination is less of a problem with single dose powder capsules as *Pseudomonas aeruginosa* can also colonise in bottles of opened solutions for nebulisers.

8. DISCUSSION

8.1 Statement of principal findings

8.1.1 Principal findings – clinical effectiveness

Three trials were included in the review. Both colistimethate sodium DPI and nebulised tobramycin DPI were reported to be non-inferior to nebulised tobramycin in pivotal Phase III non-inferiority trials, for the outcome FEV_1%, based on information from two of the trials. However, there are problems with the trials which indicate that the results should be judged with caution. None of the trials complied with the time horizon of 12 months follow-up recommended by the EMA for efficacy trials, with both following patients for 24 weeks only. As such, the existing evidence base does not include information about the long-term efficacy and safety of these treatments. Both of the large trials could also be criticised for the way they analysed the results, with the COLO/DPI/02/06 trial of colistimethate sodium DPI only reaching non-inferiority when analysed non-parametrically, and the EAGER trial of tobramycin DPI only presenting results without imputation. Study COLO/DPI/02/05 was not powered to detect an effect in FEV_1%, was only 4 weeks in duration (prior to cross over) and reported no significant differences in FEV_1% between arms and from baseline. It was not possible to draw any firm conclusions as to the relative efficacy as measured by FEV_1% of any intervention compared with any other intervention (except nebulised tobramycin) due to missing data, uncertain comparability of patient characteristics and incompatible methods of analysing the data.

As FEV_1% is a surrogate outcome, the EMA recommend that it should be considered alongside "harder" outcomes such as exacerbations, and should be supported with microbiological data. Sputum density data for tobramycin DPI supported the FEV_1% values seen with a decrease at week 20. Data on sputum density outcomes were not available for colistimethate sodium DPI. Resistance of around 20% was reported for the tobramycin arms across both Phase III trials, and of ≤1.1% for colistimethate sodium DPI. [redacted] but patients treated with DPIs spent less time on antibiotics. Adverse events were mostly similar between arms within trials, except for cough which was higher in both DPI intervention arms. More patients in the DPI intervention arms withdrew due to adverse events in both trials. The statistical and clinical significance of differences in sputum density,

resistance data, exacerbations, and adverse event data is not known. Insufficient mortality events were recorded and the study follow up was not long enough to draw conclusions as to the effect of DPI formulations on mortality in comparison to nebulised tobramycin.

8.1.2 Principal findings – cost-effectiveness

The cost-effectiveness of colistimethate sodium DPI and tobramycin DPI are subject to considerable uncertainty. This is driven by a number of factors including (1) an absence of any direct method of HRQoL elicitation within the pivotal clinical trials (2) the short-term nature of follow-up within these studies and the absence of sufficient survival data to allow extrapolation (3) the questionable validity of absolute measures of FEV_1 as an independent predictor of CF mortality and (4) gaps in the evidence base concerning the relative effectiveness of competing treatments for *Pseudomonas aeruginosa* lung infection. Given current evidence, questions relating to the long-term cost-effectiveness of the colistimethate sodium DPI and tobramycin are therefore inevitably hinged on the credibility of relationships between intermediate- and final outcomes.

A systematic review of existing cost-effectiveness studies did not identify any full economic evaluations of colistimethate sodium DPI or tobramycin DPI. Previous analyses were short-term and did not involve extrapolation to more relevant time horizons, nor did they involve the translation of intermediate outcomes to more policy-relevant economic outcome measures.

Two submissions were received from the manufacturers of colistimethate sodium DPI and tobramycin DPI. Novartis did not submit any economic evidence to support the argument that tobramycin DPI represents a cost-effective use of resources. Forest did submit an economic model to assess colistimethate sodium DPI versus nebulised tobramycin, which suggests that colistimethate sodium DPI is expected to dominate nebulised tobramycin. However, this was subject to a number of methodological problems and biases which are likely to produce overly favourable estimates of cost-effectiveness. The Forest submission was ambiguous with respect to the actual proposed price of colistimethate sodium DPI, and the net benefit estimates produced from the economic model did not include the acquisition costs of either the intervention or the comparator. This model is underpinned by the assumption that an absolute FEV_1 measurement is directly associated with survival duration (either at 1- or 2-years post-measurement). A review of the available literature suggests that the validity of this relationship is dubious and is likely to be subject to confounding due to other clinically relevant variables. Even if this relationship is considered plausible, and the methods of prediction are considered accurate, a re-analysis of the Forest model using more plausible assumptions suggests that the incremental cost-utility of colistimethate sodium DPI versus nebulised tobramycin is expected to range from dominating to £485,550 per QALY gained, depending on the price of the intervention.

The *de novo* health economic model developed by the Assessment Group is based on patient-level data from the COLO/DPI/02/06 trial augmented using external sources. This model defines differential states of HRQoL by FEV_1 strata, and extrapolates the observed FEV_1 transitions within COLO/DPI/02/06 trial to a lifetime horizon. No additional survival benefit is assumed. Whilst this extrapolation is clearly subject to considerable uncertainty, the conclusions of the analysis appear robust as the short-term 24-week analysis of the COLO/DPI/06 trial produces consistent results to the lifetime model. The results of this economic analysis suggest that colistimethate sodium DPI is expected to produce fewer QALYs than nebulised tobramycin, both in the short-term and over a lifetime horizon. If the price of colistimethate sodium DPI set at one of the prices which is higher than that of nebulised tobramycin, it is expected to be more expensive and hence dominated by nebulised tobramycin. If the price of colistimethate sodium DPI is set at £9.11, the incremental cost-effectiveness of nebulised tobramycin versus colistimethate sodium DPI is expected to be in the range £126,000 to £277,000 per QALY gained. If the price of colistimethate sodium DPI is set at £10.60, the incremental cost-effectiveness of nebulised tobramycin versus colistimethate sodium DPI is expected to be in the range £24,000 to £50,000 per QALY gained.

Insufficient data were available to produce a full economic evaluation of tobramycin DPI versus any relevant comparator. Instead, a crude threshold analysis is presented to estimate the necessary QALY gain that tobramycin DPI would need to produce in order to achieve a particular cost-utility ratio, given its incremental lifetime cost. In order to achieve a cost-utility ratio of £30,000 per QALY gained, tobramycin DPI would need to produce an estimated 1.54 additional discounted QALYs compared to nebulised tobramycin. In order to achieve a cost per QALY ratio of £20,000, tobramycin DPI would need to produce an estimated 2.31 additional discounted QALYs compared to nebulised tobramycin. The model structure suggests that neither of these QALY thresholds is achievable given the price of tobramycin DPI.

8.2 Strengths and limitations of the assessment

A key strength of this assessment is that the systematic review has been conducted to a high standard including comprehensive search strategies with study selection, data extraction and quality assessment checked by a second reviewer.

The review is limited by the small number of trials available, and methodological weaknesses and incompatibilities within the trials which inevitably limit the comparability of evidence across the trials. There are variations in the definition and measurement of the key outcomes, due to non-compliance with EMA research guidelines. No data which complies with the NICE reference case on quality of life was available from any of the trials.

The health economic model developed within this assessment was based on clinical opinion regarding current treatment pathways and systematic reviews of evidence relating to the plausibility of relationships between intermediate and final endpoints (rather than pure assumption). The model was populated using the best available evidence and was peer reviewed by several individuals with clinical and methodological expertise.

The Assessment Group model involves extrapolation of FEV_1 estimates within the COLO/DPI/06 trial. Within this analysis, the observable period is 24-weeks in duration whilst the projected period is around 43 years (when <1% patients are still alive). The considerable uncertainty surrounding the short-term evidence base inevitably results in uncertainty surrounding the long-term cost-effectiveness of colistimethate sodium DPI. One strength of the assessment is that the model considers the impact of this extrapolation on the cost-effectiveness of treatment. In addition, uncertainty surrounding the appropriate method of health state valuation is explored by applying a variety of health utility estimates within the model.

The key anticipated benefits of colistimethate sodium DPI and nebulised tobramycin concerns the increased convenience afforded by reduced treatment administration time as compared against nebulised antibiotics. In addition, the DPIs are more portable than nebulisers. These may represent "process utilities." However, none of the clinical trials attempted to capture these potential effects using a preference-based instrument. As a consequence, this potential effect is not reflected in the health economic analysis. It should be noted however that newer nebulisers such as the I-neb and eFlow devices also allow for faster treatment delivery than conventional nebulisers. The incremental benefits of this aspect of DPI delivery thus remain unclear.

8.3 Uncertainties

The key uncertainties within this assessment are:

- The relative efficacy and safety profiles of colistimethate sodium DPI and tobramycin DPI
- The long-term efficacy of treatment using colistimethate sodium DPI and tobramycin DPI versus current standard nebulised therapies
- The validity of the relationship between short-term impact on lung function and longer-term final patient outcomes (mortality and HRQoL)
- Whether there exists any long-term impact of DPI treatment on patient survival
- Long-term treatment compliance
- The clinical relevance of resistance to DPIs and its impact upon treatment efficacy
- The trade-off between ease/speed of drug administration using the inhaler devices and adverse events (and the impact of both on patients' HRQoL).

9. CONCLUSIONS

9.1 Main conclusions of the assessment

Both DPI formulations have been shown to be non-inferior to nebulised tobramycin as measured by FEV_1%. However, the results of these trials should be interpreted with caution due to means by which the results were analysed, the length of follow up, and concerns about the ability of FEV_1% to accurately represent changes in lung health. The impact of resistance to tobramycin is not known. When considered alongside other outcomes, it would appear possible that patients on DPI formulations experience more exacerbations, but spend less time on antibiotics, experience more cough adverse events and may be more likely to not tolerate the treatment. As such, the advantages and non-inferiority of DPI treatments compared to nebulised tobramycin remain unclear when all relevant outcomes are considered. Inevitably, the cost-effectiveness of the dry powder formulations is subject to considerable uncertainty. The Assessment Group model suggests that colistimethate sodium is expected to produce fewer QALYs than nebulised tobramycin. Depending on the price adopted for colistimethate sodium DPI, this results either in a situation whereby colistimethate sodium DPI is dominated by nebulised tobramycin, or one whereby the incremental cost-effectiveness of nebulised tobramycin versus colistimethate sodium DPI is in the range £24,000 to £277,000 per QALY gained. The economic analysis also suggests that given its price, it is highly unlikely that tobramycin DPI has a cost-effectiveness ratio below £30,000 per QALY gained when compared against nebulised tobramycin.

9.2 Implications for service provision

The burden upon the NHS of introducing DPIs is generally in terms of the drug acquisition cost. For many of these patients, nebulisers will still be required for administration of mucolytics and bronchodilators however there may be some reduction in the requirement for nebuliser maintenance.

9.3 Suggested research priorities

A randomised controlled trial to assess the longer-term ($\geq$ 12 months) efficacy of colistimethate sodium DPI and tobramycin DPI in comparison to nebulised treatments would be beneficial. Such a study should include the direct assessment of HRQoL using a relevant preference-based instrument. Future studies should ensure that the EMA guidelines are adhered to. In addition, high quality research concerning the relationship between FEV_1 or other measures of lung function and survival/HRQoL would be useful.

10. REFERENCES

1. Committee for Medicinal Products for Human Use (CHMP). Guideline on the clinical development of medicinal products for the treatment of cystic fibrosis. 2009; available from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/12/WC500017055.pdf. (accessed June 2011).

2. Davies, J.C., Alton, E.W., Bush, A. Cystic fibrosis. *BMJ* 2007; 335(7632):1255-1259.

3. Emerson, J., Rosenfeld, M., McNamara, S., Ramsey, B., Gibson, R.L. Pseudomonas aeruginosa and other predictors of mortality and morbidity in young children with cystic fibrosis. *Pediatr Pulmonol* 2002; 34(2):91-100.

4. Cystic Fibrosis Trust. Antibiotic treatment for cystic fibrosis: Report of the UK Cystic Fibrosis Antibiotic Working Group (3rd edition). 2009; i-100. Kent, Cystic Fibrosis Trust.

5. Yi, M.S., Tsevat, J., Wilmott, R.W., Kotagal, U.R., Britto, M.T. The impact of treatment of pulmonary exacerbations on the health-related quality of life of patients with cystic fibrosis: does hospitalization make a difference? *Journal of Paediatrics* 2004; 144(6):711-718 s.

6. Thornton, J., Elliott, R.A., Tully, M.P., Dodd, M., Webb, A.K. Clinical and economic choices in the treatment of respiratory infections in cystic fibrosis: Comparing hospital and home care. *Journal of Cystic Fibrosis* 2005; 4(4):239-247.

7. Cystic Fibrosis Trust. UK CF Registry Annual Data Report 2010. 2011; 1-67.

8. Gray, M.A. CFTR is a mechanosensitive anion channel: a real stretch? *Cell Science* 2010; 7(1):1-7.

9. Gadsby, D.C., Vergani, P., Csanady, L. The ABC protein turned chloride channel whose failure causes cystic fibrosis. *Nature* 2006; 440:477-483.

10. Mogayzel, P.J., Jr., Flume, P.A. Update in cystic fibrosis 2009. *American Journal of Respiratory & Critical Care Medicine* 2010; 181(6):539-544.

11. Moran, A., Becker, D., Casella, S.J., Gottlieb, P.A., Kirkman, M.S., Marshall, B.C. et al. Epidemiology, Pathophysiology, and Prognostic Implications of Cystic Fibrosis–Related Diabetes: A technical review. *Diabetes Care* 2010; 33(12):2677-2683.

12. Taccetti, G., Campana, S., Festini, F., Mascherini, M., Doring, G. Early eradication therapy against Pseudomonas aeruginosa in cystic fibrosis patients. *European Respiratory Journal* 2005; 26(3):458-461.

13. Griese, M., Muller, I., Reinhardt, D. Eradication of initial Pseudomonas aeruginosa colonization in patients with cystic fibrosis. *Eur J Med Res* 2002; 7:79-80.

14. Kosorok, M.R., Zeng, L., West, S.H., Rock, M.J., Splaingard, M.L., Laxova, A. et al. Acceleration of lung disease in children with cystic fibrosis after Pseudomonas aeruginosa acquisition. *Pediatr Pulmonol* 2001; 32:277-287.

15. Moreau-Marquis, S., Stanton, B.A., O'Toole, G.A. Pseudomonas aeruginosa biofilm formation in the cystic fibrosis airway. *Pulmonary Pharmacology & Therapeutics* 2008; 21(4):595-599.

16. Costerton, J.W., Philip, S., Stewart, E., reenberg, P. Bacterial Biofilms: A Common Cause of Persistent Infections. *Science* 1999; 284:1318.

17. Li, Z., Kosorok, M.R., Farrell, P.M., Laxova, A., West, S.E., Green, C.G. et al. Longitudinal development of mucoid Pseudomonas aeruginosa infection and lung disease progression in children with cystic fibrosis. *JAMA* 2005; 293(5):581-588.

18. Henry, R.L., Mellis, C.M., Petrovic, L. Mucoid Pseudomonas aeruginosa is a marker of poor survival in cystic fibrosis. *Pediatric Pulmonology* 1992; 12(3):158-161.

19. Wagener, J., Rasouliyan, L., Pasta, D.J., Mabie, J., Morgan, W., Konstan, M.W. Practice patterns for treating respiratory exacerbations in cystic fibrosis. *Pediatr Pulmonol* 2008; 43(Supplement 31):359.

20. Bilton, D., Canny, G.J., Conway, S., Dumcius, S., Hjelte, L., Proesmans, M. et al. Pulmonary exacerbation: towards a definition for use in clinical trials. Report from the EuroCareCF Working Group on outcome parameters in clinical trials. *J Cyst Fibros* 2011; 10(Suppl 2):S79-S81.

21. Dodge JA, Lewis PA, Stanton M, Wilsher J. Cystic fibrosis mortality and survival in the UK: 1947-2003. *European Respiratory Journal* 2007; 29:522-526.

22. UK CF Registry Annual Data Report 2008. 2008; available from http://www.cftrust.org.uk/aboutcf/publications/cfregistryreports/UK_CF_Registry-Annual_Data_Report_2008.pdf

23. Zemanick, E.T., Harris, J.K., Conway, S., Konstan, M.W., Marshall, B., Quittner, A.L. et al. Measuring and improving respiratory outcomes in cystic fibrosis lung disease: Opportunities and challenges to therapy. *Journal of Cystic Fibrosis* 2010; 9(1):1-16.

24. Cystic Fibrosis Trust. UK CF Registry Annual Data Report 2009. CF Registry 2011; 1-80.

25. Cystic Fibrosis Trust. Funding of clinical care for cystic fibrosis patients is revolutionised. 2011; available from www.cftrust.org.uk/pressoffice/pressreleases/PR_PbR.doc (accessed July 2011).

26. Henderson, A.J. Bronchoalveolar lavage. *Archives of Disease in Childhood* 1994; 70:167-169.

27. Consensus conference: management of patients with cystic fibrosis; pulmonary disease and infection guidelines. 2002. Paris.

28. British Society for Antimicrobial Chemotherapy. BSAC Methods for Antimicrobial Susceptibility Testing. *BSAC* 2011.

29. Miller, M.R., Hankinson, J., Brusasco, V., Burgos, F., Casaburi, R., Coates, A. et al. Standardisation of spirometry. *Eur Respir J* 2005; 26:319-338.

30. British Thoracic Society. Spirometry in practice. A practical guide to using spirometry in primary care. British Thoracic Society, London; 2005.

31. Knudson, R.J., Slatin, R.C., Lebowitz, M.D., Burrows, B. The Maximal Expiratory Flow-Volume, Curve Normal Standards, Variability and Effects of Age. *Am Rev Respir Dis* 1976; 113:589-590.

32. Hankinson, J.L., Odencrantz, J.R., Fedan, K.B. Spirometric Reference Values from a Sample of the General U.S. Population. *American Journal of Respiratory & Critical Care Medicine* 1999; 159:179-187.

33. Morris, J.F., Koski, A., Johnson, L.C. Spirometric Standards for Healthy Non-Smoking Adults. *Am Rev Respir Dis* 1971; 103:57-67.

34. Crapo, R., Morris, A.H., Clayton, P.D., Nixon, C.R. Lung Volumes in Healthy Nonsmoking Adults. *Bull Europ Physiopathol Respir* 1982; 18:419-425.

35. Cherniak, R.M., Raber, M.D. Normal Standards for Ventilatory Function Using an Automated Wedge Spirometer. *Am Rev Respir Dis* 1972; 106:38-46.

36. Gibson, R.L., Burns, J.L., Ramsey, B.W. Pathophysiology and Management of Pulmonary Infections in Cystic Fibrosis. *American Journal of Respiratory and Critical Care Medicine* 2003; 168(8):918-951.

37. Eichinger, M., Heussel, C.P., Kauczor, H.U., Tiddens, H., Puderbach, M. Computed Tomography and Magnetic Resonance Imaging in Cystic Fibrosis Lung Disease. *Journal of Magnetic Resonance Imaging* 2010; 32:1370-1378.

38. Brenner, D.J., Hall, E.J. Computed Tomography — An Increasing Source of Radiation Exposure. *N Engl J Med* 2007; 357:2277-2284.

39. Corey, M., Levison, H., Crozier, D. Five- to seven-year course of pulmonary function in cystic fibrosis. *Am Rev Respir Dis* 1976; 114:1085-1092.

40. Kerem, E., Reisman, J., Corey, M., Canny, G.J., Levison, H. Prediction of mortality in patients with cystic fibrosis. *N Engl J Med* 1992; 326:1187-1191.

41. Corey, M., Edwards, L., Levison, H., Knowles, M. Longitudinal analysis of pulmonary function decline in patients with cystic fibrosis. *Journal of Pediatrics* 1997; 131:809-814.

42. Liou, T.G., Adler, F.R., FitzSimmons, S., Cahill, B.C., Hibbs, J.R., Marshall, B.C. Predictive 5-year survivorship model of cystic fibrosis. *Am J Epidemiol* 2001; 153:345-352.

43. Hamblett, N., Rosenfeld, M., Emerson, J., Goss, C.H., Aitken, M.L. Developing cystic fibrosis lung transplant referral criteria using predictors of 2-year mortality. *American Journal of Respiratory & Critical Care Medicine* 2002; 166:1550-1555.

44. Nathanson, I., Ramirez-Garnicia, G., Wiltrout, S.A. Decreased attendance at cystic fibrosis centers by children covered by managed care insurance. *Research and Practice* 2005; 95(11):1958-1963.

45. Gee, L., Abbott, J., Conway, S.P., Etherington, C., Webb, A.K. Development of a disease specific health related quality of life measure for adults and adolescents with cystic fibrosis. *Thorax* 2000; 55(11):946-954.

46. Henry, B., Aussage, P., Grosskopf, C., Goehrs, J.M. Development of the Cystic Fibrosis Questionnaire (CFQ) for assessing quality of life in pediatric and adult patients. *Qual Life Res* 2003; 12(1):63-76.

47. Goss, C.H., Edwards, T.C., Ramsey, B.W., Aitken, M.L., Patrick, D.L. Patient reported respiratory symptoms in cystic fibrosis. *J Cyst Fibrosis* 2009; 8:245-252.

48. Goldbeck, L., Schmitz, T.G., Henrich, G., Herschbach, P. Questions on life satisfaction for adolescents and adults with cyctic fibrosis: development of a disease-specific questionnaire. *Chest* 2003; 123(1):42-48.

49. Quittner, A.L., Sweeney, S., Watrous, M., Munzenberger, P., Bearss, K., Gibson, N.A. et al. Translation and linguistic validation of a disease-specific quality of life measure for cystic fibrosis. *J Pediatr Psychol* 2000; 25(6):403-414.

50. Modi, A.C., Quittner, A.L. Validation of a disease-specific measure of health-related quality of life for children with cystic fibrosis. *J Pediatr Psychol* 2003; 28(8):535-545.

51. Jaffé A, Francis J, Rosenthal M, , B.A. Long-term azithromycin may improve lung function in children with cystic fibrosis. *Lancet* 1998; 351(9100):420.

52. Cai Y, Chai D, Wang R, Bai N, Liang BB, Liu Y. Effectiveness and safety of macrolides in cystic fibrosis patients: a meta-analysis and systematic review. *J Antimicrob Chemother* 2011; 66(5):968-978.

53. Høiby N. Recent advances in the treatment of Pseudomonas aeruginosa infections in cystic fibrosis. *BMC Medicine* 2011; 9(32).

54. Wallis C. Mucolytic therapy in cystic fibrosis. *Journal of the Royal Society of Medicine* 2001; 94(Suppl40):17-24.

55. Jarrett J. The economics of cystic fibrosis care in the East of England: PhD thesis. 2010. University of East Anglia.

56. National Institute for Health and Clinical Excellence (NICE). Mannitol dry powder for inhalation for the treatment of cystic fibrosis: A Single Technology Appraisal - Final scope. 2011; available from http://www.nice.org.uk/nicemedia/live/12224/50374/50374.pdf (accessed July 2011).

57. Lorian, V. Antibiotics in Laboratory Medicine. Williams & Wilkins Press; 1996; 589-590.

58. Novartis Pharmaceuticals. Colistimethate sodium powder (Colobreathe®) and tobramycin powder for inhalation (TOBI Podhaler®) for the treatment of pseudomonas lung infection in cystic fibrosis - Novartis submission to NICE. *Novartis Submission to NICE* 2011.

59. Association of the Royal Pharmaceutical Society of Great Britain. British National Formulary Number 62. 2011.

60. National Institute for Health and Clinical Excellence (NICE). Colistimethate sodium powder and tobramycin powder for inhalation for the treatment of pseudomonas lung infection in cystic fibrosis - Final scope. 2010; available from http://www.nice.org.uk/nicemedia/live/13068/52778/52778.pdf (accessed June 2011).

61. Centre for Reviews and Dissemination. CRD's guidance for undertaking systematic reviews in health care. 2009. University of York, CRD.

62. Paiggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJV. Reporting of noninferiority and equivalence randomized trials. *JAMA* 2006; 295:1152-1160.

63. Konstan, M.W., Flume, P.A., Kappler, M., Chiron, R., Higgins, M., Brockhaus, F. et al. Safety, efficacy and convenience of tobramycin inhalation powder in cystic fibrosis patients: The EAGER trial. *Journal of Cystic Fibrosis* 2011; 10(1):54-61.

64. Forest Laboratories UK Ltd. Colistimethate sodium powder for inhalation for the treatment of Pseudomonas lung infection in cystic fibrosis - Forest Submission to NICE. *Forest Submission to NICE* 2011.

65. Davies, J.C., Hall, P., Francis, J., Scott, S., Geddes, D.M., Conway, S. et al. A dry powder formulation of Colistimethate Sodium is safe and well tolerated in adults and children with CF. *Cystic Fibrosis Conference* 2004.

66. Konstan, M., Flume, P.A., Brockhaus, F., Angyalosi, G., He, E., Geller, D. Safety and efficacy of tobramycin inhalation powder (TIP) in treating CF patients infected with Pseudomonas aeruginosa (Pa). *Journal of Cystic Fibrosis* 2010; 9(Supplement 1):S22.

67. Forest Laboratories UK Ltd. A randomised, open label study to compare the efficacy and safety of a dry powder formulation of inhaled colistimethate sodium and nebulised TNSFI (tobramycin nebuliser solution for inhalation, TOBI®) in cystic fibrosis patients with *Pseudomonas aeruginosa* lung infection - Clinical Study Report. 2009; 1-8411.

68. Forest Laboratories UK Ltd. A randomised, open label study to compare the efficacy and safety of a dry powder formulation of inhaled colistimethate sodium and nebulised TNSFI (tobramycin nebuliser solution for inhalation, TOBI®) in cystic fibrosis patients with Pseudomonas aeruginosa lung infection. Final protocol no: COLO/DPI/02/06. 2011.

69. Hodson, M.E., Gallagher, C.G., Govan, J.R. A randomised clinical trial of nebulised tobramycin or colistin in cystic fibrosis. *The European Respiratory Journal : Official Journal of the European Society for Clinical Respiratory Physiology* 2002; 20(3):658-664.

70. Jensen, T., Pedersen, S.S., Garne, S., Heilmann, C., Hoiby, N., Koch, C. Colistin inhalation therapy in cystic fibrosis patients with chronic Pseudomonas aeruginosa lung infection. *J Antimicrob Chemother* 1987; 19(6):831-838.

71. Chuchalin, A., Csiszer, E., Gyurkovics, K., Bartnicka, M.T., Sands, D., Kapranov, N. et al. A formulation of aerosolized tobramycin (Bramitob) in the treatment of patients with cystic fibrosis and Pseudomonas aeruginosa infection: a double-blind, placebo-controlled, multicenter study. *Paediatric Drugs* 2007; 9 Suppl 1:21-31.

72. Lenoir G, Antypkin, Y.G., Miano, A., Moretti, P., Zanda, M., Varoli, G. et al. Efficacy, safety, and local pharmacokinetics of highly concentrated nebulized tobramycin in patients with cystic fibrosis colonized with pseudomonas auriginosa. *Pediatric Drugs* 2007; 9(s1):11-20.

73. Maclusky, I.B., Gold, R., Corey, M., Levison, H. Long-term effects of inhaled tobramycin in patients with cystic fibrosis colonized with Pseudomonas aeruginosa. *Pediatric Pulmonology* 1989; 7(1):42-48.

74. Ramsey, B.W., Pepe, M.S., Quan, J.M., Otto, K.L., Montgomery, A.B., Williams-Warren, J. et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. *New England Journal of Medicine* 1999; 340(1):23-30.

75. Moss, R.B. Administration of aerosolized antibiotics in cystic fibrosis patients. *Chest* 2001; 120(3 Suppl):107S-113S.

76. Moss, R.B. Long-term benefits of inhaled tobramycin in adolescent patients with cystic fibrosis. *Chest* 2002; 121(1):55-63.

77. Nasr, S.Z., Gordon, D., Sakmar, E., Yu, X., Christodoulou, E., Eckhardt, B.P. et al. High resolution computerized tomography of the chest and pulmonary function testing in evaluating the effect of tobramycin solution for inhalation in cystic fibrosis patients. *Pediatr Pulmonol* 2006; 41(12):1129-1137.

78. Nasr, S.Z., Sakmar, E., Christodoulou, E., Eckhardt, B.P., Streetman, D.S., Strouse, P.J. The use of high resolution computerized tomography (HRCT) of the chest in evaluating the effect of tobramycin solution for inhalation in cystic fibrosis lung disease. *Pediatric Pulmonology* 2010; 45(5):440-449.

79. Murphy, T.D., Anbar, R.D., Lester, L.A., Nasr, S.Z., Nickerson, B., VanDevanter, D.R. et al. Treatment with tobramycin solution for inhalation reduces hospitalizations in young CF subjects with mild lung disease. *Pediatric Pulmonology* 2004; 38(4):314-320.

80. Ramsey, B.W., Dorkin, H.L., Eisenberg, J.D., Gibson, R.L., Harwood, I.R., Kravitz, R.M. et al. Efficacy of aerosolized tobramycin in patients with cystic fibrosis. *New England Journal of Medicine* 1993; 328(24):1740-1746.

81. Konstan, M.W., Geller, D.E., Minic, P., Brockhaus, F., Zhang, J., Angyalosi, G. Tobramycin inhalation powder for P. aeruginosa infection in cystic fibrosis: the EVOLVE trial. *Pediatric Pulmonology* 2011; 46:230-238.

82. Schulz, K.F., Chalmers, I., Hayes, R.J., Altman, D.G. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995; 273(5):408-412.

83. Kjaergard, L.L., Villumsen, J., Gluud, C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Ann Intern Med* 2001; 135(11):982-989.

84. Juni, P., Altman, D.G., Egger, M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. *BMJ* 2001; 323(7303):42-46.

85. ICH Expert Working Group. ICH Harmonised tripartite guideline: Clinical safety data management - definitions and standards for expedited reporting E2A. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. 1994; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf.

86. Drummond, M.F., Sculpher, M., Torrance, G.W., O'Brien, B.J., Stoddart, G.L. Methods for the economic evaluation of health care programmes. 3rd Edition ed. Oxford University press, New York; 2005.

87. Wolter, J.M., Bowler, S.D., Nolan, P.J., McCormack, J.G. Home intravenous therapy in cystic fibrosis: a prospective randomized trial examining clinical, quality of life and cost aspects. *European Respiratory Journal* 1997; 10(4):896-900.

88. Iles, R., Legh-Smith, J., Drummond, M., Prevost, A., Vowler, S. Economic evaluation of Tobramycin nebuliser solution in cystic fibrosis. *Journal of Cystic Fibrosis* 2003; 2(3):120-128.

89. Guyatt, G.H., Berman, L.B., Townsend, M., Pugsley, S.O., Chambers, L.W. A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987; 42:773-778.

90. Grieve, R., Thompson, S., Normand, C., Suri, R., Bush, A., Wallis, C. A cost-effectiveness analysis of rhDNase in children with CF. *Int J Technol Assess Health Care* 2003; 19(1):71-79.

91. National Institute for Health and Clinical Excellence (NICE). Guide to the methods of technology appraisal. *NICE, London* 2008. 2011.

92. Rowen, D., Brazier, J. Estimation of EQ5D-Y utilities using CFQ. Preliminary Report. 2010; September 2010.

93. Eidt-Koch, D., Mittendorf, T., Greiner, W. Cross-sectional validity of the EQ-5D-Y as a generic health outcome instrument in children and adolescents with cystic fibrosis in Germany. *BMC Pediatrics* 2009; 9:55.

94. Cystic Fibrosis Foundation. 2011; available from http://www.cff.org/ (accessed Sep 2011).

95. Department of Health. NHS Reference Costs 2009-2010. 2011; available from http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_123459 (accessed Sep 2011).

96. Association of the British Pharmaceutical Society. British National Formulary number 61. 2010; available from http://bnf.org/ (accessed July 2011).

97. Wenninger, K., Aussage, P., Wahn, U., Staab, D. The revised German Cystic Fibrosis Questionnaire: Validation of a disease-specific health-related quality of life instrument. *Quality of Life Research* 2003; 12(1):77-85.

98. Wille, N., Badia, X., Bonsel, G.J., Burstrom, K., Cavrini, G., Devlin, N. et al. Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. *Quality of Life Research* 2010; 19(6):875-886.

99. Rowen, D., Longworth, L. The use of mapping methods to estimate health state utility values. 2011; available from http://www.nicedsu.org.uk/TSD%2010%20mapping%20FINAL.pdf (accessed Sept. 2011).

100. Kind, P., Hardman, G., Macran, S. UK population norms for EQ-5D. 2011; available from http://www.york.ac.uk/media/che/documents/papers/discussionpapers/CHE%20Discussion%20Paper%20172.pdf (accessed Aug 2011).

101. Taylor, R., Elston, J. The use of surrogate outcomes in model-based cost-effectiveness analyses: a survey of UK Health Technology Assessment reports. *Health Technology Assessment* 2009; 13(8).

102. International Conference on Harmonisation guidelines for the conduct of clinical trials for the registration of drugs. E9: statistical principles for clinical trials. 2012; available from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf (accessed Jan. 2012).

103. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred and conceptual framework. *Clin Pharmacol Ther* 2001; 22:485-502.

104. Johnson, J.A., Connolly, M.A., Zuberbuhler, P., Brown, N.E. Health-related quality of life for adults with cystic fibrosis: a regression approach to assessing the impact of recombinant human DNase. *Pharmacotherapy* 2000; 20(10):1167-1174.

105. Stahl, E., Lindberg, A., Jansson, S.A., Ronmark, E., Svensson, K., Andersson, F. et al. Health-related quality of life is related to COPD disease severity. *Health & Quality of Life Outcomes* 2005; 3:56.

106. Yi, M.S., Britto, M.T., Wilmott, R.W., Kotagul, U.R., Eckman, M.H., Nielson, D.W. et al. Health values of adolescents with cystic fibrosis. *Journal of Pediatrics* 2003; 142:133-140.

107. Bradley, J., Blume, S., Stafford, M., Balp, M., Elborn, S. Quality of life and health utility in patients with cystic fibrosis. *European Respiratory Society Conference* 2010.

108. Ketchell, R.I., Roughton, M., Agent, P., Gyi, K., Hodson, M.E. Predicting survival in end-stage cystic fibrosis. *Respiratory Medicine* 2009; 103(10):1441-1447.

109. Ellaffi, M., Vinsonneau, C., Coste, J., Hubert, D., Burgel, P., Dhainaut, J. et al. One-year outcome after severe pulmonary exacerbation in adults with cystic fibrosis. *Americann Journal of Respiratory and Critical Care Medicine* 2005; 171:158-164.

110. Simmonds, N.J., Macneill, S.J., Cullinan, P., Hodson, M.E. Cystic fibrosis and survival to 40 years: a case-control study. *European Respiratory Journal* 2010; 36(6):1277-1283.

111. Courtney, J.M., Bradley, J., Mccaughan, J., O'Connor, T.M., Shortt, C., Bredin, C.P. et al. Predictors of mortality in adults with cystic fibrosis. *Pediatric Pulmonology* 2007; 42(6):525-532.

112. Schluchter, M.D., Konstan, M.W., Davis, P.B. Jointly modelling the relationship between survival and pulmonary function in cystic fibrosis patients. *Statistics in Medicine* 2002; 21(9):1271-1287.

113. Augarten, A., Akons, H., Aviram, M., Bentur, L., Blau, H., Picard, E. et al. Prediction of mortality and timing of referral for lung transplantation in cystic fibrosis patients. *Pediatric Transplantation* 2001; 5(5):339-342.

114. Milla, C.E., Warwick, W.J. Risk of death in cystic fibrosis patients with severely compromised lung function. *Chest* 1998; 113(5):1230-1234.

115. Hayllar, K.M., Williams, S.G., Wise, A.E., Pouria, S., Lombard, M., Hodson, M.E. et al. A prognostic model for the prediction of survival in cystic fibrosis. *Thorax* 1997; 52(4):313-317.

116. Aurora, P., Wade, A., Whitmore, P., Whitehead, B. A model for predicting life expectancy of children with cystic fibrosis. *Eur Respir J* 2000; 16:1056-1060.

117. Mayer-Hamblett, N., Rosenfeld, M., Emerson, J., Goss, C., Aitken, M.L. Developing cystic fibrosis lung transplant referral criteria using predictors of 2-year mortality. *American Journal of Respiratory & Critical Care Medicine* 2002; 166:1550-1555.

118. Belkin RA, Henig NR, Singer LG, Chaparro C, Rubenstein RC, Xie SX et al. Risk factors for death of patients with cystic fibrosis awaiting lung transplantation. *American Journal of Respiratory & Critical Care Medicine* 2005; 173:659-666.

119. George, P.M., Banya, W., Pareek, N., Bilton, D., Cullinan, P. Improved survival at low lung function in cystic fibrosis: cohort study from 1990 to 2007. *BMJ* 2011; 342.

120. Grutters, J., Joore, M., Wiegman, E., Langendijk, H., De, R.D., Hochstenbag, M. et al. Health-related quality of life in patients surviving non-small cell lung cancer. *Radiotherapy and Oncology Conference: European Society for Therapeutic Radiology and Oncology, ESTRO 29 Barcelona Spain* 2010;S344-S345.

121. Polley, L., Yaman, N., Heaney, L., Cardwell, C., Murtagh, E., Ramsey, J. et al. Impact of cough across different chronic respiratory diseases - Comparison of two cough-specific health-related quality of life questionnaires. *Chest* 2008; 134(2):295-302.

122. Punekar, Y.S., Rodriguez-Roisin, R., Sculpher, M., Jones, P., Spencer, M. Implications of chronic obstructive pulmonary disease (COPD) on patients' health status: A western view. *Respiratory Medicine* 2007; 101(3):661-669.

123. Ko, Y., Coons, S.J. Self-reported chronic conditions and EQ-5D index scores in the US adult population. *Current Medical Research & Opinion* 2006; 22(10):2065-2071.

124. Anyanwu, A.C., McGuire, A., Rogers, C.A., Murday, A.J. Assessment of quality of life in lung transplantation using a simple generic tool. *Thorax* 2001; 56(3):218-222.

125. Department of Health. NHS Reference Costs 2010-2011. 2012. London, DH.

126. Briggs, A., Claxton, K., Sculpher, M. Decision modelling for health economic evaluation. Oxford University Press, New York; 2006.

127. Conway, S. A randomised, open label study to compare the efficacy and safety of a dry powder formulation of inhaled colistimethate sodium and nebulised TNSFI (Tobramycin Nebuliser Solution for Inhalation, TOBI) in cystic fibrosis patients with pseudomonas aerug. 2006.

128. Edenborough, F.P. Assessing total and regional lung deposition of colistin delivered using a dry powder inhaler and a nebuliser device in adult volunteers with cystic fibrosis. 2001.

129. Geller, D.E., Konstan, M.W., Smith, J., Noonberg, S.B., Conrad, C. Novel tobramycin inhalation powder in cystic fibrosis subjects: pharmacokinetics and safety. *Pediatric Pulmonology* 2007; 42(4):307-313.

130. Geller, D.E., Flume, P.A., Brockhaus, F., Zhang, J., Angyalosi, G., He, E. et al. Treatment convenience and satisfaction of tobramycin inhalation powder (TIP) versus TOBI in cystic fibrosis (CF) patients. *Journal of Cystic Fibrosis* 2010; 9(Supplement 1):S22.

131. Konstan, M. Safety of Tobramycin Inhalation Powder (TIP) vs Tobramycin Solution for Inhalation in Patients With Cystic Fibrosis. 2006.

132. Konstan, M.W., eller, D.E., rockhaus, F., hang, J., ngyalosi, G. Tobramycin Inhalation Powder Is Effective and Safe in the Treatment of Chronic Pulmonary Pseudomonas aeruginosa (Pa) Infection in Patients with Cystic Fibrosis. *American Journal of Respiratory and Critical Care Medicine* 2009.

133. Le Brun, P.P.H., De Boer, A.H., Mannes, G.P.M., de Fraeture, D.M.I., Brimicombe, R.W., Touw, D.J. et al. Dry powder inhalation of antibiotics in cystic fibrosis therapy: part 2: Inhalation of a novel colistin dry powder formulation: a feasibility study in healthy volunteers and patients. *European Journal of Pharmaceutics and Biopharmaceutics* 2002; 54(1):25-32.

134. Newhouse, M.T., irst, P.H., uddu, S.P., alter, Y.H., arara, T.E., lark, A.R. et al. Inhalation of a dry powder tobramycin PulmoSphere formulation in healthy volunteers. *Chest* 2003.

135. Novartis Pharmaceuticals. A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Phase III Study in Cystic Fibrosis (CF) Subjects to Assess Efficacy, Safety and Pharmacokinetics of Tobramycin Inhalation Powder From a Modified Manufacturing Process (TIPnew). 2009.

136. A Study of Tobramycin Inhalation Powder From a Modified Manufacturing Process Versus Placebo (EDIT). 2009.

137. Novartis Pharmaceuticals. A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase 3 Trial to Assess the Efficacy and Safety of Tobramycin Inhalation Powder (TIP) in Cystic Fibrosis (CF) Subjects. 2005.

138. Novartis Pharmaceuticals. Tobramycin Inhalation Powder (TIP) in Cystic Fibrosis Subjects. 2005.

139. Westerman, E.M., Le Brun, P.P., Touw, D.J., Frijlink, H.W., Heijerman, H.G. Effect of nebulized colistin sulphate and colistin sulphomethate on lung function in patients with cystic fibrosis: a pilot study. *Journal of Cystic Fibrosis* 2004; 3(1):23-28.

140. Westerman, E.M., De Boer, A.H., Le Brun, P.P., Touw, D.J., Roldaan, A.C., Frijlink, H.W. et al. Dry powder inhalation of colistin in cystic fibrosis patients: a single dose pilot study. *Journal of Cystic Fibrosis* 2007; 6(4):284-292.

141. Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU Technical Support Document 1: Introduction to evidence synthesis for decision making. 2011; 1-24. University of Sheffield, Decision Support Unit.

142. Alothman, G.A., Alsaadi, M.M., Ho, B.L., Ho, S.L., Dupuis, A., Corey, M. et al. Evaluation of bronchial constriction in children with cystic fibrosis after inhaling two different preparations of tobramycin. *Chest* 2002; 122(3):930-934.

143. Beringer, P.M., Vinks, A.A., Jelliffe, R.W., Shapiro, B.J. Pharmacokinetics of tobramycin in adults with cystic fibrosis: implications for once-daily administration. *Antimicrobial Agents & Chemotherapy* 2000; 44(4):809-813.

144. Denk, O., Coates, A.L., Keller, M., Leung, K., Green, M., Chan, J. et al. Lung delivery of a new tobramycin nebuliser solution (150 mg/1.5 ml) by an investigational eFlow« nebuliser is equivalent to TOBI« but in a fraction of time. *Journal of Cystic Fibrosis* 2009; 8(Supplement 2):S66.

145. Mazurek, H. A Study Comparing the Efficacy and Tolerability of TobrinebÂ®/ActitobÂ®/BramitobÂ® Versus TOBIÂ®. 2009.

146. Keller, M., Coates, A.L., Griese, M., Denk, O., Schierholz, J., Knoch, M. In-vivo data support equivalent therapeutic efficacy of a new tobramycin inhalation solution (150 mg/1.5 ml) administered by the eFlow« electronic nebuliser compared to TOBI« in the PARI LC PLUS«. *Journal of Cystic Fibrosis* 2010; 9(Supplement 1):S22.

147. Nikolaizik, W.H., Vietzke, D., Ratjen, F. A pilot study to compare tobramycin 80 mg injectable preparation with 300 mg solution for inhalation in cystic fibrosis patients. *Canadian Respiratory Journal* 2008; 15(5):259-262.

148. Winnie, G.B., Cooper, J.A., Witson, J., Cowan, R.G., Mayer, D., Lepow, M. Comparison of 6 and 8 hourly tobramycin dosing intervals in treatment of pulmonary exacerbations in cystic fibrosis patients. *Pediatric Infectious Disease Journal* 1991; 10(5):381-386.

149. Poli, G., Acerbi, D., Pennini, R., Soliani, R.A., Corrado, M.E., Eichler, H.G. et al. Clinical pharmacology study of Bramitob, a tobramycin solution for nebulization, in comparison with Tobi. *Paediatric Drugs* 2007; 9 Suppl 1:3-9.

150. Riethmueller, J., Ballmann, M., Schroeter, T.W., Franke, P., von, B.R., Claass, A. et al. Tobramycin once- vs thrice-daily for elective intravenous antipseudomonal therapy in pediatric cystic fibrosis patients. *Infection* 2009; 37(5):424-431.

151. Rietschel, E., Staab, D., Vn, K.S., Merkel, N., Heuer, H.-E., Posselt, H.-G. Pharmacokinetics of continuous treatment with o.d. or b.i.d. inhalation of tobramycin (TOBI). *Journal of Cystic Fibrosis* 2010; S23.

152. Spencer, D. Efficacy and Safety of 28 or 56 Days Treatment With Inhaled Tobramycin Nebuliser Solution for Pseudomonas Aeruginosa Infection in Children With Cystic Fibrosis. 2006.

153. Westerman, E.M., Boer, A.H., Touw, D.J., Brun, P.P., Roldaan, A.C., Frijlink, H.W. et al. Aerosolization of tobramycin (TOBI) with the PARI LC PLUS reusable nebulizer: which compressor to use? Comparison of the CR60 to the PortaNeb compressor. *Journal of Aerosol Medicine & Pulmonary Drug Delivery* 2008; 21(3):269-280.

154. Whitehead, A., Conway, S.P., Etherington, C., Caldwell, N.A., Setchfield, N., Bogle, S. Once-daily tobramycin in the treatment of adult patients with cystic fibrosis. *European Respiratory Journal* 2002; 19(2):303-309.

155. Wood, P.J., Ioannides-Demos, L.L., Li, S.C., Williams, T.J., Hickey, B., Spicer, W.J. et al. Minimisation of aminoglycoside toxicity in patients with cystic fibrosis. *Thorax* 1996; 51(4):369-373.

156. Proesmans, M., Boulanger, L., Vermeulen, F., De, B.K. Eradication of recent Pseudomonas aeruginosa isolation: TOBI versus colistin/ ciprofloxacin [abstract]. *Journal of Cystic Fibrosis* 2008; 7 Suppl 2:S64.

157. Adeboyeku, D., Scott, S., Hodson, M.E. Open follow-up study of tobramycin nebuliser solution and colistin in patients with cystic fibrosis. *Journal of Cystic Fibrosis* 2006; 5(4):261-263.

158. Webb, A.K. An open-label, randomised clinical trial of the efficacy and safety of Tobramycin solution for inhalation and aerosolised Colistin Sulphomethate Sodium in patients with cystic fibrosis. 1999.

159. Weller, P. An open label, randomised clinical trial of the efficacy and safety of Tobramycin solution for inhalation or aerosolised Colistin Sulphomethate Sodium (Colomycin) in patients with cystic fibrosis (CF). 1999.

160. Montgomery, A.B. Phase III Randomized Study of the Inhalation of Tobramycin in Patients With Cystic Fibrosis. 2000.

161. Wientzen, R., Prestidge, C.B., Kramer, R.I. Acute pulmonary exacerbations in cystic fibrosis. A double-blind trial of tobramycin and placebo therapy. *American Journal of Diseases of Children* 1980; 134(12):1134-1138.

162. Wiesemann, H.G., Steinkamp, G., Ratjen, F., Bauernfeind, A., Przyklenk, B., Doring, G. et al. Placebo-controlled, double-blind, randomized study of aerosolized tobramycin for early treatment of Pseudomonas aeruginosa colonization in cystic fibrosis. *Pediatric Pulmonology* 1998; 25(2):88-92.

163. Al Ansari, N.A., Foweraker, J., Mackeown, D., Bilton, D. Evaluation of once daily tobramycin versus the traditional three time daily for the treatment of acute pulmonary exacerbations in adult cystic fibrosis patients. *Qatar Medical Journal* 2006; 15(1):34-38.

164. Ramsey, B.W., Retsch-Bogart, G., Treggiari, M. Comparison of Two Treatment Regimens to Reduce PA Infection in Children With Cystic Fibrosis. 2004.

165. Master, V., Roberts, G.W., Coulthard, K.P., Baghurst, P.A., Martin, A., Roberts, M.E. et al. Efficacy of once-daily tobramycin monotherapy for acute pulmonary exacerbations of cystic fibrosis: a preliminary study. *Pediatric Pulmonology* 2001; 31(5):367-376.

166. Flume, P. Trial of Aeroquin Versus Tobramycin Inhalation Solution (TIS) in Cystic Fibrosis (CF) Patients. 2011.

167. Kassaa, B. Pharmacokinetic Bioequivalence Study of NebcinalÂ® 150mg/3ml Administered by AeronebÂ® IdehalerÂ® Versus TobiÂ® 300mg/5ml Administered by Pari LC PlusÂ®. 2011.

168. Smyth, A., Tan, K.H., Hyman-Taylor, P., Mulheran, M., Lewis, S., Stableforth, D. et al. Once versus three-times daily regimens of tobramycin treatment for pulmonary exacerbations of cystic fibrosis - the TOPIC study: a randomised controlled trial. *Lancet* 2005; 365(9459):573-578.

169. Canis, F., Trivier, D., Vic, P., Ategbo, S., Turck, D., Husson, M.O. [Comparison of the pharmacokinetics of tobramycin administered in a single daily dose or in 3 doses in cystic fibrosis]. [French]. *Pathologie Biologie* 1998; 46(6):449-451.

170. Trapnell, B.C., Rolfe, M., McColley, S., Montgomery, A.B., Moorehead, L., Geller, D. Fosfomycin/tobramycin for inhalation (FTI): Efficacy results of a phase 2 placebocontrolled trial in patients with cystic fibrosis and pseudomonas aeruginosa. *Pediatric Pulmonology* 2010; 302.

171. Conway, S.P., Miller, M.G., Ramsden, C., Littlewood, J.M. Intensive treatment of pseudomonas chest infection in cystic fibrosis: a comparison of tobramycin and ticarcillin, and netilmicin and ticarcillin. *Acta Paediatrica Scandinavica* 1985; 74(1):107-113.

172. De, B.K., Smet, M., Eggermont, E. Treatment of Pseudomonas lung infection in cystic fibrosis with piperacillin plus tobramycin versus ceftazidime monotherapy: preliminary communication. *Pediatric Pulmonology* 1989; 7(3):171-173.

173. Martin, A.J., Smalley, C.A., George, R.H., Gealing, D.E., Anderson, C.M. Gentamicin and tobramycin compared in the treatment of mucoid pseudomonas lung infections in cystic fibrosis. *Archives of Disease in Childhood* 1980; 55:604-607.

174. McLaughlin, F.J., Matthews, W.J., Jr., Strieder, D.J., Sullivan, B., Taneja, A., Murphy, P. et al. Clinical and Bacteriological Responses to 3 Antibiotic Regimens for Acute Exacerbations of Cystic Fibrosis Ticarcillin Tobramycin Azlocillin Tobramycin and Azlocillin Placebo. *Journal of Infectious Diseases* 1983; 147(3):559-567.

175. Parry, M.F., Neu, H.C. A comparative study of ticarcillin plus tobramycin versus carbenicillin plus gentamicin for the treatment of serious infections due to gram-negative bacilli. *American Journal of Medicine* 1978; 64(6):961-966.

176. Pedersen, S.S., Pressler, T., Pedersen, M. Immediate and prolonged clinical efficacy of ceftazidime versus ceftazidime plus tobramycin in chronic Pseudomonas aeruginosa infection in cystic fibrosis. *Scandinavian Journal of Infectious Diseases* 1986; 18(2):133-137.

177. Wesley, A.W., Quested, C., Edgar, B.W., Lennon, D.R. A double-blind comparison of ceftazidime with tobramycin and ticarcillin in the treatment of exacerbations of pseudomonas chest infection in children with cystic fibrosis [abstract]. *10th International Cystic Fibrosis Congress* 1988;R.

178. Taccetti, G., Bianchini, E., Zavataro, L., Campana, S., Defilippi, G., Ravenni, N. et al. Pseudomonas aeruginosa eradication in cystic fibrosis: Preliminary data from a randomized multicenter study of two different early antibiotic treatment protocols. *Pediatric Pulmonology* 2010; 337-338.

179. Zavataro, L., Taccetti, G., Cariani, L., Ravenni, N., Braccini, G., Bresci, S. et al. Epidemiology of first/new pseudomonas aeruginosa infection in cystic fibrosis patients. *Journal of Cystic Fibrosis* 2010; S29.

180. Gilead Sciences. Aztreonam for Inhalation Solution (AZLI) vs Tobramycin Inhalation Solution (TOBI®) in Patients With Cystic Fibrosis & Pseudomonas Aeruginosa. 2008.

181. Oermann, C.M., Assael, B., Nakamura, C., Boas, S.R., Bresnik, M., Montgomery, A.B. et al. Aztreonam for inhalation solution (AZLI) vs. tobramycin inhalation solution (TIS), a 6-month comparative trial in cystic fibrosis patients with Pseudomonas Aeruginosa. *Pediatric Pulmonology* 2010;327.

182. Gibson, R.L., Retsch-Bogart, G.Z., Oermann, C., Milla, C., Pilewski, J., Daines, C. et al. Microbiology, safety, and pharmacokinetics of aztreonam lysinate for inhalation in patients with cystic fibrosis. *Pediatric Pulmonology* 2006; 41(7):656-665.

183. Burns, J.L., Stapp, J., Lofland, D., Phase, A.I. Microbiology results from a phase 2 clinical study of aztreonam lysinate for inhalation (AI): a new inhaled antibiotic to treat CF patients with Pseudomonas aeruginosa (PA). *Journal of Cystic Fibrosis* 2005; 4 Suppl:S55.

184. McCoy, K., Retsch-Bogart, G., Gibson, R.L., Oermann, C., Braff, M., Montgomery, A.B. Investigation of susceptibility breakpoints for inhaled antibiotic therapies in cystic fibrosis. *Pediatric Pulmonology* 2010; 341.

185. Retsch-Bogart, G.Z., Burns, J.L., Otto, K.L., Liou, T.G., McCoy, K., Oermann, C. et al. A phase 2 study of aztreonam lysine for inhalation to treat patients with cystic fibrosis and Pseudomonas aeruginosa infection. *Pediatric Pulmonology* 2008; 43(1):47-58.

186. Retsch-Bogart, G.Z., Quittner, A.L., Gibson, R.L., Oermann, C.M., McCoy, K.S., Montgomery, A.B. et al. Efficacy and safety of inhaled aztreonam lysine for airway pseudomonas in cystic fibrosis. *Chest* 2009; 135(5):1223-1232.

187. Wainwright, C., Nakamura, C., Geller, D., Montgomery, A.B. A double-blind, multinational, randomized, placebo-controlled trial evaluating aztreonam for inhalation solution (AZLI) in patients with cystic fibrosis (CF), mild lung disease and P. Aeruginosa (PA). *Journal of Cystic Fibrosis* 2010; S22.

188. Salh, B., Bilton, D., Dodd, M., Abbot, J., Webb, K. A comparison of aztreonam and ceftazidime in the treatment of respiratory infections in adults with cystic fibrosis. *Scandinavian Journal of Infectious Diseases* 1992; 24(2):215-218.

189. Schaad, U.B., Wedgwood-Krucko, J., Guenin, K., Buehlmann, U., Kraemer, R. Antipseudomonal therapy in cystic fibrosis: aztreonam and amikacin versus ceftazidime and amikacin administered intravenously followed by oral ciprofloxacin. *European Journal of Clinical Microbiology & Infectious Diseases* 1989; 8(10):858-865.

190. Bosso, J.A., Black, P.G. Controlled trial of aztreonam vs. tobramycin and azlocillin for acute pulmonary exacerbations of cystic fibrosis. *Pediatric Infectious Disease Journal* 1988; 7(3):171-176.

191. McCoy, K., Quittner, A.L., Oermann, C., Gibson, R.L., Retsch-Bogart, G.Z., Montgomery, A.B. et al. Inhaled Aztreonam Lysine for Chronic Airway Pseudomonas aeruginosa in Cystic Fibrosis. *American Journal of Respiratory and Critical Care Medicine* 2008; 178:921-928.

192. Signorovitch, J., Latremouille-Viau, D., Dea, K., Wu, E., Zhang, J. Comparison of drug costs & clinical outcomes with tobramycin solution for inhalation & aztreonam lysine for inhalation in cystic fibrosis. *Pediatric Pulmonology* 2010; 309.

193. Blumer, J.L., Minkwitz, M., Saiman, L., San, G.P., Iaconis, J., Melnick, D. Meropenem (MEM) compared with ceftazidime (CAZ) in combination with tobramycin (TOB) for treatment of acute pulmonary exacerbations (APE) in patients with cystic fibrosis (CF) infected with Pseudomonas aeruginosa (PA) or burkholderia cepacia (BC) [abstract]. *Pediatric Pulmonology* 2003; Suppl 25:294.

194. Richard, D.A., Nousia-Arvanitakis, S., Sollich, V., Hampel, B.J., Sommerauer, B., Schaad, U.B. Oral ciprofloxacin vs. intravenous ceftazidime plus tobramycin in pediatric cystic fibrosis patients: comparison of antipseudomonas efficacy and assessment of safety with ultrasonography and magnetic resonance imaging. Cystic Fibrosis Study Group. *Pediatric Infectious Disease Journal* 1997; 16(6):572-578.

195. Church, D., Kanga, J., Kuhn, R., Rubio, T., Haverstock, D., Perroncel, R. et al. Prospective, double-blind, randomized comparison of ciprofloxacin (CIP) vs Ceftazidime/Tobramycin (C/T) in the treatment of pediatric cystic fibrosis (CF). *Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy* 1995; 35(0):332.

196. McCarty, J.M., Tilden, S.J., Black, P., Craft, J.C., Blumer, J., Waring, W. et al. Comparison of piperacillin alone versus piperacillin plus tobramycin for treatment of respiratory infections in children with cystic fibrosis. *Pediatric Pulmonology* 1988; 4(4):201-204.

197. Hoiby, N. Supplementary Oral Azithromycin in Treatment of Intermittent Pseudomonas Aeruginosa Colonization in CF-patients With Inhaled Colistin and Oral Ciprofloxacin; Postponing Next Isolate of Pseudomonas and Prevention of Chronic Infection. A Prospective, Double-blinded, Placebo-controlled Scandinavian Multi-centre Study. 2006.

11. APPENDICES

Appendix 1 Treatment bands for cystic fibrosis (from NHS Specialised Services)

Band 1: Patients who only receive out-patient care from doctors, nurses, physiotherapist, dieticians, social workers, etc. No intravenous antibiotics required. No in-patient admissions apart from an annual assessment and review as a day case.

Band 1a: Previously as above BUT require up to 14 days of intravenous antibiotics (at home or in hospital) and spend a maximum of 7 days in hospital over the course of a 12 month period OR receive short-term (up to 3 months) nebulised antibiotics for eradication treatment.

Band 2: Patients who require maintenance nebulised antibiotics for pseudomonas infection or maintenance nebulised Dornase alfa. Patients receive up to 28 days of intravenous antibiotics in a year OR spend a maximum of 14 days in hospital.

Band 2a: Patients who receive both nebulised antibiotics and Dornase alfa and require up to 56 days of antibiotics intravenously at home or in hospital OR a maximum of 14 days in hospital.

Band 3: Patients who have more frequent in-patient visits, have up to a maximum of 84 days on intravenous antibiotics (at home or in hospital) OR spend up to 57 days in hospital OR patients with gastrostomy feeding or any of listed CF complications namely CF related diabetes, ABPA, massive haemoptysis, pneumothorax.

Band 4: Patients who have severe disease and usually spend up to 112 days in hospital per year, although it is recognised that some patients, at this stage of their illness, prefer to be treated/supported at home with the support of the CF multi-disciplinary team. Patients require a minimum of 85 days per year on IV antibiotics (at home or in hospital). Patients have CF-related complications of diabetes, pneumothorax or haemoptysis.

Band 5: Patients are severely ill and stay in hospital for greater than 113 days per year, awaiting transplantation or receiving palliative care. As above, it is recognised that some patients, at this stage of their illness, prefer to be treated/supported at home with the support of the CF multi-disciplinary team. Patients may be receiving nocturnal ventilation and feeding gastrostomies. Patient's life expectancy is usually no more than a year to 18 months.

Appendix 2 Medline search strategy for clinical effectiveness and cost-effectiveness evidence

1 Cystic Fibrosis/ (24739)
2 cystic fibrosis.tw. (26433)
3 fibrosis cystic.tw. (46)
4 1 or 2 or 3 (31197)
5 Pseudomonas aeruginosa/ (27224)
6 Pseudomonas Infections/ (14449)
7 pseudomonas aeruginosa.tw. (31883)
8 pseudomonas infection$.tw. (728)
9 "P. aeruginosa".tw. (12458)
10 Respiratory Tract Infections/ (27457)
11 respiratory tract infection$.tw. (11475)
12 infection$ respiratory tract.tw. (57)
13 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (76944)
14 4 and 13 (4642)
15 Colistin/ (1843)
16 colistin.tw. (1557)
17 colistimethate sodium.tw. (16)
18 colobreathe.tw. (0)
19 turbospin device.tw. (1)
20 turbospin.tw. (9)
21 pentasodium colistimethanesulfate.tw. (0)
22 1066-17-7.rn. (1843)
23 12705-41-8.rn. (32)
24 polymyxin.tw. (4460)
25 promixin.tw. (0)
26 coly-mycin.tw. (10)
27 colisticin.tw. (0)
28 colimycin.tw. (216)
29 colomycin.tw. (14)
30 colymycin.tw. (12)
31 totazina.tw. (0)
32 or/15-31 (6866)
33 Tobramycin/ (3418)
34 tobramycin.tw. (4880)
35 tip.tw. (33364)

36 tobi podhaler.tw. (0)
37 podhaler.tw. (0)
38 32986-56-4.rn. (3418)
39 nebicin.tw. (1)
40 nebcin.tw. (7)
41 nebramycin factor 6.tw. (8)
42 brulamycin.tw. (13)
43 obracin.tw. (2)
44 bramitob.tw. (5)
45 tobi.tw. (74)
46 or/33-45 (39018)
47 Amikacin/ (3191)
48 amikacin.tw. (5581)
49 Gentamicins/ (15261)
50 gentamicin$.tw. (16822)
51 Ceftazidime/ (2877)
52 ceftazidime.tw. (5581)
53 Aztreonam/ (1199)
54 aztreonam.tw. (2113)
55 exp Aminoglycosides/ (113459)
56 aminoglycoside$.tw. (12835)
57 exp Cephalosporins/ (33683)
58 cephalosporin$.tw. (14765)
59 exp Fluoroquinolones/ (21184)
60 fluoroquinolone$.tw. (8258)
61 or/47-60 (179078)
62 exp "Nebulizers and Vaporizers"/ (7091)
63 (nebulis$ or nebuliz$).tw. (6454)
64 exp Administration, Inhalation/ (20759)
65 inhal$.tw. (68855)
66 exp Aerosols/ (22745)
67 aerosol$.tw. (24353)
68 eFlow.tw. (35)
69 eflow.tw. (22)
70 or/62-69 (100254)
71 61 and 70 (957)
72 32 or 46 or 71 (46179)

73 14 and 72 (557)
74 randomized controlled trial.pt. (299024)
75 controlled clinical trial.pt. (81706)
76 randomized controlled trials/ (70561)
77 random allocation/ (70117)
78 double blind method/ (108074)
79 single blind method/ (14529)
80 clinical trial.pt. (459075)
81 exp Clinical Trial/ (625172)
82 (clin$ adj25 trial$).ti,ab. (182356)
83 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (108653)
84 placebos/ (29247)
85 placebos.ti,ab. (1512)
86 random.ti,ab. (119723)
87 research design/ (61104)
88 or/74-87 (1008372)
89 Meta-Analysis/ (26827)
90 meta analy$.tw. (31188)
91 metaanaly$.tw. (962)
92 meta analysis.pt. (26827)
93 (systematic adj (review$1 or overview$1)).tw. (24154)
94 exp Review Literature/ (1576254)
95 or/89-94 (1602463)
96 cochrane.ab. (15057)
97 embase.ab. (12552)
98 (psychlit or psyclit).ab. (794)
99 (psychinfo or psycinfo).ab. (4051)
100 (cinahl or cinhal).ab. (4919)
101 science citation index.ab. (1201)
102 bids.ab. (284)
103 cancerlit.ab. (480)
104 or/96-103 (23561)
105 reference list$.ab. (5697)
106 bibliograph$.ab. (8544)
107 hand-search$.ab. (2488)
108 relevant journals.ab. (425)
109 manual search$.ab. (1419)

110 or/105-109 (16658)
111 selection criteria.ab. (13294)
112 data extraction.ab. (6142)
113 111 or 112 (18395)
114 review.pt. (1574024)
115 113 and 114 (12590)
116 comment.pt. (428431)
117 letter.pt. (699325)
118 editorial.pt. (268459)
119 animal/ (4660797)
120 human/ (11509301)
121 119 not (119 and 120) (3452597)
122 or/116-118,121 (4452285)
123 95 or 104 or 110 or 115 (1608257)
124 123 not 122 (1462773)
125 Economics/ (25932)
126 "costs and cost analysis"/ (38407)
127 Cost allocation/ (1884)
128 Cost-benefit analysis/ (49718)
129 Cost control/ (18516)
130 cost savings/ (6869)
131 Cost of illness/ (13523)
132 Cost sharing/ (1626)
133 "deductibles and coinsurance"/ (1266)
134 Health care costs/ (20501)
135 Direct service costs/ (921)
136 Drug costs/ (10095)
137 Employer health costs/ (1025)
138 Hospital costs/ (6290)
139 Health expenditures/ (11326)
140 Capital expenditures/ (1887)
141 Value of life/ (5118)
142 exp economics, hospital/ (16929)
143 exp economics, medical/ (13069)
144 Economics, nursing/ (3833)
145 Economics, pharmaceutical/ (2189)
146 exp "fees and charges"/ (24941)

147 exp budgets/ (10783)

148 (low adj cost).mp. (14051)

149 (high adj cost).mp. (5970)

150 (health?care adj cost$).mp. (2434)

151 (fiscal or funding or financial or finance).tw. (57634)

152 (cost adj estimate$).mp. (1049)

153 (cost adj variable).mp. (26)

154 (unit adj cost$).mp. (1107)

155 (economic$ or pharmacoeconomic$ or price$ or pricing).tw. (124497)

156 or/125-155 (364158)

157 73 and 88 (166)

158 73 and 124 (89)

159 73 and 156 (12)

Appendix 3 Table of excluded studies

Author	Year	Reason for exclusion
Conway et al [127]	2006	Trial record only
Edenborough[128]	2001	Trial record only
Geller et al[129]	2007	Single dose study
Geller et al[130]	2010	Satisfaction study
Konstan et al[131]	2006	Trial record
Konstan et al[132]	2009	Placebo control
Konstan et al[81]	2011	Placebo control
Le Brun et al[133]	2002	Not CF patients
Newhouse et al[134]	2003	Healthy population; non CF
Novartis[135]	2009	Trial record only
Novartis[136]	2009	Trial record only
Novartis[137]	2005	Trial record only
Novartis[138]	2005	Trial record only
Westerman et al[139]	2004	Nebulised colistin
Westerman et al[140]	2007	Single dose study

Appendix 4 Evidence network considered for meta-analysis

The purpose of a network meta-analysis is to allow comparison of the interventions defined in the scope (tobramycin DPI and colistimethate sodium DPI) with the comparators defined in the scope (antibiotics for nebulisation, defined as tobramycin and colistimethate sodium). These interventions will be referred to collectively as the decision comparator set.[141] Where there is not direct RCT evidence between these, a network can be constructed by introducing an additional treatment or treatments. The decision comparator set plus these additional treatments is known as the synthesis set. The synthesis set is usually not extended beyond studies which include at least one of the treatments in the comparator set,[141] and for a study to be included in the review it must include two of the treatments in the synthesis set.

In order for a network to be possible, a good degree of homogeneity between study characteristics within the synthesis set is needed, or where heterogeneity exists, this should be appropriately corrected for (modelled). In the context of this assessment, there are important prognostic factors which are likely to affect estimates of FEV_1%. The most significant of these are

- the mean age of participants (prognosis worsens with increasing age)
- the mean FEV_1% at baseline (prognosis worsens with decreasing FEV_1%)
- the mean BMI at baseline (prognosis worsens with lower BMI for age)

These factors are associated with life expectancy, and may be associated with treatment efficacy; e.g. patients with advanced lung damage (low FEV_1%) gain less benefit from inhaled antibiotics as bacterial plaques impede the dispersal of treatment throughout the lung. Without knowing the distribution of these factors at a patient level, correcting for them within the analysis would introduce an unacceptable level of uncertainty.

The 20 citations considered for inclusion in a NMA are listed in Table 50. Most citations related to studies of nebulised tobramycin. No head to head studies of Tobramcyin or Colistimethate sodium dry powders versus each other were identified.

A network was formed from these studies, starting with studies which included colistimethate sodium DPI or tobramycin DPI. Constructing the network involved two stages:

1. Identifying which studies used compatible interventions to those already in the network (potentially includable in the synthesis set)
2. Data extraction (from the abstract or full text if necessary) of key variables for the studies within the synthesis set.

Figures 30 and 31 of this appendix show the data available at 4 weeks after the commencement of treatment and 20 & 24 weeks after commencement of treatment. These figures also indicate where the

network was judged unviable due to heterogeneity in study variables. The data extraction of potentially includable studies is presented in Table 49 of this appendix.

At 4 weeks (Figure 38), a network could potentially be constructed which included colistimethate sodium DPI to tobramycin DPI via nebulised tobramycin. This network would depend on the published data being compatible in terms of statistical analyses performed (e.g some data is presented as logarithmic transforms). This analysis was not performed for the following reasons, which became evident during the course of the assessment:

- Data at 4 weeks is of little use to assess long term outcomes.
- There is evidence to suggest that FEV_1% measured at 4 weeks in groups treated with tobramycin (DPI or nebulised) may be unrepresentative of true long term efficacy as FEV_1% usually peaks within the first few days of treatment, and may not have levelled at 4 weeks. This would unfairly advantage tobramycin DPI and nebulised tobramycin, and disadvantage colistimethate sodium DPI.

The month-on month-off dosing of tobramycin leads to peaks and troughs in efficacy (see section 5.3). For this reason, it would see appropriate to look at outcomes at both 20 and 24 weeks, to allow for a best case and worst case scenario assessment of efficacy. Data was provided by Novartis at 20 weeks in the initial submission,[58] and data at 24 weeks was provided upon request (Novartis clarifications). The network of evidence at 20 and 24 weeks is presented in Figure 39. Data is available at both 20 and 24 weeks for colistimethate sodium DPI and tobramycin DPI, compared to nebulised tobramycin. However, no data is available for nebulised colistimethate.

Despite there being trial data with a common comparators (two trials comparing to nebulised tobramycin at 20/24 weeks, two trial comparing to nebulised tobramycin and two trials using colistimethate sodium DPI at four weeks), an indirect comparison was not performed for the following reasons:

- EAGER trial data was only presented with no imputation. An equivalent set of data was not presented for COLO/DPI/02/06 (see discussion below).
- There is a lack of certainty around the comparability of the patient populations, methods for recording FEV_1%, and definitions of acute exacerbations (see Sections 5 of main report).
- There are gaps in the data, especially at 24 weeks.
- The small number of studies may make an indirect comparison prone to being influenced by the priors and therefore potentially uninformative.

Table 49 Matrix of the studies selected for potential inclusion in the NMA

		Comparator									
		Tobi DPI	Coli DPI	Nebulised Tobramycin	Nebulised Colistimethate sodium	Placebo	Tobramycin in combination	Colistimethate sodium in combination	Aztreonam	Aztreonam in combination	Other
Intervention	Tobramycin DPI			Geller 2007[129] (90) Konstan 2011[63] (553) Konstan 2009 abstract [132] Trial record of Konstan [131] Novartis Submission[58] Konstan 2010 abstract [66]		Novartis trial records[135] (NR) [136] (NR) Novartis trial records[137] (NR) & [138] (NR) Novartis Submission[58] Konstan 2011[81]					
	Colistimethate socium DPI			Conway 2006 [127] (360) Forest Submission[64]	Westerman 2007 [140] (10) Davies 2004 [65] (12)						
	Nebulised Tobramycin			Alothman 2002[142] (19)* Beringer 2000[143] (60)* Denk 2009[144] (16)Δ Mazurek 2009[145] (NR) Δ Keller 2010[146] (92) Δ Nikolaizik 2008[147] (32)* Winnie 1991[148] (NR)* Poli 2007[149] (11) Δ	Hodson 2002[156] (NR) Adeboyeku 2006[157] (21) Unpublished study: (Taylor 1998[158] (EEN=3-5) Webb 1999[159] (NR) Weller 1999[69] (115)	Chuchalin 2007[71] (247) Poli 2007[149] (396) Montgomery 2000[160] (EEN=200) Moss 2007[18] (520) Nasr 2010[78] (32) Ramsey 1993[80] (71) Ramsey 1999[74] (520) Wientzen	Al Ansari 2006[163] (15)* Ramsey 2004[164] (NR)*	Master 2001[165] (98)*			Flume 2011 TS vs Aeroquin[166] (NR) Kassaa 2011 TS vs Nebcinal[167] (NR) Murphy 2004 TS vs routine treatment [79] (184) (unclear if chronic Pa)

				Riethmueller 2010 [150] (30) Rietschel 2010 [151] (29)* Spencer 2006[152] (EEN=121)* Westerman 2008[153] (10) Δ Whitehead 2002 [154] (60)* Wood 1996[155] (29)*		1980[161] (22) Wiesemann 1998[162] (22) Moss 2002[76] (128) Lenoir 2007[72] Maclusky 1989[73]					
	Nebulised Colistimethate sodium				Westerman 2004[139] (9)	Jensen 1987					
	Tobramycin in combination						Topic Study Grp 2005[168] (244)* Canis 1998[169] (20)* Trapnell 2010[170] (135)				Conway 1985[171] (17) De Boeck 1989 [172] (21) Martin 1980[173] (18) McLaughlin 1983[174] NR) Parry 1978[175] (82) Pederson 1986[176] (20)† Wesley 1999[177] (13)
	Colistimethate in combination						Taccetti 2010[178] (215) Zavatoro 2010[179] (198)				
	Aztreonam			Gilead Sciences trial[180] (240) Oermann		Gibson 2006[182] (12) Burns 2005[183] (105)					Salh 1992[188] Aztreonam vs Ceftazidime Schaad

				2010[181] (273)		McCoy 2010[184] (NR) Retsch-Bogart 2008[185] (131) Retsch-Bogart 2009[186] (164) Wainwright 2010[187] (157)					1989[189] IV aztreonam vs ceftazidime & amikacin (42) Bosso 1988[190] Aztreonam vs Tobramycin & Azlocillin (15) McCoy 2008[191] AS vs TS vs Placebo (211)
	Aztreonam in combination						Signorovitch 2010 [192] TS vs placebo VS AS vs placebo (692)				
	Other						Blumer 2003[193] (NR) Richard 1997[194] (108) Church 1995[195] (NR) McCarty 1988[196] (17)				Hoiby 2006[197] (NR)

Table 50 Data extracted from the abstracts of studies of potential relevance to the network meta-analysis

Study	Trial design	Age range	Mean age (years)	N (ITT)	Baseline FEV_1% Mean (SD)	Chronic Pa?	Time to outcome	Outcomes reported	Dose Dry Powder	Dose Neb. Solution	Placebo	Exclude reason
Tobramycin Dry Powder												
Konstan et al 2011a [63] (EVOLVE)	RCT	6 to 21 years	Int: 13.4 (4.42) Con: 13.2 (3.91)	517	Int: 54.7 (18.89) Con: 58.5 (20.03)	Yes	4, 8 weeks	FEV_1%; SpD; IV antibiotics; Hospitalisations; Resistance; AEs; AcEx	112mg b.i.d T-326 inhaler	n/a	Inhaler with 4 capsules b.i.d.	Placebo control
Konstan et al 2011b [81] (EAGER)	RCT, open label	≥ 6 years	Int: 26 (11.4) Con: 25 (10.2)	373	Int: 53 (14.2) Con: 53 (15.9)	Yes	4, 24 weeks	SpD; FEV_1%; AcEx; Hospitalisations; AEs; HRQoL; Compliance	112mg b.i.d T-326 inhaler	300mg/ 5ml b.i.d, PARI LC plus	n/a	n/a
Colistimethate sodium Dry Powder												
COLO/DPI/ 02/06 Forest submission[64]	RCT open label	≥ 6 years	Int: 21.3 (9.72) Con: 20.9 (9.30)	396	Int: 51.76 (1.02) Con: 50.82 (0.98)	Yes	20, 24 weeks	FEV_1%; AcEx; Hospitalisations; AEs; HRQoL; Resistance; Compliance	125mg b.i.d. Turbospin	300mg/ 5ml Tobi b.i.d	n/a	n/a
COLO/DPI/02/05 Davies et al 2004[65] Forest submission[64]	RCT with crossover	≥ 8 years	20.3yrs	16	Int: 77.14 (6.78) Con: 76.25 (7.32)	Yes	4 weeks	FEV_1%; AEs	125mg b.i.d. Turbospin	2MU Coli b.i.d	n/a	n/a
Nebulised Colistin												

Study	Trial design	Age range	Mean age (years)	N (ITT)	Baseline FEV_1% Mean (SD)	Chronic Pa?	Time to outcome	Outcomes reported	Dose Dry Powder	Dose Neb. Solution	Placebo	Exclude reason
Hodson et al 2002[69]	RCT with cross over	≥ 6 years	Coli: 30.0 Tobi: 30.2	115	Tobi: 55 Coli: 59	Yes	4 weeks (poor data for 8, 24 & 44 weeks)	FEV_1%; SpD; AEs		Tobi: 300mg, 5mL-1 b.i.d. Coli: 80mg b.i.d.	n/a	Incompatible Colistin dose
Jensen 1987[70]	RCT	≥ 7 years	Int: 13.6 Con: 14.7	40	Int: 71 (25) Con: 79 (29)	Yes	12 weeks	FVC, FEV_1%; AEs; FEF_{25-75}%; SpD;		1 MU b.i.d.	Saline b.i.d.	Incompatible Colistin dose; all dosed with IV tobramycin 2 weeks before study
Nebulised Tobramycin												
Hodson et al 2002 (also listed above)[69]	RCT with cross over	≥ 6 years	Coli: 30.0 Tobi: 30.2	115	Tobi: 55 Coli: 59	Yes	4 weeks (poor data for 8, 24 & 44 weeks)	FEV_1%; SpD; AEs		Tobi: 300mg, 5mL-1 b.i.d. Coli: 80mg b.i.d.	n/a	Incompatible Colistin dose
Chuchalin et al 2007[71]	RCT	≥ 6 yrs	Int: 14.8 Con: 14.7	247	Int: 61 Con: 64	Yes	4 weeks	FVC, FEV_1%; AEs; FEF_{25-75}%; susceptibility; MIC; hospitalisations; BMI		300mg in 4 ml b.i.d.	Saline b.i.d.	Bramitob device
Lenoir 2007[72]	RCT	≥ 6 yrs	Int: 11.0 Con: 14.2	59	Int: 58 Con: 60	No	4, 8 weeks	FEV_1%; FEF_{25-75}%; FVC; susceptibility; MIC; SpD		300mg in 4 ml b.i.d.	Saline b.i.d.	Not all chronic PA
MacLusky 1989[73]	RCT	≥7	Int: 13.9 Con: 14.3	27	Int: 70 (22) Con: 78	Yes	Up to 32 months	FEV_1%; FEF_{25-75}%; FVC; susceptibility; hospitalisations		80mg t.i.d.	Saline t.i.d.	Incompatible Tobramycin dose

Study	Trial design	Age range	Mean age (years)	N (ITT)	Baseline FEV_1% Mean (SD)	Chronic Pa?	Time to outcome	Outcomes reported	Dose Dry Powder	Dose Neb. Solution	Placebo	Exclude reason
					(21)							
Ramsey 1999;[74] Moss 2001;[75] Moss 2002[76]	RCT	≥ 6	Int: 20.8 Con: 20.6	520	Int: 49.9 (15.5) Con: 51.2 (16.8)	Unclear	20, 24 weeks	FEV_1%; SpD; Resistance		300mg (ml unclear) b.i.d.	Saline b.i.d.	Unclear if chronic infection
Nasr et al 2010,[78] Nasr et al 2006[77]	RCT	≥ 6	11.8 (tobi), 15.9 (placebo)	32	Int: 95.73 (17.21) Con: 83.71 (21.07)	Yes	4 weeks	Weight; $FEF_{25\%–75}$%; FEV_1%; Chest tomography; CFQ-R		300mg 5ml b.i.d.	Saline b.i.d.	Young participants; mild disease by FEV_1%
Murphy 2004[79]	RCT	6-15 years	10.2 (tobi group) 9.9 (placebo)	184	Int: 85.1 (12.0) Con: 86.3 (9.4)	Yes	56 weeks (no 4 week data for FEV_1)	Hospitalisations; AEs; IV antibiotics		300 mg b.i.d.	Saline b.i.d.	Young participants; mild disease; large withdrawal Ns.
Ramsey 1993[80]	RCT with crossover	NR	17.7 16.6	71	57.5 (3.5)	Unclear	4 weeks to first crossover	FVC; FEV_1%; FEF_{25-75}%; AcEx; IV antibiotics; Toxicity; Resistance		600mg t.i.d.	Saline t.i.d.	Incompatible Tobi dose

Figure 38 Network of evidence for Colistimethate sodium DPI and Tobramycin DPI with outcomes measured 4 weeks after commencement of treatment.

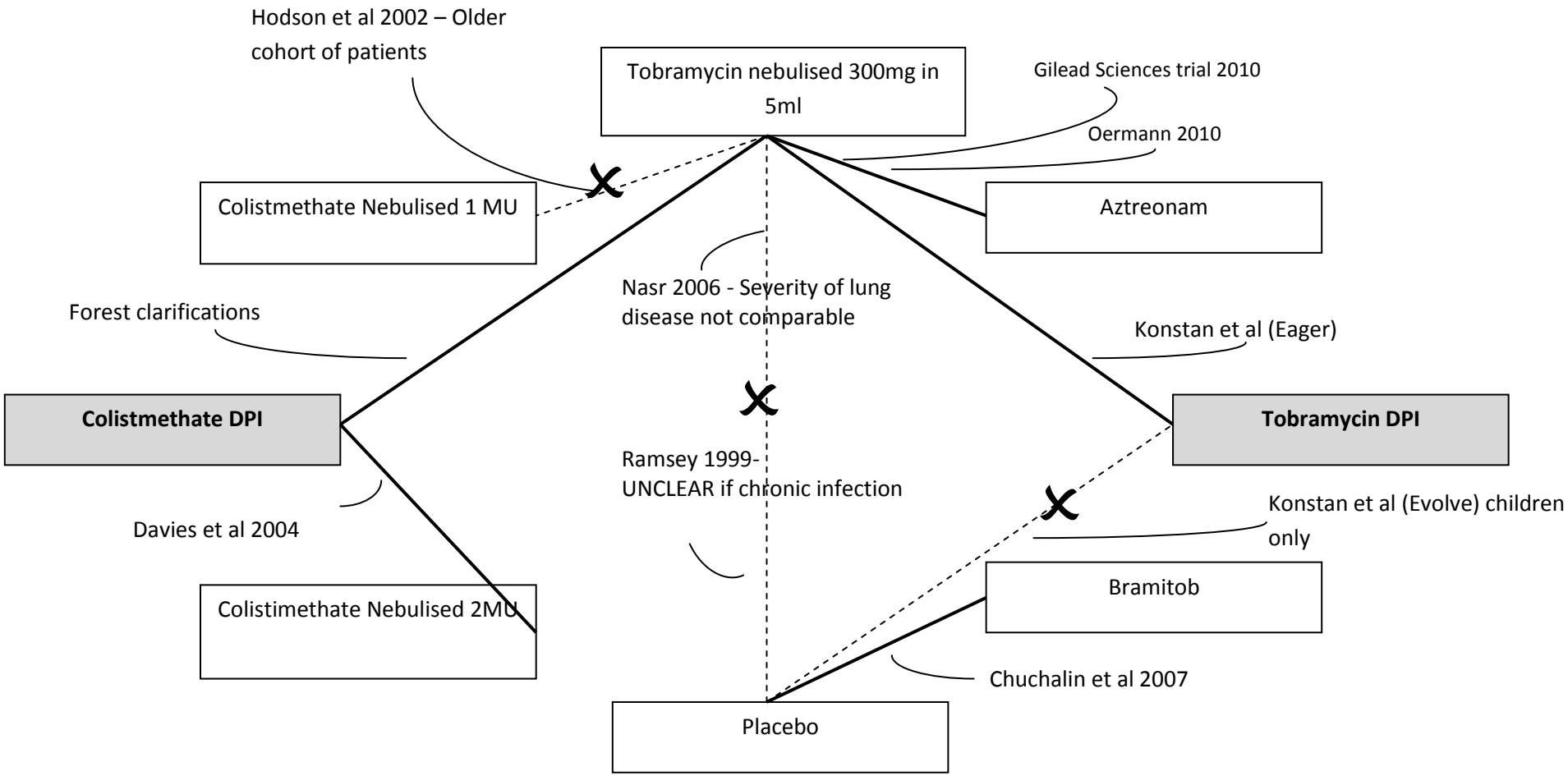
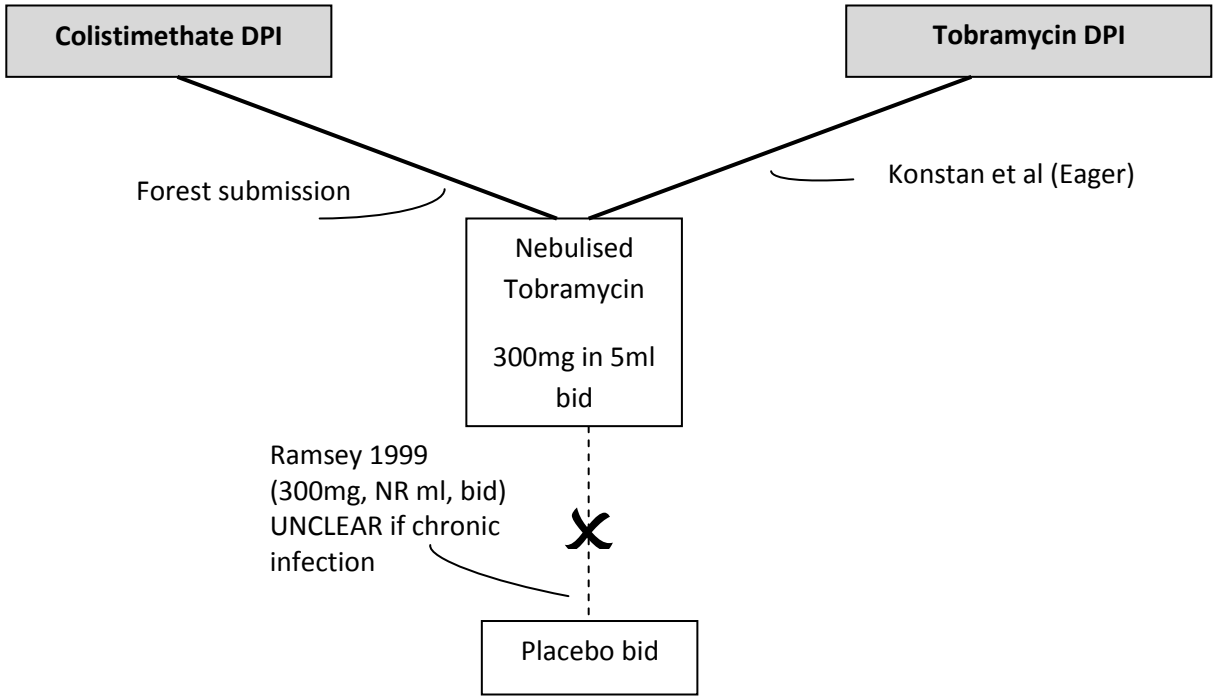


Figure 39 Network of evidence for colistimethate sodium DPI and tobramycin DPI with outcomes measured 20 and 24 weeks after commencement of treatment.



——— Studies with comparable baseline characteristics. ------- Studies with incomparable baseline characteristics or unknown characteristics.

Appendix 5 Data extraction tables

Davies et al. 2004.	
Note: data in **square brackets** denotes data extracted from the "additional sources of data" listed for the study.	
Study details	
Publication type	Davies, et al. 2004.[65] Conference abstract from Cystic Fibrosis conference.
Additional sources of data	Industry submission from Forest Laboratories UK COL/DPI/02/05 [64] (data extracted from this source indicated by square brackets)
Trial design	RCT with crossover, open label , multi-dose tolerability study
Country	UK
Dates of participant recruitment	Not reported
Sources of funding	Forest Laboratories UK Ltd.
Intervention(s) and comparator	
Treatment groups	Salbutamol followed by micronised colistin (125g) via Turbospin DPI Micronised colistin alone (125mg) b.i.d. via Turbospin DPI
Comparator	Colistimethate Sodium (2MU) solution in 4mL 0.9% NaCI b.i.d. via nebuliser
Run-in phase	[72 hours washout]
Treatment duration	8 weeks (2 x 28 day cycles) -4 weeks of powder then crossover to nebulised colistimethate sodium
Outcome(s)	
Follow-up	[4 and 8 weeks although lung function measured at 1, 2, 3 and 4 weeks]
Outcomes & Measures	[Clinical tolerability from AEs Laboratory safety from haematology, biochemistry, urinanalysis and renal markers FEV_1 Safety confirmed by CFQ for QoL]
Population	
Eligibility criteria	[Adults and children (age NR) with chronic Pa infection; Male or female aged eight years and above; If female and post menarche/pre-menopausal and sexually active, the patient had to be using adequate effective contraceptive methods (oral, depot or injectable contraception or an intra-uterine device); Patients were required to be non-smokers or a past smoker who had not smoked within the past 12 months prior to the date of entry; Patient or guardian capable of reading and understanding informed consent (assent for under 16 years) and the clinical trial information leaflet; Each patient or guardian had to have granted his or her written informed consent (assent for under 16 years) before any trial procedure was carried out; Patient had to have a documented diagnosis of CF from a specialist CF Unit (genotype and/or positive sweat tests); Current CF condition had to be clinically stable i.e. there had to be no evidence of an acute respiratory exacerbation within 28 days prior to first day of trial medication administration; Patients who had maintained stable lung function over the previous 28 days or more (as evidenced by no significant change (significant change is defined as >10% change) in

	FEV_1 OR absence of hospitalisation due to exacerbation of infection over the previous 28 days); The patient had to have been previously treated with nebulised colistimethate sodium without showing intolerance or requiring cessation of therapy; FEV_1 had to be at least 25% of predicted value Exclusion criteria: History of any form of acute respiratory exacerbation within 28 days prior to first day of trial medication administration; Known sensitivity (or previous intolerance) to colistimethate sodium or salbutamol; Administration of any investigational drug within 28 days prior to first trial medication administration; Existence of any pre-study medical conditions which, in the judgement of the investigator, warranted exclusion from the study; Patients who were pregnant or breast-feeding; Inability to communicate or co-operate with the investigator due to language problems, poor mental development or impaired cerebral function; Objection by the patient's usual CF care-giver to their participation in the study; Inability to comply with any of the study procedures or the study regimen (including inability to use study devices i.e. during dry powder inhaler and nebuliser training); Laboratory parameters falling outside the expected normal ranges for CF (Investigator decision); Children who in the opinion of the investigator would not have been reliable in handling the device; Patients whose last day of an elective course of intravenous antibiotic therapy was within 28 days of screen; Patients who, on the first day of in trial treatment, had less than 28 days off TOBI; Patients who had had less than 72-hours washout from other anti-pseudomonal agents (for example, anti-pseudomonal antibiotics including generic tobramycin, macrolides); Patients who were colonised with Burkholderia cepacia. o) Patients for whom a minimum of a 72 hour wash-out period from anti-pseudomonal agents at the beginning and in between treatments was not possible; Patients who were complicated by allergic bronchopulmonary aspergillosis (ABPA); Patients who were awaiting heart-lung or lung transplantation]
Concomitant interventions allowed or excluded	Allowed: Patients were permitted to continue with pre-existing non anti-psuedomonal CF medications. Bronchodilators: refrained from use 4 hours prior to pulmonary function test. Salbutamol administered as rescue medication for bronchoconstriction after either intervention or comparator administration.
Power calculation	NR [Sample size chosen based on practical considerations rather than formal statistical arguments, as this was a pilot study]
N randomised to treatments	[ITT 16; PP 11] 12

Treatment group	**DP Colistimethate Sodium 125mg**	**NS Colistimethate Sodium 2MU**
N randomised to treatment	12 [16]	12 [16]
Baseline characteristics	Between group characteristics NR	
Age	[Mean 20.3 (SD 12.87)]	
Sex	[M 50%; F 50%]	
FEV_1	[Mean 76.75 (SD 26.43)]	
FEV_1 % Predicted	77.14 (6.784)	76.25 (7.315)
BMI	[Mean 19.99 (SD 4.01)]	
Withdrawals	N=3 withdrew early (1=subject request, 2=adverse event)	
Withdrawals/loss to	1 discontinued due to cough, throat	0

follow-up	irritation and unpleasant taste [2 withdrew due to adverse events, having already completed nebulised treatment.]			
Results				
Notes on statistics used	[a priori: Safety set: all who received one dose of study drug. Per protocol set: all those who completed the study and had missed 20% or less of any component of their dosing regimen. No confirmatory testing was performed. Statistical tests were interpreted in a descriptive manner. Descriptive statistics used for missing observations]			
Microbial response				
	Biochemistry, haematology and Urinary N-acetyl-β-D-glucosaminidase (NAG) all showed no treatment related or consistent effects (no statistics provided).			
Lung Function				
FEV_1	No significant changes in lung function in either treatment arm. [Two-sided t-test $p < 0.05$]			
Acute exacerbations				
	NR			
Resistance				
	NA			
Compliance				
	1 discontinued use [2 left the study due to AEs]		NR	
Mortality				
	[0]		[0]	
[Adverse events (solicited and spontaneously reported)*]				
Treatment group	**[DP Colistimethate Sodium 125mg n=16]**		**[NS Colistimethate Sodium 2MU n=15]**	
	Patients (%)	No. of events	Patients (%)	No. of events
Patients with at least one treatment emergent adverse event	16 (100%)	106	9 (60.0%)	55
Gastrointestinal disorders	14 (87.5%)	18	3 (20.0%)	3
Gastrointestinal disorder[1]	14 (87.5%)	16	2 (13.3%)	2
Vomiting	2 (12.5%)	2	0	0
General disorders and administration site conditions	5 (31.3%)	8	3 (20.0%)	7
Pyrexia	2 (12.5%)	2	1 (6.7%)	1
Infections and infestation	2 (12.5%)	2	0	0
Injury, poisoning and procedural complication	2 (12.5%)	2	1 (6.7%)	1
Investigations	0	0	1 (6.7%)	1
Metabolism and nutrition disorders	1 (6.3%)	1	0	0
Nervous system disorders	5 (31.3%)	6	3 (20.0%)	6
Headache	1 (6.3%)	1	2 (13.3%)	5
Reproductive system and breast disorders	1 (6.3%)	1	0	0
Pharyngolarangeal pain	2 (12.5%)	2	2 (13.3%)	2
Throat irritation	13 (81.3%)	19	3 (20.0%)	6
Skin and subcutaneous	0	0	1 (6.7%)	1

tissue disorders				
Pruritus	0	0	1 (6.7%)	1
Severe symptoms:				
Unpleasant taste	2	NR	NR	NR
Wheezing	1	NR	NR	NR
New cough/increased cough	1	NR	NR	NR
Nasal pain	3	NR	NR	NR
Sinus pain	NR	NR	1/55 (1.8%)	NR
Comparison between groups	% of patients with related TEAEs was higher in the dry powder group than in the nebulised group for most system organ classes and preferred terms. States that unpleasant taste and new cough/increase in cough higher in DP than nebulised but don't provide the data			

1 Gastrointestinal disorder included several cases of "unpleasant taste"
*Number of patients who experienced at least one event. All adverse event data is from the sponsor submission.

EAGER trial	
Note: data in **square brackets** denotes data extracted from the "additional sources of data" listed for the study.	
Study details	
Publication type	Konstan et al 2011, [63] full report in peer reviewed journal
Additional sources of data	Novartis Industry submission[58] (data extracted from this source indicated by square brackets)
Trial design	Randomised, multicentre, two arm, open label, non-inferiority trial
Country	127 centres in 15 countries including North America, Europe, Australia, Israel and Latin America
Dates study undertaken	February 2006 to March 2009 (from clinical trial record)
Sources of funding	Novartis Pharmaceuticals
Intervention(s) and comparator	
Treatment groups	Tobramycin Inhalation Powder 112mg (4 capsules) b.i.d. with T-326 Inhaler
Comparator	Tobramycin Inhalation Solution 300mg/ 5ml TOBI b.i.d. with PARI LC PLUS jet nebuliser and DeVilbiss PulmoAide compressor
Run-in phase	NR
Treatment duration	24 weeks, (3 cycles of 28 days on, 28 days off)
Outcome(s)	
Follow-up	24 weeks.
Outcomes & Measures	[Incidence and intensity of all adverse events, changes in hematology, blood chemistry, urine protein, audiology, physical condition, body weight, audiology testing, clinical labs and vital signs] [Relative change in FEV_1% from baseline to all study treatment visits, Change in sputum density, tobramycin susceptibility to PA(mic), antipseudomonal antibiotic use, respiratory related hospitalisations, Serum and sputum pharmacokinetics, Time to first hospitalisation and duration of hospitalisation, Time to first anti-pseudomonal antibiotic use and duration of treatment]
Population	
Eligibility criteria	Inclusion: >6yrs; [Confirmed] CF patients; FEV_1 >25 to <75% predicted based on Knudson equations; Sputum or throat cultures positive for Pa within 6 months of screening [and at the the screening visit; Ability to comply with all protocol requirements; Clinically stable in the opinion of the investigator; Contraception: reliable method used (females); Consent: written informed consent Exclusion :If initiated following drugs within 28 days of study drug administration (if >28 days, they are eligible for inclusion); Chronic macrolide therapy; Dornase alpha; Inhaled steroids; inhaled hypertonic saline (but where used, must have stable regimen, consistent administration time and not within 30 mins of conducting Pulmonary Function Tests); Sputum culture with B. cepacia within 2 years prior to screening or at screening; Hemoptysis more than 60 cc at any time within 30 days prior to study drug administration; Hypersensitivity to aminoglycosides or inhaled antibiotics; Serum creatinine 2mg/dL or more, blood urea nitrogen 40 mg/dL or more, or an abnormal urinalysis defined as 2+ or greater proteinuria; Pregnant, attempting to become

	pregnant or lactating; Clinically relevant history of hearing loss or chronic tinnitus; Used systemic or inhaled antipseudomonal antibiotics within 28 days prior to study drug administration.]
Concomitant interventions allowed or excluded	Allowed: adrenergics, bile acid preparations, cephalosporins, corticosteroids, enzyme preparations, fluoroquinolones, mucolytics, multivitamins, non-drug therapies, other aminoglycosides, proprionic acid derivatives, proton pump inhibitors, selective beta2-adrenoreceptor agonists, dornase alpha, macrolides, anticholinergics, bronchodilators (patients taking short-acting bronchodilators were to take the medication 15 to 90 minutes before inhalation of study drug; patients taking long-acting bronchodilators were to take the medication as prescribed within the preceding 24 hours) and glucocorticoids.
Power calculation	[Based on primary variable of safety, 300 patients provide a 99.8% chance of observing at least one AE with a true incidence of 2% in the TIP group. Inclusion of 500 patients (TIP: 300; TIS: 200) provides 96 % power to demonstrate non-inferiority of tip to tis with non-inferiority] margin of 6% based on 500 patients for relative change from baseline in FEV after 3 cycles, with one sided significance level of 0.15 (assuming 1% true TIS-TIP treatment difference and 20% standard deviation)
N randomised to treatments included in review	553

Treatment group	**Tobramycin Inhalation Powder 112mg b.i.d.**	**Tobramycin Inhalation Solution 300mg/ 5ml TOBI b.i.d.**
N randomised to treatment	[329 randomised] 308 ITT	[224 randomised] 209 ITT
Baseline characteristics		
Age	Mean 26 (SD 11.4)	Mean 25 (SD 10.2)
Sex	M 55.5%; F 44.5%	M 55.0%; F 45.0%
FEV	Mean 53 (SD 14.2) [SE 0.81]	Mean 53 (SD 15.9) [SE 1.11]
BMI	Mean 20.7 (SD 4.0)	Mean 20.4 (SD 3.5)
Withdrawals		
	From 553 participants randomised, 36 discontinued prior to receiving study medication, [21 from TIP arm, 15 from TIS arm]. Reasons with withdrawal given, but not extracted here. A further 121 discontinued after at least one dose of study medication.	
Withdrawals/loss to follow-up	83 discontinued AE 40 (13.0%) Cough 12/308 Death 3 (1.0%) Consent withdrawn 24 (7.8%) Lost to follow up 5 (1.6%) Administrative reason 1 (0.3%) Protocol violation 6 (1.9%)	38 discontinued AE 17 (8.1%) Cough 2/209 Consent withdrawn 9 (4.3%) Lost to follow up 3 (1.4%) Inappropriate enrolment 1 (0.5%) Protocol violation 5 (2.4%) Other 3 (1.4%)

	Other 4 (1.3%)	
Results		
Notes on statistics	Population used were randomised and treated with no imputation for missing data. Information for each outcome given, but not extracted here. Non-inferiority inferential analysis: The non-inferiority of TOBI Podhaler relative to TOBI was assessed using a confidence interval approach (margin of 6%. Pharmacokinetics based on a subset of patients (30 TIP; 14 TIS) But don't report the TIS stats. Post-hoc sensitivity analyses assessed the impact of patient discontinuation. All randomised patients who received ≥1 dose of study drug were included in the safety and efficacy (ITT) populations. Efficacy (FEV_1%) measured by least square means difference. Efficacy data reported as least squares mean difference (se).	
[Microbial response at 28 days, Mean decrease log10 (SD)]		
[Mean Pa sputum density change from baseline, unspecified phenotype]	[-1.76 (SE 0.14, SD 1.96)]	[-1.32 (SE 0.17, SD 2.03)]
[Mean Pa sputum density change log 10 from baseline at week 20]		
[Mean CFU non-mucoid]	[5.17]	[6.18]
[Mean CFU mucoid]	[5.40]	[6.30]
Mean Pa sputum density change from baseline at week 20		
Non-mucoid phenotype	-1.77	-0.73
Mucoid phenotype	-1.6	-0.92
[Unspecified phenotype]	[-1.61 (SE0.16, SD 2.03)]	[-0.77 (SE0.16, SD1.78)]
Negative PA culture	11.6%	9.9%
[Lung Function 28 day data]		
[Number of patients]	[268]	[194]
[Mean FEV_1% predicted at predose]	[54.381 (SE 0.634643, SD 10.38956)]	[54.7008 (SE 0.543224, SD 7.56624)]
[Mean change from baseline(or LS mean)]	[1.48(SE 0.63)]	[1.9 (SE 0.54)]
[% mean change from baseline]	[2.80% (SD 19.64%)]	[3.60% (SD 14.33%)]
[redacted]	[redacted]	[redacted]
[Lung Function 20 week data]		
[Mean FEV_1% predicted at predose]	[55.9682(NR)]	[55.2816 (NR)]
[Mean change from baseline (or LS mean)]	[3.0682 (SE0.6546041)]	[2.4816 (SE 0.65336667)]
[% mean change from baseline]	[5.80% (SE1.24%) (least mean squares)] [	[4.70% (SE 1.24%)(least mean squares)]
[redacted]		
[redacted]	[redacted]	[redacted]
Lung function comparison between groups		
	Reported as "similar between groups using least squares mean difference 1.1% relative change	

	(SE 1.75) The lower limit (−0.67%) of the one-sided 85% [CI] (equivalent to 70% two-sided) was within the predefined 6% margin for predefined non-inferiority indicating that TIP was non-inferior to TIS.	
Least squares mean difference (PP population)	LS mean difference in FEV_1 of 1.2%, lower limit of the one-sided 85% CI was −1.02%	
[Difference in mean change from baseline(or LS mean) at 28 days]	[-0.4196 (SE0.835383114)]	
[Difference in mean change from baseline at 20 weeks]	[0.5866 (SE 0.924875414)]	
Acute Exacerbations		
Required additional antipseudomonal antibiotic	64.9%	54.5%
Oral antibiotics used	55.5%	39.7%
Mean no. of days of antibiotic use	30.9 (sd 23.34)	33.4 (sd 24.42)
Hospitalised for respiratory-related events*	24.4%	22.0%
Lung disorder †	104 (33.8%)	63 (30.1%)
[Number of patients using an PA antibiotics at 24 weeks]	[200/308 (64.9%)]	[114/209 (54.5%)]
[Number of patients with at least 1 hospitalisation]	[75 (24.4%)]	[46 (22.0%)]
[Mean (SE) days in hospital]	[15.6 (13.31)]	[15.3 (10.23)]
Resistance		
Pa isolates (all phenotypes) with MIC >8 µg/ml (resistant) at baseline	68/308 (22.1%)	
Pa isolates (all phenotypes) with MIC ≤8µg/ml (susceptible) at baseline	240/308 (77.9%)	
MIC >8 µg/ml at the end of cycle 3	19.1%	
Increased MIC of tobramycin against Pa from baseline to Day 28 of cycle 3	≥4-fold increase: 67/199 (33.7%) ≥2-fold increase: 97/199 (48.7%) (Unclear which numbers relate to which group)	
Pharmacokinetics of Pa isolates		
At baseline MIC at least 20 times lower than the mean sputum concentration observed within 30 min of the first dosing in Cycle 1	91.2% (64 µg/mL or less)	NR
At the end of Cycle 3, (all phenotypes) MIC at least 30 times lower than the mean sputum concentration observed 30-minute post-dose	86.4% (64 µg/mL or less)	NR
Compliance		
	>90%	>90%
Discontinuation rate	26.9%	18.2%
Mortality		
	3 (2 are related to acute exacerbations according to clarifications provided by	0

	manufacturer in clarifications)	
Adverse Events		
Number of patients	NR	NR
Any adverse event	90.3%	84.2%
Mild or moderate AE	73.4%	68.5%
Serious AEs	27.4%	29.2%
AEs cycle 1	77.9%	66.5%
AEs cycle 2	67.0%	66.3%
AEs cycle 3	65.8%	58.5%
Cough	149 (48.4%)	65 (31.1%)
Productive cough	56 (18.2%)	41 (19.6%)
Severe cough	2.6%	1.9%
Dyspnea	48 (15.6%)	26 (12.4%)
Oropharyngeal pain	43 (14.0%)	21 (10.5%)
Rales	22 (7.1%)	13 (6.2%)
Rhinorrhea	22 (7.1%)	15 (7.2%)
Pulmonary function test decreased	21 (6.8%)	17 (8.1%)
Pyrexia	48 (15.6%)	26 (12.4%)
[redacted]	[redacted]	[redacted]
Upper respiratory tract Infection	21 (6.8%)	18 (8.6%)
Wheezing	21 (6.8%)	13 (6.2%)
Chest discomfort	20 (6.5%)	6 (2.9%)
Sinusitis	18 (5.8%)	15 (7.2%)
Pulmonary congestion	17 (5.5%)	9 (4.3%)
Dysphonia	42 (13.6%)	8 (3.8%)
Nasal congestion	25 (8.1%)	15 (7.2%)
Vomiting	19 (6.2%)	12 (5.7%)
Hemoptysis	40 (13.0%)	26 (12.4%)
Nausea	23 (7.5%)	20 (9.6%)
Headache	35 (11.4%)	25 (12.0%)
Fatigue	20 (6.5%)	10 (4.8%)
[redacted]	[redacted]	[redacted]
Audiology from subgroup Decrease from baseline at any visit Clinically significant decrease	n=78 (25.3%) 20 (25.6%) 3 (0.97%)	n=45 (21.5%) 7 (15.6%) 2 (0.96%)
Clinically significant bronchospasm (acute relative change of ≥20% decrease in FEV_1% from pre-dose to 30-min post-dose)	5.2%	5.3%

* Data reported for % receiving antibiotics in hospital, but unclear what this refers to

† Reported by investigator as generally pulmonary or cystic fibrosis exacerbation

Forest trial 2011	
Study details	
Publication type	Industry submission from Forest Laboratories UK COL/DPI/02/06 [64]
Additional sources of	None

data	
Trial design	RCT, multicentre
Country	European Union, Russia and Ukraine
Dates of participant recruitment	NR but last patient visit was 14 August 2007
Sources of funding	Forest Laboratories UK
Intervention(s) and comparator	
Treatment groups	Colistimethate sodium dry powder 125mg b.i.d. with Turbospin device
Comparator	Tobramycin (TOBI®) nebulised solution 300mg b.i.d. with PARI LC nebuliser
Run-in phase	16 weeks, 2 cycles of TOBI® treatment
Treatment duration	24 weeks, (Intervention had continuous treatment. Control group had 3 cycles of 28 days on, 28 days off)
Outcome(s)	
Follow-up	24 weeks, with interim data at 20 weeks
Outcomes & Measures	FEV_1% predicted Antibiotic sensitivity of respiratory tract Pa isolates (MIC & BSAC) Forced vital capacity (FVC) Peak expiratory flow rate (PEFR) Forced expiratory flow between 25% and 75% of the FEV (FEF25-75) Acute exacerbations Sputum colistin levels Compliance with study medication Adverse events Dropout rates CFQ-R
Population	
Eligibility criteria	Male or female aged 6 years and above. Patients who had received a minimum of two TOBI® on/off cycles immediately prior to randomisation. Heterosexually active females had to use adequate effective contraceptive methods. Patients were required to be non-smokers or a past smoker who had not smoked within the past 12 months. Patient or parent/guardian had to be capable of reading and understanding informed consent and clinical trial information leaflet, and to have granted written informed consent. Documented diagnosis of CF from a specialist CF unit (genotype and/or positive sweat tests). Current CF condition had to be clinically stable in the investigator's opinion, i.e., there was no evidence of a current acute respiratory exacerbation within 28 days prior to the first day of trial medication administration. Patients with Pa. Patient's lung function had to be clinically stable (investigator's decision) after completing IV therapy (elective or treatment for exacerbation) at Visit 1 prior to randomisation. Patients who, on the first day of trial medication administration, had at least 28 days but no more than 35 days off TOBI®.
Concomitant interventions allowed or excluded	Allowed: Continued chronic use of bronchodilators, hypertonic saline, use of oxygen, nutritional supplements and enzymes. In addition, use of dornase alfa, inhaled steroids and macrolides (if initiated >28 days before study drug)
Power calculation	Non-inferiority of CP vs TS. 95% two-sided confidence interval (CI) for the difference between the two groups was computed, and if the lower

	limit was not less than -3.0% then non-inferiority was accepted. Based on a 2-group t-test with a 0.05 two-sided significance level and a common SD of 16%, and assume a difference of 2% in favour of Colobreathe® against TOBI® (using nQuery Advisor® 4.0). Assuming a 10% dropout/non-compliance rate, to obtain 324 evaluable patients approximately 360 patients were to be entered into the study (180 TOBI® patients and 180 Colobreathe® patients).
N randomised to treatments included in review	380

Treatment group	Colistimethate sodium dry powder 125mg b.i.d.	(TOBI®) nebulised solution 300mg b.i.d.
N randomised to treatment	187	193
Baseline characteristics		
Age	Mean 21.3 (SD 9.72)	Mean 20.9 (SD 9.30)
Sex	M 56.3%; F 43.7%	M 52.9%; F 47.1%
FEV	NR	NR
BMI	Mean 18.67 (SD 3.39)	Mean 18.46 (SD 3.58)
Medical History (ITT population)		
Respiratory, thoracic and mediastinal disorders Gastrointestinal disorders Hepatobiliary disorders Musculoskeletal and connective tissue disorders Metabolism and nutrition disorders Infections and infestations	77.0% 72.1% 29.5% 23.0% 21.3% 19.1%	73.3% 75.4% 37.7% 19.4% 17.8% 16.2%
Prior Medication		
Fluoroquinolones	11 patients (6%) 10 patients (5.5%)	6 patients (3.1%) 10 patients (3.1%)

Macrolides		
Withdrawals		
Withdrawals/ loss to follow-up	32 withdrawn (17.1%) AE: 18 (56.3%) Lack of efficacy: 2 (6.3%) Patient request: 5 (28.1%) Protocol violation: 1 (3.1%) Other: 2 (6.3%)	21 withdrawn (14.2%) AE: 3 (14.3%) Lack of efficacy: 1 (4.8%) Patient request: 11 (52.4%) Death: 2 (9.5%) Other: 4 (19.0%)
Phase of Withdrawal		
Within 4 weeks	5 (2.7%)	1 (0.5%)
Between 4 and 8 weeks	12 (6.4%)	6 (3.1%)
Between 8 and 16 weeks	9 (4.8%)	5 (2.6%)
Between 16 and 20 weeks	5 (2.7%)	5 (2.6%)
Between 20 to 24 weeks	1 (0.5%)	4 (2.1%)
Protocol violations resulting in exclusion from ITT analysis	46 patients	35 patients
Results- 24 week data		
Notes on statistics	Analysed: 380 randomised (safety population), 374 patients (intention to treat [ITT] population), 298 patients (per-protocol [PP] population). ANCOVA model using main effects treatment, baseline FEV % predicted and pooled centre. Adjusted means by treatment presented as well as an estimate of the difference between adjusted means.	
Microbial response		
Mean Pa sputum density	No sputum density tests were performed during the trials	

Lung Function		
Baseline FEV_1 % Predicted (SE)	51.76 (1.029)	50.82 (0.989)
Lung Function – data also available from manufacturer's submission but not extracted here include: Non-parametric analysis Logarithmic analysis		
Lung Function- change in FEV_1% predicted LOCF ITT population		
Number of patients	n= 183	n= 190
Mean (SD)	-0.90 (10.015)	0.35 (10.756),
Median; range FEV_1%	-1.43; min -32.9, max 43.4	-1.09; min -33.6, max 49.3
ANCOVA adjusted mean:	-1.28	-0.13.
Comparison between groups	ANCOVA adjusted least squares mean difference between treatments= -1.16 (95% CI:-3.15 to 0.84%)	
Lung Function- change in FEV_1% predicted LOCF PP population		
Number of patients	n= 141	n= 157
Mean (SD)	-0.30 (10.306),	1.12 (11.120)
Median; range FEV_1%	-1.28; min -29.0, max 43.4	-0.61, min -33.6, max 49.3
ANCOVA adjusted mean	-1.02.	-0.47.
Comparison between groups	ANCOVA adjusted least squares mean difference between treatments = -1.49 (95% CI: -3.79 to 0.81%)	

Lung Function- change in FEV_1% predicted Completers ITT population		
Number of patients	n= 153	n= 171
Mean (SD)	-0.39 (9.715)	0.78 (10.900)
Median; range FEV	-0.70, min -29.0, max 43.4	-0.58, min -33.6, max 49.3
ANCOVA adjusted mean:	-0.36	0.08
Comparison between groups	ANCOVA adjusted least squares mean difference between treatments = -0.43% (95% CI: -2.59 to 1.72%)	
Lung Function- change in FEV_1% predicted Completers PP population		
Number of patients	n= 120	n= 141
Mean (SD)	0.83 (10.236)	1.6 (11.260)
Median; range FEV_1%	-0.51, min -29.0, max 43.4	-0.26, min -33.6, max 49.3
ANCOVA adjusted mean:	-0.26	0.73
Comparison between groups	ANCOVA adjusted least squares mean difference between treatments = -0.99 (95% CI: -3.48 to 1.51%)	
Lung function FVC- adjusted treatment difference (ITT population)		
Comparison between groups	0.01 L (95% CI: -0.09, 0.10 L) not significant (p=0.886)	
Lung function PEFR- adjusted treatment difference (ITT population)		
Comparison between groups	-3.32 L/min (95% CI: -16.31, 9.67 L/min) not significant (p=0.616)	
Lung function FEF25-75- adjusted treatment difference (ITT population)		
Comparison	-0.12 L/s (95% CI:-0.23, -0.01 L/s) significant (p=0.038)	

between groups				
Lung function FEF25-75- adjusted treatment difference (PP population)				
Comparison between groups	-0.12 L/s (95% CI:-0.26, -0.01 L/s) not significant (p=0.063)			
Acute exacerbations (Mean no. days)				
Time to acute respiratory exacerbation	[redacted]		[redacted]	
Time to first additional anti-pseudomonal treatment	55.28		51.79	
Duration of use of additional anti-pseudomonal agents	[redacted]		[redacted]	
[redacted]				
[redacted]	[redacted]		[redacted]	
[redacted]	[redacted]		[redacted]	
Proportion of antibiotic resistant isolates	Colistin: ≤ 1.1%		[redacted]	
	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]		
BSAC** for resistant Pa isolates	≤ 1.1%	
BSAC** comparison between groups	No significant difference between groups until broken down by age (note: this analysis was not defined a priori and is also underpowered). In the TOBI® group, a notable increase between baseline and Week 24 in the proportion of tobramycin-resistant isolates was documented in the 6 to 12 years age group (resistant: 10.5% to 22.2%) as well as in the 13 to 17 years age group (resistant: 11.4% to 16.0%)	
Compliance		
Patients more than 75% compliant with study medication	66.7%	70.7%
Withdrew	30 (16.4%)	20 (10.5%)
< 75% of doses	31 (16.9%)	36 (18.8%)
>75% - <100% of	105 (57.4%)	120 (62.8%)

doses		
>100% of doses	17 (9.3%)	15 (7.9%)
Mortality		
	0	2 (Both deaths reported as being unrelated to study drug. One death was due to multi-organ failure and one was due to lower respiratory tract infection)
Adverse events- data by patient		
Study drug related AEs	153/187 (81.8%)	90/193 (46.6%)
Patients withdrawn due to AEs	22/187 (11.8%)	5/193 (2.6%)
Severe† (related)	AE 48/187 (25.7%)	13/193 (6.7%)
Serious AEs	8/187 (4.3%)	12/193 (6.2%)
Serious related AEs*	3/187 (1.6%)	2/193 (1.0%)
Adverse events- data by event		
Study drug related AEs	528	325
Severe (related?) AEs	73	12
Moderate dysgeusia	10.7%	5.2%
Cough	15.7%	10.3%
Dyspnoea	6.6%	8.2%
BMI mean change from baseline to week 24	<1.0kg	<0.20kg

Audiology	Not tested	Not tested
Intravenous Colistin administered during “off” periods	n/a- no off periods	7 (3.6%)
Inhaled Colistin administered during “off” periods	n/a- no off periods	4 (2.1%)
Health Related Quality of Life		
CFQ-R adjusted mean change from baseline to week 24		
Physical	0.26	-1.56
Vitality	0.86	-1.40
Emotion	2.23	0.47
Eating	0.48	0.66
Treatment Burden	5.62	2.75
Health Perceptions	0.25	-2.71
Social	3.10	0.92
Body Image	7.83	5.98
Role	0.65	1.87
Weight	0.88	-1.93
Respiratory	2.99	3.51
Digestion	5.06	2.89

Appendix 6 Medline search strategy for EQ-5D utility data on adverse events related to cystic fibrosis and its treatment

Database: Ovid MEDLINE(R) <1948 to April Week 4 2011>

Search Strategy:

---

1 eq-5d.tw. (1422)
2 eq5d.tw. (71)
3 euroqol.tw. (1254)
4 euro qol.tw. (24)
5 or/1-4 (2120)
6 Cough/ (10389)
7 cough$.tw. (27671)
8 lung disorder$.tw. (817)
9 pulmonary exacerbation$.tw. (441)
10 cystic fibrosis exacerbation$.tw. (8)
11 cf exacerbation$.tw. (15)
12 Dyspnea/ (12637)
13 dyspnea.tw. (18987)
14 (short$ adj2 breath).tw. (3582)
15 Fever/ (27386)
16 fever.tw. (96463)
17 pyrexia$.tw. (2791)
18 hyperthermia$.tw. (17458)
19 oropharyngeal pain.tw. (22)
20 mouth pain.tw. (49)
21 pharynx pain.tw. (1)
22 oropharynx pain.tw. (2)
23 Oropharynx/ (2850)
24 exp Pain/ (263562)
25 Pain Measurement/ (47304)
26 24 or 25 (279815)
27 23 and 26 (35)
28 Dysphonia/ (303)
29 dysphonia.tw. (2274)
30 phonation disorder$.tw. (19)
31 Hemoptysis/ (4409)

32 hemoptys$.tw. (4729)
33 Headache/ (19831)
34 exp Headache Disorders/ (22683)
35 headache$.tw. (46063)
36 Nasal Obstruction/ (2989)
37 nasal congestion.tw. (1103)
38 nasal block$.tw. (355)
39 block$ nasal.tw. (23)
40 nose block$.tw. (18)
41 block$ nose.tw. (104)
42 Nausea/ (11432)
43 nause$.tw. (33719)
44 Respiratory Sounds/ (5788)
45 rale$.tw. (1042)
46 rhinorrhea.tw. (2385)
47 rhinorrhoea.tw. (541)
48 runny nose$.tw. (313)
49 exp Respiratory Function Tests/ (176514)
50 respiratory function test$.tw. (832)
51 pulmonary function test$.tw. (6977)
52 49 or 50 or 51 (178682)
53 decreas$.tw. (1351277)
54 lower$.tw. (985107)
55 reduc$.tw. (1673323)
56 53 or 54 or 55 (3288804)
57 52 and 56 (59579)
58 Respiratory Tract Infections/ (27721)
59 upper respiratory tract infection$.tw. (3153)
60 infection$ upper respiratory tract.tw. (19)
61 wheez$.tw. (7993)
62 chest discomfort.tw. (719)
63 discomfort chest.tw. (13)
64 Fatigue/ (15659)
65 fatigue.tw. (42610)
66 weariness.tw. (105)
67 lassitude.tw. (291)
68 Vomiting/ (17262)

69 vomit$.tw. (39561)

70 emesis.tw. (4604)

71 exp Sinusitis/ (13915)

72 sinusiti$.tw. (10053)

73 pulmonary congestion.tw. (948)

74 pulmonary obstruction.tw. (145)

75 pulmonary blockage.tw. (0)

76 or/6-23,27-48,57-75 (444541)

77 5 and 76 (96)

Appendix 7 Medline search strategy for FEV_1 and mortality

1 exp Forced Expiratory Volume/ (17802)

2 forced expiratory volume.tw. (10738)

3 fev1.tw. (14038)

4 exp CF/ (25639)

5 CF.tw. (27580)

6 exp Mortality/ (240291)

7 mortality.tw. (357242)

8 exp Survival/ (3413)

9 survival.tw. (457634)

10 1 or 2 or 3 (28225)

11 4 or 5 (32439)

12 6 or 7 or 8 or 9 (866700)

13 10 and 11 and 12 (258)