National Institute for Health and Care Excellence

Final

Cystic Fibrosis

Diagnosis and management

NICE Guideline NG78

Methods, evidence and recommendations

25 October 2017

FINAL

Developed by the National Guideline Alliance, hosted by the Royal College of Obstetricians and Gynaecologists

Update information

December 2024: We added links to relevant technology appraisal guidance in the section on pulmonary monitoring, assessment and management. This is to provide easy access to relevant guidance at the right point in the guideline only and is not a change in practice.

See the latest version of the guideline at https://www.nice.org.uk/guidance/ng78

Contents

1 Introduction

Cystic fibrosis is a multi-system genetic disorder affecting the lungs, pancreas, liver and intestine. It can have a significant impact on life expectancy and quality of life. The current median age of those who have died is 28 years and the median predicted survival is 45.1 years.

Diagnosis is primarily made during newborn screening. The median age at diagnosis is 2 months and 1 in every 2500 babies born in the UK has cystic fibrosis. Approximately 60% of people on the UK CF registry are aged over 16 years.

Many different mutations are responsible for cystic fibrosis. The UK CF registry shows that 90.8% of people with cystic fibrosis have one known genotype. However 8.9% of people have at least one unknown genotype.

Lung function is often reduced in cystic fibrosis. The typical measure of lung function is forced expiratory volume in 1 second (FEV_1). FEV_1 is a key predictor of life expectancy in people with cystic fibrosis, and optimising lung function is a major goal of care.

Lung infections are a cause of significant morbidity in cystic fibrosis. Chronic infection (for example with *Staphlococcus aureus* and *Pseudomonas aeruginosa*) may need long-term use of antibiotics.

There is variation across the country in the multidisciplinary team structures used, the arrangements services make for providing care and in the resources available to support services. Particular problems may arise with smaller shared-care clinic arrangements. In some centres, both inpatient and outpatient facilities are limited. For example, there may be problems in arranging admission to single rooms with en-suite facilities. If adequate protocols are not in place, then there is a risk of cross-infection.

By making robust recommendations based on the available evidence and best practice in cystic fibrosis care, this guideline will help improve care for this highly complex condition.

2 Guideline summary

2.1 Guideline committee membership, NGA staff and acknowledgements

Table 1: Guideline Committee Members

Name	Role
Mandy Bryon	Senior Consultant Clinical Psychologist Head of Psychological Services, Great Ormond Street Hospital for Children NHS Trust
Janis Bloomer	Paediatric Nurse Specialist (Children and young people) Cystic Fibrosis, Great North Children's Hospital Royal Victoria Infirmary
Sarah Collins	Cystic Fibrosis Specialist Dietitian, Nutrition & Dietetic Department, Royal Brompton Hospital
Alexander Darlington	Lay Member
Iolo Doull	Consultant Respiratory Paediatrician, Children's Hospital for Wales, Cardiff
Elaine Edwards	Advanced Physiotherapist, Sheffield Children's NHS Foundation Trust
Zoe Elliott	Lay Member
Andrew Jones	Consultant and Honorary Reader in Respiratory Medicine and Cystic Fibrosis, North West Lung Centre, University Hospitals South Manchester NHS Foundation Trust
David Lacy	General Paediatrician Wirral University Teaching Hospital NHS Foundation Trust
Nichola MacDuff	Adult Specialist Nurse, Advanced Clinical Nurse Specialist & Lead Nurse, Black Country Adult CF Centre, Royal Wolverhampton NHS Trust.
Helen McCabe	Principal Paediatric Dietitian - Royal Victoria Infirmary, Newcastle upon Tyne Hospitals NHS Foundation Trust.
Helen Parrott	Physiotherapist, Clinical Specialty Lead, Adult CF Therapies Royal Brompton Hospital
Sarah Popple	Senior Pharmacist Paediatrics and Cystic Fibrosis University Hospitals of Leicester.
Keith Thompson	Senior Respiratory Pharmacist, Royal Brompton and Harefield NHS Foundation Trust
Martin Walshaw (Chair)	Consultant Physician in General and Chest Medicine at Royal Liverpool and Broadgreen University Hospitals NHS Trust, and The Liverpool Heart and Chest Hospital NHS Foundation Trust. Honorary Professor of Medicine at the University of Liverpool
Co-opted members	
Stuart Elborn	Dean, School of Medicine, Dentistry and Biomedical Sciences, Queen's University, Belfast
Stephen Holden	Consultant Medical Microbiologist Nottingham University Hospitals NHS Trust

Table 2: NGA Staff

Name	Role
Omnia Abdulrazeg	Research Fellow (until January 2016)
Stephanie Arnold	Information Scientist (from May 2016)
Alexander Bates	Guideline Lead (November 2016 – January 2017)

Name	Role
Zosia Beckles	Information Scientist (until March 2016)
Bishal Bhandari	Assistant Systematic Reviewer (September 2016 – November 2016)
Lisa Boardman	Guideline Lead (from January 2017)
Me'leshah Brown	Project Administrator
Shona Burman-Roy	Senior Systematic Reviewer (March 2015 – May 2016)
Rami Cosulich	Systematic Reviewer (from March 2016)
Katherine Cullen	Senior Health Economist (until December 2014)
Vanessa Delgado-Nunes	Guideline Lead (until November 2016)
Annabel Flint	Project Manager (until September 2016)
Paul Jacklin	Senior Health Economist (January 2015 – July 2015)
Gemma Marceniuk	Health Economist (from July 2015)
Maija Kallioinen	Systematic Reviewer (August 2016 – September 2016)
Stephen Murphy	Clinical Advisor
Fionnuala O'Brien	Project Manager (from September 2016)
Hugo Pedder	Statistician
Gemma Villanueva	Senior Systematic Reviewer (from March 2015)

Acknowledgements

Additional support was received from Ebenezer Ademoisoye (Health Economist), Alex Bates (Senior Health Economist), Maija Kallioinen (Systematic Reviewer), Abigail Moore (Assistant Systematic Reviewer), Ferruccio Pelone (Systematic Reviewer) and Natasha Pillai (Systematic Reviewer), Tim Reeves (Information Scientist).

2.2 Other versions of the guideline

NICE produces a number of versions of this guideline:

- The 'short guideline' lists the recommendations, context and recommendations for research.
- NICE Pathways brings together all connected NICE guidance.

2.3 Schedule for updating the guideline

For the most up-to-date information about guideline reviews, please see the latest version of the NICE guidelines manual available from the NICE website.

3 Development of this guideline

3.1 What is a NICE Guideline?

NICE guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our NICE guidelines on the best available research evidence, with the aim of improving the quality of healthcare. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE guidelines can:

- Provide recommendations for the treatment and care of people by healthcare professionals.
- Be used to develop standards to assess the clinical practice of individual healthcare professionals.
- Be used in the education and training of healthcare professionals.
- Help patients to make informed decisions.
- Improve communication between patients and healthcare professionals.

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- The guideline topic is referred to NICE from the Department of Health.
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the NGA.
- The NGA establishes a guideline committee.
- A draft guideline is produced after the committee members assess the available evidence and makes recommendations.
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NGA and NICE produce a number of versions of this guideline.

- The ‘full guideline’ contains all the recommendations, together with details of the methods used and the underpinning evidence.
- The ‘short guideline’ lists the recommendations, context and recommendations for research.
- NICE Pathways brings together all connected NICE guidance.

3.2 Remit

NICE received the remit for this guideline from the Department of Health. It commissioned the NGA to produce the guideline.

The remit for this guideline is to develop a NICE guideline on the diagnosis and management of Cystic Fibrosis.

3.3 Who developed this guideline?

A multidisciplinary guideline committee comprising healthcare professionals and researchers as well as lay members developed this guideline (see the list of group members and acknowledgements).

NICE funds the NGA and thus supported the development of this guideline. The guideline committee was convened by the NGA and chaired by Dr Martin Walshaw in accordance with guidance from NICE.

The group met every 4 to 6 weeks during the development of the guideline. At the start of the guideline development process all group members declared interests including consultancies, fee-paid work, shareholdings, fellowships and support from the healthcare industry. At all subsequent group meetings, members declared arising conflicts of interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest necessitated it appropriate to do so. The details of declared interests and the actions taken are shown in Appendix C.

Staff from the NGA provided methodological support and guidance for the development process. The team working on the guideline included a guideline lead, a project manager, systematic reviewers, health economists, a statistician and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the group.

3.4 What this guideline covers

3.4.1 Groups that will be covered

The guideline covers the following groups.

- Infants, children, young people and adults with cystic fibrosis, including those who have non-classic cystic fibrosis and those who have had an organ transplant.

3.4.2 Key clinical issues that will be covered

The following clinical issues will be covered in this guideline:

- The clinical manifestations of cystic fibrosis at the time of diagnosis in infants, children, young people and adults.
- The complications of cystic fibrosis.
- Management of chest disease:
  - Routine monitoring of lung disease, including microbiological surveillance, radiological imaging and pulmonary function testing.
- Antimicrobial management in cystic fibrosis to:
  - prevent bacterial colonisation
  - treat acute pulmonary infection
  - treat chronic pulmonary infection, including clinical exacerbations and colonisation.
- Immunomodulatory management in chest disease.
- Management with mucoactive or mucolytic agents.
- Chest physiotherapy.
- The role of exercise in maintaining health.
- Management of nutrition.

- Management of exocrine pancreatic insufficiency.
- Management of distal intestinal obstruction syndrome.
- Surveillance for cystic-fibrosis-related diabetes.
- Surveillance for cystic-fibrosis-related liver disease and prevention of progression.
- Surveillance for reduced bone mineral density.
- Recognising psychological and behavioural problems.
- Models for delivery of care and multidisciplinary teams.
- Provision of information and support for infants, children, young people, adults and their carers

Note that guideline recommendations will normally fall within licensed indications. Exceptionally, and only if clearly supported by evidence, the use outside a licensed indication may be recommended. This guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

For further details please refer to the scope in Appendix A and review questions in Appendix D.

3.5 What this guideline does not cover

3.5.1 Clinical issues that will not be covered

This guideline does not cover:

- Specialist management of cystic-fibrosis-related diabetes.
- Specialist management of cystic-fibrosis-related fertility and pregnancy problems.
- Specialist management of cystic-fibrosis-related liver disease.
- Specialist management of cystic-fibrosis-related bone disease.
- Specialist management of cystic-fibrosis-related ear, nose and throat (ENT) disorders.
- Specialist management of cystic-fibrosis-related renal disease.
- Surgical management of gastrointestinal complications.
- Referral for, and management of, transplantation.
- Management of specific psychological conditions.
- Management of specific behavioural problems.

3.6 Relationship between the guideline and other NICE guidance

3.6.1 Related NICE guidance

- Gastro-oesophageal reflux disease (2015) NICE guideline NG1
- Dyspepsia and gastro‑oesophageal reflux disease (2014) NICE guideline CG184
- Healthcare-associated infections: prevention and control in primary and community care (2012) NICE guideline CG139
- Constipation in children and young people (2010) NICE guideline CG99
- Depression in adults with a chronic physical health problem (2009) NICE guideline CG91
- Living-donor lung transplantation for end-stage lung disease (2006) NICE interventional procedure guidance 170

4 Guideline development methodology

This chapter describes the methods used to review the evidence and generate the recommendations presented in subsequent chapters. This guidance was developed in accordance with the methods outlined in the NICE guidelines manual 2012 (PMG 6) for the scoping phase, and the NICE guidelines manual 2014 (PMG 20) from the development phase.

Declarations of interest were recorded according to the 2014 NICE conflicts of interest policy.

4.1 Developing the review questions and outcomes

The review questions were drafted by the NGA, and refined and validated by the guideline committee. The questions were based on the key areas identified in the guideline scope (See Appendix A).

A total of 29 questions were identified (See Table 3).

The review questions were based on the following frameworks:

- intervention reviews – using population, intervention, comparator and outcome (PICO framework)
- reviews of diagnostic test accuracy – using population, diagnostic test (index tests), reference standard and target condition
- prognostic reviews – using population, presence or absence of a risk factor, and outcome
- prevalence reviews – using population and outcome (prevalence of target condition)
- qualitative reviews – using population, area of interest and themes of interest

These frameworks guided the literature searching process, critical appraisal and synthesis of evidence and facilitated the development of recommendations by the guideline committee.

Full literature searches, critical appraisals and evidence reviews were completed for all review questions.

Table 3: Description of review questions

Chapter or section number	Type of review	Review questions	Outcomes
5	Clinical prediction	In infants, children, young people and adults (including those that have undergone newborn screening) when should cystic fibrosis be suspected?	• Risk of cystic fibrosis (risk ratios and odds ratios) • Sensitivity • Specificity • Positive predictive value • Negative predictive values • Positive likelihood ratios • Negative likelihood ratios
6	Qualitative	What information and support should be given to children, young people and adults with cystic fibrosis?	Themes will be identified from the literature, but expected themes are, for example: • Timing of when support is given • Regular formal assessments tailored to needs • Psychosocial support

Chapter or section number	Type of review	Review questions	Outcomes
			• Information about named individual for point of contact. • Information at the time of diagnosis. • Clear and accurate information about cystic fibrosis • Social media, apps and technology. • Discussion about planning management of cystic fibrosis. • Information for access to resources for managing co-morbidities. • Information on pregnancy and fertility. • Education and healthcare at school.
7.1	Intervention	What is the effectiveness of different models of care (for example, specialist centre, shared care [delivered by a Network CF Clinic which is part of an agreed designated network with a Specialist CF Centre], community, telehealth and/or home care for people with cystic fibrosis?	• Lung function o Forced expiratory volume (FEV_1) o Lung clearance index (LCI) • Time to next pulmonary exacerbation • Mortality • Nutritional status • Quality of life (measured with CF-QOL or CFQR) • Patient and carer satisfaction • Frequency of cross-infections (*Pseudomonas aeruginosa, Burkholderia cepacia*) • Staff experience • Adherence to treatment
7.2	Intervention	What is the clinical and cost-effectiveness of multidisciplinary teams of various compositions?	• Lung function o Forced expiratory volume (FEV_1) o Lung clearance index (LCI) • Time to next pulmonary exacerbation • Mortality • Nutritional status • Quality of life (measured with CF-QOL or CFQR) • Patient and carer satisfaction • Frequency of cross-infections (*P aeruginosa, B cepacia*) • Staff experience • Adherence to treatment
7.3	Qualitative	What parts of the transition from children's to adult services are most important for young people with cystic	Themes will be identified from the literature, but expected themes are, for example: • Transition clinic

Chapter or section number	Type of review	Review questions	Outcomes
		fibrosis and their family members and carers?	• Transition lead (consultant/social worker) preparation of plan of transition for individual and family/carers, multidisciplinary structured approach. • Involvement of young people and family/carer in planning, implementing and reviewing transition. • Key transition therapist as part of paediatric and adult service. • Communication/co-ordination between paediatric and adult services. • Timing of transition.
8	Prevalence	What are the non-lower-respiratory complications of cystic fibrosis in infants, children, young people and adults?	Prevalence of complications of cystic fibrosis. • Malnutrition • Impaired growth • Cystic fibrosis related renal disease • Delayed puberty • Distal intestinal obstruction syndrome (DIOS) • Abdominal pain • Cystic fibrosis related diabetes • Upper airways disease • Cystic fibrosis related musculoskeletal disorders • Urinary stress incontinence • Reduced bone mineral density • Cystic fibrosis related liver disease • Infertility • Meconium ileus
10.8	Intervention	What is the effectiveness of programmes of exercise in the management of cystic fibrosis?	• Lung function ○ Forced expiratory volume (FEV_1) ○ Forced vital capacity (FVC) ○ Lung clearance index (LCI) • VO_2 • Time to next exacerbation • Body composition • Quality of life (measured with CF-QOL or CFQR) • Preference for training programme • Adverse event
10.1	Intervention	What is the clinical and cost effectiveness of nutritional interventions in people with cystic fibrosis?	• Body composition • Lung function ○ Forced expiratory volume (FEV_1) ○ Pulmonary exacerbations

Chapter or section number	Type of review	Review questions	Outcomes
			• Changes to body composition detected by anthropometric measure • Quality of life (measured with CF-QOL or CFQR) • Satisfaction • Adverse effects
10.2	Intervention	In people with cystic fibrosis, what is the most effective regimen of enzyme replacement therapy in the treatment of exocrine pancreatic insufficiency?	• Nutritional status • Reduction of steatorrhoea and faecal fat (coefficient of fat absorption and faecal fat excretion specific outcomes and others) • Resolution of symptoms of malabsorption • Quality of life (measured with CF-QOL or CFQR) • Satisfaction • Drug related side effects/ adverse events
10.3	Intervention	What are the effective strategies for treatment and secondary prevention of distal ileal obstruction syndrome?	Primary treatment of DIOS: • Reduction in clinical manifestations including • Adverse events from treatment • Patient satisfaction • Duration of hospital stay • Treatment failure (need for surgery) • Adverse events from surgery Secondary prevention of DIOS: • Reduction in clinical manifestations including • Adverse events from treatment • Patient satisfaction • Recurrence of DIOS • Admission to hospital
10.4	Diagnostic	What is the diagnostic accuracy of tests to detect or strategies to detect early and late cystic fibrosis liver disease?	For the diagnostic accuracy question: • Positive likelihood ratios/ Negative likelihood ratios (LR+/ LR-) • Sensitivity/ Specificity • Area under the curve (AUC) For the following target conditions: • Liver disease • Cirrhosis • Portal hypertension • Oesophageal varices
10.4	Prognostic	What is the diagnostic and prognostic value of different strategies to detect cystic fibrosis liver disease and	• Adjusted odds ratios (adjORs) • Adjusted hazard ratios (adjHRs) • For the identification of:

Chapter or section number	Type of review	Review questions	Outcomes
		predict progression (including progression to cirrhosis and portal hypertension with (out) oesophageal varices)?	• Liver disease • Cirrhosis • Portal hypertension
10.5	Intervention	What is the effectiveness of ursodeoxycholic acid for preventing the development or progression of liver disease in people with cystic fibrosis?	• Change of hepatocellular enzymes or bilirubin level • Liver failure • Liver transplantation • Liver related mortality • Development of portal hypertension indicated by an: ○ Enlarged spleen (increased by at least 15%) ○ Development of varices ○ Ultrasound evidence of portal hypertension ○ No development of liver disease • Quality of life (measured with CF-QOL or CFQR)
10.6	Prognostic	What is the most effective strategy to monitor for the onset of CF-related diabetes (CFRD)?	• Lung function ○ Forced expiratory volume (FEV_1) ○ Forced vital capacity (FVC) ○ Lung clearance index (LCI) • Pulmonary exacerbation • Body mass index (BMI) • Adverse events • Patient acceptability/ satisfaction (with insulin therapy)
10.7	Prognostic	What is the most effective strategy to monitor for the identification of reduced bone mineral density in people with cystic fibrosis?	• Change in body bone mineral density • Number of fractures • Quality of life (measured with CF-QOL or CFQR)
10.9	Clinical prediction	What strategies are effective at identifying people with cystic fibrosis for the presence of a psychological and/or behavioural problem?	• Sensitivity • Specificity • Positive likelihood ratio (LR+) • Negative likelihood ratio (LR-) • AUROC • Reliability and validity
9.1	Intervention	What is the value of the following investigative strategies in monitoring the onset of pulmonary disease in people with cystic fibrosis without clinical signs or symptoms of lung disease? • Non-invasive microbiological investigation: induced sputum samples, cough	• Lung function ○ Forced expiratory volume (FEV_1) ○ Lung clearance index (LCI) • Quality of life (measured with CF-QOL or CFQR) • Nutritional parameters • Time to chronic infection with *P aeruginosa* or *Staphylococcus aureus*

Chapter or section number	Type of review	Review questions	Outcomes
		swab, throat swab, and nasopharyngeal aspiration • Invasive microbiological investigation: bronchoalveolar lavage • Lung physiological function tests: cardiopulmonary exercise testing, Spirometry and Lung Clearance Index • Imaging techniques: chest x-ray and CT scan	• Clearance of the organism from the cultures
9.1	Intervention	What is the value of the following investigative strategies in monitoring evolving pulmonary disease in people with established lung disease? • Non-invasive microbiological investigation: induced sputum samples, cough swab, throat swab, and nasopharyngeal aspiration • Invasive microbiological investigation: bronchoalveolar lavage • Lung physiological function tests: cardiopulmonary exercise testing, Spirometry and lung clearance index • Imaging techniques: chest X-ray and CT scan Evolving pulmonary disease defined as decline in lung function (based on FEV_1), increased exacerbations and/or infections, and CT changes.	• Lung function ○ Forced expiratory volume (FEV_1) ○ Lung clearance index (LCI) • VO_2 max • Nutritional parameters • Time to next exacerbation • Time to chronic infection using any recognized definition with *P aeruginosa* or with *S aureus* • Mortality • Quality of life (measured with CF-QOL or CFQR)
9.1	Intervention	What is the added value of imaging and invasive microbiological testing in addition to non-invasive microbiological testing and lung function tests in monitoring the response to treatment following an acute exacerbation? Definition of stablished lung disease: clinical signs and symptoms and/or radiological signs of lung disease.	• Lung function ○ Forced expiratory volume (FEV_1) ○ Lung clearance index (LCI) • Oxygen saturation • High-resolution computed tomography (CT) appearances or Chest X-ray appearances • Nutritional parameters • Time to next exacerbation • Clearance of the organism from the cultures • Inflammatory markers • Quality of life (measured with CF-QOL or CFQR)

Chapter or section number	Type of review	Review questions	Outcomes
9.2	Intervention	What is the effectiveness of airway clearance techniques in people with cystic fibrosis?	• Lung function ○ Forced expiratory volume (FEV_1) ○ Forced vital capacity (FVC) • Oxygen saturation • Expectorated secretions (mucus, sputum, phlegm) • Sputum volume • Patient preference • Pulmonary exacerbations • Hospitalisations, change in frequency • Quality of Life (measured with CF-QOL or CFQR)
9.3	Intervention	What is the effectiveness of mucoactive or mucolytic agents, including dornase alpha, nebulised sodium chloride (isotonic and hypertonic) and mannitol in people with cystic fibrosis?	• Lung function ○ Forced expiratory volume(FEV_1) • Inflammatory markers (Serum or Sputum) • Time to pulmonary exacerbations • Need for intravenous antibiotics for pulmonary exacerbation • Quality of life (measured with CF-QOL or CFQR) • Adverse events
9.4.1	Intervention	What is the effectiveness of long-term antimicrobial prophylaxis to prevent pulmonary bacterial colonisation with *S aureus* in people with cystic fibrosis?	• Time to identification of the pathogen (*S aureus*) in sputum culture • Number of positive pathogen cultures (*S aureus*) identified during study period • Lung function ○ Forced expiratory volume(FEV_1) ○ Lung clearance index (LCI) • Time to next pulmonary exacerbation • Quality of life (measured with CF-QOL or CFQR) • Adherence to treatment • Adverse events • Emergence of resistant organisms
9.4.2	Intervention	What is the effectiveness of antimicrobial treatment for acute pulmonary infection or those with an exacerbation in children and adults with cystic fibrosis?	• For pulmonary exacerbation: • Lung function ○ Forced expiratory volume (FEV_1) ○ Lung clearance index (LCI) • Eradication of specific pathogen • Resolution of infection/exacerbation or measure of treatment failure (e.g. need for additional antibiotics) • Duration of the acute episode

Chapter or section number	Type of review	Review questions	Outcomes

			• Quality of life (measured with CF-QOL or CFQR)
			• Mortality
			• Adverse events
			• For acute infection:
			• Lung function
			  ○ Forced expiratory volume (FEV_1)
			  ○ Lung clearance index (LCI)
			• Eradication of specific pathogen
			• Time to next pulmonary exacerbation
			• Resolution of infection/exacerbation or measure of treatment failure
			• Quality of life (measured with CF-QOL or CFQR)
			• Adverse events

9.4.3	Intervention	What is the effectiveness of antimicrobial regimens in suppressing chronic pulmonary infection in children and adults with cystic fibrosis with any of the following pathogens: • *Pseudomonas aeruginosa* • *B cepacia* complex • *S aureus* • *Aspergillus fumigatus*	• Lung function ○ Forced expiratory volume (FEV_1) • Time to next pulmonary exacerbation • Number of patients with at least 1 pulmonary exacerbation • Eradication of the specified organism from sputum/airway cultures • Nutritional status • Quality of life (measured with CF-QOL or CFQR) • Adverse events • Emergence of resistant organisms/ antibiotic resistance
9.5	Intervention	What is the effectiveness of immunomodulatory agents in the management of lung disease?	• Lung function ○ Forced expiratory volume (FEV_1) • Nutritional status • Time to next pulmonary exacerbation • Quality of life (measured with CF-QOL or CFQR) • Adverse effects • Mortality
11	Intervention	What is the effectiveness of cohorting on the basis of pathogen status versus not cohorting on the basis of pathogen status in reducing transmission of CF pathogens?	• Incidence of patients infected with transmissible pathogens • Prevalence of patients infected with transmissible pathogens • Quality of life (measured with CF-QOL or CFQR) • Emotional function including anxiety and depression
11	Intervention	What is the effectiveness of different models of segregating	

Chapter or section number	Type of review	Review questions	Outcomes
		patient's in reducing transmission of CF pathogens?	• Carer satisfaction • Patient satisfaction • Staff experience • Staff and patient compliance
11	Intervention	What is the effectiveness of individual protective equipment in reducing transmission of CF pathogens?	
11	Intervention	What is the effectiveness of the combination of cohorting, segregating and protective equipment in reducing transmission of CF pathogens?	

4.2 Searching for evidence

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions from January 2015 to September 2016.

Databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to retrieve only articles published in English. All searches were conducted in MEDLINE, Embase and The Cochrane Library. The following searches were updated in January 2017.

- Monitoring for liver disease
- Airway clearance
- Monitoring pulmonary disease
- Mucoactive agents
- Immunomodulatory agents
- Antimicrobials: prophylaxis
- Antimicrobials: acute
- Antimicrobials: chronic
- Nutrition interventions
- Exercise
- Service configuration: cross-infection
- Service configuration: MDT
- Service configuration: models of care

We prioritised the list below for re-runs based on the following criteria:

- Topics where network meta-analyses (NMAs) and HE modelling work have been conducted
- Topics with significant evidence movement where it is likely that new evidence will have been published
- Topics that are part of the service delivery component of the guideline
- Topics with empty reviews (i.e. MDT)
- Topics that have been covered earlier in guideline development which may now be at greater risk of being out of date.

Any studies added to the databases after this date (even those published prior to this date) were not included unless specifically stated in the text.

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews and asking the group members to highlight any additional studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix E.

The titles and abstracts of records retrieved by the searches were inspected for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria.

During the scoping stage, a search was conducted for guidelines and reports on websites of organisations relevant to the topic. Searching for grey literature or unpublished literature was not undertaken. Searches for electronic, ahead-of-print publications were not routinely undertaken unless indicated by the guideline committee. All references suggested by stakeholders at the scoping consultation were initially considered.

4.2.1 Health economic literature search

A global search of economic evidence relating to all treatments for cystic fibrosis was undertaken in April 2015 and re-ran in January 2017. The following databases were searched:

- MEDLINE (Ovid);
- EMBASE (Ovid);
- Cochrane Central Register of Controlled Trials (CCTR);
- HTA database (HTA);
- NHS Economic Evaluations Database (NHS EED).

Further to the database searches, the committee were contacted with a request for details of relevant published and unpublished studies of which they may have knowledge; reference lists of key identified studies were also reviewed for any potentially relevant studies. Finally, the NICE website was searched for any recently published guidance relating to cystic fibrosis that had not been already identified via the database searches.

The search strategy for existing economic evaluations combined terms capturing the target condition (cystic fibrosis) and, for searches undertaken in MEDLINE, EMBASE and CCTR, terms to capture economic evaluations. No restrictions on language or setting were applied to any of the searches, but a standard exclusions filter was applied (letters, animals, etc.). Conference abstracts were considered for inclusion from 1st January 2014, as high-quality studies reported in abstract form before 2014 were expected to have been published in a peer-reviewed journal. Full details of the search strategies are presented in Appendix E.

The titles and abstracts of papers identified through the searches were independently assessed for inclusion using pre-defined eligibility criteria defined in Table 4.

Table 4: Inclusion and exclusion criteria for the systematic reviews of economic evaluations

Inclusion criteria
intervention or comparators according to the scope
study population according to the scope
full economic evaluations (cost-utility, cost-effectiveness, cost-benefit or cost-consequence analyses) that assess both the costs and outcomes associated with the interventions of interest
Exclusion criteria
abstracts with insufficient methodological details

Inclusion criteria
cost-of-illness type studies
conference papers pre January 2014

Once the screening of titles and abstracts was complete, full versions of the selected papers were acquired for assessment. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for this search on economic evaluations is presented in Appendix F.

The quality of evidence was assessed using the economic evaluations checklist as specified in the NICE guidelines manual. Quality assessments of included studies and data extraction tables are provided in Appendix L and M, respectively.

4.3 Reviewing and synthesising research evidence

4.3.1 Systematic review process

- The evidence was reviewed following these steps (See Figure 1):
- Potentially relevant studies were identified for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.
- Full papers were reviewed against pre-specified inclusion and exclusion criteria in the review protocols (in Appendix D).
- Key information was extracted on the study's methods, according to the factors specified in the protocols and results. These were presented in summary tables (in each review chapter) and evidence tables (in Appendix G)
- Relevant studies were critically appraised using the appropriate checklist as specified in the NICE guidelines manual (NICE 2014).
- Summaries of evidence were generated by outcome (included in the relevant review chapters) and were presented in committee meetings (details of how the evidence was appraised is described in Section 4.3.5 below):
    - Randomised studies: meta-analysis was carried out where appropriate and results were reported in GRADE profiles (for intervention reviews).
    - Observational studies: data were presented individually by study in GRADE profiles.
    - Prognostic studies: data were presented individually by study, usually in terms of the relative effect as reported by the authors.
    - Diagnostic studies: data were presented individually by study as measures of diagnostic test accuracy (sensitivity and specificity, positive and negative likelihood ratios) and were presented in modified GRADE profiles.
    - Prevalence studies: data were presented as measures of prevalence during a period of time (proportions with their 95% confidence intervals); the decision if meta-analysis could be conducted was based on the consideration of the heterogeneity of the studies.
    - Qualitative studies: each study was summarised by theme and meta-synthesis was carried out where appropriate to identify an overarching framework of themes and subthemes. These were then presented in GRADE-CERQual (Lewin 2015) profiles, where CERQual stands for Confidence in the Evidence from Reviews of Qualitative research.

For quality assurance of study identification, either whole study selections or a sample of the study selection results were double checked by a second reviewer. Searches related to the NMA were also double sifted.

A sample of all evidence tables, including a sample of evidence tables related to the NMA were. All drafts of reviews were checked by a second reviewer. Any discrepancies were resolved by discussion between the 2 reviewers.

Figure 1: Step-by-step review of evidence in the guideline

4.3.2 Inclusion/exclusion criteria

The inclusion and exclusion of studies was based on the review protocols, which can be found in appendix D. Excluded studies by review question (with the reasons for their exclusion) are listed in appendix H. In addition, the committee were consulted about any uncertainty regarding inclusion or exclusion.

4.3.3 Type of studies

Systematic reviews (SRs) with meta-analyses were considered the highest quality evidence to be selected for inclusion.

For most intervention reviews in this guideline, parallel RCTs were prioritised because they are considered the most robust type of study design that could produce an unbiased estimate of the intervention effects. Crossover RCTs were appropriate for some of the interventional questions. If there was limited evidence from RCTs, observational studies were included.

For diagnostic reviews, cross-sectional, retrospective or prospective observational studies were considered for inclusion. Where evidence was limited, case-control studies were also considered for inclusion.

For clinical prediction and prognostic reviews, prospective and retrospective cohort studies were included.

For prevalence reviews, the committee prioritised the UK CF registry. Where no evidence was available or the committee agreed the UK CF registry data provided limited for a particular complication, cross-sectional studies and prospective cohort studies (national registries were preferred) were also included.

For qualitative reviews, studies using focus groups, or structured or semi-structured interviews were considered for inclusion. Survey data or other types of questionnaires were only included if they provided analysis from open-ended questions, but not if they reported descriptive quantitative data only.

Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded. Conference abstracts were only considered for inclusion in the absence of full published studies.

4.3.3.1 Incorporation of technology appraisals

Two NICE Technology Appraisals were identified as relevant for this guideline (TA276 and TA266). It was agreed that the recommendations were still current, and therefore they were lifted unchanged from the original guidance.

It was also decided that full systematic reviews were to be conducted based on the review protocols agreed with the committee, as this would allow to include studies that were not included in the Technology Appraisals.

4.3.4 Types of data and methods for synthesis

4.3.4.1 Data synthesis for intervention studies

4.3.4.1.1 Pairwise meta-analysis

Meta-analysis was conducted whenever it could be robustly performed, to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software.

The generic inverse variance option in RevMan5 was used where any studies reporting solely the summary treatment effect and 95% confidence interval (95% CI) or standard error could be included.

Fixed-effect (Mantel–Haenszel) techniques were used in the first instance to calculate risk ratios (relative risk) for binary outcomes, such as rate of adverse events or rate of people with symptom improvements (Mantel 1959).

For continuous outcomes, measures of central tendency (mean) and variation (standard deviation) are required for meta-analysis. However, in cases where standard deviations were not reported per intervention group, the standard error (SE) for the mean difference was calculated from other reported statistics (p-values or 95% CIs): meta-analysis was then undertaken for the mean difference and SE using the generic inverse variance method in RevMan5

When the only evidence was based on studies summarising results by presenting medians (and interquartile ranges) or only p values were given, this information was assessed in terms of the study's sample size and was included in the GRADE tables without calculating the relative or absolute effects. Consequently, aspects of quality assessment, such as imprecision of effect, could not be assessed for evidence of this type. However, the limited reporting of this outcome was classified as a risk of bias in study limitations.

Stratified analyses were predefined for some review questions at the protocol stage when the committee identified that these strata are different in terms of biological and clinical characteristics and the interventions were expected to have a different effect.

Statistical heterogeneity was assessed by visually examining the forest plots (please see Appendix I) and by considering the chi-squared test for significance at $p<0.1$ or an I-squared inconsistency statistic (with an I-squared value of more than 50% indicating considerable heterogeneity). Where considerable heterogeneity was present, predefined subgroup analyses were performed.

Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. If no sensitivity analysis was found to completely resolve statistical heterogeneity, then a random-effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect – (DerSimonian 1986).

Where data from observational studies were included, the committee decided that the results for each outcome should be presented separately for each study and meta-analysis was not conducted.

4.3.4.1.2 Network Meta-Analysis (NMA)

In some circumstances, the results of conventional pairwise meta-analyses of direct evidence does not help assess which intervention is most effective. The challenge of interpretation may arise for two main reasons:

- Relative treatment efficacies based on separate individual pairwise comparisons across multiple treatments are difficult to assess.
- Direct RCT comparison between treatments of clinical interest are not available in published literature.

To overcome these issues, NMA can be performed. Advantages of performing this type of analysis are:

- It allows the synthesis of data from direct and indirect comparisons without breaking randomisation, to produce measures of treatment effect and ranking of different interventions. If treatment A has never been compared against treatment B head to head, but these two interventions have been compared to a common comparator, then an indirect treatment comparison can use the relative effects of the two treatments versus the common comparator. This is also the case whenever there is a path linking two treatments through a set of common comparators. All the randomised evidence is considered within the same model.
- For every intervention in a connected network, a relative effect estimate (with its 95% credible intervals (95% CrI) can be estimated versus any other intervention. These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on all of the best available evidence, whilst appropriately accounting for uncertainty. Furthermore, these estimates will be used to parameterise treatment effectiveness in the de novo cost-effectiveness modelling.

There are 3 key assumptions behind an NMA: similarity, transitivity and consistency.

Consistency is the assumption that the direct estimates are equal to the indirect estimates (i.e. that the relative effect of A *versus* C is equal to the relative effect of A *versus* B minus B *versus* C).

Similarity across trials is the critical rationale for the consistency assumption to be valid as, by ensuring the clinical characteristics of the trials are similar, we ensure consistency in the data analysis.

More specifically, randomisation holds only within individual trials, not across the trials. Therefore, if the trials differ in terms of patient characteristics, measurement and/or definition of outcome, length of follow-up across the direct comparisons, the similarity assumption is violated and this can bias the analysis. Potential sources of heterogeneity arising from trials and attempts made to identify and account for heterogeneity are:

- Different duration of treatment or study follow-up:
  - The impact of study follow-up on treatment efficacy was assessed to identify if statistically there were differences between long and short duration studies.
  - Where differences were found, or where the committee believed there were likely to be clinical differences, NMAs were conducted separately for short and long duration studies.
- Different dosages of pharmacological treatments:
  - These typically showed little variation and were within the dose ranges specified by the British National Formulary (BNF).

Transitivity is the assumption that an intervention (A) will have the same efficacy in a study comparing A *versus* B as it will in a study comparing A *versus* C. Another way of looking at it, in terms of the study participants, is that we assume that it is equally likely that any patient in the network could have been given any of the treatments in the network and would have responded to the treatments in the same way (depending on how efficacious the treatments are). This assumption is closely related to similarity in that if participants in a study comparing A *versus* B are not the same as those in a study comparing A *versus* C.

As it is the case for ordinary pairwise meta-analysis, NMA may be conducted using either fixed or random effects models. A fixed effects model typically assumes that there is no variation in relative effects across trials for a particular pairwise comparison and any observed differences are solely due to chance. For a random effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution. The variance reflecting heterogeneity is often assumed to be constant across trials.

For continuous outcomes (e.g. forced expiratory volume), where SEs could not be calculated from the data, we imputed absolute values for them from other studies that reported measures of uncertainty/variance, using the method of Stevens (2011).

In a Bayesian analysis, for each parameter the evidence distribution is weighted by a distribution of prior beliefs. Markov Chain Monte Carlo (MCMC) algorithm was used to generate a sequence of samples from a joint posterior distribution of 2 or more random variables and is particularly well adapted to sampling the treatment effects (known as posterior distribution) of a Bayesian network. A non-informative prior distribution was used to maximise the weighting given to the data and to generate the posterior distribution for each log odds ratio (OR), log rate ratio or mean difference (MD) of interest in the networks. We used the median of the distribution as our point estimate and the centiles provided the 95% Credible Intervals (CrI).

Non-informative priors were used which were normally distributed with a mean of 0 and standard deviation of 100. However, for dichotomous data, where there was sparse data within the network, we investigated whether the use of informative priors generated from empirical data would give a more stable between-study variance (Turner 2012; Appendix L).

For the analyses, a series of 40,000 (100,000 for the multivariate NMA) burn-in simulations were run to allow the posterior distributions to convergence and then a further 100,000 simulations were run to produce the outputs. Convergence was assessed by examining the history, autocorrelation and Brooks-Gelman-Rubin plots.

Goodness-of-fit of the model was also estimated by using the posterior mean of the sum of the deviance contributions for each item by calculating the residual deviance and deviance

information criteria (DIC). If the residual deviance was close to the number of unconstrained data points (the number of trial arms in the analysis) then the model was explaining the data at a satisfactory level. The choice of a fixed or random effects model can be made by comparing their goodness-of-fit to the data.

Incoherence in NMA between direct and indirect evidence can be assessed in closed treatment loops within the network. These closed treatment loops are regions within a network where direct evidence is available on at least 3 different treatments that form a closed "circuit" of treatment comparisons (for example A *versus* B, B *versus* C, C *versus* A). If closed treatment loops existed then discrepancies between direct and indirect evidence was assessed for each loop using node-splitting (van Valkenhoef 2016).

The outputs of the NMA were:

- Treatment specific log ORs, log rate ratios, and MDs with their 95% CrI were generated for every possible pairs of comparisons by combining direct and indirect evidence in each network.
- The probability that each treatment is ranked as the best treatment, based on the proportion of Markov chain iterations in which the treatment effect for an intervention is ranked best, 2nd best and so forth. This was calculated by taking the treatment effect of each intervention compared to placebo and counting the proportion of simulations of the Markov chain in which each intervention had the highest treatment effect.
- The ranking of treatments (presented as median rank and its 95% CrI).

One of the main advantages of the Bayesian approach is that the method leads to a decision framework that supports decision making. The Bayesian approach also allows the probability that each intervention is best for achieving a particular outcome, as well as its ranking, to be calculated.

We adapted a model templates for continuous and dichotomous data available from NICE Decision Support UNIT (DSU) technical support document number 2. This model accounts for the within-study correlation between treatment effects induced by multi-arm trials.

NMA was considered particularly important for the 2 review questions where it was used because it allows use of indirect evidence to make comparisons between treatments that have not been compared in head-to-head RCTs. The networks in those 2 reviews were mostly compared to a single comparator (namely placebo) and therefore NMA allows us to estimate relative effects between all active treatments. NMA also allows all treatments to be compared to a single comparator, which is useful for health economic analysis that takes a fully incremental approach to determine the most cost-effective treatment out of all treatments under consideration. The primary motivation behind NMA for the chosen review question was that health economic analysis was prioritised for both of those review questions.

4.3.4.2 Data synthesis for diagnostic test accuracy reviews

There are a number of diagnostic test accuracy measures. Sensitivity, specificity, positive and negative likelihood ratios were used as outcomes for diagnostic reviews in this guideline. These diagnostic accuracy parameters (with 95% CI) were obtained from the studies or calculated by the technical team using data from the studies (See Table 5).

Sensitivity and specificity are measures of the ability of a test to correctly classify a person as having a disorder or not having a disorder. When Sensitivity is high, a Negative test result rules out the target disorder. When Specificity is high, a Positive test result rules in the target disorder. An ideal test would be both highly sensitive and highly specific, but this is frequently not possible and typically there is a trade-off.

The following definitions were used when summarising the levels of sensitivity or specificity for the committee:

- High: 90% and above
- Moderate: 75% to 89%
- Low: 74% or below

Positive and negative likelihood ratios are measures of the association between a test result and the target disorder. A positive likelihood ratio greater than one indicates a positive test is associated with having the disorder, whilst a negative likelihood ratio less than one indicates a negative test is associated with not having the disorder.

The following definitions were used when summarising the likelihood ratios for the committee:

- Very useful test: LR+ higher than 10; LR- lower than 0.1
- Moderately useful test: LR+ 5 to 10; LR- 0.1 to 0.2
- Not a useful test: LR+ lower than 5; LR- higher than 0.2

Table 5: '2 x 2' table for calculation of diagnostic accuracy parameters

	Reference standard positive	Reference standard negative	Total
Index test result positive	True positive (TP)	False positive (FP)	TP+FP (Total number of subjects with positive result in screening tool)
Index test result negative	False negative (FN)	True negative (TN)	FN+TN (Total number of subjects with negative results in screening tool)
Total	TP+FN (Total number of subjects with diagnosis)	FP+TN (Total number of subjects without diagnosis)	TP+FP+FN+Tn=N (Total number of subjects in study)
Note: *Sensitivity=TP/(TP+FN)* *Specificity=TN/(TN+FP)* *Positive likelihood ratio=sensitivity/(1-specificity)* *Negative likelihood ratio=(1-sensitivity)/specificity*			

4.3.4.3 Data synthesis for clinical prediction and prognostic reviews

For the investigation of pre-specified prognostic/predictive factors, odds ratios (ORs), risk ratios (RRs) or hazard ratios (HRs), with their 95% confidence intervals (95% CIs) were extracted from the papers when reported. As prognostic factors are not attributes that can be randomised (either for practical or ethical reasons), evidence came from observational studies. For this type of review, we looked for studies that took into account possible key confounders as reported in multivariable analyses. The reported measures were therefore adjusted to take into account other characteristics that might explain some of the association between the prognostic factor and the outcome. Studies did this in a pre-specified manner using stratification, or used statistical methods that included confounding variables (such as multivariable logistic regression). Results from these analyses would then indicate which characteristics are most likely to be independent prognostic factors rather than confounding factors only spuriously related to the outcome.

4.3.4.4 Data synthesis for prevalence reviews

Study results were presented according to the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-analyses). Risk factors that were assessed in a multi-variated regression analysis model with adjustment for important confounders were reported. To assist with the ease of interpretation, only results from studies where outcomes were assessed dichotomously were included and reported. Prevalence estimates (proportions) with their 95% confidence intervals were reported or calculated where sufficient data were available.

Studies were categorised according to type of outcome and where data were available, results were reported by subgroups pre-specified in the review protocol.

4.3.4.5 Data synthesis for qualitative reviews

Where possible, a meta-synthesis was conducted to combine qualitative study results. The main aim of the synthesis of qualitative data was to produce a description of the topics that may influence the experience of person with cystic fibrosis, those people important to them and healthcare professionals involved in their care, rather than build new theories or reconceptualise the topic under review. Whenever studies identified a qualitative theme, this was extracted and the main characteristics were summarised. When all themes were extracted from studies, common concepts were categorised and tabulated. This included information on how many studies had contributed to an identified overarching theme.

In qualitative synthesis, a theme being reported by different studies more often than other themes does not necessarily mean that it would be more important than those other themes. The aim of qualitative research is to identify new perspectives on a particular topic. Study type and population in qualitative research can differ widely, meaning that themes identified by just one or a few studies can provide important new information for a given topic. Therefore, for the purpose of the qualitative reviews in this guideline, we did not add further studies when they reported the same themes that had already been identified from the same perspectives because the emphasis was on conceptual robustness rather than the quantitative completeness of evidence. This has implications for the types and numbers of studies that are included in the qualitative reviews. Study inclusion continued until no new relevant data could be found regarding a topic that would add to or refute it, a concept referred to in the literature as ‘theoretical saturation’ (Dixon-Woods 2005).

The most relevant evidence in this respect would originate from studies set in the target context of the UK NHS setting. Themes from individual studies were then integrated into a wider context and, when possible, overarching categories of themes with sub-themes were identified. Themes were derived from data presented in individual studies based directly on quotes from interviewees. When themes were extracted, theme names derived from the studies that provided it were used. The names of overarching themes, however, were named by the systematic reviewers.

Emerging themes were then placed into a thematic map that presents the relationship between themes and subthemes. The purpose of the map was to show relationships between overarching themes and their subthemes. The mapping part of the review was drafted by a member of the technical team, but the final framework of themes was further shaped and, when necessary, re-classified through discussion with at least one other member of the technical team. The committee could then draw conclusions from each theme in each setting or country and how they may help in forming recommendations.

4.3.5 Appraising the quality of the evidence by outcomes

4.3.5.1 GRADE methodology

For intervention reviews, the evidence for outcomes from the included RCTs and observational studies were evaluated and presented using GRADE, which was developed by the international GRADE working group. Modified GRADE assessments were also carried out for accuracy measures in diagnostic reviews. For the appraisal of the quality of the evidence from qualitative reviews an adapted GRADE-CERQual (Lewin 2015) approach was used, where CERQual stands for Confidence in the Evidence from Reviews of Qualitative research.

The software developed by the GRADE working group (GRADEpro) was used to assess the quality of each outcome, taking into account individual study quality factors and the meta-analysis results. The clinical/economic evidence profile tables include details of the quality assessment and pooled outcome data, where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate summary measures of effect and measures of dispersion (such as mean and standard deviation or median and interquartile range) for continuous outcomes and frequency of events (n/N: the sum across studies of the number of patients with events divided by sum of the number of completers) for binary outcomes. Reporting or publication bias was only taken into consideration in the quality assessment and included in the clinical evidence profile tables if it was apparent.

The selection of outcomes for each review question was decided when each review protocol was discussed with the committee. However, given the nature of most of the review questions included in this guideline (driven by short- or long-term outcomes), the categorisation of outcomes as critical and important did not follow the standard GRADE approach. The outcomes selected for a review question were critical for decision-making in a specific context.

The evidence for each outcome in interventional reviews was examined separately for the quality elements listed and defined in Table 6.

Table 6: Description of quality elements in GRADE for intervention studies

Quality element	Description
Risk of bias (study limitations)	Limitations in the study design and implementation may bias the estimates of the treatment effect. High risk of bias for the majority of the evidence decreases confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results or findings.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made, such that the effect estimate is changed. This is also related to applicability or generalisability of findings.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect. Imprecision results if the confidence interval includes the clinically important threshold. For qualitative research this can relate to the sufficiency of data within each theme.
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

The GRADE toolbox is designed only for RCTs and observational studies, but we adapted the quality assessment elements and outcome presentation for diagnostic accuracy and qualitative studies, subject to data availability.

For example, for diagnostic accuracy studies, the GRADE tables were modified to include the most appropriate measures of diagnostic accuracy (sensitivity and specificity) (See Table 7). For prognostic factors, an adapted GRADE approach was conducted. This looked at the body of the evidence for each risk factor across studies for 1 outcome (See Table 8).

Table 7: Description of the elements in GRADE and how they are used to assess the quality for diagnostic accuracy reviews

Quality element	Description
Risk of bias ('Study limitations')	Limitations in the study design and implementation may bias the estimates of the diagnostic accuracy. High risk of bias for the majority of the evidence decreases confidence in the estimate of the effect. Diagnostic accuracy studies are not usually randomised and therefore would not be downgraded for study design from the outset and start as high level evidence.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of test accuracy measures such as sensitivity and specificity between studies.
Indirectness	Indirectness refers to differences in study population, differences in index tests across studies, reference standards and outcomes between the available evidence and the review question.
Imprecision	Results are considered imprecise when studies include relatively few patients and the probability to be diagnosed correctly in this group is low. Accuracy measures would therefore have wide confidence intervals around the estimate of the effect.

Table 8: Description of the elements in GRADE and how they are used to assess the quality for prognostic reviews

Quality element	Description
Risk of bias ('Study limitations')	Limitations in the study design and implementation may bias the estimates and the interpretation of the effect of the prognostic risk factor. High risk of bias for the majority of the evidence decreases confidence in the estimate of the effect. Prognostic studies are not usually randomised and therefore would not be downgraded for study design from the outset and start as high level evidence.
Inconsistency	Inconsistency refers to an unexplained heterogeneity between studies looking at the same sign or symptom, resulting in wide variability between ORs, RRs or HRs, with little or no overlap in confidence intervals.
Indirectness	Indirectness refers to any departure from the review protocol, for instance differences in study population or risk factor, that may affect how results can be generalised from the reviewed evidence.
Imprecision	Results are considered imprecise when studies include relatively few patients and also when the number of patients is too low for a multivariable analysis (as a rule of thumb a number of 10 participants per variable). This was assessed by looking at the confidence interval and where it lies in relation to the point estimate of the study.

For qualitative studies an adapted GRADE-CERQual (Lewin 2015) approach was used, where CERQual stands for confidence in the evidence from reviews of qualitative research. This looked at the quality of evidence by theme. These themes may have originated from an individual study or may have been identified through a number of individual themes or components of themes across a number of included studies (See Table 9).

Table 9: Description of the elements in the adapted GRADE-CERQual approach used to assess qualitative evidence by theme

Quality element	Description
Risk of bias ('Study limitations')	Limitations in the study design and implementation may bias the interpretation of the qualitative themes that are identified. High risk of bias for the majority of the evidence decreases confidence in the estimate of the effect. Qualitative studies are not usually randomised and therefore would not be downgraded for study design from the outset and start as high level evidence.
Coherence of findings	The extent to which different individual themes or components of themes from studies fit into a wider network of overarching themes. For example, many components (relationship and rapport, clinical experience, information provision) can contribute to an overarching theme of healthcare professional factors in shared decision-making. Even though each individual study may not mention each factor, the overall theme is coherent.
Applicability (or relevance) of evidence	The extent to which the evidence supporting the review finding is applicable to the context specified in the review question. In the case of this guideline, qualitative evidence from the UK was prioritised over and above data from other contexts.
Theme saturation / sufficiency	Theme saturation or sufficiency refers to a similar concept in qualitative research. This refers to whether a theoretical point of theme saturation was achieved, at which point no further citations or observations would provide more insight or suggest a different interpretation of this theme. Individual studies that may have contributed to a theme or subtheme may have been conducted in a manner that by design would have not reached theoretical saturation on an individual study level.

The main criteria considered in the rating of these elements are discussed below (see section 4.3.5.2). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome.

The main criteria considered in the rating of these elements are discussed below. Footnotes beneath GRADE tables were used to describe reasons for grading a quality element as having serious or very serious limitations. The ratings for each component were summed to obtain an overall assessment for each outcome (See Table 12).

4.3.5.2 Grading the quality of clinical evidence

After results were pooled using data synthesis methods, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using the GRADE approach:

- An initial quality rating was assigned, based on the study design. RCTs start as 'High' in intervention reviews and observational studies as 'Low'. In diagnostic, prognostic and qualitative reviews, evidence from non-randomised studies start as 'High'.
- The rating was then downgraded for the specified criteria: risk of bias (study limitations); inconsistency; indirectness; imprecision; and publication bias. These criteria are detailed below. Evidence from observational studies (which had not previously been downgraded) was upgraded if there was a large magnitude of effect or a dose-response gradient, and if all plausible confounding would reduce a demonstrated effect, or suggest a spurious effect when results showed no effect.

Each quality element considered to have 'serious' or 'very serious' issues was rated down by 1 or 2 points respectively. Value based judgements for relevant interpretation of the levels of quality elements were informed by discussion with the committee for each review to balance consistency of approach across the guideline and clinical relevance within each review (see

Table 10). The downgraded/upgraded ratings were then summed and the overall quality rating was revised, taking into account the relative contributions from the individual studies within a meta-analyses, where performed. For example, RCTs start as high and the overall quality becomes moderate, low or very low if 1, 2 or 3 points are deducted respectively. The reasons or criteria used for downgrading were specified in the footnotes.

For qualitative reviews, each quality element considered to have 'minor or 'serious' limitations was rated down by 1 or 2 points respectively. A quality assessment of 'Unclear' was added to the list of possible GRADE-CERQual levels. Together with the committee, it was decided that in qualitative reviews 1 'Unclear' rating did not mean an automatic downgrade of the evidence for this theme. However, 2 'Unclear' ratings were downgraded by 1. Footnotes were not used for the CERQual tables (See Table 11).

Table 10: Levels of quality elements in GRADE for intervention, diagnostic and prognostic reviews

Level	Description
None	There are no serious issues with the evidence.
Serious	The issues are serious enough to downgrade the outcome evidence by 1 level.
Very serious	The issues are serious enough to downgrade the outcome evidence by 2 levels.

Table 11: Levels of quality elements in GRADE for qualitative reviews

Level	Description
No limitations	There are no serious issues with the evidence.
Minor limitations	The issues are serious enough to downgrade the outcome evidence by 1 level.
Serious limitations	The issues are serious enough to downgrade the outcome evidence by 2 levels.
Unclear	There is no enough information available to assess the domain.

Table 12: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

The details of the criteria used for each of the main quality elements are discussed further in sections 4.3.5.2.1 to 4.3.5.3.4 below.

4.3.5.3 Risk of bias/ methodological limitations

Intervention studies

For intervention studies, the Cochrane Risk of Bias tool was used for randomised control trials (see appendix H in the NICE guidelines manual 2014).

Bias can be defined as anything that causes a consistent deviation from the truth. Bias can be perceived as a systematic error. The risk of bias for a given study and outcome is associated with the risk of over or underestimation of the true effect. Sources of bias in RCTs are listed in Table 13).

A study with a poor methodological design does not automatically imply high risk of bias; the bias is considered individually for each outcome and it is assessed whether this poor design will impact on the estimation of the intervention effect.

Table 13: Summary of Cochrane risk of bias tool

Risk of bias	Explanation
Allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (this is a major problem in 'pseudo' or 'quasi' randomised trials with allocation by, for example, day of week, birth date, chart number).
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes or data analysts are aware of the arm to which patients are allocated.
Incomplete accounting of patients and outcome events	Missing data not accounted for and failure of the investigators to adhere to the intention to treat principle when indicated.
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results.
Other risks of bias	For example: • stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules • use of unvalidated patient-reported outcomes • recruitment bias in cluster randomised trials.

For observational studies, quality was assessed using the Newcastle-Ottawa Scale (Wells 2008) (see appendix H in the NICE guidelines manual 2014).

The risk of bias was derived by assessing the risk of bias across 3 domains – selection, comparability and outcome. Studies are given a rating depending on how they perform on each of the domains. More details about the quality assessment items for observational studies are shown in Table 14.

Table 14: Summary of Newcastle and Ottawa scale

Risk of bias category	Quality assessment item
Selection	Representativeness of the cohort
	Selection of the non-exposed cohort
	Ascertainment of exposure
	Demonstration that the outcome of interest was not present at the start of the study
Comparability	Comparability of cohorts on the basis of the design or analysis
Outcome	Assessment of outcome
	Was follow-up long enough for outcomes to occur
	Adequacy of follow-up of cohorts

Diagnostic studies

For diagnostic accuracy studies, the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS- 2) checklist was used (http://www.bristol.ac.uk/social-community-medicine/projects/quadas/quadas-2/) (see appendix H in the NICE guidelines manual 2014).

Risk of bias and applicability in primary diagnostic accuracy studies in QUADAS- 2 consists of 4 domains:

- patient selection

- index test
- reference standard
- flow and timing.

More details about the quality assessment of diagnostic studies are shown in Table 15.

Table 15: Summary of QUADAS-2

Domain	Patient Selection	Index text	Reference standard	Flow and timing
Description	Describe methods of patient selection: Describe included patients (prior testing, presentation, intended use of index test and setting):	Describe the index test and how it was conducted and interpreted:	Describe the reference standard and how it was conducted and interpreted:	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:
Signalling questions (yes/no/unclear)	Was a consecutive or random sample of patients enrolled?	Were the index test results interpreted without knowledge of the results of the reference standard?	Is the reference standard likely to correctly classify the target condition?	Was there an appropriate interval between index test(s) and reference standard?
	Was a case-control design avoided?	If a threshold was used, was it pre-specified?	Were the reference standard results interpreted without knowledge of the results of the index test?	Did all patients receive a reference standard?
	Did the study avoid inappropriate exclusions?			Did all patients receive the same reference standard?
				Were all patients included in the analysis?
Risk of bias: (high/low/unclear)	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns regarding applicability: (high/low/unclear)	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or interpretation differ from	Are there concerns that the target condition as defined by the reference standard does not match the	

Domain	Patient Selection	Index text	Reference standard	Flow and timing
		the review question?	review question?	

Prevalence studies

For prevalence studies, the quality was assessed using the checklist created by The Joanna Briggs Institute (The Joanna Briggs Institute, 2014; Munn et al., 2014) (see appendix H in the NICE guidelines manual 2014).

The quality was assessed based on answering 'yes', 'no', 'unclear', or "not applicable" to the following questions:

- Was the sample representative of the target population?
- Were the study participants recruited in an appropriate way?
- Was the sample size adequate?
- Were the study subjects and setting described in detail?
- Is the data analysis conducted with sufficient coverage of the identified sample?
- Were objective, standard criteria used for measurement of the condition?
- Was the condition measured reliably?
- Was there appropriate statistical analysis?
- Are all important confounding factors/ subgroups/differences identified and accounted for?
- Were subpopulations identified using objective criteria?

The assessment of the overall quality of the evidence was based on the reviewer's judgment considering the answers to the questions above. For example, if there were several "no" and "unclear" answers, the quality of the evidence was considered to be low, or if there were some "unclear" answers the quality of the evidence was considered to be moderate.

Prognostic studies

For prognostic studies, the quality was assessed using the checklist created by Hayden et al. (2013) (see appendix H in the NICE guidelines manual 2014).

This risk of bias for each risk factor across studies was derived by assessing the risk of bias across 6 domains for each study: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting, with the last 4 domains being assessed for each outcome. More details about the quality assessment for prognostic studies are shown in Table 16.

The assessment of the overall quality of the evidence was based on the reviewer's judgment considering the assessment of all the 6 domains, for example, if there was a high risk of bias in any domain, the evidence was considered to be of low quality and if there was low risk of bias in all domains, the evidence was considered to be of high quality.

Table 16: Assessment of risk of bias for prognostic studies based on Hayden et al. (2013)

Risk of bias	Explanation
Study participation	Assessment of whether or not there was adequate participation in the study by eligible individuals; if the population and sample were described; if the recruitment and sampling were described and considered appropriate; if inclusion and exclusion criteria were adequately described.
Study attrition	Assessment of whether there was an adequate follow-up rate for study participants; reasons for losses to follow-up were described; the individuals

Risk of bias	Explanation
	lost to follow-up were adequately described; assessment was done whether the ones lost to follow-up differed from the ones who completed the follow-up.
Prognostic factor measurement	Assessment of whether or not a clear description of the prognostic (risk) factor is provided; the method of assessing or measuring the prognostic factor is valid and reliable; and is the same for every participant.
Outcome measurement	Assessment of whether or not a clear definition of the outcome was provided; the measurement or assessment of outcome is valid and reliable; the method and setting of outcome measurement is the same for every participant.
Study confounding	Assessment of whether or not important confounders were adequately measured, described and adjusted for in the analyses.
Statistical analysis and reporting	Assessment of whether or not there is sufficient presentation of data to assess the adequacy of the analytical strategy; the statistical model is adequate; the reporting of results is adequate, clear and not selective.

Qualitative studies

For qualitative studies, quality was assessed using a checklist for qualitative studies (as suggested in Appendix H in the NICE guidelines manual 2014). This was based on the Critical Appraisal Skills Programme (CASP) checklist for qualitative studies. The quality rating for risk of bias (low, high and unclear) was derived by assessing the risk of bias across 6 domains.

The evidence was then assessed by theme using GRADE-CERQual across studies as described above and labelled (no limitations, minor limitations, major limitations and unclear), see Table 17.

Table 17: Summary of CASP tool for qualitative studies

Risk of bias	Explanation
Aim and appropriateness of qualitative evidence.	This refers to an assessment of whether the aims and relevance of the study were clearly described and whether qualitative research methods were appropriate for investigating the research question.
Rigour in study design or validity of theoretical approach	This domain assesses whether the study approach has been clearly described and is based on a theoretical framework (for example ethnography or grounded theory). This does not necessarily mean that the framework has to be explicitly stated, but that at least a detailed description is provided which makes it transparent and reproducible.
Sample selection	The background, the procedure and reasons for the chosen method of selecting participants should be stated. It should also be assessed whether there was a relationship between the researcher and the informant and if so, how this may have influenced the findings that were described.
Data collection	Consideration was given to how well the method of data collection (in-depth interviews, semi-structured interviews, focus groups or observations) was described, whether details were provided and how the data were collected (who conducted the interviews, how long did they last and where did they take place).
Data analysis	For this criterion it is assessed whether sufficient detail is provided about the analytical process and whether it is in accordance with the theoretical approach. For instance, if a thematic analysis was used, it is assessed whether there was a clear description of how the theme was arrived at. Data saturation is also part of this section. This refers to whether a theoretical point of theme saturation was achieved at which point no further citations or observations would provide more insight or suggest a different interpretation of this theme. This could be explicitly stated, or it may be clear from the citations presented that it may have been possible to find more themes.

Risk of bias	Explanation
Results	In relation to this section the reasoning about the results are important, for instance whether a theoretical proposal or framework is provided rather than being restricted to citations / presentation of data.

4.3.5.4 Inconsistency / coherence of findings

Inconsistency refers to unexplained heterogeneity of results. When estimates of treatment effect measures vary widely across studies (that is, there is heterogeneity or variability in results between studies), this suggests true differences in underlying effects.

Heterogeneity in meta-analyses was evaluated. If present, sensitivity and subgroup analyses were performed as pre-specified in the protocols (Appendix D).

When heterogeneity existed (chi-squared probability less than 0.1, I-squared inconsistency statistic of greater than 50%, or from visually examining forest plots), but no plausible explanation (for example duration of intervention or different follow-up periods) could be found, the quality of the evidence was downgraded in GRADE by 1 or 2 levels, depending on the extent of inconsistency in the results. When outcomes are derived from a single trial, inconsistency is not an issue for downgrading the quality of evidence. However, 'no inconsistency' is nevertheless used to describe this quality assessment in the GRADE profiles as this is the default option in the GRADEpro software used.

For qualitative research, a similar concept to inconsistency is coherence, which refers to the way findings within themes are described and whether they make sense. This concept was used in the quality assessment across studies for individual themes. This does not mean that contradictory data was downgraded automatically, but that it was highlighted and presented, and that reasoning was provided. As long as the themes, or components of themes, from individual studies fit into a theoretical framework, they do not necessarily have to have the same perspective. It should, however, be possible to explain these by differences in context (for example, the views of healthcare professionals might not be the same as those of family members, but they could contribute to the same overarching theme). Coherence was graded across studies with the following labels: coherent, incoherent or unclear.

4.3.5.5 Indirectness / applicability or relevance of findings

For quantitative reviews, directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

Relevance of findings in qualitative research is the equivalent of indirectness for quantitative outcomes and refers to how closely the aims and context of the studies contributing to a theme reflect the objectives outlined in the review protocol of the guideline question.

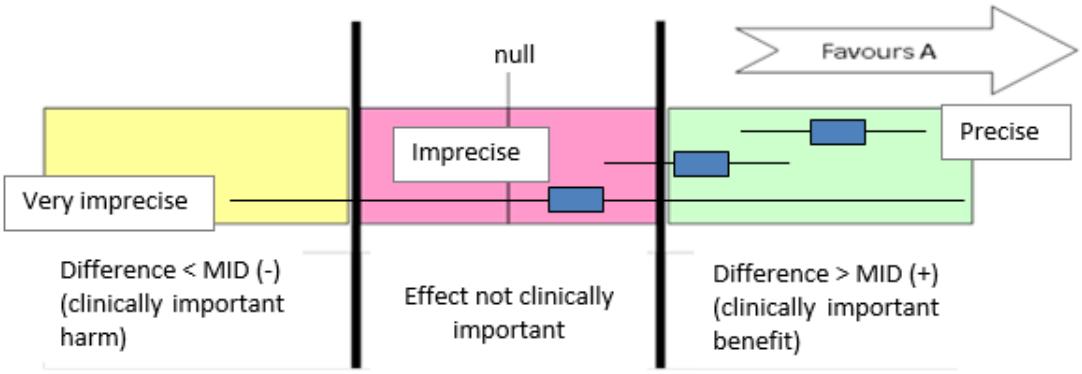
4.3.5.6 Imprecision / theme saturation or sufficiency

For quantitative reviews, imprecision in guidelines concerns whether the uncertainty (confidence interval) around the effect estimate means that it is not clear whether there is a clinically important difference between interventions or not (that is, whether the evidence would clearly support one recommendation or appear to be consistent with several different types of recommendations). Therefore, imprecision differs from the other aspects of evidence quality because it is not really concerned with whether the point estimate is accurate or correct (has internal or external validity). Instead, it is concerned with the uncertainty about what the point estimate actually is. This uncertainty is reflected in the width of the confidence interval.

The 95% confidence interval (95% CI) is defined as the range of values within which the population value will fall on 95% of repeated samples, were this procedure to be repeated. The larger the trial, the smaller the 95% CI and the more certain the effect estimate.

Imprecision in the evidence reviews was assessed by considering whether the width of the 95% CI of the effect estimate was relevant to decision-making, taking each outcome in isolation. This is explained in Figure 2, which considers a positive outcome for the comparison of treatment A versus treatment B. Three decision-making zones can be identified, bounded by the thresholds for clinical importance (minimal important difference, MID) for benefit and for harm. The MID for harm for a positive outcome means the threshold at which drug A is less effective than drug B by an amount that is clinically important to patients (favours B).

Figure 2: Illustration of precise, imprecise and very imprecise evidence based on the confidence interval of outcomes in forest plots



When the confidence interval of the effect estimate is wholly contained in 1 of the 3 zones (for example clinically important benefit), we are not uncertain about the size and direction of effect (whether there is a clinically important benefit, or the effect is not clinically important, or there is a clinically important harm), so there is no imprecision.

When a wide confidence interval lies partly in each of 2 zones, it is uncertain in which zone the true value of effect estimate lies and therefore there is uncertainty over which decision to make (based on this outcome alone). The confidence interval is consistent with 2 possible decisions and so this is considered to be imprecise in the GRADE analysis and the evidence is downgraded by 1 level ('serious imprecision').

If the confidence interval of the effect estimate crosses into 3 zones, this is considered to be very imprecise evidence because the confidence interval is consistent with 3 possible clinical decisions and there is therefore a considerable lack of confidence in the results. The evidence is therefore downgraded by 2 levels in the GRADE analysis ('very serious imprecision').

Implicitly, assessing whether the confidence interval is in, or partially in, a clinically important zone, requires the committee to estimate an MID or to say whether they would make different decisions for the 2 confidence limits.

Minimally Important Differences

The literature was searched for established minimally important differences (MIDs) for the selected outcomes in the evidence reviews, such as symptom measurement tools. MIDs specific to each review are reported in the review protocol (Appendix D), though the following MIDs were used consistently throughout the guideline:

- For CF-QOL a published MID was used (European Medicines Agency 2012) which was a difference of 5 points.
- For time to next exacerbation the committee agreed that any change was considered to be clinically important, so the MID threshold was one on a ratio scale.
- For adverse events that led to discontinuation of treatment the committee agreed that any change was considered to be clinically important, so the MID threshold was one on a ratio scale.
- For mortality the committee agreed that any change was considered to be clinically important, so the MID threshold was one on a ratio scale.

Finally, if no published or acceptable MIDs were identified, the committee considered whether it was clinically acceptable to use the GRADE default MID to assess imprecision. For binary outcomes clinically important thresholds for a risk ratio of 0.8 and 1.25 respectively were used (due to the statistical distribution of this measure this means that this is not a symmetrical interval). This default MID was used for all the binary outcomes in the interventions' evidence reviews as a starting point and decisions on clinical importance were then considered based on the absolute risk difference. For continuous outcomes GRADE default MIDs were half of the median standard deviation of the control group.

The same principle was used for prognostic factors, for example using the default MID as a starting point for the committee discussion, to assess whether the size of the outcome effect would be large enough to be meaningful in clinical practice.

In diagnostic accuracy measures, it was first considered whether sensitivity, specificity, positive likelihood ratios or negative likelihood ratios would be given more weight in the decision-making process. If one measure was given more importance than the other, then imprecision was rated on this statistical measure using the following MID thresholds:

- Sensitivity and specificity
  - High: >90%
  - Moderate: 75-90%
  - Low: <75%
- Positive likelihood ratio:
  - Very useful test: >10
  - Moderately useful test: 5-10
  - Not a useful test: <5
- Negative likelihood ratio:
  - Very useful test: <0.1
  - Moderately useful test: 0.1 to 0.2
  - Not a useful test: >0.2

Theme saturation or sufficiency refers to a similar concept in qualitative research. This refers to whether a theoretical point of theme saturation was achieved, at which point no further citations or observations would provide more insight or suggest a different interpretation of this theme. As already highlighted in a previous section on qualitative reviewing methods, it is not equivalent to the number of studies contributing to a theme, but rather to the depth of data and whether sufficient quotes or observations were provided that could underpin these findings.

4.3.5.7 NMA quality appraisal

The use of GRADE to assess the quality of studies addressing a particular review question for pairwise comparisons of interventions is relatively established. However, the use of GRADE to assess the quality of evidence across a NMA is still a developing methodology.

While most criteria for pairwise meta-analyses still apply, it is important to adapt some of the criteria to take into consideration additional factors, such as how each 'link' or pairwise comparison within the network applies to the others. As a result, we used the following adapted GRADE approach for appraising the quality of NMA.

Table 18: Rationale for downgrading quality of evidence in NMAs

GRADE criteria	Example reasons for downgrading quality
Risk of bias	Risk of bias was assessed in accordance with GRADE, as specified in 'The guidelines manual (2012)'. This includes limitations in the design or execution of the study, including concealment of allocation, blinding, loss to follow up (these can reduce the quality rating).
Inconsistency	Evidence of any inconsistency between the direct and indirect estimates of effect was assessed using the residual deviance, deviance information criterion and the statistic tau; outcome was downgraded if tau > 0.5
Indirectness	The extent to which the available evidence fails to address the specific review question (this can reduce the quality rating). This may be in relation to the setting, population, outcomes, interventions or study designs used in the evidence base. Evidence was only downgraded if this was likely to have an impact on the overall rankings (that is, within smaller networks where there is a lack of evidence or within larger networks in large trials which show large reductions in outcomes).
Imprecision	This is considered to be present when there is uncertainty around the estimate of effect, and reflects the confidence in, or 'credibility' of, the estimate of effect. It is assessed based on the overall distribution of the rankings, such that evidence was downgraded if no interventions had rank credible intervals ≤33% of total distribution of comparators.

4.3.5.8 Assessing clinical significance

Intervention and prognostic reviews

The committee assessed the evidence by outcome. To facilitate this, where possible, binary outcomes were converted into absolute risk differences (ARDs) using GRADEpro software: the median control group risk across studies was used to calculate the ARD and its 95% CI from the pooled risk ratio. For continuous outcomes, the mean difference between the intervention and control arm of the trail was calculated. This was then assessed in relation to the default MID (0.5 times the median control group standard deviation).

The clinical significance of a treatment effect or prognostic factor was evaluated as a combination of the minimally / clinically important difference (MID) thresholds and statistical significance / the null hypothesis value (zero for continuous outcomes and 1 for RRs, ORs and HRs):

- If the point estimate for a treatment effect / prognostic factor exceeded the MID and the 95% CI did not include the null hypothesis value then the result was considered to be "clinically significant"
- If the point estimate for a treatment effect / prognostic factor did not exceed the MID then the result was not considered to be "clinically significant"

Diagnostic reviews

The clinical usefulness of a test for diagnosis was determined based on either sensitivity, specificity, positive likelihood ratio or negative likelihood ratio, depending on what the committee believed was the most important – correctly identifying if a patient had the target disorder (ruling in) or correctly identifying if a patient did not have the target disorder (ruling out).

The value of the point estimate within the different MID thresholds for sensitivity, specificity, positive likelihood ratio or negative likelihood ratio were used to determine clinical usefulness.

Qualitative reviews

For themes stemming from qualitative findings, clinical significance was decided upon by the committee taking into account the generalisability of the context from which the theme was derived and whether it was convincing enough to support or warrant a change in current practice, as well as the evidence quality.

4.3.6 Evidence statements

Evidence statements are summary statements that are presented after the GRADE profiles, summarising the key features of the clinical evidence presented. The wording of the evidence statements reflects the certainty or uncertainty in the estimate of effect. The evidence statements are presented by outcome or theme and encompass the following key features of the evidence:

- the quality of the evidence (GRADE rating)
- the number of studies and the number of participants for a particular outcome
- a brief description of the participants
- the clinical significance of the effect and an indication of its direction (for example, if a treatment is clinically significant [beneficial or harmful] compared with another, or whether there is no clinically significant difference between the tested treatments).

4.3.7 Evidence of cost effectiveness

The aims of the health economic input to the guideline were to inform the guideline committee of potential economic issues related to the diagnosis and management of cystic fibrosis to ensure that recommendations represented a cost-effective use of healthcare resources. Health economic evaluations aim to integrate data on healthcare benefits (ideally in terms of quality-adjusted life-years (QALYs) with the costs of different care options. In addition, the health economic input aimed to identify areas of high resource impact; recommendations which – while nevertheless cost-effect – might have a large impact on CCG or Trust finances and so need special attention.

4.3.7.1 Undertaking new health economic analysis

As well as reviewing the published economic literature, as described above, new economic analysis was undertaken by the Health Economist in selected areas. The following priority areas for de novo economic analysis were agreed by the committee after formation of the review questions and consideration of the available health economic evidence:

- immunomodulatory agents in the management of lung disease,
- antimicrobial regimens in suppressing chronic pulmonary disease,
- configuration of services to minimise the risk of cross-infection.

A costing tool was also developed for the review question relating to models of care, where little clinical evidence was uncovered. It was thought that the committee may wish to make recommendations that would lead to a high resource impact, although current practice was recommended.

The methods and results of de novo economic analyses are reported in Appendix K. When new economic analysis was not prioritised, the committee made a qualitative judgement regarding cost effectiveness by considering expected differences in resource and cost use between options, alongside clinical effectiveness evidence identified from the clinical

evidence review. Cost descriptions used to aid considerations of cost effectiveness are also reported in Appendix K.

4.3.7.2 Cost effectiveness criteria

NICE's report Social value judgements: principles for the development of NICE guidance sets out the principles that committees should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or;
- the intervention cost less than £20,000 per QALY gained compared with the next best strategy, or;
- the intervention provided clinically significant benefits at an acceptable additional cost when compared with the next best strategy.

The committee's considerations of cost-effectiveness are discussed explicitly in the 'Consideration of economic benefits and harms' section of the relevant sections.

4.4 Developing recommendations

4.4.1 Guideline recommendations

Over the course of the guideline development process, the committee were presented with:

- evidence tables of the clinical and economic evidence reviewed from the literature: all evidence tables are in Appendix H and economic evidence tables are in Appendix L
- summary of clinical and economic evidence and quality assessment (as presented in Chapters 5 to 11)
- forest plots (Appendix I)
- a description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (Appendix K).

Recommendations were drafted on the basis of the group's interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. This was either done formally, in an economic model, or informally. Firstly, the net benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes, although most of the reviews in the guideline were outcome driven. When this was done informally, the group took into account the clinical benefits and harms when one intervention was compared with another. The assessment of net benefit was moderated by the importance placed on the outcomes (the group's values and preferences) and the confidence the group had in the evidence (evidence quality). Secondly, the group assessed whether the net benefit justified any differences in costs.

When clinical and economic evidence was of poor quality, conflicting or absent, the group drafted recommendations based on their expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs or implications compared with the economic benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The group also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation.

The wording of recommendations was agreed by the group and focused on the following factors:

- the actions healthcare professionals need to take,
- the information readers of the guideline need to know,
- the strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weak recommendations),
- the involvement of patients (and their carers if needed) in decisions about treatment and care,
- consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective intervention.

The main considerations specific to each recommendation are outlined in the 'Recommendations and link to evidence' sections within each chapter.

4.4.2 Research recommendations

When areas were identified for which good evidence was lacking, the committee considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients or the population,
- national priorities,
- potential impact on the NHS and future NICE guidance,
- ethical and technical feasibility.

4.5 Validation process

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website at publication.

4.6 Updating the guideline

Following publication, and in accordance with the NICE guidelines manual, NICE will undertake a review of whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

4.7 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The NGA disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

4.8 Funding

The NGA was commissioned by the National Institute for Health and Care Excellence (NICE) to undertake the work on this guideline.

5 Diagnosis of cystic fibrosis

Review question: In infants, children, young people and adults (including those that have undergone new-born screening) when should cystic fibrosis be suspected?

5.1 Introduction

Today, most people with cystic fibrosis will be diagnosed at birth as part of the national Newborn Screening Programme using the blood spot immunoreactive trypsin test. Screening was introduced UK-wide in 2006 and so there remains a cohort of young people and adults with cystic fibrosis who have not been screened and yet have been diagnosed through a clinical assessment. Although highly successful, the Programme is not able to screen for all cystic fibrosis associated genetic variants and so some infants will inevitably remain undiagnosed. It should be noted that over 2,000 mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene have been identified. Many of these variants are rare and have not been shown to lead to clinical disease and therefore their clinical significance can be unclear. Of these 2,000 variants, around 200 have been shown to lead to cystic fibrosis disease. Although only common disease-associated variants are tested for as part of the Newborn Screening Programme.

Additionally, infants may not undergo newborn screening due to parent's wishes or if newborn screening is not carried out in the country of birth. People with atypical manifestations of cystic fibrosis can reach adulthood undiagnosed and therefore untreated when clinical intervention would beneficial.

Given the potential for people with cystic fibrosis to remain undiagnosed at all stages in life this review aims to determine what symptoms may indicate a possibility of cystic fibrosis and so warrant further investigation.

5.2 Description of clinical evidence

The aim of this review was to support health care professionals in identifying cystic fibrosis even in people who have been through new-born screening.

In this review, our index test were clinical symptoms and signs, including:

- Respiratory features (including recurrent infection, chest x-ray evidence of chronic disease)
- Faltering growth
- Symptoms of malabsorption
- Azoospermia
- Acute pancreatitis
- Meconium ileus (in infants).

The committee agreed DIOS is known to be a symptom unique to cystic fibrosis, and therefore there was not need to include it in the review. We looked for prospective or retrospective cohort studies to identify diagnostic or prognostic factors, but no relevant studies were found. Therefore we looked for observational studies that reported the prevalence of cystic fibrosis among people presenting with one of the symptoms of interest.

As no diagnostic or prognostic data were finally included in the review, a GRADE approach (as specified in the protocol) was no longer deemed appropriate. Therefore for this review, the quality appraisal of the evidence has been conducted by study, and not by outcome.

For full details of the protocol see Appendix D.

5.2.1 Respiratory symptoms

Four observational studies were identified, 2 prospective (Ooi 2012, Seer 1997) and 2 retrospective (Hubert 2014, Grimaldi 2015).

Sample sizes ranged from 72 to 601, and the studies were conducted in Canada (Ooi 2012, Seer 1997) and France (Hubert 2014, Grimaldi 2015).

5.2.2 Faltering growth

No studies were identified.

5.2.3 Symptoms of malabsorption

No studies were identified.

5.2.4 Azoospermia

One observational study was identified (Ooi 2012).

Sample size was 92 and it was conducted in Canada.

5.2.5 Acute pancreatitis

Two observational studies were identified (Lucidi 2011, Ooi 2012).

Sample sizes ranged from 44 to 78, and the studies were conducted in Canada (Ooi 2012) and Italy (Lucidi 2011).

5.2.6 Meconium ileus

No studies were identified.

A summary of the included studies is presented in Table 19. See also study selection flow chart in Appendix F, excluded studies list in Appendix H, and study evidence tables in Appendix G.

5.3 Summary of included studies and results

A summary of the studies that were included in this review and the results is presented in Table 19.

Table 19: Summary of included studies and results

Study	Clinical symptoms & signs and reference test	Population	Findings	Comments	Quality
Respiratory symptoms					
Hubert 2004 (France) Retrospective, observational study	Symptom: • bronchiectasis • *Bronchiectasis defined as chronic mucopurulent sputum production and recurrent lower respiratory tract infection, were confirmed by high-resolution CT.* Reference test: • sweat chloride test (ST) • *Thresholds:* • *Diagnosis of CF: >60 mmol/l.* • *Suggestive, but not diagnostic of CF: 40 to 60 mmol/l.*	N=601 Adults referred for diffuse bronchiectasis from 1992 to 2001 Mean age (range): 31 years (18 to 56)	Clinical diagnosis of CF • Confirmed CF diagnosis: n=37; 6.16% • Borderline CF diagnosis: n=9; 1.50% • Sensitivity, specificity, LR+, LR-, PPV and NPV not reported and not calculable.	• It is unknown whether these patients underwent newborn screening, but seems unlikely as newborn screening was implemented in France in 2002 (Grimaldi 2015) • Two sweat test were performed for each patient. • Critical confounders not taken into consideration.	• Very low
Grimaldi 2015 (France) Retrospective, observational, multicentre study	Symptoms: • asthma, • chronic cough, • lower airway infections, • bronchiectasis • *Definition for symptoms not provided.* Reference test: • sweat chloride test (ST) • *Thresholds for patients >6 months:* • *Positive ST: ≥60 mmol/l.* • *Intermediate ST: 40 to 59 mmol/l.* • *Negative ST: ≤39 mmol/l.* • *Thresholds for infants up to 6 months:* • *Positive ST: ≥60 mmol/l.*	N=502 Infants and children who had a negative CF newborn screening presenting respiratory symptoms Mean age ± SD (range): 36±28 months (1 month to 10 years) • Asthma: n=358 • Chronic cough: n=263 • Lower airway infections: n=212	Clinical diagnosis of CF • In children with asthma: n=1; 0.3% • In children with chronic cough: n=4; 1.5% • In children with lower airway infections: n=4; 1.8% • In children with bronchiectasis: n=2; 5.7% • Sensitivity, specificity, LR+, LR-, PPV and NPV not reported and not calculable.	• All children had a negative CF newborn screening. • Critical confounders not taken into consideration.	• Very low

Study	Clinical symptoms & signs and reference test	Population	Findings	Comments	Quality
	• *Intermediate ST: 29 to 59 mmol/l.* • *Negative ST: ≤29 mmol/l.*	• Bronchiectasis: n=35			
Ooi 2012 (Canada) Prospective, observational study	Symptom: • Idiopathic chronic sinopulmonary disease *Idiopathic sinopulmonary disease defined as recurrent or chronic sinusitis (including sinusoidal pain, nasal discharge, postnasal drip), nasal polyps, recurrent or chronic bronchitis, recurrent pneumonia and/or bronchiectasis for at least 6 months. All enrolled subjects with sinopulmonary disease had three or more of these symptoms.* Reference test: • sweat chloride test (ST) • cystic fibrosis transmembrane conductance regulator gene (CFTR) *ST thresholds for the diagnosis of CF according to European consensus recommendations.* *Extensive CFTR genotyping according to European diagnostic process (interpretation of results from genotyping was based on the number of mutations identified).*	N=72 Undiagnosed individuals with single organ manifestations of CF were enrolled between 1994 and 2008 Mean age ± SD (range): 38.5±15.9 (9.9 to 66.7) years	Clinical diagnosis of CF • Classic CF: n=14; 19.4% • CFTR dysfunction: n=3; 4.2% • Inconclusive: n=1; 1.4% • Unlikely diagnosis: n=54; 75.0% • Sensitivity, specificity, LR+, LR-, PPV and NPV not reported and not calculable.	• It is unknown whether these patients underwent newborn screening, • Critical confounders not taken into consideration.	• Very low
Seear 1997 (Canada) Prospective, observational study	Symptom: • Chronic cough • *No definition given. But just children with a history of >3 months of productive cough, of unknown cause, were included* Reference test:	N=81 Children with a history of >3 months of productive cough Age: not reported	Clinical diagnosis of CF • Diagnosis of CF: n=1; 1.23% • Sensitivity, specificity, LR+, LR-, PPV and NPV not reported and not calculable.	• It is unknown whether these patients underwent newborn screening, • Critical confounders not taken into consideration.	• Very low

Study	Clinical symptoms & signs and reference test	Population	Findings	Comments	Quality
	• sweat chloride test (ST) • *Thresholds for diagnosis of CF not reported.*				
Faltering growth					
No studies were identified.					
Symptoms of malabsorption					
No studies were identified.					
Azoospermia					
Ooi 2012 (Canada) Prospective, observational study	Symptom: • Infertility due to obstructive azoospermia • *A diagnosis of obstructive azoospermia (congenital unilateral or bilateral absence of vas deferens) was confirmed by physical examination, transrectal ultrasound and evidence of azoospermia on two separate occasions.* Reference test: • sweat chloride test (ST) • cystic fibrosis transmembrane conductance regulator gene (CFTR) • *ST thresholds for the diagnosis of CF according to European consensus recommendations.* • *Extensive CFTR genotyping according to European diagnostic process (interpretation of results from genotyping was based on the number of mutations identified).*	N=92 Undiagnosed individuals with single organ manifestations of CF were enrolled between 1994 and 2008 Mean age ± SD (range): 34.8±5.3 (25.4 to 56.6) years	Clinical diagnosis of CF • Classic CF: n=19; 20.7% • CFTR dysfunction: n=21; 22.8% • Inconclusive: n=9; 9.8% • Unlikely diagnosis: n=43; 46.7% • Sensitivity, specificity, LR+, LR-, PPV and NPV not reported and not calculable.	• It is unknown whether these patients underwent newborn screening, • Critical confounders not taken into consideration.	• Very low
Acute pancreatitis					

Study	Clinical symptoms & signs and reference test	Population	Findings	Comments	Quality
Lucidi 2011 (Italy) Retrospective, observational study	Symptom: • acute recurrent pancreatitis • *Acute recurrent pancreatitis defined as 2 or more separate documented episodes of acute pancreatitis with serum amylase and/ or lipase levels at least 3 times the upper reference limit* Reference tests: • sweat chloride test (ST), • genetic test (CFTR mutation) *ST thresholds for diagnosis of CF not reported.* *CFTR genotyping diagnostic process not reported.*	N=78 Paediatric population affected by acute recurrent pancreatitis between 2003 and 2008 Mean age ± SD (range): 8.8±5.1 years (4 months to 18 years)	Clinical diagnosis of CF • Diagnosis of CF with ST: n=1; 1.3% • Borderline diagnosis of CF with ST: n=7; 9% • Diagnosis of CF by the detection of 2 CF-causing mutations: n=1 (percentage cannot be calculated as the study does not report for how many people there was data available) • CFTR mutation: 39.6% (data available for n=53) • Sensitivity, specificity, LR+, LR-, PPV and NPV not reported and not calculable.	• 42.3% (n=33) patients had a positive family history of chronic pancreatitis/ cystic fibrosis and/ or positive genetic testing and/ or altered sweat test. • However it is unknown whether all these patients underwent newborn screening. • Critical confounders not taken into consideration.	Very low
Ooi 2012 (Canada) Prospective, observational study	Symptom: • Idiopathic recurrent, acute or chronic pancreatitis *A diagnosis of idiopathic recurrent acute pancreatitis was accepted following at least two episodes of abdominal pain associated with raised serum amylase and/or lipase (more than two times the upper limit of the reference range), and/or imaging evidence of acute pancreatitis such as pancreatic oedema, haemorrhage or necrosis. Patients with chronic pancreatitis had chronic pain in association with pancreatic*	N=44 Undiagnosed individuals with single organ manifestations of CF were enrolled between 1994 and 2008 Mean age ± SD (range): 24.3±13.2 (7.9 to 59.9) years	Clinical diagnosis of CF • Classic CF: n=2; 4.5% • CFTR dysfunction: n=6; 13.6% • Inconclusive: n=1; 2.3% • Unlikely diagnosis: n=35; 79.6% • Sensitivity, specificity, LR+, LR-, PPV and NPV not reported and not calculable.	• It is unknown whether these patients underwent newborn screening, • Critical confounders not taken into consideration.	• Very low

Study	Clinical symptoms & signs and reference test	Population	Findings	Comments	Quality
	calcifications and/or characteristic ductal changes. Reference test: • sweat chloride test (ST) • cystic fibrosis transmembrane conductance regulator gene (CFTR) • *ST thresholds for the diagnosis of CF according to European consensus recommendations.* • *Extensive CFTR genotyping according to European diagnostic process (interpretation of results from genotyping was based on the number of mutations identified).*				
Meconium ileus					
No studies were identified					

Abbreviations: CF: cystic fibrosis; CFTR: CF transmembrane conductance regulator; LR: likelihood ratio; NPV: negative predictive value; PPV: positive predictive value; SDS: standardized by age and gender; ST: sweat test

5.4 Clinical evidence profile

See summary of results in Table 19.

5.5 Economic evidence

This review question is not relevant for economic analysis because it does not involve a decision between alternative courses of action.

No economic evaluations to identify the clinical manifestations suggestive of cystic fibrosis were identified in the literature search conducted for this guideline. Full details of the search and economic article selection flow chart can be found in Appendix E and F, respectively.

5.6 Evidence statements

5.6.1 Respiratory symptoms

Very low quality evidence from 1 prospective observational study showed that among 81 children with a history >3 months of productive cough 1.23% (n=1) had a diagnosis of cystic fibrosis (by means of sweat test, thresholds not reported). The study does not report whether these children had undergone newborn screening.

Very low quality evidence from 1 retrospective observational study showed that among 502 infants and children (age range: 1 month to 10 years) who had a negative cystic fibrosis newborn screening presenting respiratory symptoms:

- 0.3% (n=1; N=358) of the children presenting with asthma had a diagnosis of cystic fibrosis (sweat test ≥60 mmol/l)
- 1.5% (n=4; N=263) of the children presenting with a chronic cough had a diagnosis of cystic fibrosis (sweat test ≥60 mmol/l)
- 1.8% (n=4; N=212) of the children presenting with lower airway infections had a diagnosis of cystic fibrosis (sweat test ≥60 mmol/l)
- 5.7% (n=2; N=35) of the children presenting with bronchiectasis had a diagnosis of cystic fibrosis (sweat test ≥60 mmol/l).

Very low quality evidence from 1 retrospective observational study showed that among 601 adults (mean age: 31 years) referred for diffuse bronchiectasis:

- 6.16% (n=37) had confirmed diagnosis of cystic fibrosis (sweat test >60 mmol/l)
- 1.50% (n=9) had borderline diagnosis of cystic fibrosis (sweat test 40 to 60 mmol/l).

The study does not report whether these people had undergone newborn screening, but seems unlikely as newborn screening was implemented in France in 2003.

Very low quality evidence from 1 prospective observational study showed that among 72 children, young people and adults (mean age; range: 34.8 years; 9.9 to 66.7 years) with idiopathic chronic sinopulmonary disease:

- 19.4% (n=14) had a diagnosis of classic cystic fibrosis based on sweat test (European Consensus Recommendations)
- 4.2% (n=3) had a CFTR abnormality (based on extensive CFTR genotyping, and according to European Guidelines). This is also known as non-classic or atypical cystic fibrosis
- 1.4% (n=1) had an inconclusive diagnosis.

The study does not report whether these people had undergone newborn screening.

5.6.2 Faltering growth

No evidence was found for this sign.

5.6.3 Symptoms of malabsorption

No evidence was found for this symptom.

5.6.4 Azoospermia

Very low quality evidence from 1 prospective observational study showed that among 92 adult men (mean age; range: 34.8 years; 25.4 to 56.6 years) with infertility due to obstructive azoospermia:

- 20.7% (n=19) had a diagnosis of classic cystic fibrosis based on sweat test (European Consensus Recommendations)
- 22.8% (n=21) had a CFTR abnormality
- 9.8% (n=9) had an inconclusive diagnosis.

The study does not report whether these men had undergone newborn screening.

5.6.5 Acute pancreatitis

Very low quality from 1 retrospective observational study with 78 infants, children and young people (age range: 4 months to 18 years) affected by acute pancreatitis:

- 1.3% (n=1) had a diagnosis of cystic fibrosis based on sweat test (thresholds not reported)
- 9% (n=7) had a borderline diagnosis of cystic fibrosis based on sweat test (thresholds not reported);
- 39.6% had a single CFTR mutation on genetic testing
- n=1 had a diagnosis of cystic fibrosis based on the detection of 2 cystic fibrosis-causing mutations (the study included 78 children and young people, but it is unknown for how many of them genetic testing was available)

The study does not report whether these people had undergone newborn screening.

Very low quality evidence from 1 prospective observational study showed that among 44 children, young people and adults (mean age; range: 24.3 years; 7.9 to 59.9 years) with idiopathic recurrent, acute or chronic pancreatitis:

- 4.5% (n=2) had a diagnosis of classic cystic fibrosis based on sweat test (European Consensus Recommendations)
- 13.6% (n=6) had a CFTR abnormality
- 2.3% (n=1) had an inconclusive diagnosis.

The study does not report whether these people had undergone newborn screening.

5.6.6 Meconium ileus

No evidence was found for symptoms in infants.

5.6.7 Economic evidence statements

No evidence on cost-effectiveness in people with cystic fibrosis was available for this review.

5.7 Evidence to recommendations

The aim of this review was to support health care professionals in identifying cystic fibrosis even in people who have been through new-born screening.

The committee chose clinical diagnosis of cystic fibrosis as a critical outcome for this evidence review. Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio were rated as important outcomes.

5.7.1 Consideration of clinical benefits and harms

The committee agreed that a definition of cystic fibrosis was needed in order to emphasise that cystic fibrosis is a syndrome rather than a disease.

There are a number of investigations (such as sweat test or genetic test) that can be done in the event that cystic fibrosis is suspected, but there is no gold standard as such. These tests are useful in confirming cystic fibrosis, but they cannot completely exclude it. Ultimately, in rare cases, the diagnosis can be made based on the clinical signs and symptoms alone, even if tests results are negative. The committee discussed the emotional implications of being diagnosed with cystic fibrosis with a negative sweat test and cystic fibrosis gene mutations that have been conclusively shown to be disease causing.

The committee discussed the limitations of the available evidence. None of the studies reported diagnostic accuracy data. They agreed the usefulness of prevalence data reported in the studies was very limited as these studies did not adequately define the population and the analysis did not control for confounders. Due to this, they concluded it was not very useful in informing their recommendations and these were based on their clinical experience.

The committee discussed the relevance of each sign and symptom included in the evidence review. The committee agreed that infants (children under 1 year of age), children and young people and adults, required separate recommendations depending on the pertinence of the symptoms for each subgroup.

- The committee noted that the presence of meconium ileus in infants was considered a highly suggestive sign of cystic fibrosis that should lead to further investigation. This is because meconium ileus is a unique feature of cystic fibrosis.
- Likewise, the suspected diagnosis of DIOS in children, young people and adults (which is the equivalent to meconium ileus in infants) is also a well-known factor suggestive of cystic fibrosis that should also lead to further investigations of cystic fibrosis.
- In relation to respiratory symptoms, the committee emphasised that one single respiratory event should not necessarily lead to further investigation. The committee considered recurrent lower respiratory tract infections, chronic lung disease or chest X-ray with persistent changes as reasons for referral in infants. Similarly, chronic sinus disease and chronic wet or productive cough should also be considered as reasons for referral in children, young people and adults. They noted that children do not produce sputum and agreed to use the term wet cough. In adults, they agreed it was more appropriate to use productive sputum instead of wet cough, as adults are more aware of having sputum. Finally, they noted the presence of chronic or repeated chest infection regardless of species may raise the possibility of cystic fibrosis. They agreed not to specify pathogens causing chest infection as people with cystic fibrosis may become colonised or chronically infected with many different opportunistic infections and so highlighting any individual species is likely to confuse diagnosis.
- The committee discussed that people with cystic fibrosis often show signs of bronchiectasis due to recurrent inflammation and infection. Additionally, people with cystic fibrosis may present with asthma-like symptoms, such as wheezing, coughing, chest tightness and shortness of breath due to inflammation and infection of the airways.

- The committee acknowledged that cystic fibrosis is known to cause pancreatitis. Approximately 10-15% of people with cystic fibrosis are exocrine pancreatic sufficient and so do not show malabsorption symptoms or diabetes mellitus, however, these patients do show a high incidence of attacks of pancreatitis.
- The committee agreed that cystic fibrosis can also be suspected if there are signs of faltering growth in infants and pre-school children or undernutrition in older children, young people and adults. They noted that in young people, undernutrition can lead to delayed puberty but agreed not to include it as a sign where cystic fibrosis should be considered as there are other reasons that can lead to delayed puberty. They noted that in adults with cystic fibrosis undernutrition normally goes in association with other symptoms, such as pancreatitis and malabsorption.
- The committee stressed that malabsorption should be separated from undernutrition as malabsorption, such as steatorrhea, may be indicative of pancreatic insufficiency, a common complication of cystic fibrosis (as discussed above), whereas undernutrition has a variety of non-cystic fibrosis causes.
- The committee highlighted that azoospermia showed an important association with a diagnosis of cystic fibrosis. They noted that this was consistent with previous findings, as it is estimated 99% of men with cystic fibrosis are infertile. They also noted that some men can produce sperm, but they are still infertile. They discussed whether this symptom applied to young people too, but agreed that generally it will not be apparent to people under 18 years. It was also discussed that women may present with sub-infertility, but agreed that this is rather unusual and that clinically it is not possible to use the term sub-infertility.

The committee also discussed other signs and symptoms not included in the review protocol, such as congenital intestinal atresia, DIOS, rectal prolapse, pseudo-Bartter syndrome and diabetes mellitus.

- The committee noted congenital intestinal atresia is a rare condition that leads to the complete occlusion of the intestinal lumen in neonates. It has been associated with the presence of cystic fibrosis.
- As highlighted in the protocol, DIOS is considered a symptom of cystic fibrosis. Therefore, the committee agreed that the suspected diagnosis of DIOS in children, young people and adults (which is the equivalent to meconium ileus in infants) should lead to further investigations of cystic fibrosis.
- They noted that rectal prolapse can be a sign that health care professionals should be aware of. However, this sign does not present on its own and it is associated with pancreatitis.
- Cystic fibrosis may present as Pseudo-Bartter Syndrome, dehydration and salt depletion due to dysregulation of salt homeostasis in cystic fibrosis. But this is rare in the UK and more common in warmer climates.
- They also discussed whether the presence of diabetes mellitus in young people could be a sign of cystic fibrosis. However, they agreed not to include it in the recommendations as cystic fibrosis-related diabetes is diagnosed in the presence of other symptoms related to cystic fibrosis.

In addition to the signs and symptoms mentioned above, the committee noted that family history could also prompt an assessment for cystic fibrosis.

The committee agreed that a sweat test should be recommended in infants, children and young people. If the test was positive or borderline, the person should be referred for further investigations at a specialist cystic fibrosis centre.

Furthermore, the committee were concerned about carrying out genetic testing in a child carrier to determine their carrier status (for example if the child is heterozygous), as they cannot give consent. Thus, they agreed that genetic testing should only be considered when

sweat tests results are uncertain. In adults, however, the sweat test is less reliable and cystic fibrosis gene testing is preferred.

With regards to gene testing, the committee noted that over 2000 variants in the CFTR have been identified but at present only around 10% of these have been linked to the development of cystic fibrosis. At present genetic tests only return results for the most common variants associated with the disease. Clinicians should be aware this means results from genetic tests cannot rule out a diagnosis of cystic fibrosis.

The committee discussed how the results of genetic testing results related to the obligation of clinicians to refer people to a specialist cystic fibrosis centre. They agreed that a gene test revealing 1 or more cystic fibrosis mutations was a reason for referral. It was also decided that due to the possibility that negative results do not entirely rule out cystic fibrosis, a referral should be based on the clinician's judgement in light of gene test results and apparent symptoms (as discussed above).

The committee noted that these recommendations are consistent with the NHS Service Specifications for cystic fibrosis.

5.7.2 Consideration of economic benefits and harms

The committee advised that their recommendation to offer a sweat test or gene test follows current clinical practice to identify the clinical manifestations of cystic fibrosis and its complications. The committee also added that this was reflected in the Guidelines for the Performance of the Sweat Test for the Investigation of Cystic Fibrosis in the UK 2nd Version 2014. Overall, the committee agreed their recommendations promoted a cost-effective use of resources as those tests would subsequently inform the patient's management which may potentially improve their health-related quality of life and outweigh the relatively cheap cost of those tests.

Moreover, knowing what clinical manifestations suggest a diagnosis of cystic fibrosis and the complications of cystic fibrosis may lead to better identification. This may result in more timely management and therefore has potentially important resource implications, albeit indirectly. Therefore, it was important those manifestations and complications were included in the committee's recommendations.

5.7.3 Quality of evidence

Prospective and retrospective observational studies were included in the review. The quality of evidence as assessed per individual studies was very low. The main sources of bias in the studies were:

- Selection bias: It was noted that most studies do not indicate whether children had undergone newborn screening. Although committee members were able to assume that in some of the studies it was likely the participants were not assessed based on the date of the study and the country (Hubert 2004 - France).
- Prognostic factor of interest or outcome of interest not defined: It was noted that some studies did not adequately define the symptom evaluated. Other studies did not provide details about how sweat test was conducted or the thresholds used for diagnosis.
- Lack of control of potential confounders: Studies did not indicate if the people included in the studies presented with other sign or symptoms suggestive of cystic fibrosis. This was considered a very serious limitation.

Due to all these limitations, the committee considered that the usefulness of prevalence data reported in the studies is very limited.

None of the studies reported diagnostic accuracy data or enough data to calculate diagnostic outcomes.

5.7.4 Other considerations

No equality issues were identified by the committee for this review question.

The committee agreed there was no need to prioritise a research recommendation for this topic. They noted that a universal screening programme is in place in the UK since 2006. In addition, they agreed their clinical experience and expertise was sufficient to draft recommendations regarding the clinical features that should lead to investigation of cystic fibrosis.

The committee noted that there are useful publications on diagnosing cystic fibrosis that health care professionals can refer to, such as the Guidelines for the Performance of the Sweat Test for the Investigation of Cystic Fibrosis in the UK, 2nd Version, by the Royal College of Paediatrics and Child Health (2014); and the supporting publications by Public Health England (2012) on the newborn blood spot screening programme in relation to cystic fibrosis, which are available online.

5.7.5 Key conclusions

The committee concluded that cystic fibrosis is a clinical syndrome that is diagnosed based on clinical presentation. This diagnosis can be confirmed by sweat test and a genetic test. In infants, children, young people and adults that have not been previously diagnosed with cystic fibrosis, including those who had a negative newborn screening test, cystic fibrosis can be suspected based on family history or if one or more of the following signs or symptoms are present: meconium ileus or DIOS, respiratory symptoms, pancreatitis, faltering growth or malnutrition, symptoms of malabsorption, rectal prolapse or pseudo-Bartter syndrome.

5.8 Recommendations

1. **Be aware that cystic fibrosis can be diagnosed based on:**
    - positive test results in people with no symptoms, for example infant screening (blood spot immunoreactive trypsin test) followed by sweat and gene tests for confirmation **or**
    - clinical manifestations, supported by sweat or gene test results for confirmation **or**
    - clinical manifestations alone, in the rare case of people with symptoms who have normal sweat or gene test results.

2. **Assess for cystic fibrosis and, when clinically appropriate, perform a sweat test (for children and young people) or a cystic fibrosis gene test (for adults) in people with any of the following:**
    - family history
    - congenital intestinal atresia
    - meconium ileus
    - symptoms and signs that suggest distal intestinal obstruction syndrome
    - faltering growth (in infants and young children)
    - undernutrition
    - recurrent and chronic pulmonary disease, such as:
        - recurrent lower respiratory tract infections
        - clinical or radiological evidence of lung disease (in particular bronchiectasis)
        - persistent chest X-ray changes

    - chronic wet or productive cough
  - chronic sinus disease
  - obstructive azoospermia (in young people and adults)
  - acute or chronic pancreatitis
  - malabsorption
  - rectal prolapse (in children)
  - pseudo-Bartter syndrome.

3. Refer people with suspected cystic fibrosis to a specialist cystic fibrosis centre if:

  - they have a positive or equivocal sweat test result
  - their assessment suggests they have cystic fibrosis but their test results are normal
  - gene testing reveals 1 or more cystic fibrosis mutations.

6 Information and Support

Review question: What information and support should be given to children, young people and adults with cystic fibrosis?

6.1 Introduction

People with cystic fibrosis and their families and carers often report that the information and support available to them at different stages of diagnosis and management is inconsistent. While the information needed differs between people, it is widely acknowledged that they need information and support at all stages of life with cystic fibrosis. Having the right information and support is an important factor in the effective management of cystic fibrosis, for example in order to achieve optimal health and quality of life.

Access to the right information and support can help to reduce anxiety and increase empowerment and confidence in managing symptoms and providing effective care for someone with cystic fibrosis. Equally, not having access to the right information and support can hinder people to make informed decisions about treatment and management.

Due to the variations in the provision of information and support, the committee agreed it was important to consider what information and support people with cystic fibrosis and their family and carers need.

The committee considered not only the type of information and support available but also the format in which it was delivered. Providing too much information in an inaccessible format may be as detrimental as not enough quality information. They considered some of the concerns people might have about access to reliable sources of information or support. An example of this is the increasing use of online forums or online communities. People who have cystic fibrosis, their carers or family members may use these resources to look for answers to questions to supplement information gaps from their health care providers. The committee did not want to negate the applicability of such avenues of support. But they did want to consider how they may be useful as an adjunct to other sources of information rather than as a replacement.

6.2 Description of clinical evidence

The aim of this review was to identify the information and support that should be provided to people with cystic fibrosis and their parents and carers.

Studies were considered for inclusion if they collected data using qualitative methods (such as semi-structured interviews, focus groups and surveys with open-ended questions) in which the authors analysed the data qualitatively (including thematic analysis, framework thematic analysis or content analysis). Survey studies restricted to reporting descriptive data that was analysed quantitatively were excluded.

Given the nature of qualitative reviews, findings or themes were summarised from the literature. They were not restricted to those identified as likely themes by the committee at protocol stage.

For full details see review protocol in Appendix D.

There were 31 studies included in this review.

All the studies were qualitative studies except 1 which used mixed methods (Hilliard 2014) and 2 studies based on questionnaires that included open questions (Fair 2000 and Widerman 2003). All qualitative studies included semi-structured interviews except 2 which

used in-depth interviews (D'Auria 2000, Johannesson 1998), 1 study that used unstructured interviews (Jessup and Parkinson 2010), 1 study that used an online ethnographical approach, which involved observing, downloading and analysing discussion group postings (Kirk 2016). There were 3 studies which used focus groups in addition to semi-structured interviews (Braithwaite 2011, MacDonald and Greggans 2010, Tipping 2010).

The size of the studies ranged from 4 to 203 participants. There were 2 studies which included parents of infants with cystic fibrosis (Tluczek 2006, Tluczek 2009), 1 study included parents of infants and children with cystic fibrosis (Jessup 2016), 4 studies included parents of children with cystic fibrosis (Coates 2007, Filigno 2012, Grob 2008, Whyte 1995), 5 studies included parents of children and young people with cystic fibrosis (Grossoehme 2014, Hodgkinson and Lester 2002, Hummelinck and Pollock 2006, Lang 2005, Miller 2009), 1 study included children with cystic fibrosis and their parents (Angst and Deatrick 1996), 1 study included infants, children, young people and adults with cystic fibrosis and their families (Roehrer 2013), 1 study included children, young people and adults with cystic fibrosis and their parents (Jessup and Parkinson 2010), 1 study included young people with cystic fibrosis and their parents (Kirk 2016), 7 studies included adults with cystic fibrosis (Braithwaite 2011, Hilliard 2014, Johannesson 1998, Kazmerski 2016, Widerman 2002, Widerman 2003, Widerman 2004), 2 studies included children and young people with cystic fibrosis (Barker 2012, Beresford 2002), 2 studies included young people and adults with cystic fibrosis (D'Auria 2000, Fair 2000), 1 study included pediatric nurses for cystic fibrosis (Bagnasco 2013), 1 study included physicians that cared for either children with cystic fibrosis, adults with cystic fibrosis or both children and adults with cystic fibrosis (Dellon 2012), 1 study included children and young people with cystic fibrosis, their parents, befrienders, play therapists and education liaison personnel (MacDonald and Greggans 2010), 1 study included parents or children and young people with cystic fibrosis and physiotherapists (Tipping 2010).

There were 9 studies conducted in the UK (Beresford 2002, Coates 2007, Fair 2000, Hodgkinson and Lester 2002, Hummelinck and Pollock 2006, Kirk 2016, Lang 2005, MacDonald and Greggans 2010, Whyte 1995), 13 in the USA (Angst and Deatrick 1996, Barker 2012, D'Auria 2000, Dellon 2012, Filigno 2012, Grob 2008, Grossoehme 2014, Hilliard 2014, Kazmerski 2016, Tluczek 2006, Tluczek 2009, Widerman 2002, Widerman 2004), 5 in Australia (Braithwaite 2011, Jessup 2016, Jessup and Parkinson 2010, Roehrer 2013, Tipping 2010), 1 in Italy (Bagnasco 2013), 1 in Sweden (Johannesson 1998), 1 in Canada (Miller 2009), 1 in multiple countries (Widerman 2003).

A summary of the included studies is presented in Table 159. See study selection flow chart in Appendix F, study evidence tables in Appendix G and list of excluded studies in Appendix H. For the presentation of findings, a theme map was generated according to the themes emerged from studies (Figure 1). Due to the qualitative nature of these studies, the evidence is summarised in GRADE-CERQual tables within the evidence report. Therefore no separate Appendix is provided for this.

6.3 Summary of included studies

A summary of the studies that were included in this review are presented in Table 20.

Table 20: Summary of included studies

Study	Study design/ methods	Participants /respondent	Aim of the study	Comments
Angst and Deatrick (1996) USA	Semi-structured interviews (secondary	N=28 mixed population N=20 children with CF and both	To describe how children with chronic illness and their parents are	• Overall quality: low • Sample selection was not reported.

Study	Study design/ methods	Participants /respondent	Aim of the study	Comments
	analysis of two data sets)	parents of each child Age of children: range 7 to 11 years (median 9 years).	involved in health care decisions.	• Description of data collection method was vaguely described. • The analytical process was reported vaguely. Description of emerging and overarching themes was reported, but saturation of data was not reported.
Bagnasco et al. (2013) Italy	Semi-structured interviews	N= 12 paediatric nurses N=7 paediatric nurses for CF	To explore how nurses perceived autonomy in parents, adolescents, and children related to the management of chronic disease.	• Overall quality: low • Mixed sample with Neuro muscular and CF unit. No clear differentiation with overlap between samples. • No information on structure of interview or whether topic guide reported. Description of how "themes" were arrived at was discussed but information was not sufficient to conclude if data collection process was robust. No information on data saturation and full exploration of theme. • The analytical process was described with description of themes and categories. • Researchers' role and potential influences in the analytical process not critically reviewed. • Consistency between the researchers not reported.
Barker et al. (2012) USA	Semi-structured interviews	N= 24 children and young people with CF Age range: 11 to 18 years; mean age: 15.7	To explore the role of family and friends in supporting cystic fibrosis disease management during adolescence.	• Overall quality: moderate • Sample selection was clearly reported. • Data collection relied on the semi-structured interviews. Process for semi structured interview was clearly reported but topic guide was not reported. • The analytical process was described, with the use of predefined

Study	Study design/ methods	Participants /respondent	Aim of the study	Comments
				template analysis from the literature. No description of how "themes" were arrived at • The researchers' roles and potential influences in the analytical process not critically reviewed • Multiple researchers but consistency between them not reported
Beresford et al. (2002) UK	Semi-structured interviews	N= 63 children and young people with chronic condition (n=11 with CF) Age: 11 to 16 years	To explore the experiences of chronically ill adolescents in communicating with health professionals, including the identification of factors which hinder or facilitate their use of health professionals as an information source.	• Overall quality: low • Sample selection was clearly reported. • Unclear about topic guides and limited information about group meetings. • The analytical process was not described in detail, no description of how "themes" were arrived at; researchers did not critically review their own roles in the process. • The study was not clear about the number of researchers involved in data collection or interviews.
Braithwaite et al. (2011) Australia	Focus groups (with staff) and semi-structured interviews (with people with CF and with family members)	N= 42 • n=12 people with CF • n=10 family members of people with CF who had died • n=20 staff • Age range of people with CF: 26 to 53 years; mean age: 35 years •	To explore the unmet needs and key issues for people with CF, their families and the staff providing their care while awaiting organ transplantation.	Overall quality: high • Sample selection was clearly reported. • Structure of interview and topic guide decided by the experts within the hospital • The analytical process was described in detail. • Study conducted by lone researcher and may lack some of the formal research vigour.
Coates et al. (2007) UK	Semi-structured interviews	N=8 mothers of children with CF Children's age: 3 to 7	To supplement existing research to gain insight into mothers' experiences of informing relatives about	• Overall quality: moderate • Sample selection was clearly reported • Structure of interview and topic guide reported. Description of how "themes" were

Study	Study design/ methods	Participants /respondent	Aim of the study	Comments
			CF and to look at patterns of communication within these families.	arrived at was discussed. Data saturation and full exploration of theme not clear. • The analytical process was described with description of themes and categories. Whether sufficient data were gathered to fully explore the themes is not clear. No critical review of the researchers' role in the process. • Discrepancies between the researchers were addressed by the senior researcher with oversight.
D'Auria et al. (2000) USA	In-depth interviews	N=15 young people and adults with CF Age of respondents with CF: between 17 - 22 years with mean age of 19 years.	To explore the influence of peer relationships on adjustment to CF.	Overall quality: low • Sample selection was not clearly reported. • Structure of interview and topic guide not reported. No discussion on whether saturation has been reached for any of the themes reported. • Description of how "themes" were arrived at was discussed. No critical review of the researchers' role in the process • Study conducted by multiple researchers but the level of consistency between them not reported
Dellon et al. (2012) USA	Follow-up semi-structured interviews after surveys	N=26 physicians at two major CF centres Physicians worked with either children, or adults, or both children and adults.	To give an account of the physician perspective on communication with patients about the use of non-invasive and invasive mechanical ventilation for respiratory failure.	Overall quality: low • Sample selection was process was not clearly reported. • The relationship between the researcher and the participants was not reported. • Description of data collection method was vaguely described and the setting of the interview was unclear.

Study	Study design/ methods	Participants /respondent	Aim of the study	Comments
				• The analytical process was reported vaguely. • Description of emerging themes and data saturation was not reported. • Results were presented clearly (e.g., citation/data and the researchers' own input distinguished)
Fair et al. (2000) UK	Survey (postal questionnaire with open-ended questions)	N=136 young people and adults with CF Age: ≥16 years	To determine: • attitudes about fertility and pregnancy among subjects with CF • satisfaction with communication on this issue from health care professionals	Overall quality: Low • Sample selection was not clearly reported. • The relationship between the researcher and the participants was not reported. • Limited information on the development of questionnaire. • Study design limits the exploration of themes or development and eliciting further information. • The analytical process of interpreting open ended question was not reported although use of specific qualitative software (NUD*ist) reported. • No information on data saturation or identification of specific themes • Results were presented clearly (e.g., citation/ data and the researchers' own input distinguished).
Filigno et al. (2012) USA	Semi-structured interviews	N=8 parents of children with CF Mean age of children at the time of interview=8.2 years (SD 0.8).	To: • better understand how families used the strategies taught in a behaviour-nutrition intervention • identify the challenges with CF management	• Overall quality: moderate • Sample selection was clearly reported. • Data collection method was described • The analytical process was reported. • Description of emerging and overarching themes, and saturation was reported. • Findings or results:

Study	Study design/ methods	Participants /respondent	Aim of the study	Comments
			families experienced during the developmental transition from toddlerhood to school-age, particularly nutrition.	○ Results were presented, however, quotations/citations from respondents were not reported clearly
Grob (2008) USA	Semi-structured interviews	N=35 parents of children with CF (33 mothers and 2 fathers) (16 parents received a newborn screening diagnosis; 4 received a prenatal diagnosis; 4 received a diagnosis within a few days or weeks of birth for an asymptomatic child; 11 received a later diagnosis for a symptomatic child (between 2 months and 7 years). Age of children at the time of the interviews: Not reported	To examine how the expansion of mandatory genetic testing at birth structures, for parents, specific kinds of disjuncture between their child's medically defined disorder and the manifest illness.	• Overall quality: Low • Sample selection was not reported. • Data collection method was not described clearly. • The analytical process was reported, but vague in description. • Description of emerging and overarching themes was reported, but saturation of data was not reported.
Grossoehme (2014) USA	Semi-structured interviews	N=25 parents of children and young people with CF Age of children and young people: < 13 years	To describe parent experiences developing and utilizing CF care routines.	• Overall quality: moderate • Sample selection was clearly reported. • Structure of interview reported. Description of how "themes" were arrived at was discussed in depth. • Data saturation and full exploration of theme reported. • The analytical process was described with description of themes and categories and use of specific software for processing. • Researchers' role and potential influences in the analytical process not critically reviewed.

Study	Study design/ methods	Participants /respondent	Aim of the study	Comments
				• Study conducted by multiple researchers but the level of consistency between the researchers not reported.
Hilliard et al. (2014) USA	Mixed-methods study including semi-structured interviews	N=16 adults with CF Age: 21 to 48 years	To involve individuals with CF in guiding the development of future mHealth apps for adherence promotion.	• Overall quality: high • Sample selection was clearly reported. • The analytical process was described in detail. • Description of how "themes" were arrived at; saturation of data and exploring all the themes in detail was reported
Hodgkinson and Lester (2002) UK	Semi-structured interviews	N=17 mothers of children and young people with CF Age range of people with CF: 2-13 years	To explore the current stresses and coping strategies used by mothers and to identify roles and strategies that nursing professionals could extend or adopt to support them and families of children with CF.	• Overall quality: moderate • Sample selection was clearly reported. • Data collection method was appropriately described, including saturation of themes • The analytical process was reported, but not in detail. Saturation of themes was described in the data collection section
Hummelinck and Pollock (2006) UK	Semi-structured interviews	N=27 parents from 20 families with a child with a chronic condition (n=4 children and young people with CF) Age range of children and young people: 0-16	To explore the complexity of parents' information needs and how current information provision is evaluated.	• Overall quality: low • Sample selection was clearly reported. The relationship between the researcher and the respondents clearly reported • Data collection method was not described in detail and cross referenced to other study for detail information • The analytical process was clearly reported. Unclear if saturation of data was achieved. Development of theme was described. No report on transcribing interview, validation or use of qualitative

Study	Study design/ methods	Participants /respondent	Aim of the study	Comments
				software for processing of information • Results were presented clearly and the findings discussed in detail (e.g., citation/data and the researchers' own input distinguished)
Jessup et al. (2016) Australia	Semi-structured interviews	N=10 parents from 7 families of infants and children with CF Age of infants and children: 1 to 8 years	To explore the education needs of 10 parents following their infant's diagnosis with CF via newborn screening.	Overall quality: moderate • Sample selection was clearly reported. • Structure of interview and topic guide reported. Description of how "themes" were arrived at was discussed. • Data saturation determining further sample recruitment was reported. • The analytical process was described with description of themes and categories. • Researchers' role and potential influence s in the analytical process not critically reviewed • Study conducted by multiple researchers but the level of consistency not reported.
Jessup and Parkinson (2010) Australia	Un-structured interviews	N=8 families with a son/daughter with CF (n=7 people with CF, n=17 parents either as couples or individually) Age of people with CF: range: 2-21, average: 10.5	To explore the experiences of living with CF.	• Overall quality: moderate • Sample selection was clearly reported. • The authors clearly explained and justified clearly how the data were collected. However, the authors did not discuss data saturation. • There was an in-depth description of the analysis process. It is clear how the themes were derived from the data. However, there was no critical review of the researcher's role in the process. • A colleague with expertise in phenomenology

Study	Study design/ methods	Participants /respondent	Aim of the study	Comments
				challenged perceived anomalies in the analysis. However, the total number of analysts involved was unclear. There was no respondent validation due to concerns about the research burden on the CF population.
Johannesson et al. (1998) Sweden	In-depth interviews	N=14 women with CF Age: 22 to 34 years	To investigate psychosocial issues concerning puberty and motherhood among CF adult females, to see how they had obtained and conceived information on these matters and how they would like information to be given.	• Overall quality: low • Sample selection was clearly reported. The relationship between the researcher and the respondents was clearly reported. • Description of data collection method was vaguely described • The analytical process was not clearly reported. • Description of how emerging and overarching themes were reached was not reported, saturation of data was not reported. • Results were presented clearly supported with quotes and findings discussed in depth (e.g., citation/data and the researchers' own input distinguished)
Kazmerski et al. (2016) USA	Semi-structured interviews	N=22 women with CF Age: 18 to 30 years N=16 CF program directors	To explore the attitudes, preferences, and experiences of patients with CF and CF providers toward sexual and reproductive health care for young women with CF.	Overall quality: moderate • Sample selection was clearly reported. • Structure of interview and topic guide reported. • Description of how "themes" were arrived at was discussed. Data saturation and full exploration of theme reported. • The analytical process was described with description of themes and categories. • Researchers' role and potential influences in the analytical process not critically reviewed.

Study	Study design/ methods	Participants /respondent	Aim of the study	Comments
				• Study conducted by multiple researchers but the level of consistency between the researchers not reported. • Findings cannot be generalised to all CF care providers (for example those who are not directors).
Kirk et al. (2016) UK	Online ethnographical approach, involving observing, downloading and analysing discussion group postings	N= 182 participants on the parent's discussion group (103 discussion threads) and 97 participants on the young people's discussion group (48 discussion threads). Age of participants: not reported	To explore how online peer support is used by young people and parents to support self-care in relation to CF.	• Overall quality: moderate • Sample selection was clearly reported. Whether the sample is genuine representative of the CF population is unclear and it was based on a single online discussion forum. • Data collection relied on the discussion thread. • Description of how "themes" were arrived at was unclear or whether data saturation reached. • The analytical process was described but was inadequate in description. • Researchers' role and potential influences in the analytical process not critically reviewed.
Lang et al. (2005) UK	Semi-structured interviews	N=8 parents of children and young people with CF Age of children and young people: 3 to 16 years	To explore the experiences of parents of children with CF who had been asked to consider lung transplantation as a treatment choice and subsequently referred to one of two national lung transplant centres. Especially to explore their views on how the flow of information should be	Overall quality: Moderate • Sample selection was clearly reported. • The relationship between the researcher and the participants was not reported. • Description of data collection method was vaguely described although validated qualitative research tool was used. • The analytical process was reported vaguely. Description of emerging and overarching themes was reported, but saturation of data was not reported. Coding

Study	Study design/ methods	Participants /respondent	Aim of the study	Comments
			managed, and how the process of initial introduction by the referring centre could be improved.	and category identification by two independent researchers suggest reliability of findings • Findings/results: Results were presented clearly. Discussion of the finding was limited and cross reference to citation/data and the researchers' own input was not adequately presented
MacDonald and Greggans (2010) UK	Semi-structured interviews and focus groups	N=17 participants of which n=10 were children or young people with CF or their parents, n=3 were befrienders, n=2 play therapists, n=2 education liaison personnel Age of children and young people with CF: 8 to 18 years	To evaluate the impact of a community youth befriending programme on a group of young people with CF and their carers.	• Overall quality: moderate • Sample selection was clearly reported. • Structure of interview and topic guide reported. Description of how "themes" were arrived at was discussed. Data saturation and full exploration of theme not reported. • The analytical process was described with description of themes and categories. • Researchers' role and potential influences in the analytical process not critically reviewed. • Study conducted by multiple researchers but the level of consistency between the researchers and rigour of the process reported.
Miller et al. (2009) Canada	Semi-structured interviews	N=47 parents of children and young people with complex chronic health conditions (n=7 with CF) Age of participants with CF not reported.	To examine how the experiences and perceptions of parents of children with complex chronic health conditions fit with the perspectives of academic and service providers on continuity of care. To identify the salient	• Overall quality: moderate • Sample selection was clearly reported. • Structure of interview process reported but no information on use of topic guide. Description of how "themes" were arrived at was discussed. Data saturation and full exploration of theme reported.

Study	Study design/ methods	Participants /respondent	Aim of the study	Comments
			factors in the experience of continuity in this population.	• The analytical process was described with description of themes and categories and use of specific technology. No critical review of the researchers' role in the process. • Interview conducted by single researcher but the level of consistency and accuracy not reported.
Roehrer et al. (2013) Australia	Semi-structured interviews	N= 15 people with CF and their families Age of people with CF: 19 months to 52 years	To provide an overview of the evaluation of a pilot trial of an information system conceptualised to develop to assist people with CF and their families, to enhance their skills and communication in relation to self-management for their condition.	• Overall quality: low • Sample selection was clearly reported. • Data collection method was described. • The analytical process was reported. Description of emerging and overarching themes was reported, but saturation of data was not reported. • Results were not presented clearly (e.g., citation/data and the researchers' own input distinguished).
Tipping (2010) Australia	Focus group of physiotherapists and semi-structured interviews with parents	N=11 • n=5 physiotherapists • n=6 parents of children or young people with CF Age of children: 2 to 16	To identify factors that impair the delivery and retention of physiotherapy education for parents of children with CF and factors that impair effective physiotherapy treatment in the home environment.	• Overall quality: moderate • Sample selection was clearly reported. • Data collection was clearly reported, including the number of interviews, data saturation and the use of an interview map and digital recording. • The analysis process was described in detail, including details on how categories, sub-categories and themes were developed. However, there was no mention of contradictory data and researchers did not critically examine their own role, potential bias and influence during analysis and data selection.

Study	Study design/ methods	Participants /respondent	Aim of the study	Comments
				• Data analysis was completed independently by two researchers to enhance credibility. Moreover, participants were asked to review the emerging themes and comment on their accuracy.
Tluczek (2006) USA	Semi-structured interviews	N= 33 families of infants with abnormal newborn results (8 with CF confirmed after sweat test) Age of infants: 1.5 to 6 months	• To • understand parents' perceptions about genetic counselling received while awaiting their infant's sweat test results, • identify conditions that may affect the quality of their experience, • develop a model for genetic counselling under the conditions of NBS using CF as a prototype for NBS programs using gene technologies.	• Overall quality: moderate • Sample selection including process of recruitment was clearly reported. • Structure of interview and topic guide not reported. • Description of how "themes" were arrived at was discussed. Data saturation and full exploration of theme reported. • The analytical process was described with description of themes and categories. • Researchers' role and potential influences in the analytical process not critically reviewed.
Tluczek (2009) USA	Semi-structured interviews	N= 193 parents of 100 infants (100 interviews) with abnormal newborn screening results for CF (n=16 diagnosed with CF) Age of infants: <6 months	To examine how, when and from whom parents were informed about NBS, as well as to obtain their perspectives about how to improve parent education about NBS.	• Overall quality: moderate • Sample selection was reported. The relationship between the researchers was reported. • Description of data collection method was reported. • The analytical process was reported. • Description of emerging and overarching themes was reported, but saturation of data was not reported.
Whyte et al. (1995) UK	Semi-structured interviews	N=16 families (n=4 with CF)	To increase understanding of the needs of	• Overall quality: low • Sample selection was clearly reported.

Study	Study design/ methods	Participants /respondent	Aim of the study	Comments
		Age of children: 4 years	families caring for children with chronic illness; to investigate the continuity, effectiveness and acceptability of care from the parents' perspectives.	• Description of data collection method was not clearly described • The analytical process was reported. Description of methodology of emerging and overarching themes was not clearly reported, and saturation of data was not reported.
Widerman (2002) USA	Semi-structured interviews	N= 36 adults who received a diagnosis of CF at age 20 years or older	To determine the extent to which the needs and issues attendant to the adult CF interview are addressed by existing bad-news and paediatric CF recommendations and, if necessary, to develop and present recommendations to supplement them.	• Overall quality: moderate • Sample selection was clearly reported. • Data collection method was appropriately described • The analytical process was reported. Authors' interpretation was checked independently. Unclear if saturation of themes was achieved
Widerman (2003) International	Survey (survey instrument included open-ended questions)	N=130 adults diagnosed with CF after age 18	To address evidence gap about the actual and self-perceived knowledge of people diagnosed with CF as adults in order to inform the development of educational materials for this sub-population and to guide caregivers in educating them.	• Overall quality: low • Research method was not the most appropriate for answering the research question. Qualitative semi structured interview would have been better. • Sample selection was unclear. The need for international sample solicited through email was not justified. • Data collection relied on the postal questionnaire with open ended question. Survey instrument described. There was no theme or topic guide or report of data saturation. • The analytical process was poorly described

Study	Study design/ methods	Participants /respondent	Aim of the study	Comments
				and involved grouping information based on frequency. No further analysis of the qualitative information. • Researchers' role and potential influences in the analytical process not critically reviewed. • Was sponsored by pharmaceutical company.
Widerman (2004) USA	Semi structured interview	N=36 young adults with CF	To explore the experience of receiving a diagnosis of cystic fibrosis after age 20.	Overall quality: Moderate • Sample selection: Sample selection was clearly reported. The relationship between the researcher and the respondents clearly reported • Data collection method was appropriately described • The analytical process was reported but was unclear on use of analytical software. Authors' interpretation was checked independently. • Unclear if saturation of themes was achieved • Results were presented clearly (e.g., citation/data and the researchers' own input distinguished).

Abbreviations: CF-cystic fibrosis; NBS-newborn screening; SD- standard deviation; UK-United Kingdom; USA-United States of America.

6.4 Clinical evidence profile

6.4.1 Theme maps

The theme maps are presented in Figure 3 and Figure 4.

Figure 3: Theme map: information needs for people with cystic fibrosis and their parents or carers

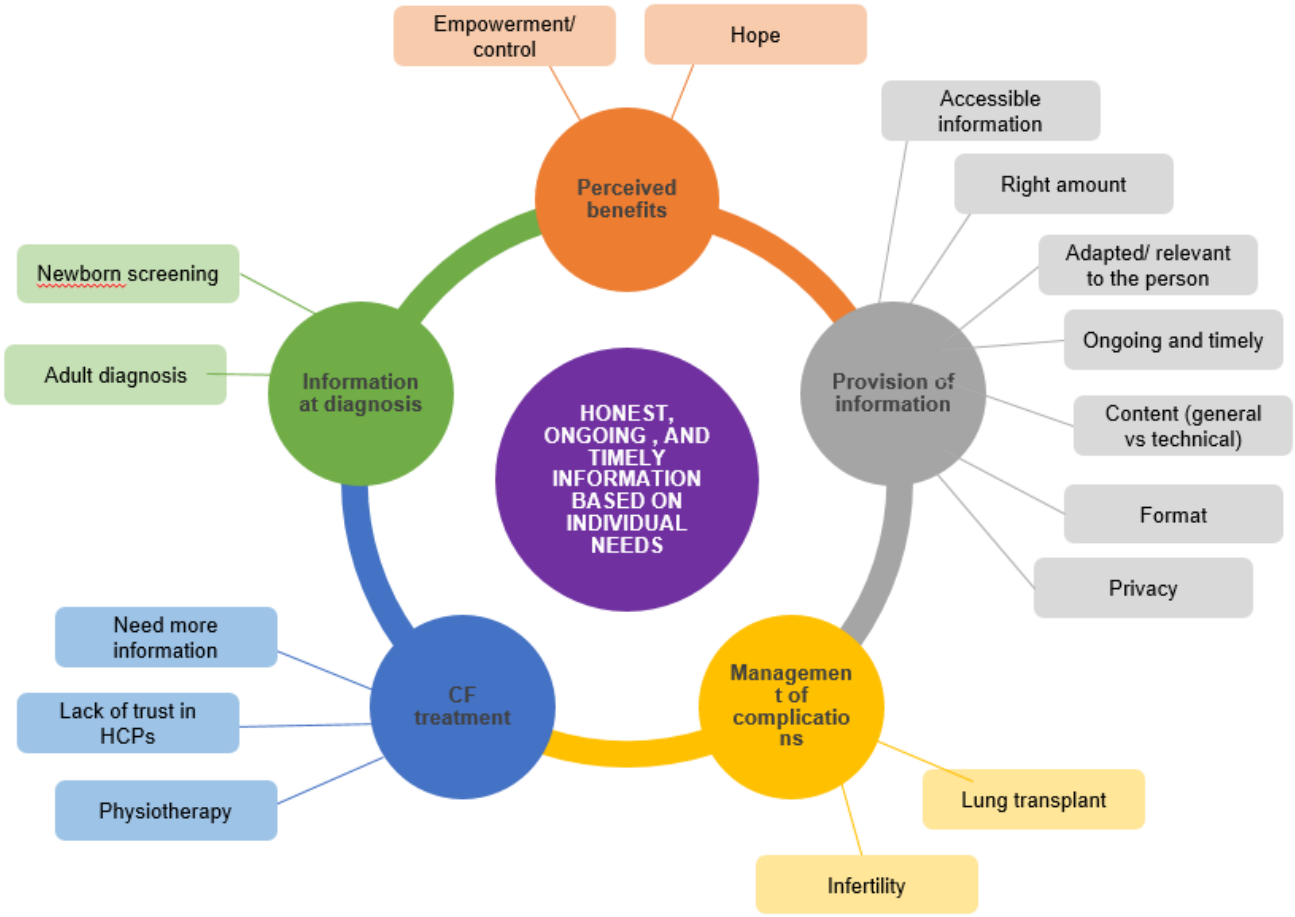
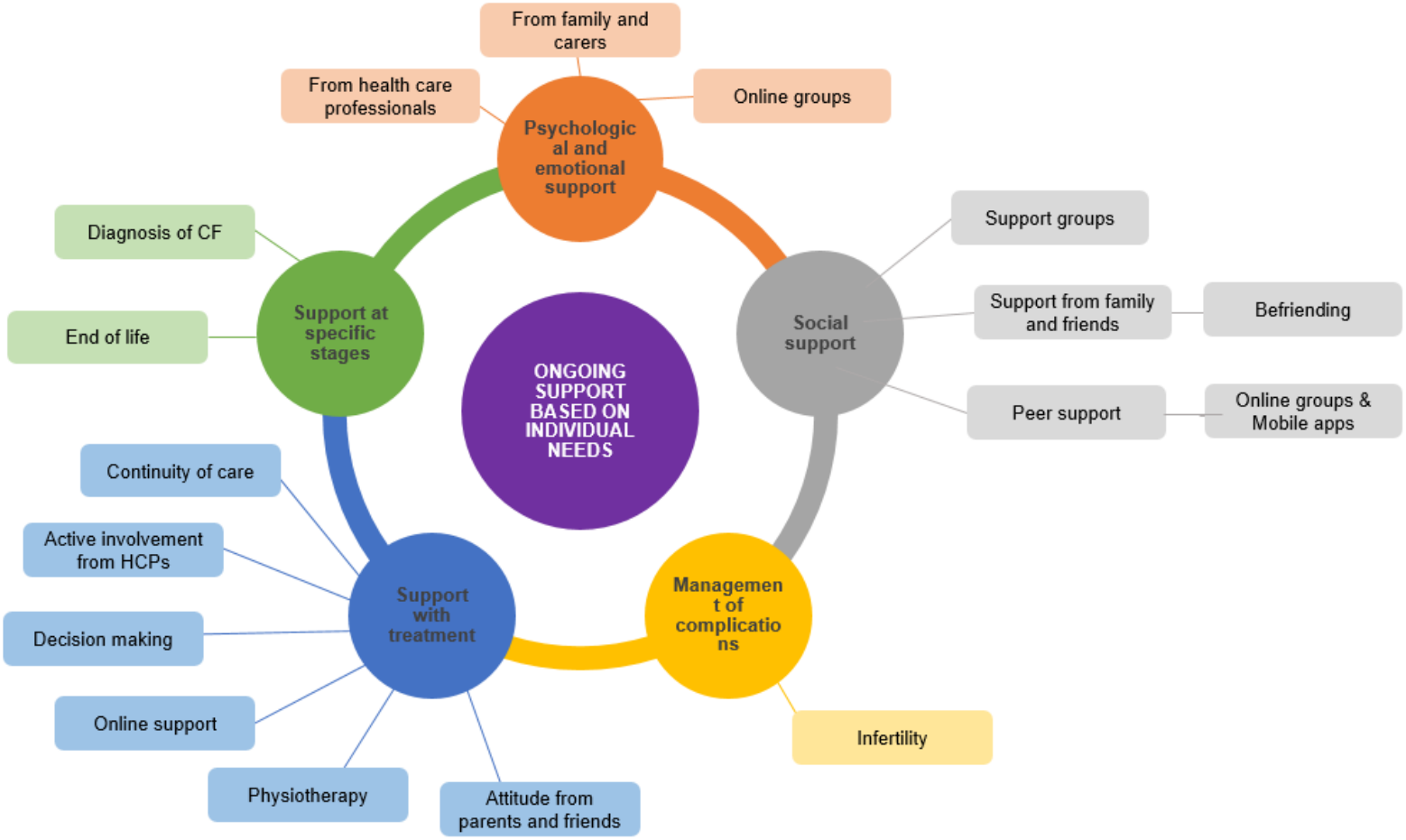


Figure 4: Theme map: support needs for people with cystic fibrosis and their parents or carers



The clinical evidence (GRADE-CERQual) for the information and support question is presented in Table 21 to Table 30.

6.4.2 Clinical evidence profile: information needs for people with cystic fibrosis and their parents or carers

Table 21: Summary of clinical evidence (GRADE-CERQual): Theme 1. Information at diagnosis

Study information			Quality assessment		
Number of studies	Design	Description of theme or finding	Criteria	Rating	Overall
Sub-theme 1: new-born screening					
5 studies (Grob 2008, Jessup 2010, Tipping 2010, Tluczek 2006, Whyte 1994	5 studies using interviews	5 studies conducted in Australia, the UK, the USA explored the information needs of the families of infants with abnormal newborn screening or children with cystic fibrosis. Parents reported they were **relieved** when they received the diagnosis of cystic fibrosis: *"..when we got it I was totally relieved. Even though he cystic fibrosis and I knew what it was and I knew the outcome of it, it was a relief, because I knew I was gonna be treated correctly. I knew..that I wasn't crazy, that I wasn't looking for something to be wrong with him, you know?" (mother of a child aged 7 years with delayed diagnosis of cystic fibrosis)* The issue of **delayed diagnosis** was also discussed. Parents were concerned about their observations and suggestions being dismissed by the health care professional regarding their child's health: *"At the doctor's office, I would cry every time because he wasn't gaining [weight]. I think they kind of looked at me like this hysterical first-time mother, and the doctor whom I kept going to see kept saying 'Oh he'll kick in, some babies take a while to kick in.' That was really hard, being so powerless..." (mother of child who had delayed diagnosis)* Some parents discussed about the information needs they had before or after receiving the results of the test: *"I want all the information. That way I know what I'm waiting to hear about. So it's not this black box that I don't know anything about and when I find out.. I think it was good that we had the*	Limitation of evidence	Minor limitations	MODERATE QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Saturated	

Study information			Quality assessment		
Number of studies	Design	Description of theme or finding	Criteria	Rating	Overall
		information ahead of time. And, in fact, we were even seeking it out." *"I'm the kind of person, I'm really proactive, so if I find out about a problem or an issue I want to dive into it and figure out what's the best way to do this, or what should we do? So I want all the information I can get.. I don't just want to be clueless and think, 'Oh she'll be fine, she'll beat the odds.' I want to know the dirty truth. I want to know what these people [with CF] go through so that I know how I can prepare myself and how I can prepare Alexandra". (parent of child with cystic fibrosis diagnosis)* Another mother reported she did not know of cystic fibrosis until she received a positive new-born screen result for cystic fibrosis: *"[Margo was] chunky,'' she recalls. ''She was over nine pounds at birth, so I mean there was no indicators, you know, I mean visually, you knowlooking at her there wasn't anything to think therewas anything wrong with her..'' (mother of child of 2.5 years diagnosed at birth).* Following diagnosis, parents sought information on **future implication of cystic fibrosis**: *"I think probably for his future. What is it going to mean for (him) when he gets married and has his own kids? How is that (being a CF carrier) going to play a role? How do we tell him about all this and explain it to him so that he understands? And I think more of how is it going to affect him then us, now? How in the future is it going to affect him?" (mother of carrier infant)* Information is seen as helpful to find reassurance. Parents experienced difficulties immediately after diagnosis as they felt confused and frightened when presented with information because they could not find answers to specific questions or resolve anxieties that confronted them: *"I felt I was standing outside, watching it all going on, I did not even know...the IV's he was having straight away and I did not*			

Study information			Quality assessment		
Number of studies	Design	Description of theme or finding	Criteria	Rating	Overall
		even know what that was all about. And they were just pumping all these drugs into him. It was just one injection after the other in, pretty scary actually. You are left on your own in a room, you know. Sitting there, waiting for the next lot of IV's which of course I did not know when that would be. I did not know how many he had to have. It was difficult. " (Mother of a child with cystic fibrosis age 7 years) Some parents reported they received **too much information** at the time of diagnosis, and found this overwhelming. They felt they were *"snowed under"* by initial information *"blah, blah, blah"* (parent). Another parent also said *"I think firstly in that first week we felt information overload... to be told like especially with the physiotherapy...that you've got to do this every single day for your child's life it's just overwhelming."* Whereas some parents felt they had to fight to get the information they wanted: *"We wanted to know all the details, and there would be things where we would ask the question and they would hedge as if to say, "We really don't like to tell everybody all those details to start with." Because we were both biology trained, we just wanted the absolute details . . . it seemed like getting blood out of a stone." (couple of parents)* *"not just the stuff they want the parents to hear" (one parent who read whatever she could and said that she could recognize the erroneous facts she received from health care professionals)* *"I didn't know anything about it and I got sent home with a little bit of information but it was like a week later before I had my first clinic. I was there all by myself and calling like half of [city name] it felt like trying to find somebody that...was home and that could talk...They told me it was genetics but I didn't understand what genetics truly meant either so I was like well what did I do and you know what I can have done different.."*			

Study information			Quality assessment		
Number of studies	Design	Description of theme or finding	Criteria	Rating	Overall
		(mother of a one month old infant diagnosed with cystic fibrosis). Or that they have to look the information themselves: *"I got the initial diagnosis over the phone…. they don't tell you much. It's like: "We think she's got cystic fibrosis and we want you to come in and talk about, and I can see you in two or three days' time'. And then it's like: 'Oh my God,' and 'Help, Google!'… (parent)* Parents appreciate **honesty**, and did not want professionals to withhold information: *"One problem I have with some doctors is that they talk down to you and don't explain things thoroughly". (Parent of a child with cystic fibrosis diagnosis) (parent)* However, they also appreciate information that is **simple**, and *"not scary":* *"We had one doctor. and we walked into the room and she sat down and we sat down and she said, 'Having cystic fibrosis is not a good prognosis.' And I sort of thought 'I don't really need to hear this. I'm well aware of what it does.' I didn't really think that was very thoughtful to say to someone while holding their new baby.. This one doctor. could be quite callous. And not really think about how you might be feeling as a parent..[What I needed was] the basics for the moment. You can find out everything else as you go along. It's not necessary to know everything right from the start". (mother of a child with cystic fibrosis diagnosis) (mother)* And **timely**, at a rhythm that is comfortable for them: *"They had some hand-outs and things...as far as treatment and dietary concerns, you know," "But "there was just too much at that time to absorb, so we [would] look at it a little bit [at a time].." (mother of a child with cystic fibrosis diagnosis)*			

Study information			Quality assessment		
Number of studies	**Design**	**Description of theme or finding**	**Criteria**	**Rating**	**Overall**
Sub-theme 2: adult diagnosis					
2 studies (Widerman 2002, Widerman 2003)	1 study using questionnaires and 1 study using interviews	2 studies conducted in USA and Europe with 166 adults with cystic fibrosis explored the experience of receiving a diagnosis of cystic fibrosis as adults. Some adults with suspected of cystic fibrosis were told by their physicians not to be concerned as they would probably test negative. Participants would have appreciated more clarity in this regard, as they were left confused and questioning whether they actually had cystic fibrosis: *"[My doctor] decided to have me tested for CF...He said, 'Don't worry, you're too old'. It can't be, blah, blah, blah, blah. And it came back positive. So they did it again. And it was positive again" (46 year old woman)* *"OK you tested positive for CF, but we wanted to make sure you really have the illness. So, therefore we are going to forward you another clinic for confirmation" (Participant comment)* Participants highlighted the need for information following diagnosis. *"What do I do now?" or "how do I care for myself?"* However, they noted information was non-specific and not relevant to them: *"I wanted to know everything" (participant comment)* *"I got a booklet from the CF Foundation listing the median age of survival as 21. I was diagnosed at 24!"* (woman diagnosed as adult) *"I immediately went to the library the next day and looked up CF. And, everything said you were going to die by the time you were 16. And here I was 40". (man diagnosed as adult)*	Limitation of evidence	Major limitations	LOW QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Saturated	

Study information			Quality assessment		
Number of studies	Design	Description of theme or finding	Criteria	Rating	Overall
		"None (of the materials) addressed social, economic, psychological, or political issues and obstacles." (man diagnosed as adult) *"We were given two books, but only one little paragraph really applied to me." (man diagnosed as adult)* *"I want to know about adult stuff. I want to know what to look for in symptoms, hints to better activities now, not to think I am going to die soon so often". (male participant)* Some participants questioned why they were diagnosed with a paediatric condition, why they had not experienced symptoms, and how many others are diagnosed as adults. (author comment) Participants said that health care professionals should offer **more information** and spend more time with them: *"'Doctors need to have more information available. I had 15 min counsel with my diagnosis and that was it. I would call with a question. They would answer, but otherwise I have been on my own for information. It's scary to have a bomb dropped on you and then it's like here, deal with it." (female, 31 years)* *"My physicians gave me no information. I actually supplied them with articles and I have continued my self-education once I realized that physicians often do not keep up on the literature." (young woman with cystic fibrosis)* They also found difficult to make questions at the time of diagnosis, as they knew nothing about the condition: *"Because how can you ask questions about something you know nothing about? First you assimilate the disease, then you question it" (female participant)* *"I was confused. I didn't know what to ask" (male participant)* In particular, newly diagnosed adults would like to know about general aspects, such as treatment available and impact of cystic fibrosis in their lives.			

Study information			Quality assessment		
Number of studies	Design	Description of theme or finding	Criteria	Rating	Overall
		For example they wanted to know how cystic fibrosis would change their lives (whether they could or should have children), and what to expect in the future. (author comments) They also wanted to know what treatments would be effective, and signs to look out for as indicators of their health status, and if their symptoms could be controlled (authors comments). They also wanted to know how long they could expect to live and whether being diagnosed as an adult was associated with longer life expectancy. (author comment)			

Table 22: Summary of clinical evidence (GRADE-CERQual): Theme 2. Information about treatment

Study information			Quality assessment		
Number of studies	Design	Description of theme or finding	Criteria	Rating	Overall
Sub-theme 1: trust in healthcare professionals					
1 study (Hodgkinson 2002)	1 study using interviews	In 1 study conducted in the UK with mother of children with cystic fibrosis, mothers reported that the primary care team's unfamiliarity with cystic fibrosis drugs, which contributed to distrust of primary care advice: *"The GP says-'what do you normally have?' and it's sort of, well it would be nice if they could tell me what they think". (mother)*	Limitation of evidence	Minor limitations	VERY LOW QUALITY
			Coherence of findings	Unclear	
			Applicability of evidence	Unclear	
			Saturation	Not saturated	
Sub-theme 2: more information					
2 studies (Angst 1996, Lang 2005)	2 studies using interviews	In 1 study conducted in the USA with children with cystic fibrosis and their parents, most families reported they were not given information about alternative care (for example, home vs hospital antibiotic therapy, and different means to enhance their child's nutritional status). (author comment) In another study conducted in the UK with families of children with cystic fibrosis, parents agreed that a gradual and informal	Limitation of evidence	Major limitations	VERY LOW QUALITY
			Coherence of findings	Unclear	
			Applicability of evidence	Unclear	
			Saturation	Not saturated	

Study information		Description of theme or finding	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
		process of discussing cystic fibrosis and treatment options prior to crisis-point was recommended as a means of preparing and supporting families more effectively. (author comment)			
Sub-theme 3: physiotherapy					
2 studies (Jessup 2016, Tipping 2010)	2 studies using interviews	In 1 study conducted in Australia with families of infants with cystic fibrosis, several parents referred the usefulness of the practical instructions given by the physiotherapist, which represented something they could do: *"You know what was terrific was the little physio card that she made up for us…So when we're home going 'What do we do next?' we could go back to the card and check." (parent)* However, in another study conducted in Australia with parents of young children with cystic fibrosis and physiotherapist, parents reported the information given was really outdated: *"They gave us a video as well, really outdated ... I didn't think it was the greatest video but anyway it was a bit old fashioned." (parent)*	Limitation of evidence	Minor limitations	LOW QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Not saturated	

Table 23: Summary of clinical evidence (GRADE-CERQual): Theme 3. Information about management of complications

Study information		Description of theme or finding	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Sub-theme 1: lung transplant					
1 study (Lang 2005)	1 study using interviews	One study conducted in the UK with 10 families of children explored the role of information in relation to lung **transplantation**. Most of the parents thought information helped them to prepare and face the reality of the situation: *"Distressing but facing reality"*	Limitation of evidence	Minor limitations	LOW QUALITY
			Coherence of findings	Unclear	
			Applicability of evidence	Applicable	

Study information			Quality assessment		
Number of studies	**Design**	**Description of theme or finding**	**Criteria**	**Rating**	**Overall**
		"I wanted to be told everything (eg. Assessment criteria, procedures, complications and outcomes, including statistics, quality of life, drug-side effects and long-term prognosis". *"Information makes you more aware and prepared"* *"I would have liked more information"* However, other parents were reluctant to receive information: *"I didn't want information"* *"I didn't really want to deal with it"* *"Having the information is depressing"*	Saturation	Not saturated	
Sub-theme 2: infertility					
3 studies (Fair 2000, Johannesson 1998, Kazmerski 2016)		In 3 studies conducted in Sweden, the USA, and the UK with adults with cystic fibrosis and centre directors discussed the role of information in the context of **sexual health and fertility**. People with cystic fibrosis and care providers said they felt uncomfortable discussing these issues, as they are **too intimate**. Solutions to overcome this barrier were proposed: *"Sometimes women are afraid to speak up and they keep these things [SRH issues] personal to them… and might feel uncomfortable." (woman with cystic fibrosis)* *"I think the number 1 [reason] is that a lot of the younger women are …embarrassed, especially because I'm a middle aged man, they're just a little embarrassed to bring it up." "You do what you're comfortable with. I'm not good at fielding questions about sexuality, so I probably don't bring it up as often as I should." (male care provider)* *"Sometimes, if people were to feel uncomfortable… maybe be given a pamphlet. Or some papers that have Web sites that you can, you know, go on… or maybe there would be an online thing where you can actually ask questions, kinda like be*	Limitation of evidence	Major limitations	LOW QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Saturated	

Study information			Quality assessment		
Number of studies	Design	Description of theme or finding	Criteria	Rating	Overall
		anonymous because maybe some people are embarrassed." (woman with cystic fibrosis) *Providers: "…a concise booklet that was […] very accurate [with] all the different [SRH] subjects at a comprehensive level. Because some [patients] probably don't necessarily want to talk about it in the clinic, but … we could provide accurate information to them that they could access at their own convenience." (care provider)* Timing of these discussions was also identified as important: *"[SRH] was brought up in school when I was in 4th or 5th grade, so I was probably 9…I think between 8 and 10, depending on if puberty is starting, I think you should be informed." (person with cystic fibrosis)* *"Honestly, for me, the easiest thing would be to just start [SRH discussions] young and have it be an expectation. We walk in here and know that people are going to talk to us about bowel movements, that's just part of what we know is gonna be asked. So, if you start [SRH discussions] at a young age, I think it just becomes part of the routine and it doesn't become as uncomfortable as it would be." (young person with cystic fibrosis)* Women described satisfactory and unsatisfactory discussions with doctors and nurses: *"I felt no one would help me at least try and come to a decision. I had so little information. I was constantly told the risks were too high and now it's too late and I feel there's a huge gap in my life" (F, 33 years,* FEV_1 *62% predicted).* They also indicated they want more information about health consequences of **pregnancy**: *"(explain that) you will feel ill during and maybe for years after giving birth and when you have your baby, there's almost no*			

Study information			Quality assessment		
Number of studies	Design	Description of theme or finding	Criteria	Rating	Overall
		time to be unwell yourself which can cause problems" (F, 23 years, FEV_1 *44% predicted).* *"Information about general health during pregnancy and risks about the actual birth" (F, 16 years,* FEV_1 *50% predicted).* *"To let them know that 14 days of IVS will be administered at home after the birth of the baby" (F, 29 years,* FEV_1 *60% predicted).* Men suggested they wanted to know "the facts: *"Simple cans and can'ts, facts ... to the point, no 'maybe you can but ... etc'." (M, 20 years)* *"I feel that there should be discussions and literature handed out in CF Clinic at an earlier stage e.g. not later than 16" (M, 20 years,* FEV_1 *65% predicted).* *"Facts as they stand with hope via assisted fertility information" (M, 28 years,* FEV_1 *22% predicted).* *"Make sure he knows about it early so he can learn to accept it easier" (M, 27 years,* FEV_1 *40% predicted).* The authors of 1 study noted that most men did not seem to be aware of the relatively low success rate of assisted fertility treatment. Of 30 comments from men, 9 were on the positive chance that they would be able to have children through assisted fertility and no man commented on the low success rate of fertility programmes. (author comment) In particular they noted that younger men aged < 20 years were much less likely than women or older men to make any comment on what information they wanted. Older men with good lung function seemed most likely to be distressed by their infertility: *"I would like more information on how other people are handling the fact that they cannot have children" (M, 35 years,* FEV_1 *84% predicted).*			

Table 24: Summary of clinical evidence (GRADE-CERQual): Theme 4. Provision of information

Study information			Quality assessment		
Number of studies	**Design**	**Description of theme or finding**	**Criteria**	**Rating**	**Overall**
Sub-theme 1: accessible information					
2 studies (Dellon 2012, Hilliard 2014)	1 study using surveys and 1 study using interviews	In 1 study conducted in the USA with adults with CF, participants expressed the need for an accessible resource for general information about cystic fibrosis: *"Sometimes I'll [wonder when] something happens health-related to me, 'Is that normal for everyone or…is that happening to me because I have CF?' And it's hard to find particular sources where I can find that out." (Age 35, Female)* In another study conducted in the UK with health care professionals (pulmonologists), participants also highlighted the need to ensure **access to same information** for all patients and families: *"It would be helpful to formalize the structure. We do a lot of this stuff in a pretty informal ad-hoc fashion." (health care professional)*	Limitation of evidence	Minor limitations	LOW QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Not saturated	
Sub-theme 2: adapted information/ relevant to the person					
5 studies (Beresford 2003, Hilliard 2014, Jessup 2016, Tluczek 2006, Widerman 2004)	5 studies using interviews	In 1 study conducted in the UK with young people with cystic fibrosis, 2 studies conducted in the USA with adults with cystic fibrosis and 2 studies conducted in Australia and the USA with parents of children with cystic fibrosis reported on the importance of giving adapted information. Participants highlighted that information has to be **relevant** to the person: *"We just got a booklet that was produced in America and it wasn't relevant here, and there was so much ambiguity." (parent)* *"Sometimes I'll [wonder when] something happens health-related to me, 'Is that normal for everyone or…is that happening to me because I have CF?' And it's hard to find particular sources where I can find that out." (Age 35, Female)*	Limitation of evidence	Minor limitations	MODERATE QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Saturated	

Study information			Quality assessment		
Number of studies	**Design**	**Description of theme or finding**	**Criteria**	**Rating**	**Overall**
		Many participants who were diagnosed with cystic fibrosis as adults said they were given information addressed to a paediatric audience, and that few adult materials were available: *"It seems there is not enough information for me to research on my own out there. I want to know about adult stuff" (man recently diagnosed with cystic fibrosis)* A woman wanted directions on how to do chest percussions; she was given a booklet with illustrations of an infant. (author comment) Young people with cystic fibrosis also noted that healthcare professionals should communicate adequately, as sometimes they do not feel part of the conversation: *"I go to see him, but not sure why 'cos mum talks about things."* *"He doesn't talk at my level. He ignores me and talks to my mum."* The use of **simple language** was also important to parents: *"We like to know that he does or he does not have this, instead of using all these big, giant words that make your head swim. It is confusing because one (test) could be a good thing that he's negative, another one could be a bad thing that he's negative." (mother)* Participants also discussed about relevance of information at diagnosis. Please see Table 1.			
Sub-theme 3: right amount					
3 studies (Braithwaite	3 studies using interviews	There were 3 studies conducted in Australia and the UK with parents of children with cystic fibrosis which explored parents'	Limitation of evidence	Minor limitations	MODERATE QUALITY

Study information			Quality assessment		
Number of studies	**Design**	**Description of theme or finding**	**Criteria**	**Rating**	**Overall**
2011, Hummelinck 2006, Jessup 2016)		views on information needs, and reported on adequacy of information provided. Family members of children with cystic fibrosis sometimes felt that they were given **too much information** without giving them time to process it. *"You get a bit overwhelmed by the information … when you think about it later you think, Oh, what did they say?" (parent)* Similarly, the authors of another study noted that parents of children with cystic fibrosis (that strictly required multidisciplinary care input and secondary care management) reported receiving an *'information overload'*, particularly at the time of diagnosis. (author comment) This presents a challenge when people may have differing requirements. For one parent: *"We were just trying to get everything we could";* Whereas for another: *"I think at that point for us it was probably all we needed"* As 1 parent reflected, in reality there is no easy way: *"You're given probably more than you want but it's what you need. I don't think there's anything that you could stop or take away from that process. I don't think there is any right way to do it… It's just a process that you have to go through."* Participants also discussed about adequacy of information at diagnosis. Please see Table 1.	Coherence of findings Applicability of evidence Saturation	Coherent Applicable Saturated	
Sub-theme 4: ongoing and timely					
5 studies (Braithwaite 2011,	4 studies using interviews and 1	Two studies conducted in Australia and the UK with parents of children with cystic fibrosis, 1 study conducted in Australia with	Limitation of evidence	Minor limitations	MODERATE QUALITY

Study information			Quality assessment		
Number of studies	**Design**	**Description of theme or finding**	**Criteria**	**Rating**	**Overall**
Dellon 2012, Jessup 2016, Lang 2005, Widerman 2004)	study using surveys	children and young people with cystic fibrosis and their parents and 1 study conducted in the USA with adults with cystic fibrosis identified receiving ongoing information as important. In 1 study, parents wanted **information at different times**, either as soon as possible or when the treatment became an option for their child. Therefore, it seems beneficial to have information available for parents to access as and when they wish. (author comment) For example, some parents felt they needed developmentally relevant information delivered at intervals during their child's first year: *"So I think It'd be better to have a booklet day one up to may be six months pre food and then another booklet that's relevant for that time ….Some more of these fact sheets….and use those as a thing to go through with parents over time, rather than overload with information all at once." (parent of an infant with cystic fibrosis)* *"… Just the practical day to day stuff would be great … maybe when the baby is about 6 months, it would be great to have some day to day tips about CF: things to avoid, things to do."* *"You're not ready to hear what'll happen in three years or things like that. You're more ready to hear that stuff once you've found your platform of confidence and comfort." (parent)* Families also sought **timely information** to help them prepare. Participants showed their frustration, as they were not given information at time of diagnosis. (author comment) *"I would have liked more information when (patient)'s health was better so I wasn't in shock." (parent)*	Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Saturated	

Study information			Quality assessment		
Number of studies	**Design**	**Description of theme or finding**	**Criteria**	**Rating**	**Overall**
		In another study conducted in the USA with a group of pulmonologists, they suggestive to take a **proactive** rather than a reactive **approach** to information giving: *"Maybe if we can find a way of bringing this up at earlier points in the disease it wouldn't become such a heavy weight on the patient. It would be helpful to be able to say, 'This is not something we are doing uniquely for you, this is just part of what we do.'" (healthcare professional)*			
Sub-theme 5: content					
2 studies (Jessup 2016, Widerman 2004)	2 studies using interviews	One study conducted in the USA with adults with cystic fibrosis and 1 study conducted in Australia with parents of children with cystic fibrosis participants discussed about the information they need. Many participants reported they needed general information, rather than **illness-specific**. Participants were not particularly interested in biomedical descriptions of cystic fibrosis, or even in instructions on self-care. (author comment) A woman recently diagnosed with cystic fibrosis lamented her education involved *"technical things"* and *"nothing about what life would be like".* Another man said: *"We need more on everyday stuff"* Several people referred to the practical instructions given by the physiotherapist, which represented something they could do: *"You know what was terrific was the little physio card that she made up for us…So when we're home going 'What do we do next?' we could go back to the card and check."*	Limitation of evidence	Minor limitations	LOW QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Not saturated	

Study information			Quality assessment		
Number of studies	**Design**	**Description of theme or finding**	**Criteria**	**Rating**	**Overall**
		Some participants complained the information was unnecessarily "**frightening or upsetting**": *"We received a sheet … with genetics with some basic pointers about cystic fibrosis… but the very first line on it was the life expectancy for CF… and the number … it's really confronting to have that as one of the first pieces of information."* *"The first thing you see when you open their website is that 30% of teenagers died from CF … To see that figure is like 'Oh my God.'" and one father explained: 'This is what we got at the time … All we could see, there's a little kid in jail: 'Just one cell mutation can trap you for life'…. It's just awful."*			
Sub-theme 6: format					
3 studies (Jessup 2016, Hilliard 2014, Lang 2005)	3 studies using interviews	In 2 studies conducted in Australia and the UK with families of children with cystic fibrosis, participants commented on the format, with recommendations from simple fact sheets, to brochures, booklets, DVDs, a map, personal accounts, specific transplant group meetings and counselling. They needed developmentally relevant information delivered at intervals during their child's first year. (author comment) *"So I think It'd be better to have a booklet day one up to may be six months pre food and then another booklet that's relevant for that time ….Some more of these fact sheets….and use those as a thing to go through with parents over time, rather than overload with information all at once."* One study conducted in the USA with adults with cystic fibrosis explored the use of online information and mobile applications. Although some participants noted the benefits of using mobile applications as a way of contacting with healthcare professionals, others reported that cystic fibrosis providers may	Limitation of evidence	Minor limitations	LOW QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Unclear	
			Saturation	Unclear	

Study information		Description of theme or finding	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
		not be responsive if contacted via telephone or email between visits, and would prefer to see the provider in person: *"I'm not always in a place where I can call them, so if I can just shoot a text…that would be convenient…If they want me to do something out of the ordinary...I want to [ask], 'How exactly did you want me to do this?' " (Age 23, Male)* *"In the everyday world [electronic communication] just seems to be replacing talk and conversation and you know, communicating that way, I don't want that to happen [with my doctors]." (Age 35, Female)* Similarly, some participants reported that they would not need another channel of communication with their family: *"I would use other more direct messages." (Age 28, Male)* *"I would probably continue to communicate with them the way I already do." (Age 33, Female)*			
Sub-theme 7: privacy					
1 study (Beresford 2003)	1 study using interviews	In 1 study conducted in the UK with young people with cystic fibrosis, some participants felt the privacy was important to communicate freely. *"You don't tell the doctor anything because you don't want them [student doctors] to hear." (young person with cystic fibrosis)*	Limitation of evidence	Major limitations	LOW QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Saturated	

Table 25: Summary of clinical evidence (GRADE-CERQual): Theme 5. Perceived benefits of receiving information

Study information		Description of theme or finding	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Sub-theme 1: empowerment and control					

Study information			Quality assessment		
Number of studies	**Design**	**Description of theme or finding**	**Criteria**	**Rating**	**Overall**
4 studies (Braithwaite 2011, Hummelinck 2006, Jessup 2016, Lang 2005)	4 studies using interviews	Four studies conducted in Australia and the UK with parents of children with cystic fibrosis and people with cystic fibrosis explored the reasons why parents want to receive information. Participants thought that they required information so that they could ask relevant questions when required: *"I need to ask more questions but sometimes I don't even know what to ask" (adult with cystic fibrosis)* Parents wished for more information to feel involved in management of their child's illness and to be able to understand decisions being made. Understanding what was happening helped some parents to cope with the illness and re-establish a sense of control: *"I want everything [all there is to know about cystic fibrosis] now. Because then when something arises, you can go [snaps his fingers] 'Right, I recognise that, we have got to do this' or 'I know what that is, we do not need to panic'. We know, we are in control. I think we are in control anyway, but when he's not well...It might not be nice, knowing what might be, but it's better to know. At least you are in control that way". (Father of a child with cystic fibrosis age years)* Some parents also saw information as crucial to prepare. (author comment) In addition, parents of children with cystic fibrosis reported that information gives them reassurance and empowerment: *"It would have been a bit more empowering if I'd more information … Because you kind of want parents to become experts." (parent)* One parent also mentioned that the unknown exacerbated fear:	Limitation of evidence	Minor limitations	MODERATE QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Saturated	

Study information			Quality assessment		
Number of studies	**Design**	**Description of theme or finding**	**Criteria**	**Rating**	**Overall**
		"I think the biggest thing was not knowing what might happen, which gives you a bit of a panic." (parent)			
Sub-theme 2: hope					
2 studies (Jessup 2016, Widerman 2002)	2 studies using interviews	In 1 study conducted in Australia with 10 parents of infants with cystic fibrosis, parents saw information as a source of hope: *"So that's the most important thing, that optimism is really important for parents."* This was particularly so because it: *"…moves you out of a 'victim' state to a 'move on with it' state."* As one mother declared: *"I just wanted to get on with bringing up my baby".* Parents sought information that enabled them to assign their child's position on the 'severity spectrum' of cystic fibrosis disease, explained by this father: *"I want to kind of put the severity of CF on a spectrum, and then ask: 'Where does my child fit? Is she worse or better off compared to someone else?'"* However, in spite of the best intentions and sources of current information, prognosis evolves and eludes: *"I know obviously they can't tell you for various reasons because they don't know themselves, but that's one question that I was asking myself a lot … because we still don't know."* Similarly, in another study conducted in the USA with adults newly diagnosed with cystic fibrosis, participants reported that they reacted in a positive manner when their questions were answered, and given information about cystic fibrosis, as well as positive messages to promote hope. (author comment)	Limitation of evidence	Minor limitations	LOW QUALITY
			Coherence of findings	Unclear	
			Applicability of evidence	Applicable	
			Saturation	Not saturated	

6.4.3 Clinical evidence profile: support needs for people with cystic fibrosis and their parents or carers

Table 26: Summary of clinical evidence (GRADE-CERQual): Theme 1. Support at specific stages in the course of the condition

Study information			Quality assessment		
Number of studies	Design	Description of theme or finding	Criteria	Rating	Overall
Sub-theme 1: new-born screening and diagnosis of cystic fibrosis					
1 study (Grob 2008, Whyte 1994, Widerman 2003)	2 studies using interviews and 1 study using a questionnaire	Three studies conducted in the UK, USA and Europe with parents of children diagnosed with cystic fibrosis reported on the experience following diagnosis. Parents felt overwhelmed and distress when they found out about the diagnosis and following discharge from hospital: *"My husband and I were completely traumatised at first and only kept going on adrenalin for the first year. Now I grieve for the baby I wanted and didn't get. However, we still love Jane" (mother of infant diagnosed at birth)* *"we were told that she might die when she was in her teens-I shall always remember the doctor saying that, and the effect it had on us" (mother of an infant diagnosed at 15 months age, who had symptoms of loose stools)* *"..It just seemed like everything changed.. It was like there is so much more now to taking care of her, and are we really fit to do that?.. [I]t was just so overwhelming. I mean the first time we went to the clinic they were like well, you have to do this and this. And we met with nutritionists, respiratory therapists and pulmonologists and social workers and you know it was just all so overwhelming, all this stuff we were going to have to do. I remember leaving there thinking "how am I going to do all this stuff in one day?' ". (parent of infant diagnosed with cystic fibrosis, after discharge from hospital)* Mothers reported that they seek support from professionals upon receiving a positive screening test for cystic fibrosis: *"Well, I would say in the very beginning [when we got the NBS diagnosis]. me and my husband, we were both kind of like what do you [doctors] want to do, what do you think we should*	Limitation of evidence	Major limitations	LOW QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Saturated	

Study information			Quality assessment		
Number of studies	Design	Description of theme or finding	Criteria	Rating	Overall
		do, what do you think we should do, what do you think is best? You guys are the doctors, you know" (mother of infant diagnosed with cystic fibrosis). Mothers reported that they contacted the health care professional for advice, expertise, reassurance and instructions about caring for their infant: *"Once I found out that she possibly could have the cystic fibrosis, I called so many times in the middle of the night. I'm like 'Oh my god, she's breathing really heavy, I don't know if this is right..' There was just a lot of follow-up that came from the hospital that helped.' (mother of one month old infant)* One mother found it difficult to approach the health care professional as they regarded her as being overly needy: *"What was hard I think in the beginning [was] being new as a parent for one and not knowing what was normal for children. and then dealing with the disease, the health care.. The people in health care were somewhat hard to deal with... because I would call a lot because I didn't know, because I was so scared, because there was such a fear..I would call the nurse a lot and say 'I don't know if this normal or not, this doesn't seem right.' (mother of new born infant diagnosed with cystic fibrosis).* With regards to diagnosis of cystic fibrosis as adults, 1 study conducted across different centres in the USA and Europe explored the experience of people who receive the diagnosis of cystic fibrosis as adults. A 51-year-old man diagnosed 2 years previously said, *"The concern for my emotional health by the medical professionals was almost non-existent."* A 37-year-old male simply wrote, *'It seems like care is lacking.'*			

Study information		Description of theme or finding	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Sub-theme 2: support through end of life					
1 study (Braithwaite 2011)	1 study using interviews and focus groups	One study conducted in Australia with 42 participants, including people with cystic fibrosis, their parents and the healthcare professionals looking after them noted that family members needed support to address the imminent death of their children: *"We had spoken about death and his wishes ....I could just focus on (patient), say the things I needed to say… have no regrets… prepare myself for the worst…which I think helped me to accept" (parent)* Likewise, people with cystic fibrosis felt vulnerable and thought they needed psychological support: *"I would need some psychological support … I worry about my family and how they will cope… knowing there is counselling is a comfort to me." (person with cystic fibrosis)*	Limitation of evidence	No limitations	MODERATE QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Not saturated	

Table 27: Summary of clinical evidence (GRADE-CERQual): Theme 2. Support with treatment

Study information		Description of theme or finding	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Sub-theme 1: continuity of care					
2 studies (Beresford 2003, Miller 2009)	2 studies using interviews	One study conducted in Canada that included 7 parents of children with cystic fibrosis and another study conducted in the UK with young people with cystic fibrosis noted the importance of continuity of care. They reported lack of coordination between different organisations. *"To me, it was like you were cut off from life. You turn six, that's it. You're gone. When they do it from zero to six, they coordinated. They stayed on top of it, they tell you what they*	Limitation of evidence	Major limitations	LOW QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Saturated	

Study information			Quality assessment		
Number of studies	**Design**	**Description of theme or finding**	**Criteria**	**Rating**	**Overall**
		need. As soon as they get into the school system ... I'm not even sure who coordinates it then." (parent) *"It would be better just to have one doctor so we could move on to different parts …. instead of getting the same questions again and again." (young person with cystic fibrosis)* Parents believed that knowledge of the child, according to parents, developed through relationships with a consistent set of service providers, both in and outside of medical settings. *"You need to see the regular faces, because they're the ones you feel at least know your child best," the mother said. "They know the history," the father added, "so you feel they have the whole story." (parent)* *"It's nice when relationships do develop, you know. Kate knows the nurses [in the cystic fibrosis clinic] and she likes them, and ... she's not scared when she goes down there. Those faces are familiar to her, and if she is sick, it's not scary, it's not somebody she doesn't know." (parent)*			
Sub-theme 2: active involvement from health care professionals					
1 study (Hodgkinston 2002)	1 study using interviews	In 1 study conducted in the UK with 17 mothers of children with cystic fibrosis, some participants reported that there was a need for GPs to become more involved in their children's treatment as their role was limited: *"Well basically he [GP] just writes prescriptions for us…he hasn't played a big part in the cystic fibrosis part of it". (mother)* Many mothers turned to nurse specialists for support and advice, and was critical in interpreting information and aiding understanding of treatment and compliance: *"If we do have any worries or concerns [we] just contact the hospital straight away…we never bother going up to the doctors, we always just contact S, she's one of the nurses". (mother)*	Limitation of evidence	Minor limitations	VERY LOW QUALITY
			Coherence of findings	Unclear	
			Applicability of evidence	Unclear	
			Saturation	Not saturated	

Study information			Quality assessment		
Number of studies	**Design**	**Description of theme or finding**	**Criteria**	**Rating**	**Overall**
Sub-theme 3: decision making					
2 studies (Angst 1996, Dellon 2012)	1 survey using interviews and 1 study using a survey	Two studies conducted in the USA, 1 with 34 healthcare professionals (pulmonologists) and another with 20 children with cystic fibrosis and their parents, reported on the importance of supporting parents in relation to decision making. Most parents viewed themselves as involved in the decision making process (discussion with the healthcare provider, decisions at home regarding enzymes and respiratory therapies). (author comment) However, some parents did not see themselves as having much room to make decisions. They noted decisions were based on recommendations made by health care professionals. (author comment) *"We pretty much get the plan from [the doctor] and then we just implement it...I just do what he tells me, basically. I think if I had something that was a nagging concern, I certainly know he would listen and respond to those concerns, but to date I've just not had any...I figure when he wants to change the programme, he'll tell me and we'll just do it" (mother of child with cystic fibrosis).* Parents viewed the outcome of decisions about their child's health as potentially very serious. They identified the outcome of making the wrong decision as illness progression and even death, which is why they considered the healthcare professional's recommendations seriously. (author comment) With regards to children, some parents reported they did not involve children in decision making: *"It was presented as a need for him to get back to approximately where he was on the growth curve. And if he*	Limitation of evidence	Major limitations	LOW QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Saturated	

Study information			Quality assessment		
Number of studies	Design	Description of theme or finding	Criteria	Rating	Overall
		does, then he avoids the tube. If he doesn't, then he gets the tube...We don't have that much that's negotiable...I don't see that there's two equivalent paths of therapy that are offered. Generally there's only one. Therefore, there's no need for discussion." (father) *"I don't think he really should have much choice. I think we should just tell him. He certainly has as much right to ask questions and get answers as I do, but I want him to know that it's very important to do what we're told in this case. Not to be a creative thinker." (mother's comment)* Other parents did not previously think about involving their children in decision making as they waited for a cue from the healthcare providers as to when it was appropriate to involve their children: *"I guess I never thought to ask [child]...I guess as he's gotten older, there's no reason not to ask his opinion". (mother)* *"As a parent, I guess I need to push or just be told it's OK to do this now. You know that this is the stage that the child can handle it. You know, because when [the health care professional] tells you it's OK, it's a lot easier than you making that decision". (father)* Children did not see themselves as involved in planning or decision making either: *"When I go to clinic, he doesn't usually talk to me...when I loose weight, he yells at my mom for it". (girl with cystic fibrosis)* Most children liked being uninvolved; however, many children wanted greater involvement: *"Sometimes they want me to take more medicine, and I don't even know what the medicine is, and if I stop taking other medicines. And so I have to ask my parents and they have to*			

Study information			Quality assessment		
Number of studies	**Design**	**Description of theme or finding**	**Criteria**	**Rating**	**Overall**
		ask. If they at least told me, I think I would feel a little better about why I'm taking this medicine..I think I'd feel more comfortable if I got to talk to them". (girl's comment) HCPs suggested that educational and decision support tools were seen as useful prompt in-depth discussions about treatment options and preferences: *"Having tools to facilitate the discussion would help. We may misread the kind of information people want. And if you are trying to explain treatments, I have no materials to give people about things like bilevel pressure ventilation." (HCP)*			
Sub-theme 4: online support					
1 study (Kirk 2016)	1 study using information from online forums	1 study conducted in the UK explored how online peer support is used by young people and parents (n=279) to support self-care in relation to cystic fibrosis. They noted the group sought advice and support about how to manage different treatments and therapies. *"Have you tried going swimming together just the girls in yr family make exercise fun and then when she has done it go and have lunch together or buy her a treat, That has worked with my son 13." (parent)* *"We used to use straws – blowing cotton wool balls across the kitchen table – actually our physio who has retired showed us this one – it was great fun when we all joined in as a family. " (parent)*	Limitation of evidence	Minor limitations	LOW QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Unclear	
			Saturation	Not saturated	
Sub-theme 5: physiotherapy					
2 studies (Tipping 2010, Whyte 1994)	2 studies using interviews	2 studies conducted in the UK and Australia with families of children with cystic fibrosis and physiotherapists noted parents found helpful learning about physiotherapy in hospital and they	Limitation of evidence	Major limitations	LOW QUALITY
			Coherence of findings	Coherent	

Study information			Quality assessment		
Number of studies	**Design**	**Description of theme or finding**	**Criteria**	**Rating**	**Overall**
		considered the hospital as a primary source of professional support, for problems with their child adhering to physiotherapy: *"we do it three times a day mostly-on different parts. We do front and back in the mornings, sides at lunch time and tops in the evening. We learnt that in hospital, it was helpful" (parent of a child with cystic fibrosis)* *"the new physiotherapist came out to get the message over. 'If you won't let mum do it, someone else has to come'" (mother of a child with cystic fibrosis)* Similarly, they also reported that the visit of the physiotherapist to the school was helpful: *"the physiotherapist went to the school and told them all about CF, and that helped the teachers to understand Rachel's problems" (mother of a child with cystic fibrosis, at school)* Mothers reported that continued support from the physiotherapist was helpful in crisis situations: *"I wasn't coping and I went to the hospital before my appointment was due and I just broke down in tears. The physiotherapist was very good, and said it wasn't a unique situation, and that I was coping well. I was happy that I had spoken to someone about it-it helped" (mother of a child with cystic fibrosis)* *"I asked to see the physio at the time... it was just impossible to try and keep someone of that age still for 20 min to half an hour to finish the treatment... he started telling us about doing some bubble games" (parent of a young child with cystic fibrosis)*	Applicability of evidence	Applicable	
			Saturation	Saturated	
Sub-theme 6: nutrition					
1 study (Filigno 2012)	1 study using interviews		Limitation of evidence	Major limitations	VERY LOW QUALITY

Study information			Quality assessment		
Number of studies	**Design**	**Description of theme or finding**	**Criteria**	**Rating**	**Overall**
		In 1 study conducted in the USA with 8 parents of children with cystic fibrosis highlighted the difficulties parents experience in relation to nutrition. Parents recalled that learning how to deliver both positive consequences (praises and rewards) and negative consequences (removal of privileges) to manage mealtime behaviour was helpful. They also reported intense desperation to get their child to eat, inkling preparing meals for the child so that the child would eat. Parents found that an ongoing challenge was general behavioural non-compliance including refusal to eat, take enzymes, and complete a fecal fat test. Parents found challenges with transfer of treatment responsibility from them to their child for certain aspects of cystic fibrosis management. Parents/families reported that managing transition to school was difficult as parents were not able to monitor their child's nutrition during the school day, and found that they were compensating their child's food intake at home (dinner). Parents also reported that there was a negative impact of missing school due to hospitalisation and illness. Parents struggled with partnering with schools to ensure that their children received appropriate accommodations.	Coherence of findings	Unclear	
			Applicability of evidence	Unclear	
			Saturation	Not saturated	
Sub-theme 7: attitude from parents and friends					
1 study (Barker 2012)	1 study using interviews	In 1 study conducted in the USA with 24 children and young people with cystic fibrosis participants perceived treatment-related behaviours as non-supportive, although they were	Limitation of evidence	Minor limitations	LOW QUALITY
			Coherence of findings	Unclear	

Study information			Quality assessment		
Number of studies	**Design**	**Description of theme or finding**	**Criteria**	**Rating**	**Overall**
		reluctant to rate family members or friends as being *'unsupportive'* even when annoyed by them. One young person stated, *"Their intentions are good but the way they pursue it isn't that wonderful. I'd rather them tell me to do it instead of them yelling at me to do it. I mean I'm a person, too, I forget things."* Young adults reported becoming annoyed when reminders were given after the treatment was completed or when the adolescent has a plan to complete the treatment. *"I get annoyed 'cause sometimes [mom] reminds me and I already did them. When talking about support from a close friend," another participant said, "It starts to get a little nagging at times, he's like 'You gotta do it, you gotta do it.' And I'm like, 'I know, I have a set time for this. I'll do 'em, don't worry!"* They also found reminders annoying when the reminder interrupted other activities. "*Well, like they'll tell me to do stuff. And if I'm talking on the phone or hanging out with my friends, then I don't want to do it and it gets on my nerves." Another participant said, "Well sometimes like when I want to watch a show or something, she tells me to do my treatment, so I have to stop the activity and I go do it – that gets annoying."* One adolescent said, *"cause sometimes she'll say it and it'll really get to me and I'll be like, 'Don't tell me what to do' or 'I'll do whatever I want', you know, 'I can take care of myself '. So it's not that she's saying anything differently, it's just the way I'm perceiving it that day."* However they recognized the need for persistent reminders and their benefits even when they are annoyed by them.	Applicability of evidence	Unclear	
			Saturation	Saturated	

Study information			Quality assessment		
Number of studies	Design	Description of theme or finding	Criteria	Rating	Overall
		One participant reported, *"[Mom] keeps telling me to do it whether I want to or not, she knows that it's going to help me so it's pretty supportive."* While another stated, *"[Mom] usually tells me to do [airway clearance] daily 'cause sometimes I don't like doing it so she usually has to tell me or else I won't do it."* Similarly, one adolescent talked about reminders from her friend, She pretty much says, *"Hey ok, if we're going to go out, you know, just like, let's get your meds done.' She wouldn't say, 'Ok you have to do your meds now' she'd say, 'So let's get your meds done just before we go or whatever so we don't have to do it later.' She'll present it in the way that it's not like something I have to do."* She rated her friends' reminders as very supportive because they were as encouraging and not as demanding the treatment be completed.			

Table 28: Summary of clinical evidence (GRADE-CERQual): Theme 3. Management of the complications of cystic fibrosis

Study information			Quality assessment		
Number of studies	Design	Description of theme or finding	Criteria	Rating	Overall
Sub-theme 1: infertility					
2 studies (Fair 2000, Kazmerski 2016)	1 study using interviews and 1 study using a questionnaire	2 studies conducted in the UK and the USA with young people and adults with cystic fibrosis and HCPs discussed about the support needed regarding fertility issues. Participants reported they want the emotional impact of infertility to be recognised by their health professionals: *"I do feel this can be a very emotional issue" (M, 23 years,* FEV_1 *45% predicted).* *"Give some hope of being able to father and try and make them not feel a failure if they can't father children" (M, 31 years,* FEV_1 *96% predicted).*	Limitation of evidence	Major limitations	VERY LOW QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Not saturated	

Study information			Quality assessment		
Number of studies	Design	Description of theme or finding	Criteria	Rating	Overall
		"It is terrifying for men not to be able to father a child" (M, 34 years, FEV_1 *84% predicted).* Both professionals and people with cystic fibrosis reported this issue is often neglected: *"It's always just like you don't talk about it [SRH], it's one of those things that's left to the side, it's […] like they [CF providers] feel it's not as important as everything else, but sometimes it is. I mean, it [SRH] wasn't life or death threatening, but it could've changed my life a lot." (person with cystic fibrosis)* *We've been so focused on nutrition and liver disease and lung disease and diabetes, but now that […] quality of life continues to improve, this will be a big issue, a more important issue for everyone." (HCP)*			

Table 29: Summary of clinical evidence (GRADE-CERQual): Theme 4. Psychological and emotional support

Study information			Quality assessment		
Number of studies	Design	Description of theme or finding	Criteria	Rating	Overall
Sub-theme 1: from healthcare professionals					
6 studies (Braithwaite 2011, Hodgkinton 2002, Jessup 2016, Kazmerski 2016, Lang 2005 Tipping 2010)	6 studies using interviews	4 studies conducted in Austria and the UK with parents of children with cystic fibrosis, and another study conducted in Australia with parents of children with cystic fibrosis and healthcare professionals commented on the perceived emotional support from healthcare professionals Many parents felt supportive by the staff, and they found this to be important and encouraging, and also helpful to achieve a good relationship with staff: For example one parent commented about their physiotherapist: *"I wasn't coping very well… the physio was*	Limitation of evidence	Minor limitations	MODERATE QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Saturated	

Study information			Quality assessment		
Number of studies	Design	Description of theme or finding	Criteria	Rating	Overall
		very good. I don't know why, but for some reason I think the physio part of Cystic Fibrosis, not only is it huge because of what it does, I just think it's huge in terms of support. We just asked them so many questions … I've placed my baggage on them and they've taken that really well." (parent of a toddler with cystic fibrosis) Another mother commented: *"He will always, without fail, give you praise…and he'll say Wonderful specimen mother. Well done, keep it up, wont you, you're doing marvellous', and it's what you need".* Having a good relationship with the clinician introducing and discussing was seen as essential. Parents felt the process would also be less formal and less distressing if the cystic fibrosis nurse, who knew the family and who had perhaps been previously emotionally supportive, was central to this. (author's comment) Family members said they needed timely reassurances that their children are looked after: *"Even though there is no new information we still want to hear from the team …otherwise you know you're not being abandoned but you feel abandoned". (parent)* They also expect this support to continue throughout their illness: *"The team has rescued me a number of times now and I hope they can just keep doing that until transplant" (parent)* However, some parents raised that they were overwhelmed by the number of different people involved with their care and not being empathetic: "All I can remember is five people in a room watching me cry, feeling like a real goose." (parent)			

Study information			Quality assessment		
Number of studies	**Design**	**Description of theme or finding**	**Criteria**	**Rating**	**Overall**
		"I felt quite teary. It was really, really draining …I remember people asking me questions…and I didn't know who to ask, and I just felt like I was surviving." (parent) *"We came in on the three days. It was sort-of like people came and saw you and then you waited for the next lot of people to come through, and then you waited some more…It was such a nightmare… It was the actual doing, it was terrible." (mother)*			
Sub-theme 2: from family and carers					
1 study (Widerman 2004)	1 study using interviews	In 1 study conducted in the USA with 16 people diagnosed with cystic fibrosis as adults, moderate or seriously ill participants admitted feeling self-pity and wanting sympathy, particularly from family members and caregivers. *"Once in a while, I'd like someone to feel sorry for me" (woman diagnosed with cystic fibrosis as adult)* Participants said they envied and resented the concern of the public for cystic fibrosis "poster children". But because cystic fibrosis is not outwardly apparent in most adults, participants felt their families, friends and coworkers underestimated its impact (authors' comment).	Limitation of evidence	Major limitations	VERY LOW QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Not saturated	
Sub-theme 3: online support					
1 study (Kirk 2016)	1 study using information from online forums	1 study conducted in the UK explored how online peer support is used by young people and parents (n=279). The results suggested that online peer support groups are useful for managing emotions, as group discussion provided an outlet for parents and young adults to express their emotions: *"Hey, You are certainly not alone! I think everyone with CF has felt like tha sometimes. I know for a fact I hve felt like why do I bother but I tend to do it when i'm well bcoz i cant see any difference when i take my tablet sna if i miss them but I've learnt now that i have to do my nebs and stuff"*	Limitation of evidence	Minor limitations	LOW QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Not saturated	

Study information			Quality assessment		
Number of studies	Design	Description of theme or finding	Criteria	Rating	Overall
		Some parents tried to validate their identity and to justify that they were good parents *"my daughter is 15 now but i remember like it was yesterday going through the stuff u r now and to be honest u sound like a great mum and my only advice is a mum knows best just listen to your heart and u wont go far wrong."* Although the groups were a place where negative emotions could be expressed, it appeared that there were boundaries to this. Indeed, the online group was not always seen as being an appropriate place to discuss certain experiences and feelings: *"This is a short post. I ashamed to say I often feel the same (perhapes manage it a little better though). I dont want to open up on this subject on here though. Feel free to email me on XXX" (Parent)* Participants advised parents to take an assertive stance and question medical decision making. *"I just wanted to say that I think your attitude towards your son's care is fantastic. I know a lot of parents struggle to stand up to/question medical staff (including my mum when I was younger) so it's great that you have already managed to gain the confidence to do it when your son is still at such a young age."*			

Table 30: Summary of clinical evidence (GRADE-CERQual): Theme 5. Social support

Study information			Quality assessment		
Number of studies	Design	Description of theme or finding	Criteria	Rating	Overall
Sub-theme 1: support groups					

Study information			Quality assessment		
Number of studies	**Design**	**Description of theme or finding**	**Criteria**	**Rating**	**Overall**
2 studies (D'Auria 2000, Whyte 1994)	2 studies using interviews	In 1 study conducted with 15 young people and adults with cystic fibrosis, participants commented on the usefulness of attending support groups with other people with cystic fibrosis. *"There were 16 cystic fibrosis patients on the floor that holds maybe 30. We all went out to dinner. That's the kind of thing that balances out even though you miss school and the occasional homecoming dance. You have at least something to balance out and just say, Yeah, I missed that, but I've made a lot of good friends here, too."* Similarly, in another study conducted in the UK with 4 families of children with cystic fibrosis some parents found that joining support groups was helpful, and parents considered volunteering to work with families who were newly-diagnosed with cystic fibrosis: *"I would like to work with newly-diagnosed families. I needed much more help with the emotional side of things during the whole of the first year" (mother of a child with cystic fibrosis)*	Limitation of evidence	Major limitations	VERY LOW QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Not applicable	
			Saturation	Not saturated	
Sub-theme 2: support from family and friends					
4 studies (Hodgkinson 2002, MacDonald 2010, Tipping 2010, Whyte 1984)	3 studies using interviews and 1 study using both interviews and focus groups	2 studies conducted in the UK with parents of children with cystic fibrosis and 1 study conducted in Australia with parents of young children with cystic fibrosis and HCPs explored the roles of families and friends in providing social support. Mothers found support from various sources including family, partner, friends, cystic fibrosis liaison nurses and their primary health care team. (authors comment) Family was perceived as supportive by some people: "At the time we also had a bit of support unit with my mum and sister in law there and they were taught [physiotherapy techniques] as well for back up and a bit of emotional and moral support for me." (parent)	Limitation of evidence	Major limitations	LOW QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Unclear	

Study information			Quality assessment		
Number of studies	Design	Description of theme or finding	Criteria	Rating	Overall
		But it was described as unsupportive by others: *“My husband who is an angel, he is fantastic, he also wasn’t 100% support[ive] in that manner, he left most of it (physiotherapy) for me” (parent)* Friends were identified as an important source of support because they could talk about other things than cystic fibrosis: *"If I visit my friend who lives round the corner, we don’t sit there talking about S, you know, we can have a gossip and just things like that. CF isn’t the centre of the conversation all the time, which like, it shouldn’t have to be" (mother)* A mother of twins with cystic fibrosis found that the help she received from the community support scheme was not helpful: *"The help I got was not the same as help from the family. if only my mum had been around...we do miss a granny figure"* One study conducted in the UK with children and young people with cystic fibrosis, their parents and the healthcare professionals looking after them, explored the benefits of a befriending programme. Befriending was seen as helpful by both parents and young adults. For example a young adult of 15 years was happy in the company of befriender: *"it’s what I expected, going out having a wee bit of a laugh and when I come back my dad says I’m always happier than when I left home."* In particular, young adults understood that having a befriender took the pressure of parents: *"when they first asked me if I wanted a befriender, I just wanted to go through it myself, saves my mum and dad having to do all that stuff." (young person with cystic fibrosis)* Parents also recognise that their children might share their emotion with befriender when they sometime struggle to share with them:			

Study information			Quality assessment		
Number of studies	**Design**	**Description of theme or finding**	**Criteria**	**Rating**	**Overall**
		"… this is one of the reasons that the befriender … plays a role in it … that builds up a sort of friendship with (son) … that if he's got any fears like that, hopefully he'll speak tae the befriender." (parent of a befriendee) Some criticism of befriending was around the continuity, as befrienders were mostly young people who were in transition between education and employment and continuity was thus difficult: For example 1 young adult was unhappy about the lack of continuity *"Don't know what happened to the first one……I thought it was me…. I could never get in touch with her."* Similarly, a parent of a 16 year old befriendee said *"They'd be better if the lassies were a wee bit older, ken they're away on holiday, I dunno what age, she can only be in her 20s, changing jobs, its months since we've seen her."* In relation to this, a parent shared the same concern *"I feel let down and (son) has been let down because he was getting close to her."* Another difficulty raised is that befrienders also faced challenges in building and boundaries of the relationship: *"…It can take a while to get to that stage, I'm now totally comfortable with (child), we can talk about anything…"* *"He doesn't understand why he can't come to my house, or I can't bring my child along and neither do I."* Befrienders were also concerned about their **lack of knowledge** when discussing with parent or young adult about cystic fibrosis. *"I would like more training about CF, the parents talk to you in jargon you don't understand – what's IV's?*			
Sub-theme 3: peer support/ virtual support					

Study information			Quality assessment		
Number of studies	**Design**	**Description of theme or finding**	**Criteria**	**Rating**	**Overall**
2 studies (Hilliard 2014, Kirk 2016)	1 study using interviews and 1 study using information from online forums	One study conducted in the UK with 279 young people with cystic fibrosis and their parents explored the use of an online forum as means of social support. While parents mainly used the site to seek specific advice or emotional support (as seen before), young people used it as a **social networking site**. *"hey Tina welcome back! how did you get on with the exams? i'm good thanx, back on the IV's in June. how are you?" (young person with cystic fibrosis)* *"aww i'm gd. on my Iv's atm. halfway there! yay! a week is too long though. i feel like pulling the needle out! glad to hear you're feeling good. i think i need a bronch to! havent had one in ages and sometimes you can just tell you need one! now is one of these times! (but don't tell the doctor!" (young person with cystic fibrosis)* Another study conducted in the USA with 15 adults with cystic fibrosis using a **mobile application** showed that some people saw this as a novel **opportunity to network**, given prohibitions on face-to face contact. *"Because people with CF can't be in the same room as each other,…being able to see someone else with CF is much more profound than just exchanging emails with some anonymous person." (Age 28, Male)* *"I think that support for the family and friends is important…for people who have CF…talking to significant others of people who have CF." (Age 28, Male)* Others could feel **discouraged or guilty** seeing others "*doing better or worse than you*": *"I don't like hearing about CF people that aren't doing well. I have a hard time distancing myself from it. It's hard having to*	Limitation of evidence	Minor limitations	MODERATE QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Unclear	

Study information			Quality assessment		
Number of studies	Design	Description of theme or finding	Criteria	Rating	Overall
		filter through all this sadness to get kind of connected with someone." (Age 26, Female) *"I didn't really like it only because some people had it worse than me and if it kind of brought me down because I felt like this is where I'm heading and I just didn't like that…So I don't know if I'd really want to talk to any other people with CF, I don't want to like be depressed." (Age 32, Male)*			

6.5 Economic evidence

No economic evaluations related to information and support in cystic fibrosis were identified in the literature search conducted for this guideline. Full details of the search and economic article selection flow chart can be found in Appendix E and F, respectively.

This review question is not relevant for economic analysis because it does not involve a decision between alternative courses of action.

6.6 Evidence statements

6.6.1 Information needs for people with cystic fibrosis and their parents or carers

Information at diagnosis

Low to moderate quality evidence from 7 qualitative studies conducted with parents of children with abnormal newborn screening results, children with cystic fibrosis or adults recently diagnosed with cystic fibrosis discussed the information needs prior to and following diagnosis. Both parents and adults wanted to know information about the condition and the future implications of cystic fibrosis. However, some discrepancies were found between those parents who felt they received too much information and those who felt they had to fight to get the information they needed or to look for information themselves. In balance, parents appreciate timely information, at a pace that it is convenient for them. Adults were particularly concerned about not being given information specifically related to them.

Information about treatment

Very low to low quality evidence from 5 qualitative studies conducted with children with cystic fibrosis and parents of children with cystic fibrosis noted the importance of trusting healthcare professionals in relation to the information received about the treatment. They wanted to know about the available treatment options and about alternative care. Parents particularly welcomed practical instructions in relation to the physiotherapy treatment.

Information about management of complications

Low quality evidence from 4 qualitative studies conducted with families of children with cystic fibrosis, adults with cystic fibrosis and healthcare professionals looked at specific complications related to cystic fibrosis. With regards to lung transplant, most parents found information helped them to face the situation, although some parents found it difficult to deal with it. Adults reported they were concerned in relation to fertility issues, but it seemed they sometimes found it difficult and uncomfortable to discuss their worries and questions with the healthcare professionals. To overcome this barrier, some participants suggested this topic should be discussed earlier and these discussions should be part of the routine. Women, in particular, reported that they would like more information about the consequences of pregnancy and the risks of the actual birth.

Provision of information

Low to moderate quality evidence from 10 qualitative studies with young people and adults with cystic fibrosis, parents of children with cystic fibrosis and healthcare professionals discussed aspects relevant to the provision of information. People valued receiving relevant information for them, accessibility to information resources, the use of simple language and privacy. In relation to the content, people wanted to get general information that is practical rather than technical information. They noted that information can sometimes be upsetting.

The amount of information needed was discussed. People have different needs, those who required lots of information and those who preferred information to be delivered at intervals. Ultimately, people seemed to prefer timely information that helps them to prepare. With regards to the format, people commented on different possibilities, such as written information, specific groups and DVDs. Many people felt reluctant to use online resources or mobile applications, as a way of getting information or communicating with healthcare professionals or the family.

Perceived benefits of receiving information

Low to moderate quality evidence from 5 qualitative studies conducted with parents of children with cystic fibrosis and with people with cystic fibrosis reported on the benefits of receiving information. Most participants reported that information helped them to understand the condition and gave them a sense of control. It helped them to prepare for treatments and to ask meaningful questions when needed. Information was seen as reassuring. Both adults with cystic fibrosis and parents of children with cystic fibrosis saw information as a source of hope.

6.6.2 Support needs for people with cystic fibrosis and their parents or carers

Support at specific stages

Low to moderate quality evidence from 2 qualitative studies conducted with people with cystic fibrosis, parents of children with cystic fibrosis, and healthcare professionals reported on the support needed at important stages during the condition, including newborn screening, diagnosis and end of life care. Parents reported feeling overwhelmed after the diagnosis and wanting to contact healthcare professionals for advice, expertise and reassurance, although some felt difficult to approach professionals. Similarly, people with cystic fibrosis and their parents indicated they needed support to address the end of life care.

Support with treatment

Very low to low quality evidence from 10 qualitative studies conducted with children and young people with cystic fibrosis, parents of children and healthcare professionals explored the support needed in relation to treatment. Parents and young people with cystic fibrosis noted the lack of continuity of care and emphasised that having a consistent set of providers would be beneficial. Parents would also appreciate GPs to be more involved in the care of their child. Parents seek help in relation to treatment either from professionals or other parents. They particularly noted the need for help with practical aspects in relation to nutrition and physiotherapy. Finally, the role people should take in decision making regarding treatment was discussed by several participants. Parents viewed themselves as being involved in the process, although they acknowledged their decisions were based on the recommendations of healthcare professionals because of the seriousness of the condition. Children felt they were not very involved in decision making and they noted they would like to have a more active role. In relation to this, parents said they did not want their children to be involved, or that they were waiting for the right time.

Management of complications

Very low quality evidence from 2 qualitative studies conducted with young people with cystic fibrosis, parents of children with cystic fibrosis and healthcare professionals explored the issue of fertility and the support needed in this regard. They all agreed the issue of fertility is often neglected as it is not considered life-threatening. Young people, in particular, highlighted they need healthcare professionals to recognise the emotional impact of infertility.

Psychological and emotional support

Very to moderate quality evidence from 5 qualitative studies conducted with young people with cystic fibrosis, people diagnosed with cystic fibrosis as adults, parents of children with cystic fibrosis and healthcare professionals explored the importance of emotional and psychological support. Parents highlighted they needed timely reassurance and continuous support from staff. Feeling emotionally supported by staff was very encouraging for them and helped build a good relationship with them. Some parents had experienced a lack of empathy and this made them feel misunderstood. Similarly, people that had been diagnosed as adults felt the need for emotional support and sympathy from their relatives and friends. The use of online groups was described as helpful for managing emotions.

Social support

Very low to moderate quality evidence from 7 qualitative studies conducted with young people and adults with cystic fibrosis, parent of children with cystic fibrosis and healthcare professionals explored the benefits of social support. Young people with cystic fibrosis and parents of children with cystic fibrosis described attending support groups as useful. Furthermore, the use of virtual support, either online support or mobile applications, was also found to be very useful to meet people with the same condition. This is particularly useful given the recommendations to avoid face to face contact and risk of cross infection. However, some felt it could be discouraging seeing other people doing better or worse than them.

Families and friends were seen as supportive and unsupportive. A befriending programme was described as helpful by both young people with cystic fibrosis and their parents as it took the pressure off parents and allowed for young people to share their emotions. However, they were concerned about the lack of continuity.

6.6.3 Economic evidence statements

No evidence on cost-effectiveness in people with cystic fibrosis was available for this review.

6.7 Evidence to recommendations

6.7.1 Relative value placed on the themes considered

The aim of this review was to identify what information and support should be provided to people with cystic fibrosis and their parents and carers. Although there were many themes in the literature, the committee identified those that they thought would be important when the protocol was developed. They agreed that the following themes would provide useful perspectives: provision and timing of psychosocial support, regular individualised assessment, support groups, support at school, information at the time of diagnosis, social media, care planning and social services and benefits.

6.7.2 Consideration of clinical benefits and harms

While acknowledging the limitations of the evidence, the committee agreed that the themes and sub-themes identified in the literature were useful and relevant.

The committee discussed the evidence regarding information and support needs around the time of diagnosis. The literature reported that people with cystic fibrosis and their parents want to receive information following diagnosis primarily about the condition and the future implications. In addition, the committee emphasised that receiving the diagnosis of cystic fibrosis is a stressful event and it is important that information is delivered by a specialist in cystic fibrosis.

As highlighted in the evidence, the committee acknowledged there is a need for honest dialogue between people with cystic fibrosis, their parents or carers and health care professionals. They agreed information should be relevant and adequate for the person, but not overwhelming to the receivers. They agreed general information should be readily available, but the detail people want may differ and should be based on individual needs.

The committee discussed that it is important to offer ongoing and staggered information, as reported in the evidence. They agreed that the person or their family may require information at specific times, for example before and after diagnosis, or for specific topics, such as treatment for cystic fibrosis-related complications (for example liver disease, cystic fibrosis-related diabetes, lung transplant or fertility issues). They suggested having honest and open dialogue on the symptoms of cystic fibrosis and possible complications. They also agreed that information on coping with anxiety from cystic fibrosis is important. They agreed that the person, or their family, should be offered opportunities to discuss the following issues with relevant professionals: managing the risks of cross infection, the implications of the condition for school and education, career planning, transition to adult care, foreign travel (for example on specific risks such as insurance, fitness to fly, carrying medications and nebulisers), pregnancy and parenting, organ transplantation and end of life care. The committee noted that all people with cystic fibrosis have a pathway of care, which describes the care they are receiving, and that they should be able to have access to it.

The committee noted it is important to deliver information through different formats in a way that can be understood by people with suspected, or diagnosed, cystic fibrosis and their family members or carers (as appropriate). As suggested in the literature, information should take into account individual variances in literacy and comprehension levels.

The committee underlined that emotional support is important for people with cystic fibrosis and their families or carers and some may need specialist psychological support. The literature highlights the time of diagnosis and when approaching end of life as key periods when psychological support is needed. They highlighted additional support may be needed during times of change, such as starting or changing school, moving from education to work, changing to living independently. The committee noted that social work support is important at these times, especially liaison with local Social Care services as appropriate. They agreed that support would be needed in relation to: fertility issues, including family planning, infertility, complications and issues which may arise in pregnancy for expectant mothers with cystic fibrosis, awaiting or undergoing organ transplantation and when approaching end of life.

The committee discussed the use of online support, including social media, as reported in the literature. They expressed potential concerns that social media is unregulated and so information may be inaccurate. However, they highlighted that monitoring and regulating online discussion forums is far beyond the remit of healthcare professionals. Based on this, they agreed it is important to advise people with cystic fibrosis and their parents to be aware of the potential issues when they use the internet to look up for health information. However, information and support available from trustworthy sources of information, such as the NHS, CF Trust (and its international counterparts) could be signposted to. They agreed it is important to give the person with cystic fibrosis and the families an opportunity to discuss what they have read.

Some reports in the literature suggest that support groups can be perceived as beneficial by some people with cystic fibrosis. However, the committee strongly recommends these groups do not take place face to face in order to prevent cross-infection which can lead to further complications. Information about online support groups and advocacy services would be beneficial. Facilitating access to parent or carer only face to face social support groups can be considered if there is a demand. But with these, the risk to their children meeting socially must be emphasised.

6.7.3 Consideration of economic benefits and harms

This review question is not relevant for economic analysis because it does not involve a decision between alternative courses of action. Even so, there are considerations for the resources and costs providing information and support may entail.

Whilst there are aspects of providing information and support which have opportunity costs, such as the staff time and some of the different communication formats that may be useful in this population, these are typically small and would ordinarily be considered within the provision of standard services and care. Good communication is recognised as important generally within healthcare provision and that patient care can suffer as a result of poor or ineffective communication. The committee considered that, overall, their recommendations regarding information and support would have a minimal resource impact and that they would promote the cost-effective use of NHS resources.

6.7.4 Quality of evidence

Moderate to very low-quality evidence was presented in this review, as assessed by GRADE-CERQual. Below the main reasons leading to downgrading the evidence are described.

The methodological limitation of the studies, especially the inadequate reporting on processing and analysis of the data. Some of the studies reported were descriptive when thematic analysis would have been more appropriate and informative. In the studies where thematic analysis was done, the authors did not always report in detail how findings or themes were derived or emerged from the data in their research.

Another methodological limitation was the inadequate information on the researcher's role in sample recruitment, data collection or data analysis. Few studies clearly reported the relationship between researchers, interviewers and the respondents, whether the researchers had a preunderstanding about the topic or the possible influence of that in data collection and analytical process. Lack of verification of findings was not reported either in any of the studies.

Downgrading of evidence was also related to data saturation, applicability and incoherence. Some of the studies did not report whether saturation was achieved in terms of data collection or data analysis. It was difficult to ascertain from the information reported in those studies whether all possible views had been explored. Some other studies were done in an isolated group or population in other countries and were not applicable to UK population. Incoherence was also a factor in downgrading the quality of evidence in few of the studies.

6.7.5 Other considerations

No equality issues were identified by the committee for this review question.

The recommendations related to this evidence review were based on the evidence and the committee's clinical experience. In addition, the committee acknowledged some of the principles about communication and information in the NICE guideline on "patient experience in adult NHS services: improving the experience of care for people using adult NHS services" (NICE CG138) could also be applied here. Therefore they agreed to draft a recommendation which directed readers to this guideline. The committee concluded that a research recommendation was not needed as the guidance provided in the guideline combined with an individual healthcare professional's experience is sufficient to provide the necessary support and information. Given the limitations in research funding, it was determined that this should not be a priority for further research.

6.7.6 Key conclusions

The committee concluded that receiving a diagnosis of cystic fibrosis is a stressful event. It is important to ensure that information and support is provided by healthcare professionals with expertise in cystic fibrosis. Information should be tailored to the individual needs and given on an ongoing and staggered basis. They agreed that information and support may also be needed regarding new treatments, management of comorbidities and fertility.

6.8 Recommendations

4. **Provide people who are newly diagnosed with cystic fibrosis and their family members or carers (as appropriate) with opportunities to discuss their concerns.**

5. **Information and support should be provided by healthcare professionals with expertise in cystic fibrosis.**

6. **Provide people with suspected or diagnosed cystic fibrosis and their family members or carers (as appropriate) with relevant information that they can understand, and opportunities for discussion on topics such as:**
    - their diagnosis
    - monitoring of their condition
    - management choices for their condition
    - possible or existing complications or comorbidities
    - implications for living independently.

7. **Provide people with cystic fibrosis and their family members or carers (as appropriate) with information about their care pathway.**

8. **Give information to people with cystic fibrosis and to family members or carers in ways that are individually appropriate. Avoid jargon and use formats that they prefer, for example:**
    - face-to-face discussions
    - copies of correspondence
    - written information (such as leaflets)
    - any digital media and reliable internet sources that are available.

9. **When appropriate, provide people with cystic fibrosis and their family members or carers with opportunities for discussion with relevant expert professionals on:**
    - available resources and support, such as local support and advocacy services
    - managing the risks of cross-infection
    - implications of the condition for school and education
    - career planning
    - transition to adult care
    - foreign travel
    - fertility and contraception
    - pregnancy and parenting
    - organ transplantation
    - end of life care.

10. **Provide people with cystic fibrosis with information about how to contact other people with cystic fibrosis without risking cross-infection (see Prevention of cross infection), for example by directing them to online support groups.**

11. **For more information on communication, providing information and shared decision-making in adult NHS services, see the NICE guideline on patient experience in adult NHS services.**

12. **Be aware that people with cystic fibrosis and their family members or carers will need emotional support and some may need specialist psychological support (see Psychological assessment), in particular:**
    - at diagnosis
    - at times of transition (for example, when starting or changing school, moving from education to work, or changing to living independently for the first time)
    - in relation to fertility, including family planning, pregnancy and infertility
    - to cope with complications of cystic fibrosis
    - when waiting for or having organ transplantation
    - when approaching the end of life.

7 Service delivery

7.1 Service configuration

Review question: What is the effectiveness of different models of care (for example, specialist centre, shared care [delivered by a Network CF Clinic which is part of an agreed designated network with a Specialist CF Centre], community, telehealth and/or home care) for people with cystic fibrosis?

7.1.1 Introduction

There is a wide range of ways in which care for people with cystic fibrosis is organised and delivered.

In the UK, care for adults with cystic fibrosis is primarily concentrated in specialist cystic fibrosis centres.

Children with cystic fibrosis may be cared for solely by a specialist cystic fibrosis centre. But there are some circumstances where they may also be seen in conjunction with a team in a local hospital as part of a paediatric network (shared-care clinic). Such an arrangement reduces disruption to schooling and improves the family's local support.

In addition, there are other models of care and service which people with cystic fibrosis may utilise including telemedicine, clinical review and treatment at home, outreach care and community care by primary health care professionals.

Each of these models provides a different patient experience and may be associated with different outcomes and cost effectiveness. Additionally, limitations in a patient's socio-economic background and local geography have significant impacts on how care can be arranged and delivered.

7.1.2 Description of clinical evidence

The aim of this review was to assess the effectiveness of different models of care (for example specialist centre, shared care, community care, telehealth and home care) for the care of people with cystic fibrosis.

For the purpose of this review, the different models of care were defined as follows:

- Specialist centre:
  - normally with >100 patients and minimum of >50 patients
  - commissioned by NHS England to provide care for people with cystic fibrosis
  - will have the core MDT available.
- Shared care (delivered by a network clinic):
  - local hospital looking after a small number of children with cystic fibrosis
  - has input from a specialist centre at least twice a year, which is responsible for the standard of care
  - may not have the core MDT and may not be full time.
- Community care:
  - community nurses of the region who look after people with cystic fibrosis and will administer treatments such as home intravenous (IV) antibiotics
  - normally delivered by health visitors and school nurses.
  - might include palliative services.

- Home care:
  - care that would normally be given at hospital which is given at home
  - delivered by cystic fibrosis specialist (e.g. nurse, dietitian, physiotherapist).
- Outreach:
  - specialist centre team conduct a clinic in a local hospital.
- Telemedicine:
  - involves video conferencing patients and remote monitoring.

As per protocol, studies that assessed the effectiveness of different models of care were eligible for inclusion in this review if they were RCTs or comparative cohort studies that were conducted in Western countries. Studies based on registry and audit data from the UK were also eligible for inclusion. Conference abstracts of RCTs were considered if RCTs were unavailable. Prospective studies were prioritised over retrospective studies, therefore retrospective studies were excluded if there were prospective studies which covered the same intervention and outcomes. Evidence from questionnaires conducted within cross-sectional studies was included (for example, for quality of life, or patient satisfaction).

For full details see review protocol in Appendix D.

Two Cochrane systematic reviews were included:

- Balaguer 2015 evaluated the effectiveness of IV antibiotic therapy administered at home compared to IV antibiotic therapy administered in hospital, 1 RCT was included from this review (Wolter 1997).
- Goldbeck 2014 evaluated the effectiveness of psychological interventions compared to standard care, 1 RCT was included from this review (Wilkinson 2008)
- In addition, 4 prospective cohort studies (Donati 1987, Esmond 2006, Riethmueller 2002, van Koolwijk 2002), 3 retrospective cohort studies (Bosworth 1997, Thomas 2008, Finkelstein 1992) and 2 cross-sectional studies (Thomas 2006, Walters 1994) were included.

Where possible, data and risk of bias assessment were taken directly from the Cochrane systematic reviews. Individual studies were retrieved for completeness and accuracy and were also checked for additional outcomes of interest.

The size of the studies ranged from 6 to 746 participants. Three studies included adults only (Esmond 2006, Wilkinson 2008, Wolter 1997), 1 study included people aged ≥ 15 years (Walters 1994), 1 study included people aged ≥12 years (Donati 1987), 5 studies included children, young people and adults (Bosworth 1997, Finkelstein 1992, Riethmueller 2002, Thomas 2006, Thomas 2008), 1 study included children and young people (Van Koolwijk 2002).

Three studies were conducted in the UK (Esmond 2006, Walters 1994, Wilkinson 2008), 3 in the USA (Bosworth 1997, Donati 1987, Finkelstein 1992), 3 in Australia (Thomas 2006, Thomas 2008, Wolter 1997), 1 in Germany (Riethmueller 2002), 1 in the Netherlands (van Koolwijk 2002).

Four studies (Bosworth 1997, Donati 1987, Esmond 2006, Wolter 1997) compared the effectiveness of IV antibiotics for treatment of pulmonary exacerbations administered at home and in the hospital. One study (Riethmueller 2002) compared the effectiveness of IV antibiotics for people with a chronic infection administered at home and in the hospital. Three studies compared centre care to shared care (Thomas 2006, Thomas 2008, Van Koolwijk 2002). Two studies (Thomas 2008, Van Koolkwijk 2002) compared centre care to local care (below UK standards). One study (Thomas 2008) compared shared care above UK standards to shared care at UK standards. One study (Walters 1994) compared centre care to usual care (by non-cystic fibrosis specialists). One study (Finkelstein 1992) compared a telemedicine intervention (daily recording of physical measurements and symptoms) to usual

care. One study (Wilkinson 2008) compared a telemedicine intervention (weekly video conferences for clinical assessment and psychological support) to usual care.

A summary of the included studies is presented in Table 159. See study selection flow chart in Appendix F, study evidence tables in Appendix G, list of excluded studies in Appendix H, forest plots in Appendix I, and full GRADE profiles in Appendix J.

7.1.3 Summary of included studies

A summary of the studies that were included in this review are presented in Table 31.

Table 31: Summary of included studies

Study	Intervention/ Comparison	Population	Outcomes	Comments
Cochrane reviews				
Balaguer 2015 Cochrane SR	Comparison 1: home-based care (IV antibiotic therapy administered at home) versus hospital-based care (IV antibiotic therapy administered in hospital) (Wolter 1997)	Children, young people and adults with CF	• Change in FEV_1 (% predicted) • Weight gain (kg) • Not reported: • Mortality • Patient and carer satisfaction • Lung Index Clearance • Time to next pulmonary exacerbation • Quality of life • Frequency of cross-infections • Staff experience • Adherence to treatment	
Goldbeck 2014 Cochrane SR	Comparison 1: Psychological intervention versus usual care (Wilkinson 2008)	Children, young people and adults with CF	• Change in quality of life • Not reported: • FEV_1 % predicted • Mortality • Patient and carer satisfaction • Lung Index Clearance • Time to next pulmonary exacerbation • Nutritional status • Frequency of cross-infections • Staff experience • Adherence to treatment	
Primary studies included in the Cochrane SR				

Study	Intervention/ Comparison	Population	Outcomes	Comments
Wilkinson 2008 (UK) RCT	Intervention: telemedicine • weekly videoconferences from home for a clinical assessment, psychological support and the opportunity for discussion with any member of the multidisciplinary team Control: Standard care	N=7 adults with CF on a transplantation list (16 recruited, 11 completed the baseline assessment and 7 completed the study) • Telemedicine: n=4 • Control arm: n=3 Age range of people who were randomized (median): 21 to 41 (27)	• Change in quality of life	Included in Goldbeck 2014 SR Follow-up: 6 months
Wolter 1997 (Australia) RCT and cross-over open study	Intervention: home-based care spent 2 - 4 days in hospital before discharge people with CF were taught to prepare and administer their own intravenous antibiotics home visits were conducted Comparison: hospital-based care whole treatment was administered in the hospital	N=17 adults with CF with an infective exacerbation (31 admissions: home care: n=13 admissions hospital care: n=18 admissions) Age range (median): 19-41 (22)	• Change in FEV_1 (% predicted) at 21 days • Weight gain (kg) at 10 days	Included in Balaguer 2015 Follow-up: 21 days for FEV_1% predicted, 10 days after treatment for weight gain
Additional primary studies				
Home care and community care: IV antibiotics for treatment of pulmonary exacerbations				
Bosworth (1997) USA Comparative cohort study	Intervention: Home-based care • Prior to receiving home care, people with CF stayed in the hospital for up to 4 days • IV antibiotics and chest physiotherapy administered at home either by self or family with the same	N= 40 people with CF who required IV antibiotic therapy for a pulmonary exacerbation (59 courses) • Home group: n=19 people with CF (27 courses). Age range: 7-31. Mean (SEM): 18.8 (1.2) • Hospital group: n= 21 people with CF (32	• Time to next exacerbation	Although not explicitly reported, likely to be a retrospective study. Mean follow-up: 18 days

Study	Intervention/ Comparison	Population	Outcomes	Comments
	frequency as in hospital • Home visits from nurses at least once a week Comparison: hospital-based care • IV antibiotics in the hospital • Chest physiotherapy administered in the hospital 4 times a day	courses). Age range: 8-29. Mean (SEM): 17.05 (0.9)		
Donati 1987 (USA) Comparative prospective cohort study	Intervention: Home-based care • Daily visits from nurses Comparison: hospital-based care • IV antibiotics administered at the hospital	N=64 people with CF (82 treatments) who required IV antibiotic therapy for a pulmonary exacerbation Age: ≥12 years • home group: n= 26 people (41 treatments) • hospital group: n=38 people (41 treatments)	• Change in FEV_1 (% predicted) • Change in weight (kg)	Follow-up: 18 days
Esmond 2006 (UK) Quasi-experimental design: prospective comparative cohort	Intervention: home-based care • Home IV antibiotic treatment. • All patients who chose home therapy had previously self-administered IV antibiotics at home. • People performed their own chest physiotherapy Comparison: hospital-based care • IV antibiotic treatment administered at the hospital. • Chest physiotherapy performed by experienced	N=28 adults with CF experiencing an acute respiratory exacerbation. (30 treatments) Age: ≥18 years • Home group: n=15 treatments • Hospital: n=15 treatments	• Change in FEV_1 (% predicted) • Change in BMI Change in quality of life measured with CFQoL questionnaire (Gee et al. 2000)	Follow-up: 15 days

Study	Intervention/ Comparison	Population	Outcomes	Comments
	respiratory physiotherapists.			
Home care/ community care versus hospital: IV antibiotics for patients with chronic infection				
Riethmueller 2002 (Germany) Prospective comparative cohort study	Intervention: home-based care • IV antibiotic treatment at home • People did their daily training and were supervised once per week by a physiotherapist specialized in CF. • People were offered a visit by a specialized nurse if intravenous line or other problems occurred. Comparison: hospital-based care • IV antibiotic treatment in hospital. • Two daily courses of supervised physiotherapy (1 h). • Diets were supervised by a dietitian specialised in CF care.	N=36 people with CF (58 courses) • Home group: n=17 people (30 courses). Mean (SD) age: 16 (5) • Hospital group: n=19 people (28 courses). Mean (SD) age: 15 (4) Inclusion criteria included *P aeruginosa* in sputa over a time period of more than 6 months before entering, good compliance and regular home physiotherapy.	• Change in FEV_1 % predicted • Change in weight (kg) • Change in weight for height (%)	Follow-up: 14 days
CF centre care versus. shared care or local care				
Thomas 2006 (Australia) Cross-sectional study	Intervention: CF centre care • Children are reviewed at least 3 times a year and have full access to the MDT. Comparison: shared care • Children are managed by their local paediatrician or general practitioner and	N=162 people with CF (and/or their parents when relevant) Age range: 2-19 • Specialist centre: n=91 • Shared care: n=71	• HRQOL measured with CFQ questionnaire (Quittner et al. 2005)	In the paper, different terminology is used compared to this review: • CF centre care is called “Cystic Fibrosis Centre (CFC)” in the study • Shared care is called “Cystic Fibrosis Outreach

Study	Intervention/ Comparison	Population	Outcomes	Comments
	local hospital, and they also attend outreach clinics visited by CFOS. • Regional staff are invited to attend the clinics. • Outreach clinics occur twice per year except for 1 site, which has 1 clinic and 2 tele health clinics per year.			Service (CFOS)" in the study
Thomas 2008 (Australia) Retrospective comparative cohort study	Intervention: CF centre care • All care is provided by the Cystic Fibrosis Centre (CFC) • Admission to the CFC when required • Outpatient review at CFC 3 or more times per year Comparison 1: shared care, review 3+times a year (above UK standards) • Children living in regional centres and attending Cystic Fibrosis Outreach Service (CFOS) as well as attending CFC regularly. • Admission to CFC or local hospital with local hospital care provided by local paediatrician. • Outpatient review by CFC or CFOS 3 or more times per year. • Children attending outreach clinics are also managed by their	N=150 people with CF born between 1982 and 2002. Age range: 0-20 • Specialist centre: n=74 • Shared care review 3+ times a year: n=21 • Shared care review 2+ times a year: n=37 • Local care: n=18	• Change in FEV_1 % predicted from first to last per year • FEV_1 % slope per year	273 people were included in the study, however the analysis on FEV_1 % predicted focused on 150 people. Follow-up: 3 years Only longitudinal data on FEV_1 were extracted; cross-sectional data on FEV_1, height z scores and weight z scores were not extracted In the paper, different terminology is used compared to this review: • CF centre care is called "LOC1" in the study • Shared care, review 3+times a year, is called "LOC2" in the study • Shared care, review 2+

Study	Intervention/ Comparison	Population	Outcomes	Comments
	local paediatrician or general practitioner. Comparison 2: shared care, review 2+times a year (at UK standards) • Care is predominantly provided by the local paediatrician with consultation with CFC • Admission to local hospital with care provided by local paediatrician. • Outpatient review by CFOS at least twice a year Comparison 3: local care • Involvement by CFC or CFOS once a year or no CFC/CFOS involvement. • Includes children seen by respiratory physicians but with no CFC or CFOS multidisciplinary health care involvement • Alternatively, care provided by local paediatrician or general practitioner or unknown			times a year, is called "LOC3" in the study • Local care is called "LOC4" in the study
Van Koolwijk 2002 (The Netherlands) Prospective comparative cohort study	Intervention: CF centre care • Patients receive their treatment completely in the centre • Regular visits at minimum	N= 105 young people and children with CF. Age range: 5-17: • CF centre care: n=41. Mean (SEM) age: 10.8 (0.5) years	• Change in FEV_1 % predicted • Change in BMI (kg/m2)	In the paper, similar terminology to this review is used: • CF centre care is called "centralized

Study	Intervention/ Comparison	Population	Outcomes	Comments
	intervals of 3 months Comparison 1: Shared care • Includes a half-yearly visit to the Centre (annual check-up and an MDT outpatient clinic visit) combined with regular visits to the local paediatrician • The local paediatrician comes to the centre during the annual check-up and participates in the multidisciplinary consultation • Regular visits at minimum intervals of 3 months Comparison 2: Local care • Patients visit the centre only once a year at the annual check-up, but remain fully treated at their local hospitals. • The local paediatrician comes to the centre during the annual check-up and participates in the multidisciplinary consultation • Regular visits at minimum intervals of 3 months	• Shared care: n=41. Mean (SEM) age: 10.7 (0.5) years • Local care: n=23. Mean (SEM) age: 9.4 (0.5) years		care" in the study • Shared care is called the same ("shared care") in the study • Local care is called "local care" in the study
CF centre versus usual care by non-specialists in CF				
Walters 1994 (UK) Cross-sectional study	Intervention: CF centre care • Large special cystic fibrosis clinics	N= 746 people with CF aged ≥15 years • Specialist centre: n=494	• Patient satisfaction	Questionnaires were sent to all 1052 members of the Association of

Study	Intervention/ Comparison	Population	Outcomes	Comments
	Comparison: Usual care • Non-CF general clinics at local hospitals	• General clinic: n=252		Cystic Fibrosis Adults.
Telemedicine				
Finkelstein 1992 (USA) Retrospective comparative cohort study (follow-up of a RCT)	Intervention: Home monitoring with diary recording • Daily recording of physical measurements and symptoms • Diary sent to the data coordinating centre weekly for analysis. Comparison: usual care • No diary recording, no home monitoring	N=50 people with CF • Intervention: n=25 • Control: n=25 Age range: 6 to 43 years	• Change in predicted FEV_1 (%) at 4 years	Participants were randomly selected from a bigger RCT Follow-up: 4 years

Abbreviations: CF-Cystic Fibrosis; IV-intravenous; FEV-forced expiratory volume in 1 second; BMI-Body Mass Index; QoL-Quality of Life; HRQOL- Health-Related Quality of Life; CFC-Cystic Fibrosis Centre; CFOS-Cystic Fibrosis Outreach Service; LOC-Level of Care; RCT-Randomised Controlled Trial.

7.1.4 Clinical evidence profile

The summary clinical evidence profiles for this review question are presented in Table 32 to Table 40.

7.1.4.1 Home-based care

Table 32: Summary clinical evidence profile: Comparison 1.1. Home versus hospital care for the administration of IV antibiotics in people with CF experiencing an acute pulmonary exacerbation

Comparison 1.1. Home care compared to hospital care for the administration of IV antibiotics for people with CF experiencing an acute pulmonary exacerbation						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of treatments (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Hospital care for the administration of IV antibiotics	Home care for the administration of IV antibiotics				
Lung function: change in FEV_1 % predicted	The mean change in FEV_1 %	The mean change in FEV_1 % predicted in		31[a] (Wolter 1997)[1]	⊕⊖⊖⊖	

Comparison 1.1. Home care compared to hospital care for the administration of IV antibiotics for people with CF experiencing an acute pulmonary exacerbation						
Scale from: 0 to 100. Follow-up: 21 days	predicted in the hospital care group was 7	the home care groups was 3 lower (13.61 lower to 7.61 higher)			very low[2,3]	
Lung function: change in FEV_1 % predicted Scale from: 0 to 100. Follow-up: mean 18 days	The mean change in FEV_1 % predicted in the hospital care group was 12.3[c]	The mean change in FEV 1 % predicted in the home care groups was 5.60 lower (12.29 lower to 1.09 higher) [a]		63[b] (Donati 1987	⨁⊖⊖⊖ very low[4]	
Lung function: change in FEV_1 % predicted Scale from: 0 to 100. Follow-up: 15 days	The mean change in FEV_1 % predicted in the hospital care group was 5.1	The mean change in FEV 1 % predicted in the intervention groups was 3.1 lower (6.93 lower to 0.73 higher)		30[d] (Esmond 2006)	⨁⊖⊖⊖ very low[4,5]	
Patients starting next course of antibiotics more than 12 weeks after completing the previous course (proxy outcome for time to next exacerbation) Follow-up: mean 18 days	875 per 1000	481 per 1000 (315 to 726)	RR 0.55 (0.36 to 0.83)	59[e] (Bosworth 1997)	⨁⊖⊖⊖ very low[6]	
Weight change (kg) Follow-up: mean 18 days	The mean weight change in the hospital care group was 1.6 [c]	The mean weight in the home care groups was 1.10 lower (4.29 lower to 2.09 higher) [a]		74[b] (Donati 1987)	⨁⊖⊖⊖ very low[6]	
Weight change (kg) Follow-up: 10 days post treatment	The mean weight change in the hospital care group was 0.7	The mean weight change (kg) in the home care groups was 0.5 lower (8.06 lower to 7.06 higher)		31[a] (Wolter 1994)	⨁⊖⊖⊖ very low[7]	
BMI change Follow-up: 15 days	The mean BMI change in the hospital care group was 0.7	The mean BMI change in the home care groups was 0.2 lower (0.63 lower to 0.23 higher)		30[d] (Esmond 2006)	⨁⊖⊖⊖ very low[5,6]	

Comparison 1.1. Home care compared to hospital care for the administration of IV antibiotics for people with CF experiencing an acute pulmonary exacerbation						
Change in quality of life - CF-QOL-Physical. Scale from: 0 to 100. Follow-up: 15 days	The mean change in CF-QOL-physical in the hospital care group was 12.2	The mean change in CF-QOL-physical in the home care groups was 2.2 lower (13.21 lower to 8.81 higher)		30[d] (Esmond 2006)	⨁⊖⊖⊖ very low[3,5 f]	
Change in quality of life - CF-QOL-Social. Scale from: 0 to 100. Follow-up: 15 days	The mean change in CF-QOL-social in the hospital care group was 6.4	The mean change in CF-QOL-social in the home care groups was 3.4 lower (18.87 lower to 12.07 higher)		30[d] (Esmond 2006)	⨁⊖⊖⊖ very low[3,5, f]	
Change in quality of life - CF-QOL-Treatment. Scale from: 0 to 100. Follow-up: 15 days	The mean change in CF-QOL-treatment in the hospital care group was 8.2	The mean change in CF-QOL-treatment in the home care groups was 2 lower (17.15 lower to 13.15 higher)		30[d] (Esmond 2006)	⨁⊖⊖⊖ very low[3,5, f]	
Change in quality of life - CF-QOL-Symptoms. Scale from: 0 to 100. Follow-up: 15 days	The mean change in CF-QOL-symptoms in the hospital care group was 23.3	The mean change in CF-QOL-symptoms in the home care groups was 17.1 lower (31.25 to 2.95 lower)		30[d] (Esmond 2006)	⨁⊖⊖⊖ very low[4,5, f]	
Change in quality of life - CF-QOL-Emotional. Scale from: 0 to 100. Follow-up: 15 days	The mean change in CF-QOL-emotional in the hospital care group was 8.3	The mean change in CF-QOL-emotional in the home care groups was 4.2 higher (8.67 lower to 17.07 higher)		30[d] (Esmond 2006)	⨁⊖⊖⊖ very low[3,5, f]	
Change in quality of life - CF-QOL-Future. Scale from: 0 to 100. Follow-up: 15 days	The mean change in the hospital care group was 9.3	The mean change in CF-QOL-future in the home care groups was 5.5 lower (17.96 lower to 6.96 higher)		30[d] (Esmond 2006)	⨁⊖⊖⊖ very low[3,5, f]	
Change in quality of life - CF-QOL-Relationships. Scale from: 0 to 100. Follow-up: 15 days	The mean change in CF-QOL-relationships in the hospital care group was -0.5	The mean change in CF-QOL-relationships in the home care groups was 7.4 higher		30[d] (Esmond 2006)	⨁⊖⊖⊖ very low[3,5, f]	

Comparison 1.1. Home care compared to hospital care for the administration of IV antibiotics for people with CF experiencing an acute pulmonary exacerbation						
		(5.6 lower to 20.4 higher)				
Change in quality of life - CF-QOL-Body image. Scale from: 0 to 100. Follow-up: 15 days	The mean change in CF-QOL-body image in the hospital care group was 1.8	The mean change in CF-QOL-body image in the home care groups was 0.9 higher (13.92 lower to 15.72 higher)		30[d] (Esmond 2006)	⊕⊖⊖⊖ very low[3,5, f]	
Change in quality of life - CF-QOL-Career. Scale from: 0 to 100. Follow-up: 15 days	The mean change in CF-QOL-career in the hospital care group was 1.7	The mean change in CF-QOL-career in the home care groups was 8.3 higher (5.76 lower to 22.36 higher)		30[d] (Esmond 2006)	⊕⊖⊖⊖ very low[3,5, f]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: BMI: body mass index; CI: confidence interval; CF: cystic fibrosis; CF-QOL: cystic fibrosis quality of life questionnaire; FEV_1: forced expiratory volume in 1 second; IV: intravenous; MD: mean difference; RR: risk ratio

1 Cross-over trial
2 The quality of the evidence was downgraded by 1 as this is an open-label study
3 The quality of the evidence was downgraded by 2 because the 95% CI crosses 2 clinical MIDs.
4 The quality of the evidence was downgraded by 1 because the 95% CI crosses 1 clinical MID
5 The quality of the evidence was downgraded by 1 as there is a high-risk of bias in relation to the comparability of the groups
6 The quality of the evidence was downgraded by 1 because the 95% CI crosses 1 default MID
7 The quality of the evidence was downgraded by 2 because the 95% CI crosses 2 default MIDs
a Number of people in each group not reported
b Number of people included in the analysis in each group unclear
c The mean difference was calculated by the NGA technical team after calculating mean change and related SD in each group using the mean and SE at baseline and follow-up and assuming a correlation of 0.75
d There were 15 people in each group, but the total N of people is 28. Two people had both home care and hospital care.
e There were 19 people in the home group, 21 people in the hospital group (40 in total)
f Imprecision for quality of life was assessed using a clinical MID of 5 because the study by Esmond et al. used the CF-QOL questionnaire (Gee et al.2000)

Table 33: Summary clinical evidence profile: comparison 1.2. Home versus hospital care for the administration of IV antibiotics in people with CF and chronic pulmonary infection with *P aeruginosa*

Comparison 1.2 Home versus hospital care for the administration of IV antibiotics for people with CF and chronic pulmonary infection						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Treatments (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Hospital care for the administration of IV antibiotics	Home care for the administration of IV antibiotics				

Comparison 1.2 Home versus hospital care for the administration of IV antibiotics for people with CF and chronic pulmonary infection						
Lung function: Change in FEV_1 % predicted Scale from: 0 to 100. Follow-up: 14 days	The mean change in the hospital care group was 6	The mean change in FEV_1 in the home care groups was 2 higher (9.81 lower to 13.81 higher)		56[a] (Riethmueller 2002)	⊕⊖⊖⊖ very low[1,2]	
Nutritional status: change in weight (kg) Follow-up: 14 days	The mean change in the hospital care group was 1.1	The mean change in weight in the home care groups was 0 higher (4.38 lower to 4.38 higher)		57[a] (Riethmueller 2002)	⊕⊖⊖⊖ very low[1,3]	
Nutritional status: change in weight for height (%) Follow-up: 14 days	The mean change in the hospital care group was 4	The mean change in weight for height (%) in the home care groups was 1 lower (4.64 lower to 2.64 higher)		57[a] (Riethmueller 2002)	⊕⊖⊖⊖ very low[1,4]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: CI: confidence interval; CF: cystic fibrosisFEV_1: forced expiratory volume in 1 second; IV: intravenous; MD: mean difference

1 The quality of the evidence was downgraded by 1 due to high risk of bias in relation to the comparability of the groups
2 The quality of the evidence was downgraded by 2 because the 95% CI crosses 2 clinical MIDs
3 The quality of the evidence was downgraded by 2 because the 95% CI crosses 2 default MIDs
4 The quality of the evidence was downgraded by 1 because the 95% CI crosses 1 default MID
a Number of people included in the analysis in each group unclear

7.1.4.2 CF centre care

Table 34: Summary clinical evidence profile: Comparison 2.1. CF centre care versus shared care (care by non-specialist in CF)

Comparison 2.1. CF centre care compared to shared care (UK equivalent) for people with CF						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Shared care (UK equivalent)	CF centre care				
Change in FEV_1 % predicted. Scale from: 0 to 100. Follow-up: 1 year	The mean change in FEV_1 % predicted in the shared care group was -2.4	The mean change in FEV_1 % predicted in the CF centre care groups was 0.5 lower (3.05 lower to 2.05 higher)		82 (Van Koolwijk 2002)	⊕⊖⊖⊖ very low[1]	

Comparison 2.1. CF centre care compared to shared care (UK equivalent) for people with CF						
First to last FEV_1 (% per year) Scale from: 0 to 100. Follow-up: 3 years	The mean first to last FEV_1 (% per year) in the shared care group was 1	The mean first to last FEV_1 (% per year) in the CF centre care groups was 2.4 lower (5.72 lower to 0.92 higher)		97 (Thomas 2008)	⊕⊖⊖⊖ very low[2,3]	
Slope FEV_1 (% per year) Scale from: 0 to 100. Follow-up: 3 years	The mean slope FEV_1 (% per year) in the shared care group was 0.7	The mean slope FEV_1 (% per year) in the CF centre care groups was 2.2 lower (5.37 lower to 0.97 higher)		97 (Thomas 2008)	⊕⊖⊖⊖ very low[2,3]	
Change in BMI Follow-up: 1 year	The mean change in BMI in the shared care group was 0.54	The mean BMI in the CF centre care groups was 0.12 lower (0.44 lower to 0.2 higher)		82 (Van Koolwijk 2002)	⊕⊖⊖⊖ very low[1]	
Quality of life: CFQ-Teen - Physical Scale from: 0 to 100.	The mean CF-QOL teen - physical in the control shared care was 90.4	The mean CF-QOL teen - physical in the CF centre care groups was 17.8 lower (30.28 to 5.32 lower)		34 (Thomas 2006)	⊕⊖⊖⊖ very low3,4 , a	
Quality of life: CFQ-Teen - Role Scale from: 0 to 100.	The mean CF-QOL teen - role in the shared care group was 86.6	The mean CF-QOL teen - role in the CF centre care groups was 10.4 lower (26.45 lower to 5.65 higher)		34 (Thomas 2006)	⊕⊖⊖⊖ very low[3, 4, a]	
Quality of life: CFQ-Teen - Vitality Scale from: 0 to 100.	The mean CF-QOL teen - vitality in the shared care group was 74.2	The mean CF-QOL teen - vitality in the CF centre care groups was 18.2 lower (32.5 to 3.9 lower)		34 (Thomas 2006)	⊕⊖⊖⊖ very low[3, 4, a]	
Quality of life: CFQ-Teen - Emotional Scale from: 0 to 100.	The mean CF-QOL teen - emotional in the shared care group was 82.7	The mean CF-QOL teen - emotional in the CF centre care groups was 5.5 lower (18.35 lower to 7.35 higher)		34 (Thomas 2006)	⊕⊖⊖⊖ very low[3, 4, a]	
Quality of life: CFQ-Teen - Social	The mean CF-QOL teen - social in the	The mean CF-QOL teen - social in the CF centre care groups was		34 (Thomas 2006)	⊕⊖⊖⊖ very low[3, 4, a]	

Comparison 2.1. CF centre care compared to shared care (UK equivalent) for people with CF						
Scale from: 0 to 100.	shared care group was 94	17.6 lower (26.71 to 8.49 lower)				
Quality of life: CFQ-Teen - Body Scale from: 0 to 100.	The mean CF-QOL teen - body in the shared care group was 76.7	The mean CF-QOL teen - body in the CF centre care groups was 4.5 lower (21.56 lower to 12.56 higher)		34 (Thomas 2006)	⊕⊖⊖⊖ very low[5, 4,a]	
Quality of life: CFQ-Teen - Eating Scale from: 0 to 100.	The mean CF-QOL teen - eating in the shared care group was 76.7	The mean CF-QOL teen - eating in the CF centre care groups was 4.5 lower (21.56 lower to 12.56 higher)		34 (Thomas 2006)	⊕⊖⊖⊖ very low[5, 4, a]	
Quality of life: CFQ-Teen - TB Scale from: 0 to 100.	The mean CF-QOL teen - TB in the shared care group was 65.6	The mean CF-QOL teen - TB in the CF centre care groups was 9.6 lower (28.01 lower to 8.81 higher)		34 (Thomas 2006)	⊕⊖⊖⊖ very low[5, 4, a]	
Quality of life: CFQ-Teen - Health Scale from: 0 to 100.	The mean CF-QOL teen - health in the shared care group was 72.2	The mean CF-QOL teen - health in the CF centre care groups was 14.8 lower (31.75 lower to 2.15 higher)		34 (Thomas 2006)	⊕⊖⊖⊖ very low[3,5, a]	
Quality of life: CFQ-Teen - Weight Scale from: 0 to 100.	The mean CF-QOL teen - weight in the shared care group was 72.2	The mean CF-QOL teen - weight in the CF centre care groups was 12.5 lower (29.45 lower to 4.45 higher)		34 (Thomas 2006)	⊕⊖⊖⊖ very low[3,5, a]	
Quality of life: CFQ-Teen - Respiratory Scale from: 0 to 100.	The mean CF-QOL teen - respiratory in the shared care group was 72.8	The mean CF-QOL teen - respiratory in the CF centre care groups was 4.5 lower (15.25 lower to 6.25 higher)		34 (Thomas 2006)	⊕⊖⊖⊖ very low[3, 4, a]	
Quality of life: CFQ-Teen - Digestion Scale from: 0 to 100.	The mean CF-QOL teen - digestion in the shared care group was 92.2	The mean CF-QOL teen - digestion in the CF centre care groups was 7.9 lower (17.14 lower to 1.34 higher)		34 (Thomas 2006)	⊕⊖⊖⊖ very low[3, 4, a]	

Comparison 2.1. CF centre care compared to shared care (UK equivalent) for people with CF						
Quality of life: CFQ-Child - Physical Scale from: 0 to 100.	The mean CF-QOL child - physical in the shared care group was 77.2	The mean CF-QOL child - physical in the CF centre care groups was 1.2 lower (10.97 lower to 8.57 higher)		83 (Thomas 2006)	⨁⊖⊖⊖ very low[5, 4, a]	
Quality of life: CFQ-Child - - Emotional Scale from: 0 to 100.	The mean CF-QOL child - emotional in the shared care group was 74.8	The mean CF-QOL child - emotional in the CF centre care groups was 1.3 higher (5.13 lower to 7.73 higher)		83 (Thomas 2006)	⨁⊖⊖⊖ very low[4, a]	
Quality of life: CFQ-Child - - Social Scale from: 0 to 100.	The mean CF-QOL child - social in the shared care group was 71.9	The mean CF-QOL child - social in the CF centre care groups was 1.7 lower (9.46 lower to 6.06 higher)		83 (Thomas 2006)	⨁⊖⊖⊖ very low[3, 4, a]	
Quality of life: CFQ-Child - - Body Scale from: 0 to 100.	The mean CF-QOL child - body in the shared care group was 81.1	The mean CF-QOL child - body in the CF centre care groups was 2.8 lower (13.64 lower to 8.04 higher)		83 (Thomas 2006)	⨁⊖⊖⊖ very low[3, 4, a]	
Quality of life: CFQ-Child - - Eating Scale from: 0 to 100.	The mean score in the shared care group was 76.6	The mean CF-QOL child - eating in the CF centre care groups was 0.5 lower (11.94 lower to 10.94 higher)		83 (Thomas 2006)	⨁⊖⊖⊖ very low[5, 4, a]	
Quality of life: CFQ-Child - - TB Scale from: 0 to 100.	The mean CF-QOL child - TB in the shared care group was 63.7	The mean CF-QOL child – TB in the CF centre care groups was 4.7 higher (5.88 lower to 15.28 higher)		83 (Thomas 2006)	⨁⊖⊖⊖ very low[3, 4, a]	
Quality of life: CFQ-Child - - Respiratory Scale from: 0 to 100.	The mean CF-QOL child - respiratory in the shared care group was 66.9	The mean CF-QOL child - respiratory in the CF centre care groups was 3.9 higher (5.69 lower to 13.49 higher)		83 (Thomas 2006)	⨁⊖⊖⊖ very low[3, 4, a]	
Quality of life:	The mean CF-QOL child - digestion in	The mean CF-QOL child - digestion in the		83 (Thomas 2006)	⨁⊖⊖⊖ very low[3, 4, a]	

Comparison 2.1. CF centre care compared to shared care (UK equivalent) for people with CF						
CFQ-Child - - Digestion Scale from: 0 to 100.	the shared care group was 72.1	CF centre care groups was 4 higher (8.38 lower to 16.38 higher)				
Quality of life: CFQ-Parent - Physical Scale from: 0 to 100.	The mean CF-QOL parent - physical in the shared care group was 71.7	The mean CF-QOL parent - physical in the CF centre care groups was 2.5 higher (6.96 lower to 11.96 higher)		80 (Thomas 2006)	⊕⊖⊖⊖ very low[3, 4, a]	
Quality of life: CFQ-Parent - Vitality Scale from: 0 to 100.	The mean CF-QOL parent - vitality in the shared care group was 65	The mean CF-QOL parent - vitality in the CF centre care groups was 0.7 lower (7.78 lower to 6.38 higher)		80 (Thomas 2006)	⊕⊖⊖⊖ very low[4, a]	
Quality of life: CFQ-Parent - Emotional Scale from: 0 to 100.	The mean CF-QOL parent - emotional in the shared care group was 75	The mean CF-QOL parent - emotional in the CF centre care groups was 1.1 higher (7.52 lower to 9.72 higher)		80 (Thomas 2006)	⊕⊖⊖⊖ very low[3, 4, a]	
Quality of life: CFQ-Parent - Body Scale from: 0 to 100.	The mean CF-QOL parent - body in the shared care group was 69.2	The mean CF-QOL parent - body in the CF centre care groups was 3 higher (9.12 lower to 15.12 higher)		80 (Thomas 2006)	⊕⊖⊖⊖ very low[5, 4, a]	
Quality of life: CFQ-Parent - Eating Scale from: 0 to 100.	The mean CF-QOL parent - eating in the shared care group was 70.5	The mean CF-QOL parent - eating in the CF centre care groups was 7.5 lower (20.22 lower to 5.22 higher)		80 (Thomas 2006)	⊕⊖⊖⊖ very low[3, 4, a]	
Quality of life: CFQ-Parent - TB Scale from: 0 to 100.	The mean CF-QOL parent - TB in the control group was 51.4	The mean CF-QOL parent - TB in the CF centre care groups was 6.2 lower (14.63 lower to 2.23 higher)		80 (Thomas 2006)	⊕⊖⊖⊖ very low[3, 4, a]	
Quality of life: CFQ-Parent - Health	The mean CF-QOL parent - health in the	The mean CF-QOL parent - health in the CF centre care groups was 1.1 higher		80 (Thomas 2006)	⊕⊖⊖⊖ very low[3, 4, a]	

Comparison 2.1. CF centre care compared to shared care (UK equivalent) for people with CF						
Scale from: 0 to 100.	shared care group was 68.3	(8.6 lower to 10.8 higher)				
Quality of life: CFQ-Parent - Weight Scale from: 0 to 100.	The mean CF-QOL parent - weight in the shared care group was 57.1	The mean CF-QOL parent - weight in the CF centre care groups was 0.8 lower (16.4 lower to 14.8 higher)		80 (Thomas 2006)	⊕⊖⊖⊖ very low[5, 4, a]	
Quality of life: CFQ-Parent - Respiratory Scale from: 0 to 100.	The mean CF-QOL parent - respiratory in the shared care group was 74.8	The mean CF-QOL parent - respiratory in the CF centre care groups was 0.5 lower (10.33 lower to 9.33 higher)		80 (Thomas 2006)	⊕⊖⊖⊖ very low[5, 4, a]	
Quality of life: CFQ-Parent - Digestion Scale from: 0 to 100.	The mean CF-QOL parent - digestion in the shared care group was 77.1	The mean CF-QOL parent - digestion in the CF centre care groups was 0.6 lower (8.76 lower to 7.56 higher)		80 (Thomas 2006)	⊕⊖⊖⊖ very low[3, 4, a]	
Quality of life: CFQ-Parent - School function Scale from: 0 to 100.	The mean score in the share care group was 65.1	The mean CF-QOL parent - school function in the CF centre care groups was 0.60 lower (11.63 lower to 10.43 higher)		80 (Thomas 2006)	⊕⊖⊖⊖ very low[5, 4, a]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: BMI: body mass index; CI: confidence interval; CF: cystic fibrosis; CFQ: cystic fibrosis questionnaire; FEV_1: forced expiratory volume in 1 second; IV: intravenous; MD: mean difference

1 The quality of the evidence was downgraded by 2 because of the differences between groups.
2 The quality of the evidence was downgraded by 2 due to high risk of bias in relation to the selection of the population and high loss to follow-up
3 The quality of the evidence was downgraded by 1 as the 95% CI crosses 1 clinical MID
4 The quality of the study was downgraded by 2 due to high risk of bias in relation to comparability of the groups, and significant differences at follow-up between groups
5 The quality of the evidence was downgraded by 2 as the 95% CI crosses 2 clinical MIDs
a Imprecision for quality of life was assessed using a clinical MID of 8.5 because the paper by Thomas et al. uses the CFQ- Teen, CFQ-Child and CFQ-Parent (Quittner et al. 2005)
** CFQ-Teen: data not available for the following domain: school function*
*** CFQ-Child: data no reported for the following domains: role, vitality, health and weight; data not available for school function*
**** CFQ-Parent: data no reported for the following domains: role and social*

Table 35: Summary clinical evidence profile: Comparison 2.2. CF centre care versus local care (below CF Trust recommendations)

Comparison 2.2. CF Centre compared to Local care (below CF Trust recs) for people with CF						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Local care (below CF Trust recs)	CF Centre				
Change in lung function: FEV_1 % predicted Scale from: 0 to 100. Follow-up: 1 year	The mean change in FEV_1% predicted in the local care group was -5.6	The mean change in FEV_1 % predicted in the CF centre groups was 2.7 higher (0.55 lower to 5.95 higher)		64 (Van Koolwijk 2002)	⊕⊖⊖⊖ very low[1,2]	
Lung function: First to last FEV_1 (% per year) Scale from: 0 to 100. Follow-up: 3 years	The mean first to last FEV_1 (% per year) in the local care group was 4.3	The mean first to last FEV_1 (% per year) in the CF centre groups was 5.7 lower (10.99 to 0.41 lower)		78 (Thomas 2008)	⊕⊖⊖⊖ very low[2,3]	
Slope FEV_1 (% per year) Scale from: 0 to 100. Follow-up: 3 years	The mean slope FEV_1 (% per year) in the local care group was 1.8	The mean slope FEV_1 (% per year) in the CF centre groups was 3.3 lower (6.13 to 0.47 lower)		78 (Thomas 2008)	⊕⊖⊖⊖ very low[2,3]	
Change in BMI Follow-up: 1 year	The mean BMI change in the local care group was 0.51	The mean BMI change in the CF centre groups was 0.09 lower (0.42 lower to 0.24 higher)		64 (Van Koolwijk 2002)	⊕⊖⊖⊖ very low[1]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: BMI: body mass index; CI: confidence interval; CF: cystic fibrosis; FEV_1: forced expiratory volume in 1 second; IV: intravenous; MD: mean difference

1 The quality of the evidence was downgraded by 2 because of the differences between groups.
2 The quality of the evidence was downgraded by 1 because the 95% CI crosses 1 clinical MID
3 The quality of the evidence was downgraded by 2 due to high risk of bias in relation to the selection of the population and high loss to follow-up

Table 36: Summary clinical evidence profile: Comparison 2.3. CF centre care versus general clinic (non-CF)

Comparison 2.3. CF specialist clinic compared to general (not CF) clinic for people with CF					
Outcomes	Illustrative comparative risks* (95% CI)			Quality of the	Comments

Comparison 2.3. CF specialist clinic compared to general (not CF) clinic for people with CF						
	Assumed risk	Corresponding risk	Relative effect (95% CI)	No of Participants (studies)	evidence (GRADE)	
	General (not CF) clinic	CF specialist clinic				
Patient satisfaction with care overall	The overall patient satisfaction rating in the general clinic group was 4.20	The overall patient satisfaction rating in the CF specialist clinic group was 3.76	0.44 higher (0.29 higher to 0.58 higher)	686 (Walters 1994)	⊕⊖⊖⊖ very low[1]	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Abbreviations: CI: confidence interval; CF: cystic fibrosis; MD: mean difference						

1 The quality of the evidence was downgraded by 1 because the authors did not control the analysis for any of the confounding factors

7.1.4.3 Shared care

Table 37: Summary clinical evidence profile: Comparison 3.1. Local care (below CF Trust recs) compared to shared care (UK equivalent)

Comparison 3.1. Local care (below CF Trust recs) compared to shared care (UK equivalent) for people with CF						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Shared care (UK equivalent)	Local care (below CF Trust recs)				
Change in lung function: FEV_1 % predicted Scale from: 0 to 100. Follow-up: 1 year	The mean change in FEV_1% predicted in the shared care group was -2.4	The mean change in FEV_1 % predicted in the local care groups was 3.2 lower (6.84 lower to 0.44 higher)		64 (Van Koolwijk 2002)	⊕⊖⊖⊖ very low[1,2]	
First to last FEV_1 (% per year) Scale from: 0 to 100. Follow-up: 3 years	The mean first to last FEV_1 (% per year) in the shared care group was 1	The mean first to last FEV_1 (% per year) in the local care groups was 3.3 higher (2.59 lower to 9.19 higher)		41 (Thomas 2008)	⊕⊖⊖⊖ very low[2,3]	
Slope FEV_1 (% per year)	The mean slope FEV_1 (% per year) in	The mean slope FEV_1 (% per year) in the local care		41 (Thomas 2008)	⊕⊖⊖⊖ very low[3]	

Comparison 3.1. Local care (below CF Trust recs) compared to shared care (UK equivalent) for people with CF						
Scale from: 0 to 100. Follow-up: 3 years	the shared care group was 0.7	groups was 1.1 higher (2.69 lower to 4.89 higher)				
Change in BMI Follow-up: 1 year	The mean BMI change in the shared care group was 0.54	The mean BMI change in the local care groups was 0.03 lower (0.43 lower to 0.37 higher)		64 (Van Koolwijk 2002)	⊕⊖⊖⊖ very low[1]	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval;						

1 The quality of the evidence was downgraded by 2 because of the differences between groups.
2 The quality of the evidence was downgraded by 1 because the 95% CI crosses 1 clinical MID
3 The quality of the evidence was downgraded by 2 due to high risk of bias in relation to the selection of the population and high loss to follow-up

Table 38: Summary clinical evidence profile: Comparison 3.2. Shared care (above UK equivalent) compared to shared care (UK equivalent) for people with CF

Comparison 3.2. Shared care (above UK equivalent) compared to shared care (UK equivalent) for people with CF						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Shared care (UK equivalent)	Shared care (above UK equivalent)				
Lung function: First to last FEV_1 (% per year) Scale from: 0 to 100. Follow-up: 3 years	The mean in first to last (% per year) FEV_1% in the shared care group was 1	The mean change first to last FEV_1 (% per year) in the shared care + groups was 0.5 lower (5.63 lower to 4.63 higher)		49 (Thomas 2008)	⊕⊖⊖⊖ very low[1,2,3]	
Lung function: Slope FEV_1 (% per year) Scale from: 0 to 100. Follow-up: 3 years	The mean slope FEV_1 (% per year) in the shared care group was 0.7	The mean slope FEV_1 (% per year) in the shared care + groups was 2.1 lower (6.52 lower to 2.32 higher)		49 (Thomas 2008)	⊕⊖⊖⊖ very low[1,2,3]	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Abbreviations: CI: confidence interval; CF: cystic fibrosis; FEV_1: forced expiratory volume in 1 second; MD: mean difference						

1 The quality of the evidence was downgraded by 2 due to high risk of bias in relation to the selection of the population and high loss to follow-up

2 The quality of the evidence was downgraded by 1 because 1 of the comparators is not representative of current UK practice
3 The quality of the evidence was downgraded by 1 because the 95% CI crosses 1 clinical MID

7.1.4.4 Telemedicine

Table 39: Summary clinical evidence profile: Comparison 4.1. Home monitoring programme + diary recording versus usual care

Comparison 4.1. Home monitoring program with diary and usual care compared to usual care for people with CF						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Usual care	Home monitoring program with diary and usual care				
Change in FEV 1 (% predicted). Scale from: 0 to 100. Follow-up: 4 years	The mean FEV_1 % predicted in the usual care group was 11.5	The mean FEV_1 (% predicted) in the home monitoring groups was 8 lower (17.01 lower to 1.01 higher)		50 (Finkelstein 1992)	⊕⊖⊖⊖ very low[1,2]	
**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).* *Abbreviations: CI: confidence interval; CF: cystic fibrosis; FEV_1: forced expiratory volume in 1 second; MD: mean difference*						

1 The quality of the evidence was downgraded by 1 due lo unclear comparability between groups
2 The quality of the evidence was downgraded by 1 because the 95% CI crosses 1 clinical MID

Table 40: Summary clinical evidence profile: Comparison 4.2. Telemedicine versus usual care

Comparison 4.2. Telemedicine compared to standard care for people with CF						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Standard care	Telemedicine				
Change in quality of life – CF-QOL. Scale from: 0 to 100. Follow-up: 6 months	Not reported	The mean in CQ-QOL body in the intervention groups was not reported There was a significant improvement at 6 months, p=0.02		7 (Wilkinson 2008)	⊕⊖⊖⊖ very low[1]	The study does not report on differences between groups.
**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).* *Abbreviations: CI: confidence interval; CFQOL: cystic fibrosis quality of life questionnaire*						

1 The quality of the evidence was downgraded by 2 because of incomplete reporting and high-loss to follow-up

7.1.5 Economic evidence

Three economic evaluations were identified that compared home-care IV antibiotic therapy to hospital IV antibiotic therapy. Wolter 1998 conducted a cost–consequence analysis in Australia based on a, RCT that included 17 adult patients, whilst Thornton 2005 and Elliott 2005 performed a cost-effectiveness analysis and cost-benefit analysis, respectively, using the same data collected retrospectively from 116 adults with cystic fibrosis at The Manchester Adult CF Unit. The methods and results of these studies are described in more detail in Appendix K.

Full details of the search and economic article selection flow chart can be found in Appendix E and F, respectively. Data extraction tables and quality assessments of included studies can be found in Appendix L and M, respectively.

This review question was not prioritised for de novo economic modelling. To aid consideration of cost-effectiveness a costing tool that utilised a "what-if" approach was developed to estimate the annual cost per patient per model of care for a given MDT composition. The methods and results of this analysis are reported in Appendix K. The results are reproduced in Table 41 for ease of reference, where the cheapest model of care is the Specialist Centre (£9,247) followed by Outreach Care (£10,126) and Shared Care (n=150, £14,440; n=250, £13,220).

Table 41: Annual cost across the recognised models of care [a]

Model of care	Clinic size [b]	Annual travel costs incurred by the Specialist Centre MDT	Annual MDT staff costs	Total annual cost/ clinic	Total annual cost/ person
Specialist Centre	250	None	£2,311,670 (Specialist Centre MDT)	£2,311,670	£9,247
Shared Care	250	£11,760 (25 days of travel totalling 3,000 miles @ 56p/ mile for 7 HCPs)	£1,384,445 (paediatric Shared Care MDT for 150 people) + £1,895,215(Specialist Centre for 250 people[c]) + £13,567 (0.5 administrator)	£3,304,987	£13,220
Shared Care	150	£6,115 (13 days of travel totalling 1,560 miles @ 56p/ mile for 7 HCPs)	£747,951 (paediatric Shared Care MDT for 75 people) + £1,398,431 (Specialist Centre for 150 people[c]) + £13,567 (0.5 administrator)	£2,166,064	£14,440
Outreach Care	1	£627 (1 day of travel totalling 160 miles @ 56p/ miles for 7 HCPs) shared by 2 people	£9,247 (Specialist Centre MDT divided by a clinic size of 250) + £60 (administrator, 0.5 days) + £440 (capital costs, 0.5 days)	NC	£10,126

HCP, health care professional; NC, not calculable; MDT, multidisciplinary team

(a) Excluding diagnosis and treatment costs

(b) Number of people with cystic fibrosis managed by the model of care
(c) Using paediatric WTE figures, see Appendix K

7.1.6 Evidence statements

7.1.6.1 Home-based care

7.1.6.1.1 Comparison 1.1. Home versus hospital care for the administration of IV antibiotics in people with cystic fibrosis experiencing an acute pulmonary exacerbation

Lung function: FEV_1

Very low quality evidence from 1 RCT demonstrated no clinically significant difference in lung function (measured as a change in FEV_1 % predicted) following 31 admissions of 17 adults with cystic fibrosis who received IV antibiotic treatment at home or within hospital for the treatment of an acute pulmonary exacerbation at 21 days follow-up.

Very low quality data from 1 prospective cohort study of 63 IV antibiotic treatments of people with cystic fibrosis aged ≥ 12 years found no clinically significant difference in lung function (measured as a change in FEV_1% predicted) at 18 days following IV antibiotic treatment at home and in hospital for the treatment of acute pulmonary exacerbation. The number of people included in the analysis was not reported.

Very low quality evidence from 1 prospective cohort study of 30 IV antibiotic treatments in 28 adults with cystic fibrosis showed that there was no clinically significant difference in lung function (measured as change in FEV_1 % predicted) at 15 days following home IV antibiotic treatment (with self-performed chest physiotherapy) compared with hospital administered IV antibiotic treatment with chest physiotherapy performed by experienced respiratory physiotherapists.

Mortality

No evidence was found for this critical outcome.

Patient and carer satisfaction

No evidence was found for this critical outcome.

Lung function: LCI

No evidence was found for this important outcome.

Time to next pulmonary exacerbation

Very low quality evidence from 1 prospective cohort study of 59 IV antibiotic treatments in 40 children, young people and adults with cystic fibrosis aged ≥ 8 years receiving IV antibiotics for acute pulmonary exacerbations identified that more patients treated in hospital did not require a further course of antibiotics at 12 weeks compared to those receiving antibiotics at home and this represents a clinically significant benefit.

Nutritional status

Very low quality evidence from 1 prospective cohort study of 74 antibiotic treatments in people with cystic fibrosis aged ≥12 years found no clinically significant difference in weight (measured as a change in kg) following IV antibiotic treatment at home and in hospital for the treatment of acute pulmonary exacerbation at 18 days follow-up. The number of people included in the analysis was not reported.

Very low quality evidence from 1 RCT of 31 admissions with 17 adults with cystic fibrosis found that at 10 days following treatment, there was no clinically significant difference in weight change between those who received IV antibiotics at home compared to those receiving IV antibiotics in hospital

Very low quality evidence from 1 prospective cohort study of 30 IV antibiotic courses for the treatment of an acute respiratory exacerbation in 28 adults with cystic fibrosis showed no clinically significant difference in BMI between the participants receiving therapy at home or in the hospital at 15 days follow-up.

Quality of life

Very low quality evidence from 1 prospective cohort study of 30 IV antibiotic courses for the treatment of acute respiratory exacerbations in 28 adults with cystic fibrosis showed no clinically significant difference in relation to the quality of life (measured as change in the CF-QOL domains – physical, social, treatment, emotional, future, relationships, body image and career) between the participants receiving therapy at home or at hospital at 15 days follow-up. The same evidence found a clinically significant lower score in quality of life (measured as a change in the domain CF-QOL – symptoms) in the group of participants receiving therapy at home compared to those receiving therapy in the hospital at 15 days follow-up.

Frequency of cross-infection

No evidence was found for this important outcome.

Staff experience

No evidence was found for this important outcome.

Adherence to treatment

No evidence was found for this important outcome.

7.1.6.1.2 Comparison 1.2: home versus hospital care for the administration of IV antibiotics in people with cystic fibrosis and chronic pulmonary infection with P aeruginosa

Lung function: FEV_1

Very low quality evidence from 1 prospective cohort study of 56 courses of IV antibiotics for the treatment of chronic pulmonary infection with *P aeruginosa* in children, young people and adults with cystic fibrosis showed no clinically significant difference in lung function (measured as change in FEV_1 % predicted) between receiving therapy at home or at hospital at 14 days follow-up. The number of people included in the analysis was not reported.

Mortality

No evidence was found for this critical outcome.

Patient and carer satisfaction

No evidence was found for this critical outcome.

Lung function: LCI

No evidence was found for this important outcome.

Time to next pulmonary exacerbation

No evidence was found for this important outcome.

Nutritional status

Very low quality evidence from 1 prospective cohort study of 57 courses of IV antibiotics in children, young people and adults with cystic fibrosis for the treatment of chronic pulmonary infection with *P aeruginosa* showed no clinically significant difference in nutritional status (measured as change in kg or as weight/ height %) between receiving therapy home or at hospital at 14 days follow-up. The number of people included in the analysis was not reported.

Quality of life

No evidence was found for this important outcome.

Frequency of cross-infection

No evidence was found for this important outcome.

Staff experience

No evidence was found for this important outcome.

Adherence to treatment

No evidence was found for this important outcome.

7.1.6.2 Cystic fibrosis centre care

7.1.6.2.1 Comparison 2.1. Cystic fibrosis centre care versus shared care

Lung function: FEV_1

Very low quality evidence from 1 prospective cohort study with 82 children and young people with cystic fibrosis aged 5 to 17 years showed no clinically significant difference in lung function (measured as change in FEV% predicted) between the group of participants attending a cystic fibrosis centre and the participants receiving shared care at 1 year follow-up.

Very low quality evidence from 1 retrospective cohort study with 97 people with cystic fibrosis aged 0 to 20 years showed no clinically significant differences in lung function (measured as change from first to last FEV_1 % predicted per year and slope FEV_1% per year) between the group of participants attending a cystic fibrosis centre and the participants receiving shared care during the 3 years follow-up.

Mortality

No evidence was found for this critical outcome.

Patient and carer satisfaction

No evidence was found for this critical outcome.

Lung function: LCI

No evidence was found for this important outcome.

Time to next pulmonary exacerbation

No evidence was found for this important outcome.

Nutritional status: BMI

Very low quality evidence from 1 prospective cohort study with 82 children and young people with cystic fibrosis aged 5 to 17 years showed no clinically significant difference in the change in BMI between the group of participants attending a cystic fibrosis centre and the participants receiving shared care at 1 year follow-up.

Quality of life

Very low quality evidence from 1 cross-sectional study with 34 young people with cystic fibrosis showed a clinically significant lower score in the quality of life for the domains physical, vitality and social(measured with the CFQ-R Teen questionnaire) in the group of participants attending a cystic fibrosis centre compared to the group of participants receiving shared care. However, no clinically significant differences were found in the rest of the domains (role, emotional, body, eating, treatment burden, health, weight, respiratory and digestion).

Very low quality evidence from 1 cross-sectional study with 83 children with cystic fibrosis showed no clinically significant differences in the reported quality of life between the group of participants attending a cystic fibrosis centre and the group of participants receiving shared care (measured with the following CFQ-R child domains: physical, emotional, social, body, eating, treatment burden, respiratory and digestion).

Very low quality evidence from 1 cross-sectional study with 80 parents of people with cystic fibrosis showed no clinically significant differences in the parent-reported quality of life of their children between the group of participants attending a cystic fibrosis centre and the group of participants receiving shared care (measured with the following CFQ-R parents domains: physical, vitality, emotional, body, eating, treatment burden, health, weight, respiratory, digestion and school function).

Frequency of cross-infection

No evidence was found for this important outcome.

Staff experience

No evidence was found for this important outcome.

Adherence to treatment

No evidence was found for this important outcome.

7.1.6.2.2 Comparison 2.2. Cystic fibrosis centre care versus local care (below CF Trust recommendations)

Lung function: FEV_1

Very low quality evidence from 1 prospective cohort study with 63 children and young people with cystic fibrosis aged 5 to 17 years showed no clinically significant difference in lung function (measured as change in FEV_1 % predicted) between those receiving cystic fibrosis

centre care and participants receiving local care (only annual check-up at the cystic fibrosis centre) at 1 year follow-up.

Very low quality evidence from 1 retrospective cohort study with 78 children and young people with cystic fibrosis aged 0 to 20 years showed a clinically significant lower lung function (measured as change from first to last FEV_1% predicted per year) in the group of participants receiving cystic fibrosis centre care compared to those receiving local care (care by non-specialists in cystic fibrosis, with involvement by the cystic fibrosis centre once a year for some people) during the 3 years follow-up. However, the same evidence found no clinically significant difference in lung function (measured as slope FEV_1% predicted per year) between those receiving cystic fibrosis centre care and participants receiving local care during the 3 years follow-up.

Mortality

No evidence was found for this critical outcome.

Patient and carer satisfaction

No evidence was found for this critical outcome.

Lung function: LCI

No evidence was found for this important outcome.

Time to next pulmonary exacerbation

No evidence was found for this important outcome.

Nutritional status: BMI

Very low quality evidence from 1 prospective cohort study with 64 children and young people with cystic fibrosis aged 5 to 17 years showed no clinically significant difference in the change in BMI between those receiving cystic fibrosis centre care and the participants receiving local care (only annual check-up at the cystic fibrosis centre) at 1 year follow-up.

Quality of life

No evidence was found for this important outcome.

Frequency of cross-infection

No evidence was found for this important outcome.

Staff experience

No evidence was found for this important outcome.

Adherence to treatment

No evidence was found for this important outcome.

7.1.6.2.3 Comparison 2.3. Cystic fibrosis centre care versus general clinic (non-cystic fibrosis)

Lung function: FEV_1

No evidence was found for this critical outcome.

Mortality

No evidence was found for this critical outcome.

Patient and carer satisfaction

Very low quality evidence from 1 cross-sectional study with 686 people with cystic fibrosis aged ≥15 years showed a significant difference in overall patient satisfaction between the participants receiving cystic fibrosis centre care and the participants receiving usual care (care by non-specialists in cystic fibrosis). The clinical significance and the imprecision for this outcome could not be calculated.

Lung function: LCI

No evidence was found for this important outcome.

Time to next pulmonary exacerbation

No evidence was found for this important outcome.

Nutritional status: BMI

No evidence was found for this important outcome.

Quality of life

No evidence was found for this important outcome.

Frequency of cross-infection

No evidence was found for this important outcome.

Staff experience

No evidence was found for this important outcome.

Adherence to treatment

No evidence was found for this important outcome.

7.1.6.3 Shared care

7.1.6.3.1 Comparison 3.1. Local care (below CF Trust recommendations) versus shared care (UK equivalent)

Lung function: FEV_1

Very low quality evidence from 1 prospective cohort study with 64 children and young people with cystic fibrosis aged 5 to 17 years showed no clinically significant difference in lung function (measured as change in FEV_1 % predicted) between those receiving local care (below the standards recommended by the CF Trust) and the participants receiving shared care (as in current UK practice) at 1 year follow-up.

Very low quality evidence from 1 retrospective cohort study with 41 people with cystic fibrosis aged 0 to 20 years showed no clinically significant difference in lung function (measured as change from first to last FEV_1 % predicted per year and slope FEV_1% per year) between

those receiving local care (below the standards recommended by the CF Trust) and the participants receiving shared care (as in current UK practice) during the 3 years follow-up.

Mortality

No evidence was found for this critical outcome.

Patient and carer satisfaction

No evidence was found for this critical outcome.

Lung function: LCI

No evidence was found for this important outcome.

Time to next pulmonary exacerbation

No evidence was found for this important outcome.

Nutritional status: BMI

Very low quality evidence from 1 prospective cohort study with 64 children and young people with cystic fibrosis aged 5 to 17 years showed no clinically significant difference in the change in BMI between the participants receiving local care (below the standards recommended by the CF Trust) and the participants receiving shared care (as in current UK practice) at 1 year follow-up.

Quality of life

No evidence was found for this important outcome.

Frequency of cross-infection

No evidence was found for this important outcome.

Staff experience

No evidence was found for this important outcome.

Adherence to treatment

No evidence was found for this important outcome.

7.1.6.3.2 Comparison 3.2. Shared care (above UK equivalent) versus shared care (UK equivalent)

Lung function: FEV_1

Very low quality evidence from 1 retrospective cohort study with 49 people with cystic fibrosis aged 0 to 20 years showed no clinically significant difference in lung function (measured as change from first to last FEV_1% predicted per year and slope FEV_1% per year) between the participants receiving intensive shared care (above UK equivalent) and usual shared care (UK equivalent) during the 3 years follow-up.

Mortality

No evidence was found for this critical outcome.

Patient and carer satisfaction

No evidence was found for this critical outcome.

Lung function: LCI

No evidence was found for this important outcome.

Time to next pulmonary exacerbation

No evidence was found for this important outcome.

Nutritional status

No evidence was found for this important outcome.

Quality of life

No evidence was found for this important outcome.

Frequency of cross-infection

No evidence was found for this important outcome.

Staff experience

No evidence was found for this important outcome.

Adherence to treatment

No evidence was found for this important outcome.

7.1.6.4 Telemedicine

7.1.6.4.1 Comparison 4.1. Home monitoring programme + diary recording versus usual care

Lung function: FEV_1

Very low quality evidence from 1 observational study with 50 people with cystic fibrosis > 6 years old showed no significant difference in lung function (measured as a change in FEV_1 % predicted) between the participants in the home monitoring programme and the participants receiving usual care at 4 years follow-up. The uncertainty for this outcome could not be calculated.

Mortality

No evidence was found for this critical outcome.

Patient and carer satisfaction

No evidence was found for this critical outcome.

Lung function: LCI

No evidence was found for this important outcome.

Time to next pulmonary exacerbation

No evidence was found for this important outcome.

Nutritional status

No evidence was found for this important outcome.

Quality of life

No evidence was found for this important outcome.

Frequency of cross-infection

No evidence was found for this important outcome.

Staff experience

No evidence was found for this important outcome.

Adherence to treatment

No evidence was found for this important outcome.

7.1.6.4.2 Comparison 4.2. Telemedicine versus usual care

Lung function: FEV_1

No evidence was found for this critical outcome.

Mortality

No evidence was found for this critical outcome.

Patient and carer satisfaction

No evidence was found for this critical outcome.

Lung function: LCI

No evidence was found for this important outcome.

Time to next pulmonary exacerbation

No evidence was found for this important outcome.

Nutritional status

No evidence was found for this important outcome.

Quality of life

Very low quality evidence from 1 RCT with 7 adults with cystic fibrosis on a transplantation list showed that the participants in the telemedicine group experienced a significant improvement in the quality of life, measured as the subjects' perception of body image (with CF-QOL body domain), at 6 months follow-up. The clinical significance and imprecision for this outcome could not be calculated.

Frequency of cross-infection

No evidence was found for this important outcome.

Staff experience

No evidence was found for this important outcome.

Adherence to treatment

No evidence was found for this important outcome.

7.1.6.5 Economic evidence statements

One cost-consequence analysis (Wolter 1997) on people with cystic fibrosis in Australia found that managing exacerbations at home was less expensive compared to those managed in hospital over 5 years. This analysis is partially applicable as the type of economic evaluation applied is difficult to assess cost-effectiveness and a societal perspective is inferred. This evidence is associated with serious limitations from the small number of participants (n=17).

One cost-benefit analysis (Elliot 2005) on people with cystic fibrosis in the UK found that hospital-based care was more expensive than home-based care over 1 year. This analysis is partially applicable with minor limitations.

One cost-effectiveness analysis (Thornton 2005) on people with cystic fibrosis in the UK found that the ICER (cost per decline in FEV1% ≤0%) was £46,098 (the cost to obtain 1 more year of effective treatment with hospital care for 1 person) for hospital IV therapy compared to home-care IV therapy. This analysis has minor limitations and is directly applicable given that the type of economic evaluation is unlikely to change the conclusions about cost-effectiveness and all other applicability criteria are met.

7.1.7 Evidence to recommendations

7.1.7.1 Relative value placed on the outcomes considered

The aim of this review was to assess the effectiveness of different models of care (for example specialist centre, shared-care, community care, telehealth and home care) for the care of people with cystic fibrosis.

The committee identified the following outcomes as critical: lung function (FEV_1% predicted), mortality and patient satisfaction. LCI, time to next pulmonary exacerbation, nutritional status, quality of life, carer satisfaction, frequency of cross-infections (*P aeruginosa, B cepacia*), staff experience and adherence to treatment were considered to be important outcomes.

7.1.7.2 Consideration of clinical benefits and harms

A number of comparisons between different models of care were covered in this review. Overall, no clinically significant differences in outcomes were found to favour a particular model.

In relation to the administration of IV antibiotics for an acute pulmonary disease exacerbation, all evidence was of very low quality; 3 studies found no significant difference in lung function between home and hospital care; there was no evidence on the other 2 critical outcomes of mortality and patient satisfaction. With regards to the important outcomes, the evidence showed a clinically significant reduction in the risk of experiencing an exacerbation at 12 weeks in the group treated in hospital. Very low quality evidence from 3 studies found no clinically significant differences in nutritional status between home and hospital care. Very

low quality evidence from 1 study found no clinically significant difference in 8 domains of quality of life but found a clinically significant lower score in the symptoms domain of quality of life in the home care group compared to the hospital group. There was no evidence on LCI, carer satisfaction, frequency of cross-infections, staff experience and adherence to treatment. Likewise, in relation to the comparison between home and hospital administration of IV antibiotics for chronic pulmonary infection, very low quality evidence from 1 study found no clinically significant differences in lung function and nutritional status. There was no evidence on the other outcomes. Following this, the committee concluded that a recommendation in favour of home IV therapy could only be supported if training and equipment were available to people with cystic fibrosis who are willing and competent to self-administer their treatment.

With regard to the comparison between cystic fibrosis management based on specialist centre care and the use of shared-care, all evidence was of very low quality; there was evidence from 2 studies on the critical outcome of lung function and evidence on nutritional status and quality of life from 1 study. No clinically significant differences were found between these 2 models of care except for a clinically significant difference in favour of shared care for the physical, vitality and social domains of quality of life measured with the CFQ-Teen questionnaire. However, the committee noted that this study was conducted in Australia, where people often need to travel long distances for review and management, this does not reflect the situation for most in the UK. There was, therefore, an issue of indirectness with regard to this evidence, and it could not be readily applied to a typical UK arrangement. There was no evidence on the other outcomes.

With regards to the comparison between cystic fibrosis specialist centre care and local care (below CF Trust recommendations), very low quality evidence from 2 studies showed mixed results in relation to lung function and very low quality evidence showed no clinically significant difference in nutritional status between these 2 models of care. There was no evidence on the other outcomes. With regards to the comparison between cystic fibrosis specialist centre care and care in a general non-cystic fibrosis clinic, there was very low quality evidence from 1 study on patient satisfaction which showed a significant difference in favour of centre care, but there was no evidence on the other outcomes.

With regards to the comparison between local care below CF Trust recommendations and shared care (UK equivalent), there was very low quality evidence from 2 studies which showed no clinically significant difference in lung function between these two models of care, and very low quality evidence from 1 study which showed no clinically significant difference in nutritional status. With regards to the comparison between shared care and intensive shared care, very low quality evidence from 1 study found no clinically significant difference in lung function. There was no evidence on the other outcomes.

The committee noted that there were 2 published studies (Doull 2012, Mahadeva 1998) conducted in the UK that compared cystic fibrosis specialist care with other alternative models of care. These studies had been identified in the evidence search but were not included in the review because they used a cross-sectional design, and therefore did not meet the protocol criteria. However, the committee considered that they were relevant as they reflected UK practice. In 1 of these studies (Doull 2012), the children who received either full cystic fibrosis centre care or hybrid care (cystic fibrosis centre care + local clinic) had better lung function than those who only received local hospital-based care. The second of these studies (Mahadeva 1998) found that adults attending a specialist cystic fibrosis centre who had received treatment in a paediatric cystic fibrosis specialist centre (group A) had better lung function and better nutritional status than those who received their paediatric cystic fibrosis care at a non-specialist centre followed by an adult cystic fibrosis specialist centre (group B).

In relation to telemedicine, very low quality evidence from 1 study on daily home monitoring (daily recording of symptoms and physical measurements sent to the centre weekly), did not

show a clinically significant beneficial effect on lung function compared to usual care. No evidence was available for the other outcomes. However, based on very low quality evidence home telemedicine (weekly video conference with the patient and members of the MDT to provide psychological support) appeared to be beneficial in improving the quality of life of people with cystic fibrosis that were terminally ill, compared to standard care alone. The committee noted that this benefit applied only to that specific population of people with cystic fibrosis. However, based on their clinical experience and expertise, the committee members agreed that people with cystic fibrosis who are severely ill are likely to benefit from face-to-face appointments for appropriate diagnosis and management. No evidence was available on the other outcomes.

7.1.7.3 Consideration of economic benefits and harms

The committee agreed that providing cystic fibrosis care outside of the specialist centre incurs greater costs from travel and administration and for shared-care an additional MDT. However, the committee felt it was unrealistic and unethical to recommend the specialist centre alone as people with cystic fibrosis may be unable to travel greater distances than they would under a shared-care or outreach care model.

The committee iterated that the burden of travel could negatively impact a patient's usual activities and, in some cases, increase their anxiety. Furthermore, long distances may reduce attendance to hospital for treatment, potentially resulting in downstream costs from delayed diagnosis and management. The committee added that this would include factors beyond someone's control which may affect their ability to travel when they are willing to do so. For these reasons, the committee agreed that a cost-effective recommendation would say how geography and the MDT indicate that care could be delivered through a shared-care network or outreach care clinic for paediatrics and adults respectively.

To reduce the burden of visits to a clinic, the committee considered a role for telemedicine as a supplementary model of care for routine monitoring in people with cystic fibrosis who are clinically stable. The committee also noted that this model could prevent cross-infection at the clinic, which can be costly to prevent and treat. However, people with cystic fibrosis who are unwell must not utilise telemedicine as they would require additional face-to-face appointments to obtain the correct diagnosis and management. Telemedicine would lead to a change in clinical practice as it is currently performed in a small proportion of clinics. According to the committee, this would incur a small injection of resources to set up if people with cystic fibrosis did not possess the necessary testing equipment such as spirometry. However, the cost of equipment would be negligible (approximately £50) and would last several years before it needed to be replaced (approximately 5 years).

The committee advised that people with cystic fibrosis should be able to telephone for urgent specialist advice as this could lead to more timely management. The committee added that such a recommendation would not lead to a change in current practice, but would increase the awareness of this service to people with cystic fibrosis and their parents or carers.

The committee agreed that home-care monitoring was an unsustainable model for routine monitoring when they considered the opportunity cost of staff time travelling long distances. Conversely, IV antibiotic therapy can be administered at home without health care professional supervision provided that training is given during routine clinic visits. The committee noted that the potential cost savings from this type of administration can only be realised if people with cystic fibrosis are willing and competent to do so, as further costs will be incurred to treat unsuccessful cases. Therefore, to ensure self-administered IV therapy is cost-effective, the committee made a recommendation to ensure that arrangements are in place for people to have IV antibiotic therapy at home, by transferring the necessary equipment and expert support provided in a clinic setting, to a home setting. Given that the equipment and expert support from a healthcare professional is part of an attendance to the clinic, no additional resources are anticipated from this move. The committee added that if

the IV training provided during routine clinic visits is successful, the frequency and duration of expert support anticipated for this model would be relatively low compared to the level of contact provided during an attendance at the clinic.

The committee discussed and agreed the review frequencies for people with cystic fibrosis based on their knowledge and experience. After a diagnosis of cystic fibrosis, it is important to review frequently, given the immediate polypharmacy, to prevent the potentially lethal consequences of giving an inappropriate treatment. Following those initial years, the person's treatment schedule and condition are likely to stabilise. As a result, less frequent monitoring would be considered cost-effective as the potential to miss a negative change in their condition is unlikely to escalate between those reviews. Furthermore, the CF Trust Standards of Care 2011 advises that people with cystic fibrosis are seen at least twice a year by the Specialist Centre. Finally, given that the NHS service specifications for cystic fibrosis and committee agreed that review frequency should be based on individual circumstances, no significant impact on resource is anticipated from the review frequencies provided by the committee.

7.1.7.4 Quality of evidence

The quality of the evidence presented in this review was very low as assessed by GRADE.

One of the main reasons that led to downgrading the quality of the evidence was the quality of the studies. Most of the included studies used an observational design and presented problems in the comparability of the groups. Data was poorly reported across studies and some of them reported the results narratively only.

Another reason was the lack of generalisability of the interventions to the UK context. Many of the studies were conducted in countries outside the UK, and the service delivery models evaluated differed from current UK practice.

The committee considered that it was important to note that no evidence was identified for the critical outcomes for many of the comparisons.

7.1.7.5 Other considerations

Given the scarcity and poor quality of the evidence, the recommendations were mainly based on the committee members' clinical experience and consensus on good clinical practice (NHS service specifications for cystic fibrosis; CF Trust Standards of Care 2011, which are mentioned in the NHS service specifications as the standards to follow; and European Cystic Fibrosis Society Standards of Care 2014).

The committee agreed that care for people with cystic fibrosis should be provided by a specialist MDT based at a cystic fibrosis specialist centre. MDT care is current practice in cystic fibrosis given that the condition is a multi-system chronic disease (please see the review on MDTs in this guideline for further details). The expertise of the MDT is key for effective management, therefore specialist cystic fibrosis centres should plan patient care, including measures to avoid cross-infection. Moreover, they should maintain local and national registers of patients that include information about their clinical condition, treatment and outcomes, as these are important for care, and audit and research purposes; the specialist centres should also audit practice and outcomes. These recommendations are consistent with the NHS service specifications for cystic fibrosis, which state that care is to be directed by the specialist centres and that individuals are to be seen by MDTs. The committee noted that local circumstances, such as the distance to the specialist centre for some people, might support the need for arrangements in which members of the specialist MDT either worked with the local hospital team or came to the local hospital to provide specialist care. Network based shared-care might be appropriate for some. This could be provided by local hospitals that have relatively small numbers of people with cystic fibrosis attending (for example, fewer than 50, given that the CF Trust Standards of Care 2011

mention that the number of patients in a specialist CF centre should not be less than 50). These people would receive their care at their local hospital, but with input from the specialist centre (members of the specialist centre MDT coming to work with the local team in clinic) at least twice yearly, which would remain responsible for ensuring the quality of the standard of care provided. Such shared-care models are consistent with current practice for the management of children and young people in the UK. The NHS service specifications for children with cystic fibrosis mention that network care is provided in partnership with the specialist CF centre that coordinates the network.

The committee noted that in adult practice shared-care was not the norm and an outreach clinic model was an alternative and more accepted model. The NHS service specifications for adults with cystic fibrosis state that centres serving more rural areas should be able to demonstrate an ability to provide outreach care when appropriate. With the outreach model the cystic fibrosis specialist team directly cares for adults with cystic fibrosis but comes to their local hospital to provide a local cystic fibrosis clinic. In relation to this, the committee noted that this might pose an equality issue, and more importantly, that it may increase the risk of cross-infection as local hospitals may not have the facilities required to cohort people according to their microbiological profile.

In both cases, all people with cystic fibrosis should be managed by a cystic fibrosis core MDT with access to an extended MDT if necessary, as discussed in the MDT review.

With regard to monitoring in network-based shared-care, the committee agreed that all people with cystic fibrosis should have an annual assessment and at least one other review per year with the specialist centre MDT. This is consistent with the CF Trust Standards of Care 2011, which are referred to in the NHS service specification for cystic fibrosis. This would be in addition to reviews by the local paediatric team (please see below for the committee's discussion on the frequency of regular routine reviews). They also agreed that these reviews can be conducted at the specialist centre, the network clinic, by telemedicine or at home.

Home visits were also considered an appropriate option for some people. Home care is consistent with the NHS service specifications for cystic fibrosis, which state that where appropriate the model of care must ensure access to care at home or close to home and home treatment is encouraged.

Given the scarcity and very low quality of the evidence on telemedicine, the committee used their clinical experience and expertise to make a recommendation. The committee agreed that it can sometimes be a suitable alternative to outpatient visit for routine monitoring, depending on individual circumstances. The NHS service specifications for cystic fibrosis do not mention telemedicine. However, as explained in the economic benefits and harms section, this can be a supplementary model of care for routine monitoring which has a negligible cost and may be useful to prevent cross-infection. It was discussed that, in addition to this, people should be able to access specialist advice 24/7 for urgent situations. Therefore, the specialist cystic fibrosis centre should have a point of contact available day and night for urgent enquiries related to their cystic fibrosis. This is consistent with current practice, with the NHS service specification for cystic fibrosis, and adheres to good clinical practice recommendations.

In relation to the administration of intravenous antibiotics in people with cystic fibrosis experiencing an acute exacerbation or with chronic pulmonary disease, this could sometimes have advantages for the person with cystic fibrosis, but the choice between home or hospital therapy would depend on individual circumstances. This is consistent with the NHS service specifications for cystic fibrosis, which recommend that intravenous antibiotics may be provided at home where appropriate. The committee agreed that it was important to ensure that appropriate training is provided for those involved in providing home IV therapy.

The committee agreed that routine monitoring is key in ensuring effective management because early detection of declining health can prompt early intervention, which in turn can prevent or limit symptoms and complications of cystic fibrosis. Moreover, routine monitoring allows healthcare professionals to regularly review and adjust management and self-management interventions, which supports people's adherence to treatment. Additionally, the committee agreed that annual assessments are important to ensure that progress is regularly assessed and that a 12-month management plan is agreed.

The committee made a recommendation that detailed all the assessments that should be included at the annual review. This recommendation was based on evidence from a wide range of reviews and consensus discussions about annual reviews and assessments that are outlined more in detail in different sections of the guideline. The committee agreed that they wanted one overarching recommendation that summarised all reviews that were required annually.

The committee discussed the frequency with which people with cystic fibrosis should be reviewed. Current practice is usually to review 6 times per year, but they agreed that the frequency would vary considerably depending on individual circumstances. Elsewhere, for example, the committee had made specific recommendations for monitoring pulmonary disease, where the advice varied depending on age and the clinical situation. Based on their clinical experience and expertise, the committee agreed to recommend more frequent routine reviews after diagnosis and in early life, when carers are not yet familiar with the condition and need more guidance to identify any issues and provide appropriate care. Moreover, as mentioned above in the economic benefits and harms section, after a diagnosis of cystic fibrosis frequent reviews are important to prevent the potentially lethal consequences of inappropriate polypharmacy. Following those initial years, the person's condition is likely to become more predictable. Therefore, the committee gave some examples of review frequency for different age groups, with frequency decreasing with age, from weekly reviews in the first month of life to every 3 to 6 months for adults. The examples for each age group were based on the committee's clinical experience and expertise. The NHS service specifications for cystic fibrosis state that routine outpatient appointments should be every 2 to 3 months when stable and more often if not for both adults and children. However, the NHS service specifications for cystic fibrosis also refer to the CF Trust Standards of Care 2011, which specify that patients should be reviewed with a frequency appropriate to their individual needs and that newly diagnosed infants should be seen more frequently (initially weekly). The committee's examples indicated the need to review children up to 5 years old more frequently (6 to 8 weeks) than the NHS service specifications for cystic fibrosis, and to review adults less frequently than the NHS service specifications. However, the NHS service specifications and the committee agreed that review frequency should be based on individual circumstances.

The committee discussed potential equality issues. They noted that people who live far from a specialist centre may be disadvantaged. However, they agreed no additional recommendations were needed as the use of alternative models of care had already extensively been discussed (for example, the access to shared-care in paediatrics, outreach clinics for adult care or telemedicine).

The committee agreed that research recommendations were not prioritised for this topic because clinical practice and the available models of care are already well established. Models of care need to be responsive to, and developed according to, local needs and factors (such as geography, as outlined above) which, by definition, are not suited to a general research recommendation.

7.1.7.6 Key conclusions

The committee concluded that care for all people with cystic fibrosis should be the responsibility of a recognised specialist centre, but in paediatrics this could be provided

through shared-care clinics as part of a network arrangement (between the specialist cystic fibrosis centre and the district general hospital). All people should have an annual assessment with their core MDT and regular monitoring should be scheduled depending on their individual needs. The core MDT should either include or have access to relevant specialists with experience of cystic fibrosis.

7.1.8 Recommendations

13. Care for people with cystic fibrosis should be provided by a specialist cystic fibrosis multidisciplinary team based at a specialist cystic fibrosis centre (see Multidisciplinary team).

14. Specialist cystic fibrosis centres should:

- plan patient care (including outpatient and inpatient care), taking into account the risk of cross-infection (see Prevention of cross infection)
- maintain local and national registers of patients that include information about their clinical condition, treatment and outcomes
- audit practice and outcomes.

15. When a shared-care model is used for children and young people, it should include:

- formal arrangements between the local paediatric team at the shared-care centre and the multidisciplinary team at the specialist cystic fibrosis centre
- direct involvement of specialist cystic fibrosis multidisciplinary team members
- an annual assessment and at least one other review per year by the specialist cystic fibrosis multidisciplinary team, in addition to reviews by the local paediatric team (see recommendations 20 to 23**Error! eference source not found.**).

16. If available and when clinically appropriate, outreach care for adults with cystic fibrosis may be provided by the specialist cystic fibrosis multidisciplinary team at a local hospital.

17. The specialist cystic fibrosis centre should have a point of contact available at all times (day or night) for urgent enquiries from people with cystic fibrosis and their family members or carers (as appropriate).

18. Consider telemedicine or home visits for routine monitoring when they are more appropriate than outpatient visits and if the person with cystic fibrosis prefers it.

19. Make arrangements (including providing equipment and expert support) for people to have intravenous antibiotic therapy at home, when this is appropriate.

Annual and routine reviews

20. Be aware that:

- the aim of cystic fibrosis care is to prevent or limit symptoms and complications of the condition
- routine monitoring and annual assessments are crucial in providing effective care.

21. **Offer people with cystic fibrosis a comprehensive annual review that includes the following:**
    - a pulmonary assessment (see Pulmonary monitoring)
    - an assessment of nutrition and intestinal absorption (see Nutritional Interventions and Exocrine pancreatic insufficiency)
    - as assessment for liver disease (see Monitoring for liver disease)
    - testing for cystic-fibrosis-related diabetes, from 10 years of age (see Monitoring for cystic fibrosis related diabetes)
    - an assessment for other potential or existing cystic fibrosis complications (see Complications of cystic fibrosis)
    - a psychological assessment (see Psychological assessment)
    - assessments by a specialist nurse, physiotherapist, pharmacist and social worker (see Service delivery)
    - a review of their exercise programme (see Exercise).

22. **Provide regular routine reviews for people with cystic fibrosis, and do these more frequently immediately after diagnosis and in early life. For example:**
    - weekly in their first month of life
    - every 4 weeks when they are between 1 and 12 months old
    - every 6 to 8 weeks when they are between 1 and 5 years old
    - every 8 to 12 weeks when they are over 5 years old
    - every 3 to 6 months as adults.

7.2 Multidisciplinary team

Review question: What is the clinical and cost-effectiveness of multidisciplinary teams of various compositions?

7.2.1 Introduction

Cystic fibrosis is a multi-system chronic disease that affects the respiratory tract and lungs, digestive system, sweat glands and reproductive organs. The condition is typically identified in infancy and care is required throughout an individual's lifetime through to end of life. The care aims to address the biological and psychosocial needs of the patient and their families or carers. As cystic fibrosis is associated with poor quality of life and clinical outcomes, it is important that care adequately addresses the needs of patients by allowing flexibility for individual circumstances. This requires an experienced MDT of cystic fibrosis-specialist healthcare professionals to ensure optimal care with continuity. This brings up the question of what would represent an ideal MDT.

7.2.2 Description of the clinical evidence

The aim of this review was to compare different combinations of the individuals working together as a core MDT with combinations of the individuals working together as an extended MDT and examines key patient and clinical outcomes.

As per protocol, studies that assessed the effectiveness of multidisciplinary teams of various compositions were eligible for inclusion in this review if they were RCTs or comparative prospective and retrospective cohort studies from Western countries. Studies based on registry and audit data from the UK were also eligible for inclusion. Moreover, conference abstracts of RCTs were also considered if the full papers were unavailable. However, no

relevant studies were identified for inclusion and no evidence was available to inform the review.

For full details see review protocol in Appendix D.

See also study selection flow chart in Appendix F, and excluded studies list in Appendix H.

7.2.3 Summary of included studies

Not applicable, as no studies were included in this review.

7.2.4 Clinical evidence profile

Not applicable, as no studies were included in this review.

7.2.5 Economic evidence

No economic evaluations of MDTs were identified in the literature search conducted for this guideline. Full details of the search and economic article selection flow chart can be found in Appendix E and F, respectively.

This review question was not prioritised for de novo economic modelling. To aid considerations of cost-effectiveness a costing tool was developed that utilised a "what-if" approach to estimate the cost of providing the core MDT specified in the protocol. This tool enables the user to vary the composition of the MDT, the number of whole time equivalents and the size of the clinic the MDT manages.

The cost of health care professionals included in the protocol are provided in Table 42, whilst a full description of the methods and results of the analysis are presented in Appendix K.

Table 42: Cost of providing the MDT at the Specialist Centre

Health care professional	Cost per annum	Cost per hour	Source (bands informed by the committee)
Core MDT			
Specialist CF Clinician	£190,408 [a]	£105 [b]	PSSRU 2016: Hospital-based doctors, medical consultant
Specialist Nurse	£83,628 [c]	£53 [d]	PSSRU 2016: Band 7, hospital-based nurses
Specialist Dietitian	£85,739 [f]	£54 [e]	PSSRU 2016: Band 7, scientific and professional staff
Specialist Physiotherapist	£87,381 [g]	£55 [e]	PSSRU 2016: Band 7, scientific and professional staff [h]
Specialist Pharmacist	£101,367 [i]	£64 [e]	PSSRU 2016: Band 8a, scientific and professional staff
Specialist Psychologist	£101,367 [i]	£64 [e]	PSSRU 2016: Band 8a, scientific and professional staff
Specialist Social worker	£61,730 [j]	£40 [k]	PSSRU 2016: Social worker (adult services)
Specialist Social worker	£58,947 [l]	£39 [k]	PSSRU 2016: Social worker (children's services)
Extended MDT			
Paediatric Diabetic Medicine	£253 per attendance		NHS Reference Costs 2015/16: WF01A, Non-Admitted Face to Face Attendance Follow-up,

Health care professional	Cost per annum	Cost per hour	Source (bands informed by the committee)
			Consultant-led, Paediatric Diabetic Medicine 263
Diabetic Medicine	£159 per attendance		NHS Reference Costs 2015/16: WF01A, Non-Admitted Face to Face Attendance Follow-up, Consultant-led, Diabetic Medicine 307
Paediatric ENT surgeon	£103 per attendance		NHS Reference Costs 2015/16: WF01A, Non-Admitted Face to Face Attendance, Follow-up, Consultant led, Paediatric Ear Nose And Throat 215
ENT surgeon	£89 per attendance		NHS Reference Costs 2015/16: WF01A, Non-Admitted Face to Face Attendance, Follow-up, Consultant led, Ear Nose And Throat 120
Obstetrician	£121 per attendance		NHS Reference Costs 2015/16: WF01A, Non-Admitted Face to Face Attendance, Follow-up, Consultant-led, Obstetrics 501
General surgeon	£123 per attendance		NHS Reference Costs 2015/16: WF01A, Non-Admitted Face to Face Attendance, Follow-up, Consultant led, General Surgery 100
Gastroenterologist/ hepatologist	£253 per attendance		NHS Reference Costs 2015/16: WF01A, Non-Admitted Face to Face Attendance, Follow-up, Consultant led, Hepatology 306

(a) Including wages/salary £87,449; salary oncosts £23,198; management, admin and estates staff overheads £26,777; non-staff overheads £47,689 and capital overheads £5,295
(b) Working time 42.3 weeks (1,838 hours) per year 43.3 hours per week
(c) Including wages/salary £38,550; salary oncosts £9,605; management, admin and estates staff overheads £11,653; non-staff overheads £20,755 and capital overheads £3,065
(d) Working time 42 weeks (1,572 hours) per year, 37.5 hours per week
(e) Working time 42.7 weeks (1,603 hours) per year, 37.5 hours per week
(f) Band 7 Dietitian. Including wages/salary £38,786; salary oncosts £9,670; management, admin and estates staff overheads £11,726; non-staff overheads £20,885 and capital overheads £4,672
(g) Band 7 Physiotherapist. Including wages/salary £38,786; salary oncosts £9,670; management, admin and estates staff overheads £11,726; non-staff overheads £20,885 and capital overheads £6,314
(h) Specialist Centre must be led by a Principal CF Physiotherapy Practitioner (Band 8)
(i) Band 8a. Including wages/salary £46,095; salary oncosts £11,702; management, admin and estates staff overheads £13,987; non-staff overheads £24,911 and capital overheads £4,672
(j) Including wages/salary £31,288; salary oncosts £9,463; direct overheads £11,818; indirect overheads £6,520 and capital overheads £2,641
(k) Working time 41 weeks (1,517) 37 hours per week
(l) Including wages/salary £29,854; salary oncosts £8,978; direct overheads £11,261; indirect overheads £6,213 and capital overheads £2,641

7.2.6 Evidence statements

Not applicable, as no clinical or economic studies were included in this review.

7.2.7 Evidence to recommendations

7.2.7.1 Relative value placed on the outcomes considered

The aim of this review was to compare different combinations of individuals working together as a core MDT with combinations of the individuals working together as an extended MDT and examines key patient and clinical outcomes.

The committee identified the following outcomes as critical: mortality, forced expiratory volume in one second (FEV_1) and patient satisfaction. Lung clearance index (LCI), time to next pulmonary exacerbation, nutritional status, quality of life, carer satisfaction, frequency of

cross-infections (*P aeruginosa, B cepacia*), staff experience and adherence to treatment were rated as important outcomes.

7.2.7.2 Consideration of clinical benefits and harms

Cystic fibrosis is a multi-system chronic disease that affects the respiratory tract, digestive system, sweat glands and reproductive organs. The condition is typically identified in infancy and care is required throughout an individual's lifetime through to end of life. The care aims to address the biological and psychosocial needs of the person with cystic fibrosis and their families or carers. In the UK, care is provided by a specialist cystic fibrosis centre. As cystic fibrosis is associated with poor quality of life and clinical outcomes, it is important that care adequately addresses the needs of patients by allowing flexibility for individual circumstances.

Given the nature of this condition, the committee considered it important to provide guidance on the professionals that should be responsible for the provision of care as well as examples of the sorts of care and support to be provided by different members of the MDT. Due to the lack of evidence, the recommendations were based on the committee's knowledge and expertise and were agreed by consensus.

In relation to the composition of the MDT, the committee discussed which healthcare professionals should be part of the core team. It was agreed the core team should include the following specialists: cystic fibrosis clinicians, nurses, dietitians, physiotherapists, pharmacists and psychologists. Moreover, the core team should include, or have access to, a social worker. This is consistent with the NHS service specifications for cystic fibrosis.

The committee agreed that within the MDT there should be a specialist paediatrician or adult physician that provides leadership for the MDT. Specialist paediatricians and adult physicians would have the necessary breadth and depth of experience and knowledge regarding cystic fibrosis to equip them for this role.

The committee agreed that key clinical roles of specialist nurses include: support during and following diagnosis and periods of change, triage, advanced clinical assessment, initiation of treatment, coordination and management of home IV services and IV access. The committee also noted that specialist nurses communicate with people with cystic fibrosis and their family members or carers about their overall care needs rather than focusing on one area of specialisation. Therefore, they are best placed to coordinate their care and facilitate communication between the members of the team, and act as advocates for the person's best possible care. The committee noted that this recommendation reflects current practice.

The committee agreed that, in their experience, people with cystic fibrosis benefit from regular meetings with a specialist physiotherapist who advises them on, airway clearance, nebuliser use, musculoskeletal disorders, exercise and physical activity and urinary incontinence. People with cystic fibrosis also benefit from regularly seeing a specialist dietitian who advises them on nutrition. Normally, a review from a physiotherapist and a dietitian would be an integral part of a clinic visit. These reviews should be available at clinic visits, however the frequency of these reviews would be a matter for individual consideration. The committee considered that every person should have a physiotherapist and a dietitian review as part of their annual review. Moreover, they agreed that the input of a physiotherapist and a dietitian would be important during inpatient admissions. Finally, they recommended physiotherapist assessments during pulmonary exacerbations. The committee agreed that the recommendations on the role of the physiotherapist and the dietitian reflect current practice.

The committee agreed that the specialist pharmacist should be available when necessary to advise on matters related to medications during inpatient admissions, on discharge from hospital, at outpatient clinic visits and at annual review. They agreed people with cystic fibrosis should have a pharmacist review as part of their annual review. Moreover, the

specialist pharmacist should advise health care professionals on all aspects of medicines use and prescribing. The specialist pharmacist should also support GPs, community pharmacists and homecare providers to ensure that people with cystic fibrosis get the medicines they need without interruption. The committee noted that this recommendation reflected current practice.

The committee agreed that people with cystic fibrosis should have a specialist clinical psychologist review as part of the annual review to identify psychological and behavioural problems and offer advice. Moreover, the specialist clinical psychologist should assess and advise people with cystic fibrosis, and their families and carers, at cystic fibrosis clinical visits, inpatient admissions and at further outpatient consultations (such as community visits, schools or social care meetings) or telephone calls when required. The committee agreed that the frequency of visits should be based on individual needs. The committee noted that the recommendation on the role of the clinical psychologist reflected current practice.

The committee agreed that social workers should provide advice, and support people with cystic fibrosis, and their families and carers, on adjusting to long-term treatment (such as taking regular medicines), educational or employment needs, government benefits and respite care needs. The committee noted that this recommendation reflected current practice.

The committee noted that the CF Trust Standards of Care 2011 (which are mentioned in the NHS service specifications for cystic fibrosis as the standards to follow) offered a detailed description of the role of each professional included in the core MDT.

In addition, the committee discussed the health care professionals that should also be involved in the MDT depending on the person's circumstances. This extended team should include: diabetologists, obstetricians, ear, nose and throat (ENT) surgeons, general surgeons and gastroenterologists or hepatologists. The committee emphasised the importance of the health care professionals having cystic fibrosis expertise or interest.

Although not specifically covered in the protocol, the committee agreed that microbiologists, interventional radiologists, pulmonary physiologists, rheumatologists, thoracic surgeons and palliative care specialists can play an important role in the management of people with cystic fibrosis and the MDT should have access to them where appropriate. This is consistent with current practice.

The committee agreed that access to the aforementioned professionals would be necessary to provide high quality care in the areas of microbiology, pulmonary physiology, diabetes, gastroenterology, hepatology, rheumatology, psychiatry, interventional radiology, surgery (gastrointestinal, thoracic and ENT surgery), obstetrics and palliative care. The committee noted that people with cystic fibrosis would have access to these professionals either through the specialist centre or through referral from their GP.

The committee also discussed the need to have access to secretarial and data entry support. This is already current practice, whether the staff is only dedicated to the MDT or not, and it is supported by other consensus recommendations.

The committee agreed that the specialist cystic fibrosis multidisciplinary team should work with the person's GP. They agreed that they should provide timely information in order to ensure the person's GP is able to support them in the following ways: prescribe routine cystic fibrosis medication (minimum one month at a time), medicines prescribed for longer periods and arrangements for prescriptions of unlicensed medicines, routine annual immunisation including alternations for people with cystic fibrosis and flu vaccinations for family members and carers, management of non-cystic fibrosis related health issues, certification of illnesses, partnership working with cystic fibrosis homecare team (particularly in relation to end of life issues), and care of family and carers. The committee noted that this recommendation reflected current practice.

7.2.7.3 Consideration of economic benefits and harms

The committee agreed that the core MDT composition should follow previous guidance (such as recommendations of the Cystic Fibrosis Trust's and NHS service specifications for cystic fibrosis) as this represents current clinical practice and resource use in England. Moreover, the core MDT would have expertise in the specialities regularly needed by people with cystic fibrosis and can provide a cost-effective full-time composition.

The committee considered the whole time equivalent (WTE) recommendations reported in the CF Trust Standards of Care 2011 for a given clinic size. They concluded that the values they specified were insufficient to provide a high quality service given the need for the core MDT to be spread over acute hospital work, outpatient clinics, network clinics and community work, such as home visits. The committee also highlighted that the number of WTEs did not allow for the provision of annual leave or sick leave cover. However, the committee were reluctant to suggest a minimum WTE for each of the core members as this would depend on the complexity of the people with cystic fibrosis at each clinic and the size of the clinic.

The committee highlighted the importance of administrative support to disseminate information across the models of care and provide data entry into the UK CF Registry, which is useful to monitor the complications and comorbidities of cystic fibrosis and its management. The committee considered this to be a cost-effective use of an administrator's time when the collected data can be used to improve people's knowledge of cystic fibrosis. Despite this, a recommendation on their role was not prioritised, as evidence on the effects of administrative professionals was not considered during protocol development.

The committee agreed the extended MDT would not be full-time members of the MDT as their case load would include people without cystic fibrosis. One defined person within the specialty would be called upon on a case-by-case basis as this would promote continuity and cystic fibrosis expertise which promotes effectiveness. As a result, the committee considered the opportunity cost of the extended MDTs time to care for people without cystic fibrosis and made a recommendation for the core MDT to have access to those (extended) specialists who can provide advice and accept referrals for people with cystic fibrosis.

In addition to the extended MDT outlined in the protocol, the committee discussed how the wider MDT service specification reported by NHS England should reflect current NHS commissioning. However, it was noted that such service specifications by NHS England are not evidence based and could not justify an increase in current resource use where they are not followed as there is no evidence that those specifications are a cost-effective use of resources for wider implementation.

The committee stated that people with cystic fibrosis should have access to a physiotherapist, dietitian, pharmacist and psychologist at outpatient clinic visits and annual reviews, to ensure changes to their health and goals are identified and managed without potentially harmful delays. Consequently, the committee made recommendations to that effect and added that the CF Trust Standards of Care 2011 (which are mentioned in the NHS service specifications for cystic fibrosis as the standards to follow) offered a detailed description of the role of each professional included in the core MDT.

Furthermore, during inpatient admissions, dietitians and physiotherapists need to ensure that their patient's exercise programmes and nutritional requirements compliment their inpatient treatment schedules (see recommendations in sections 10.1.8 and 10.8.8 for nutrition and exercise, respectively). For these reasons, the committee agreed their recommendations to ensure access during inpatient admissions promoted a cost-effective use of resources as management strategies usually need to be modified during inpatient care.

7.2.7.4 Quality of evidence

Not applicable as no evidence was found for this review.

7.2.7.5 Other considerations

Given the lack of evidence, the recommendations were based on the committee' clinical experience and consensus on good clinical practice (NHS service specifications for cystic fibrosis; CF Trust Standards of Care 2011, which are mentioned in the NHS service specifications as the standards to follow; and European Cystic Fibrosis Society Standards of Care 2014).

No equality issues were identified by the committee for this review question.

The committee felt a research recommendation into the MDT was not needed as their clinical experience and expertise was sufficient to show the need for all members outlined above.

7.2.7.6 Key conclusions

The committee concluded that the core MDT team should include the following specialist: cystic fibrosis clinicians, nurses, dietitians, physiotherapists, pharmacists, psychologists and should either include, or have access to, social workers. The MDT team should work with the person's GP, providing timely information so that the GP can offer appropriate care and support to the person with CF and their family and carers. In addition, the following professionals with expertise in cystic fibrosis may also be included in the MDT if appropriate: diabetologists, obstetricians, ENT surgeons, general surgeons and gastroenterologists or hepatologists. Although not strictly part of the team, the MDT should have access to administrative and cystic fibrosis registry data entry staff.

7.2.8 Recommendations

23. **The specialist cystic fibrosis multidisciplinary team should include at least one of each (depending on the size of the clinic) of the following professionals, who should have specialist expertise in the condition:**
    - specialist paediatricians or adult physicians
    - specialist nurses
    - specialist physiotherapists
    - specialist dietitians
    - specialist pharmacists
    - specialist clinical psychologists.

24. **The specialist cystic fibrosis multidisciplinary team should be led by a specialist paediatrician or adult physician.**

25. **The specialist cystic fibrosis multidisciplinary team should either include or have access to social workers.**

26. **Social workers should provide advice and support to people with cystic fibrosis and their family members or carers (as appropriate), for example on:**
    - help with adjusting to long-term treatment (such as taking regular medicines)
    - education
    - employment
    - government benefits
    - respite care.

27. **Specialist nurses (working with specialist paediatricians or physicians) should coordinate care and facilitate communication between other members of the cystic fibrosis team, and act as advocates for people with cystic fibrosis and their family members or carers (as appropriate). Key clinical roles could include:**
    - support during and after diagnosis and when starting treatment
    - triage
    - advanced clinical assessment
    - coordinating home intravenous antibiotic services, including intravenous access.

28. **Specialist physiotherapists should assess and advise people with cystic fibrosis at clinic, at inpatient admissions, during pulmonary exacerbations and at their annual review. Assessment and advice could cover airway clearance, nebuliser use, musculoskeletal disorders, exercise, physical activity and urinary incontinence.**

29. **Specialist dietitians should assess and advise people with cystic fibrosis about all aspects of nutrition at outpatient clinic visits, during inpatient admissions and at their annual review (see Nutritional Interventions).**

30. **Specialist pharmacists should advise people with cystic fibrosis on medicines optimisation at outpatient clinic visits, during inpatient admissions, on discharge from hospital and at annual review. They should advise healthcare professionals on all aspects of medicines use and prescribing, and support GPs, community pharmacists and homecare providers to ensure that people with cystic fibrosis get the medicines they need without interruption.**

31. **Specialist clinical psychologists should assess and advise people with cystic fibrosis and their family members or carers (as appropriate) at outpatient clinic visits and (if needed) at other outpatient appointments, during inpatient admissions, and at their annual review (see Psychological assessment).**

32. **The specialist cystic fibrosis multidisciplinary team should either include or have access to specialist expertise relevant to cystic fibrosis in the following areas:**
    - microbiology
    - pulmonary physiology
    - diabetes
    - gastroenterology
    - hepatology
    - rheumatology
    - psychiatry
    - interventional radiology
    - surgery (gastrointestinal, thoracic, and ear, nose and throat)
    - obstetrics
    - palliative care.

33. **The specialist cystic fibrosis multidisciplinary team should work with GPs, and provide timely information so that GPs can support people with cystic fibrosis by:**
    - prescribing routine cystic fibrosis medicines:
        - in batches of at least 1 month at a time for routine medicines

    - for longer periods be advised by the specialist team
    - following guidance on arrangements for prescriptions of unlicensed medicines
- providing routine annual immunisation including any alterations for people with cystic fibrosis and flu vaccinations for family members and carers
- managing health problems not related to cystic fibrosis
- certification of illnesses
- working in partnership with cystic fibrosis homecare teams, particularly for end of life care
- providing care for the person's family members or carers.

7.3 Transition to adult services

Review question: What parts of the transition from children's to adult services are most important for young people with cystic fibrosis and their family members and carers?

7.3.1 Introduction

Young people themselves are nervous of change and worried about the new responsibility. Parents are concerned about the level of care provided by a new team and fear the loss of their child to adulthood with resultant loss of control over their care. Additionally, transition often occurs during a time of emotional and social flux for the young person as in addition to their change in treatment they are undergoing the changes in schooling, work and relationships which all people go through on maturity to adulthood.

Transition must be a collaboration between paediatric and adult centres, the person with cystic fibrosis and their family. There must be input for psychological and practical preparation and adjustment. It is important to equip young adults with cystic fibrosis with the skills to negotiate the adult system of health care. Paediatric centres cannot offer emotional support nor offer the surroundings or service appropriate for adults. Paediatric centres focus on the wellbeing of the whole family whereas adult centres focus on the patient. This can lead to emotional strains as parents or caregivers begin to 'take a backseat' in the management of their child's heath. This fundamental difference in approach has major implications for the emotional care of the young person and their families and adjustments or interventions may be needed. Preparation for the change can greatly affect the ease of transition. The role of the paediatric team must be to not show bias, respect the rights of the teenager, offer guidance and support, discuss the future, provide information about the adult services and facilitate the move both practically and emotionally. There is a role for social work and social care services for support regarding transfer of financial benefits and assistance with employment and further education. The adult service needs to be aware of these concerns and act to manage the transition not just from paediatrics to the adult centre but also the transition of the young person from a dependent child to independent young adult, including support for primary caregivers.

Transitional care from paediatrics to adult services is a complex process that involves a multidisciplinary team approach. There is an obligation to ensure that the person's health care needs are met at each step of the way. Young people should be transferred to the adult service when they have completed growth and puberty. Where possible, they should be largely independent of parents and staff, for example, with regards to communication and decision making. Transition planning must begin well before the anticipated transfer time. A transition programme is an essential part of quality care for young people with cystic fibrosis and their parents or carers. In early adolescence, it is favourable that a series of education

sessions take place. These should include understanding the disease, the rationale behind therapy and recognising and responding to symptoms and deterioration. Cystic fibrosis teams, as well as people with cystic fibrosis, have found that the transfer of care from one centre to another must be a gradual process rather than an abrupt shift. Transition is not synonymous with transfer. It is an active process and not a single event. It must begin early, be planned and regularly reviewed and be age and developmentally appropriate. There is a lack of standardisation currently in transition practices and people with cystic fibrosis and their families report inconsistencies.

The committee recognises that effective transition is important for all young people with health needs, as outlined in the NICE guideline on transition from children's to adult's care (NG43). However, they specifically focused on aspects that are particularly important or unique for young people with cystic fibrosis, their families and carers.

7.3.2 Description of clinical evidence

The aim of this review was to identify elements of the transition process (for example, transition planning involvement) from paediatric to adult services from perspectives of young people with cystic fibrosis and their family and carers.

We looked for studies that collected data using qualitative methods (such as semi-structured interviews, focus groups and surveys with open-ended questions) in which the authors analysed the data qualitatively (including thematic analysis, framework thematic analysis or content analysis). Survey studies restricted to reporting descriptive data that were analysed quantitatively were excluded.

Given the nature of qualitative reviews, findings or themes were summarised from the literature and were not restricted to those identified as likely themes by the guideline committee at protocol stage.

For full details see review protocol in Appendix D.

Eleven qualitative studies were included in this review (Al-Yateem 2012, Al-Yateem 2013, Begley 2013, Brumfield 2004, Depuis 2011, Iles 2010, Moola 2011, Russell 1996, Tierney 2013, Tuchman 2008, Van Staa 2011).

Seven studies used semi-structured interviews (Dupuis 2011, Iles 2010, Moola 2011, Russell 1996, Tierney 2013, Tuchman 2008, van Staa 2011), 2 studies used in-depth interviews (Al-Yateem 2013, Brumfied 2004), 1 study used a postal survey (Begley 2013) and 1 study used focus groups (Al-Yateem, 2013). The most common data analysis method employed across studies was thematic analysis.

With regards to the population, 9 studies included young people and young adults (age range: (Al-Yateem 2012, Brumfield 2004, Depuis 2011, Iles 2010, Moola 2011, Russell 1996, Tierney 2013, Tuchman 2008, Van Staa 2011), 4 studies included parents (Dupuis 2011, Moola 2011, Russell 1996, Van Staa 2011) and 4 studies included healthcare professionals working with young people and young adults with cystic fibrosis (Al-Yateem 2013, Begley 2013, Iles 2010, Van Staa 2011).

The sample size of the studies ranged from 4 (Brumfield 2004) to 132 participants (Begley 2013). Three studies included a mixed population (Begley 2013, Moola 2011, Tuchman 2008), but only quotes from people with cystic fibrosis were retrieved.

Two studies were conducted in the UK (Iles 2010, Tierney 2013), 3 in Ireland (Al-Yateem 2012, Al-Yateem 2013, Begley 2013), 2 in Australia (Brumfied 2004, Russell 1996), 2 in Canada (Dupuis 2011, Moola 2011), 1 in the USA (Tuchman 2008), and 1 in the Netherlands (van Staa 2011).

See study selection flow chart in Appendix F, study evidence tables in Appendix G and list of excluded studies in Appendix H. For the presentation of findings, a theme map was generated according to the themes emerged from studies (Figure 1). Due to the qualitative nature of these studies, the evidence is summarised in GRADE-CERQual tables within the evidence report. Therefore no separate Appendix is provided for this.

7.3.3 Summary of included studies

A summary of the studies that were included in this review are presented in Table 43.

Table 43: Summary of included studies

Study	Study design/ methods	Participants /respondent	Aim of the study	Comments
Al-Yateem (2012) Ireland	In-depth interviews	N=15 young adults with CF Age of young adults: Not reported	To explore and understand the experience of young people before and after their transitional care, and the factors that both contribute to and hinder that experience.	• Overall quality: low • Age of young adult not reported. • Description of data collection method was vaguely described. • The analytical process was reported vaguely. • Description of emerging and overarching themes was reported, but saturation of data was not reported.
Al-Yateem (2013) Ireland	Focus groups	Health care professional working with young adults with CF Sample size and age group not reported	To develop relevant and feasible guidelines for transition care, based on perspectives of stakeholders.	• Overall quality: low • Number of participants and age group not reported. • Description of data collection method was vaguely described. • The analytical process poorly described.
Begley (2013) Ireland	Postal survey	N=132 healthcare professionals	To evaluate how the transition from child to adult healthcare is managed in young people with CF or diabetes in Ireland.	• Overall quality: low • The sample selection process was not clearly reported, although the authors tried to involve all participants caring after young people before the transition process, 56% response rate. • Description of data collection method and data analysis was vaguely described. • The authors do not explain whether data saturation was reached, but given the limited number of quotes

Study	Study design/ methods	Participants /respondent	Aim of the study	Comments
				presented in the study it is unlikely. • This study includes healthcare professionals looking after young people with CF and diabetes. Only quotes relevant to CF have been extracted.
Brumfield (2004) Australia	In-depth interviews	N=4 young adults with CF Age: 19 to 22 years	To explore the experiences of Australian adolescents with CF as they made the transition from paediatric to adult care.	• Overall quality: moderate • Small sample size. • Data collection was described in detail but no information on data saturation. • Robustness of the finding not discussed considering the low sample.
Dupuis (2011) Canada	Semi-structured interviews	N=26 • 7 young people with CF • 7 mothers, 4 fathers • 8 members of the healthcare team Age of people with CF: 15 to 18 years	To explore the experience of parents and adolescents living with cystic fibrosis prior to the transfer of the adolescent's care from a paediatric to an adult healthcare facility.	• Overall quality: low • No information on structure of interview or whether topic guide reported. • Themes and categories used but no information on data saturation and full exploration of theme. • Most of the findings unrelated to transitions process.
Iles (2010) UK	Semi-structured interviews	N=73 • 50 young people and young adults with CF • 23 healthcare professionals Age of people with CF: 13 to 24 years	To examine how young people and staff perceive the nature of parental care and support for those with CF who have left paediatric services.	• Overall quality: moderate • Sample selection was clearly reported. The relationship between the researcher and the respondents was reported. • Information on structure of interview or topic guide reported. • The analytical process was described with description of themes, categories and use of qualitative software.
Moola (2011) Canada	Semi-structured interviews	N=78 • 50 young people; • 28 parents	To understand the transition experiences of young people with CF and coronary heart disease.	• Overall quality: moderate • The sample selection process was vaguely reported, and the

Study	Study design/ methods	Participants /respondent	Aim of the study	Comments
		• affected by CF and coronary heart disease Age of young people: 11 to 17 years		relationship between the researcher and the respondents was not reported. • All the steps of the thematic analysis were reported, but it was unclear whether data saturation was reached. • Results were presented clearly, but very few themes referred to the transition from child to adult services. • This study includes a mixed population. Only quotes relevant to CF have been extracted.
Russell (1996) Australia	Semi structured interviews	N=15 • 7 young people and young adults with CF and • 8 parents Age of young people with CF: 11 to 20 years	To investigate the experience of transferring to adult healthcare from the perspective of adolescents with CF and their parents.	• Overall quality: moderate • Data collection method was well described and consistency in the interview process reported. • Description of emerging and overarching themes was reported, but saturation of data was not reported.
Tierney (2013) UK	Semi-structured interviews	N=19 young people and young adults with CF Age: 17 to19 years	To explore the experiences of young people with cystic fibrosis of transferring to adult services.	• Overall quality: moderate • Data collection and analysis method was well described and consistency in the interview process reported. • Findings were presented clearly. Robust ness of the overall findings discussed.
Tuchman (2008) USA	Semi-structured interviews	N=5 young people and young adults with CF Age: 15 to 21 years	To describe expectations and concerns of adolescents with chronic illness regarding transition from sub-speciality paediatric to adult-centred care during the transition process in order to guide effective programme	• Overall quality: low • Mixed sample with other chronic diseases. • No inclusion criteria reported. • Data collection and analysis was vaguely described and lacked detailed information.

Study	Study design/ methods	Participants /respondent	Aim of the study	Comments
			design and implementation.	
van Staa (2011) Netherlands	Semi-structured interviews	N=8 • 3 young people and adults with CF; • 3 parents; • 2 healthcare providers Age of people with CF: 15 to 22 years	• To explore map experiences with the transfer to adult care of young adults with chronic conditions. • To identify recommendations for transitional care of young adults, their parents and healthcare providers.	• Overall quality: moderate • Mixed sample with other chronic diseases. • Sample selection process was vaguely reported. • Data collection and analysis process was well described. • Findings were well presented but use of quotes was inadequate.

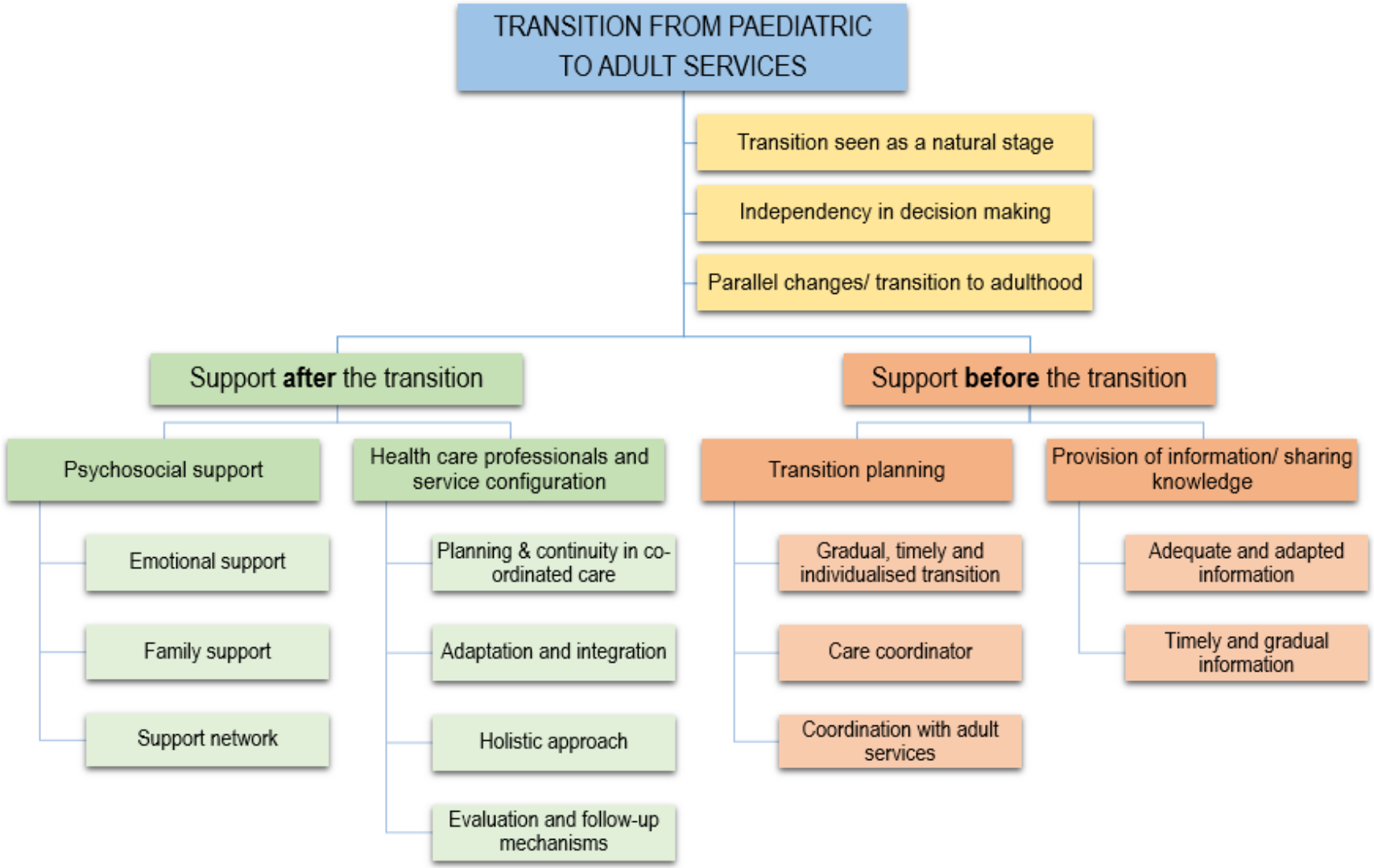
Abbreviations: CF: cystic fibrosis; UK: United Kingdom

7.3.4 Clinical evidence

7.3.4.1 Theme map

The theme map is presented in Figure 5.

Figure 5: Theme map: Needs of young adults in transition to adult health services



7.3.5 Clinical evidence profile

The clinical evidence (GRADE-CERQual) for the transition review question is presented in Table 44 to Table 48.

7.3.5.1 Overarching themes

Table 44: Summary of clinical evidence (GRADE-CERQual): Overarching themes

Study information			Quality assessment		
Number of studies	**Design**	**Description of theme or finding**	**Criteria**	**Rating**	**Overall**
Sub-theme 1: Transition as natural stage					
3 studies (Brumfield 2004, Moola 2011, van Staa 2001)	3 studies using interviews	Two studies conducted in Australia, Canada and the Netherlands with young people and young adults with cystic fibrosis, parents and healthcare professionals noted that transition was seen as a natural process. Age appropriate treatment was considered and issue by people with cystic fibrosis: *"As I grew up, he (paediatric doctors) sort of treated me . . . as if I was older . . . he didn't start treating me like a little kid and stuff, so that was good." (19 year old with cystic fibrosis)* However, another individual said that they were treated as children even when they were young adults ready for transition: *"I thought . . . if only the (paediatric) doctors knew that we were becoming adults, you know, we were in our mid-teens thinking, they still treat us as if we were ten years old." (20 year old with cystic fibrosis)* Young people, young adults and their parents recognised the inevitability that they will be transferred to adult healthcare and the fact they will have to get more involved in their future care: *"My mum usually takes care of all the appointments and everything… it will probably change when I get older. When I'm an adult, I'll probably have to make all the appointments and everything" (young girl with cystic fibrosis, age 13).*	Limitation of evidence	Minor limitations	LOW QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Not saturated	

		"I'll need to get used to it. I've known my doctor awfully long, for 18 years. But I'll just see what's going to happen. [. . .] Actually, I'm getting too old now for a children's hospital. Seems to be the right age [for transfer] because I'm an adult now, aren't I?" (19-year-old male, cystic fibrosis) Healthcare providers recognised transfer as *'a natural process'* that is *'age-appropriate'.*			
Sub-theme 2: Parallel changes or transition to adulthood					
2 studies (Moola 2011, Tierney 2013)	2 studies using interviews	In 1 study conducted in the UK with young people and young adults with cystic fibrosis, participants highlighted that relocating to a new healthcare system is a of several transitions young people with a long-term condition. Hence, transfer takes place against a backdrop of additional pressures and might not be a top priority: *"It was very busy actually because you know you've got to come in here at some point but then you've also just started at college, a new course, you don't want to miss all the beginning of your course. It's a new start both sides so you don't want to miss either one." (young person with cystic fibrosis)* In another study conducted in Canada with young people with chronic conditions and parents, the authors concluded that young people projected their lives into the future. Although they showed future aspirations, they contemplated if their health would deteriorate in the future, and the impact this would have on their lives. For example, they suggested it might be important to choose a school or work environment that is in close proximity to a hospital: *"I will probably not live in the residence in the future and I will probably live at home with all the medicine near and staff right near me… It is easier to get all of the medicine and stuff; my mum is always driving down to get the medicine. And then I can just bring it home and get it right away. Instead of me living somewhere else and then having to get it. It would be so much more complicated" (young female with cystic fibrosis, age 15)*	Limitation of evidence Coherence of findings Applicability of evidence Saturation	Minor limitations Coherent Applicable Not saturated	LOW QUALITY

		In 1 study, young women expressed sadness and resignation regarding the potential impact that illness could have on fertility. They were worried that illness would preclude them from being able to have a normal pregnancy: *"I want to have a family, but I cannot have children because of cystic fibrosis" (young female with cystic fibrosis, age 16)* Young people with cystic fibrosis and their parents described they feel threatened by cystic fibrosis, and expressed sadness for the lost time that would result in an early death: *"I also know that I am not going to live as long as everybody else, so that is hard. I feel like it is out of my control, I feel helpless, how I used to be able to do it (physical activity), and now, I can't. It is kind of depressing. It makes me think that it is a progressive disease, and it makes me think that it is getting worse… it makes me worried" (young female with cystic fibrosis, age 15)* *"A parent never wants to have a kid die before her and what is what she (wife) was upset about. That is why I was trying to tell her to spend as much time as you can, with her (child with cystic fibrosis). And just think; every waking moment that you have, spend it with her. Even if you have both of them, of one by themselves, spend that time with her. I had her quit her job and that is why I work 16 hours a day. So that she can spend more time with them) (parent of a young person with cystic fibrosis).* *"It (cystic fibrosis) is part of who I am… I was thinking about life in general and how I knew that my disease was going to kill me off younger – I will probably not be able to see my grandchildren grow up, kind of thing… It really got to me that whole year and eventually, I just accepted the fact that everybody dies. It does not matter when you go, but you go. I just kind of got a positive attitude, that I might as well be happy and make the most of it" (young male with cystic fibrosis, age 17)*			
Sub-theme 3: independency in decision making					

5 studies (Al-Yateem 2013, Iles 2010, Russell 1996, Tuchman 2008, van Staa 2011)	4 studies using interviews and 1 study using focus groups	Five studies conducted in Australia, Ireland, the Netherlands, the UK and the USA with young people and young adults with cystic fibrosis, parents and healthcare professionals reported on the importance of being allowed to make choices, self-advocacy and build independence gradually. ***Promoting independence*** One participant suggested that young adults should be more involved in decision making process: *"I think it is important to keep them involved … and take part in all decisions and activities during clinic and so on". (healthcare professional working with young people)* ***Increasing active involvement ("parent-as-partner")*** Young adults noted that more independence and self-reliance was expected of them. Parents wondered whether their children could take up the full responsibility for their treatment. Healthcare providers recognised cultural differences between the paediatric and adult specialities that complicated transfer. The adult care had a more 'business-like approach' which often contrasted with the paediatric 'holistic, system-oriented approach' Young adults want to create their own identity and perform task to gain independence. To gain independence, the young adults were in the process of developing autonomous and self-determined lives and separating from their parents. They also preferred active involvement in their clinic appointments and their desire for a confidential consultation. Many young people reported embracing opportunities to take the lead in adult clinic consultations, negotiating with their parents to facilitate this: *"Since I went over to the adults' [clinic] it's been me more involved and she's just sat back and she'll take me if I want her to and she'll sit there and she won't say anything unless I ask her." (17 year old with cystic fibrosis)* Some young adults did not even want their parents to be involved during hospital consultations:	Limitation of evidence Coherence of findings Applicability of evidence Saturation	Minor limitations Coherent Applicable Saturated	MODERATE QUALITY

		"My mum used to come with me to the clinic when I first transferred. I mean she'd come with me now if she could get time off work, if I'd let her, but sometimes I'd rather she wasn't there because there are obviously personal things you want to talk to the doctor about, like when I got my first boyfriend and stuff, I didn't want her to be there." (23 year old with cystic fibrosis) *"I didn't tell my mum I was transferring. I didn't tell her, because my mum's a bit obsessive about the clinic and she feels she has to know everything, you know, even though I'm 17... I mean I know it's the duty of the parent, I know that's their job…But that's the good thing about the adult clinic, is the parents don't have to be there, just the child or the patient's wishes. That's the good thing about being in the adult [service]." (17 year old with cystic fibrosis)* Health professionals stressed the need for understanding the family dynamics but also recognised that young adults are decision makers: *"I think that when they move to the adult side we very much leave it up to the young person. Some of them leave their parents in the waiting room, others very firmly bring them in." (Specialist physician)* *"I make it very clear to the parents, when they come up, that I am quite happy to discuss anything with them that the patients want me to discuss with them, but that they are now adults and it's up to them if I speak to them. I mean I will ask my patients, 'Do you mind if I discuss your treatment options with your parents?' And nine times out of ten, they have no problem with it. But I make it very, very clear to the parents that I can't talk to them the way that I could do or [others] used to when they were children and it's really part of learning to let go for them." (Cystic fibrosis Nurse Specialist)* In spite of this, the parents persisted in their attempts to be included until they were recognised as an integral part of the adolescent's care. One mother described this as, *"I don't know whether they realized that we just weren't going to go away, that they would*			

		then have to get on with us and we were going to have to get on with them." *"My mom doesn't want to let go. She has flat out told me. You put 18 years into your child's health and it becomes your health as well" (young adult with cystic fibrosis)* *"My mom has mixed emotions about it because she's not sitting back in the room with me anymore. She likes being able to put her two cents in. And I like being able to do it myself." (young adult with cystic fibrosis)* However, in some situations parents were still regarded as protectors. The main way in which young people perceived their parents to protect them was in withholding information during childhood about the terminal nature of cystic fibrosis: *"You know, I know a person [with cystic fibrosis], my mum knew him. And my mum never wanted to tell me [he had died] until I had turned 15." (16 year old with cystic fibrosis)* Staff also acknowledged the difficulties communicating limited life expectancy with parents because of their protective nature, where it seemed that young people were perhaps more able than their parents to have these discussions with staff: *"We had to have a discussion whether to go on to mechanical ventilation would be the right thing ..... And she was able to have that discussion. And I asked her did she want me to let her mother know, if she wasn't going to tell her, that we had had that discussion? She asked me to tell her [mother]. And her mother was initially comfortable that we had had that discussion. Then over the space of about two or three hours, became very agitated and very upset that we'd had it… it was a huge stress for the mother, whereas her daughter, although finding it very difficult, was actually able to have [the conversation] and was – in the end, I think, glad she had had it." (Chest Physician)* Although some young adults had also started to protect their parents from knowing the extent of their deteriorating health: *"Mum always used to sit in on consultations until, until I could get rid of her about three years ago. That made it really hard to*			

		talk about anything, because Mum obviously gets upset if you mention stuff like dying. So you have to be really careful. (23 year old with cystic fibrosis)			

7.3.5.2 Support before transition to adult services

Table 45: Summary of clinical evidence (GRADE-CERQual): Theme 1. Provision of information/ sharing knowledge

Study information			Quality assessment		
Number of studies	**Design**	**Description of theme or finding**	**Criteria**	**Rating**	**Overall**
Sub-theme 1: adequate and adapted information					
3 studies (Al-Yateem 2012, Al-Yateem 2013, Tierney 2013)	2 studies using interviews, and 1 study using focus groups	Three studies conducted in Ireland and the UK with young people and young adults with cystic fibrosis and healthcare professionals reported on the need for more information throughout the process of transition. ***Adequate information*** Participants noted a lack of adequate information about the transition process, especially about the different aspects of this process. One young adult with cystic fibrosis noticed a lack of detail: *"Ah, very little, almost nothing. I mean all they do is to tell you that you are transferring."* Another was not aware of the hospital or cystic fibrosis service to which he would be referred. He said: *"I don't really know, it might be either X hospital or Y hospital. I don't know we have to go and see. I don't know how they will be like?"* Lack of sharing knowledge led to unmet information needed for people with cystic fibrosis: *"Well the thing that they don't talk with us enough about cystic fibrosis, how it will be ... you know, and what it will be like in the future." (young adult with cystic fibrosis)* ***Adapted information*** Participants suggested that information should be appropriate to the person's age and developmental stage and supplemented with extra printed or digital material.	Limitation of evidence	Major limitations	VERY LOW QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Not saturated	

Study information			Quality assessment		
Number of studies	**Design**	**Description of theme or finding**	**Criteria**	**Rating**	**Overall**
		"Anyway, providing information should be given extra attention, and possibly information sessions could solve this problem" (young adult with cystic fibrosis). *Sources of information* Online forums were a good source of information for young adults about to transfer to adult services. As a person with cystic fibrosis stated: *"…since it was mentioned in the [adult] clinic about the forums…I went on there and it's a big eye opener that there's loads of people going through it, been through it, and they can just offer you a lot more advice from a patient side of it..."*			
Sub-theme 2: timely and gradual information					
1 study (Al-Yateem 2012)	1 study using interviews	In 1 study conducted in Ireland with young adults with cystic fibrosis, participants stated that information should be provided at a timely interval: *"Actually, we haven't been told about the transfer yet, nobody talked to us about it…"* *"Yes, I know about transition…last month the cystic fibrosis nurse told me that I will be going to another hospital next year when I turn 18…"*	Limitation of evidence	Major limitations	VERY LOW QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Not saturated	

Table 46: Summary of clinical evidence (GRADE-CERQual): Theme 2. Transition planning

Study information			Quality assessment		
Number of studies	**Design**	**Description of theme or finding**	**Criteria**	**Rating**	**Overall**
Sub-theme 1: gradual, timely and individualised transition					
5 studies (Al-Yateem 2012, Al-Yateem 2013, Brumfield	4 studies using interviews, and 1 study using focus groups	Five studies conducted in Australia, Ireland, the UK and the USA with young people and young adults with cystic fibrosis and healthcare professionals reported the need of careful transition planning, especially with regards to the timing	Limitation of evidence	Major limitations	LOW QUALITY
			Coherence of findings	Coherent	

2004,Tierney 2013, Tuchman 2008)		involved, The topic of transition with cystic fibrosis to adulthood should not be a new concept. ***Timely transition*** Some participants noted that the timing of transition seemed arbitrary and unfair: *"Actually, we haven't been told about the transfer yet, nobody talked to us about it…" (young adult with cystic fibrosis)* *"Yes, I know about transition…last month the cystic fibrosis nurse told me that I will be going to another hospital next year when I turn 18…" (young adult with cystic fibrosis)* *"And right now it's like, maybe in a year, but right now I'm, I've just gone off to college. It's like, I don't want to make that transition now. And they're like, well you need to. It's like, and you have patients here that are 30 years old and you're telling me I have to go?" (young adult with cystic fibrosis)* *"I think maybe if it wasn't just an all of a sudden strange situation. Slam the door behind you, you know. You're at university, you can't come back." (young adult with cystic fibrosis)* ***Structured transition service*** Participants stated that the service provided was amorphous and appeared to lack a comprehensive and coherent structure to transitional programming: *"There was no real discussion … it was just the cystic fibrosis nurse who told us last year that it would be when I finish the leaving cert. It would not be straight away when I turned 18, so it would be after." (young adult with cystic fibrosis)* Good paediatric care not only optimizes the health of people with cystic fibrosis, but also prepares them for a change to adulthood: *"Sometimes it was like he (paediatric doctor) could read your mind . . . he always eased you, whatever your problem was, if you had a problem, you always went out feeling better." (22 year old with cystic fibrosis)* One 18-year-old young adult with cystic fibrosis anticipating transition explained: *"I think it would have been easier if they*	Applicability of evidence	Applicable	
			Saturation	Saturated	

		would have really started pushing when I was younger. Like, even at 15 or 16, start really suggesting it. Really being like, you know you might want to look into this. You might want to start meeting some of the doctors over there." Positive and supportive attitude helped in transition from children to adult health services: *"He (paediatric doctor) really highly recommended Dr B. (adult doctor), which was good . . . the fact that he recommended him strongly would have helped." (21 year old with cystic fibrosis)* ***Individualised assessment and care*** Planning and care tailored for the individual person for transition was considered important: *"The assessment will highlight to us what the adolescents actually need, and what might affect his or her transition in terms of information, family, or any other issues". (young adult with cystic fibrosis)* *"It will be good for everyone [planning] adolescent, parents, and even us… everybody will know what to do" (healthcare professional).*			
Sub-theme 2: care coordinator					
1 study (Tierney 2013)	1 study using interviews	In 1 study conducted in the UK with young people and young adults, some interviewees believed their needs were neglected while they waited to move and described being uncertain about who was responsible for their care because they were straddled between 2 services: *".. they [paediatric staff] knew I was moving up so they'd gone a bit, put me last kind of thing, so I wasn't a priority because they knew I was going to be moving up soon that they'd lost interest but they were making sure that the younger ones were alright because they knew I was going soon" (young adult with cystic fibrosis).*	Limitation of evidence Coherence of findings Applicability of evidence Saturation	Minor limitations Coherent Applicable Not saturated	LOW QUALITY
Sub-theme 3: coordination with adult services					
1 study (Tierney 2013)	1 study using interviews	In 1 study conducted in the UK with young people and young adults, some participants described their feelings about moving	Limitation of evidence	Minor limitations	LOW QUALITY

		to adult services as superseded by procedural tasks, such as gathering relevant documents to forward to the adult team. *"… didn't seem to show interest in how you felt about moving over. It was more like we've sent your notes over to that side so we're just waiting for them to reply." (young adult with cystic fibrosis).* Young adults suggested that clinicians form paediatrics could be involved to provide continuous and optimal care: *"…he [paediatric consultant] could tell if I was ill. I've got like a problem with my stomach and he could feel straight away if I was having, if it was worse or if it was manageable…So he's known me for a long time. That's why I was worried about moving here…he knew a lot of the problems that I've had..." (young adult with cystic fibrosis).*	Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Not saturated	

7.3.5.3 Support after transition to adult services

Table 47: Summary of clinical evidence (GRADE-CERQual): Theme 1. Healthcare professionals and services configuration

Study information			Quality assessment		
Number of studies	**Design**	**Description of theme or finding**	**Criteria**	**Rating**	**Overall**
Sub-theme 1: planning and continuity in co-ordinated care					
4 studies (Brumfield 2004, Tierney 2013, Tuchman 2008, van Staa 2011)	4 studies using interviews	Four studies conducted in Australia, the Netherlands, the UK and the USA with young people and young adults with cystic fibrosis, parents and healthcare professionals reported that participants felt they have lost the resources available to them in the paediatric system. It is the abruptness of the transition that was most disruptive to participants, and lack of time and resources in the adult healthcare system. ***Familiarity*** Participants valued having a familiar face around after transition to adult services was reassuring for people with cystic fibrosis:	Limitation of evidence	Minor limitations	MODERATE QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Saturated	

Study information			Quality assessment		
Number of studies	Design	Description of theme or finding	Criteria	Rating	Overall
		"I knew her from before . . . even though it might not be a lot of contact with her, um, it was still a familiar face, and that was enough to give me reassurance in that regard." (20 year old with cystic fibrosis) ***Fracturing*** However, some participants reported that transition disrupts the bond which have developed between the person with cystic fibrosis and healthcare personnel looking after them. Some participants described being ignored and their need was not addressed during transition phase. As a young adult with cystic fibrosis stated: *"… didn't seem to show interest in how you felt about moving over. It was more like we've sent your notes over to that side so we're just waiting for them to reply."* Some interviewees believed their needs were neglected while they waited to move and described being uncertain about who was responsible for their care because they were straddled between 2 services: *".. they [paediatric staff] knew I was moving up so they'd gone a bit, put me last kind of thing, so I wasn't a priority because they knew I was going to be moving up soon that they'd lost interest but they were making sure that the younger ones were alright because they knew I was going soon" (young adult with cystic fibrosis).* One group suggested that handover should be staggered over time to make transition easier for young adults. *"I think staff from the ... hospital can come over here and do their first few clinics with adolescents…this might help… and we can give them better information about our patients"* ***Appraisal of the experience of transition***			

Study information			Quality assessment		
Number of studies	Design	Description of theme or finding	Criteria	Rating	Overall
		Some parents and young adults looked back at transfer as *'no big deal'* and even as *'peanuts*', when the process had been smooth or *'seamless'*. But most young adults and especially parents said it had been more stressful and difficult than anticipated. Parents and young adults said that paediatric was more warm and friendly. On the other hand, they used metaphors like *'being lost', 'falling into a deep hole', 'feeling abandoned'* and even *'waking up in a horror movie'* for adult care. However, this was seen as temporary; transition was perceived as a rite of passage: *"you have to get used to it, that's all."* A bad transition experience created a negative impact and discouraged people in seeking care. *"I always say to Mum that it's a waste of time going . . . I don't . . . I don't really trust them, because of the way they treat you, because you are a number . . . if it was up to me I probably wouldn't go back to clinic, but Mum has always told me that you've got to keep your foot in the door in case we need them (the clinic) . . . So I sort of go back on the off chance that I may need them." (22 year old with cystic fibrosis)* Another person stated that the service provided was amorphous and appeared to lack a comprehensive and coherent structure to transitional programming: *"There was no real discussion … it was just the cystic fibrosis nurse who told us last year that it would be when I finish the leaving cert. It would not be straight away when I turned 18, so it would be after."* This lack of structure created anxiety and negative feeling: *"I don't really like to come here…like, they don't do much for me…if they just listen I would have told them what I want to know…or how they can help…this is very annoying…"*			

Study information			Quality assessment		
Number of studies	**Design**	**Description of theme or finding**	**Criteria**	**Rating**	**Overall**
Sub-theme 2: adaptation and integration					
3 studies (Begley 2013, Tierney 2013, Van Staa 2011)	2 studies using interviews and 1 study using a survey	In 3 studies conducted in Ireland, the Netherlands and the UK with young people and young adults with cystic fibrosis, parents and healthcare professionals, participants highlighted the challenges encountered during this process: ***Not being understood*** Integrating with the adult services was a of the challenges for young adults and was difficult to begin with. They believed that their issues would not be easily understood in adult health services. *"…I was with them for so long I got to know them really well and they knew I was a fussy person. But I'm sure it will all be the same with the adults." (person with cystic fibrosis)* ***Different culture between paediatric and adult care*** Parents and young adults said that paediatric staff were more warm and friendly. On the other hand, they used metaphors like *'being lost', 'falling into a deep hole', 'feeling abandoned'* and *even 'waking up in a horror movie'* for adult care. However, this was seen as temporary; transition was perceived as a rite of passage: *"you have to get used to it, that's all."* Young adults noted that more independence and self-reliance was expected of them. Parents wondered whether their children could take up the full responsibility for their treatment. *"The adult care had a more 'business-like approach' which often contrasted with the paediatric 'holistic, system-oriented approach."*	Limitation of evidence	Minor limitations	MODERATE QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Unclear	

Study information			Quality assessment		
Number of studies	Design	Description of theme or finding	Criteria	Rating	Overall
		Young adults appreciated the efficiency of adult services whereas others were concerned about the shorter appointment with less information and the less frequent appointments: *"We used to do it (sputum test) every month in x hospital, but they just do it every 3 months in here, so you kind of stay anxious for a long time ... you don't know when the infection is going to hit … it will be late…"* *"It's just different. I mean I like how you kind of rush through it. It's not like where you have to talk to a million people. They don't seem as qualified there, it seems like the people that I talk to at Children's really knew what they were doing. Maybe it's because they don't talk to me as much."* Young people with cystic fibrosis and parents were also concerned about the lack of single rooms for people with cystic fibrosis, which lead to a fear of cross-infection: *"Young people and their parents have real concern re cross-infection in mixed wards. They do not want to share wards with elderly patients" (healthcare professional)* ***Transition at an early age*** Healthcare professionals found problematic for young people to be transferred at an "early age". *"Historically the age at which children attend adult services in this hospital is 14, which I consider too young and my training as an adult physician leaves me less able to deal with the 14-16 age group. I have difficulty in managing patients who in my mind are "children" and I find teenage/ adolescent emotional aspects of illness to be an unwelcome challenge" (healthcare professional)* ***Involvement in decision making***			

Study information			Quality assessment		
Number of studies	**Design**	**Description of theme or finding**	**Criteria**	**Rating**	**Overall**
		The main positive differences that subjects noted between paediatric and adult care were feeling greater control over and more involvement in decision making. (See overarching theme) One participant with cystic fibrosis who was very resistant to transition was impressed with the pulmonologist: *"She gave me this big talk about some of the new things [I'm] going to encounter as an adult with cystic fibrosis. And she just opened my eyes to a lot of things."*			
Sub-theme 3: holistic approach					
2 studies (Al-Yateem 2012, Depuis 2011)	2 studies using interviews	In 2 studies conducted in Canada and Ireland with young adults with cystic fibrosis, parents and healthcare professionals, participants suggested that the focus of some health professionals on clinical activities, rather than focusing on the actual individual needs of the young adult, was source of frustration in people with cystic fibrosis. *"People need to be looked at and listened to …and then you make your diagnosis from there, but sometimes they are over reliant on paperwork that is obsolete and doesn't give any function. It doesn't solve problems...". (young adult with cystic fibrosis)* Healthcare professionals in adult services appeared to concern themselves mainly with giving information around clinical parameters rather than dealing with emotional factors in young adults associated with transition. As stated by a healthcare professional: *"We talk to them about their medications, about physiotherapy, the respiratory therapist sees them at every visit to go over the techniques. But other times, we show them that their X-ray has deteriorated. We show them the film, we explain that it's important for them to take control. We shake them up a bit."*	Limitation of evidence	Major limitations	VERY LOW QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Not saturated	
Sub-theme 4: evaluation and follow up mechanisms					

Study information		Description of theme or finding	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
1 study (Al-Yateem 2013)	1 study using focus groups	In 1 study conducted in Ireland with healthcare professionals, it was suggested that monitoring the process can help to improve the care during transition. One participant said: *"Based on the transition plan you can later on evaluate whether the child has made any progress, or any further intervention might be needed".*	Limitation of evidence	Major limitations	VERY LOW QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Not saturated	

Table 48: Summary of clinical evidence (GRADE-CERQual): Theme 2. Psychosocial support

Study information		Description of theme or finding	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Sub-theme 1: family support					
1 study (Tierney 2013)	1 study using interviews	In 1 study conducted in the UK with young people and young adults with cystic fibrosis, the presence of parents was described as reassuring, especially during the early transition phase: *"…if my mum hadn't come, I wouldn't have asked half as many questions. I don't think I'd have been as open with the doctors talking to me…I think I'd have been a little bit more introvert and worried…I know it sounds dead daft, me mum was there and I'm 19 but because me mum was there I was more confident in asking questions because I knew if I'd said something that had come out a funny way or the wrong way, mum would go well what she actually means is this" (young person with cystic fibrosis).*	Limitation of evidence	Minor limitations	LOW QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Not saturated	
Sub-theme 2: support network					
1 study (Brumfield 2004)	1 study using interviews	In 1 study conducted in Australia with young adults with cystic fibrosis, a support network was considered important for transition. Participants noted they are anxious and the lack of support network does not help in fully utilising the services:	Limitation of evidence	Minor limitations	VERY LOW QUALITY
			Coherence of findings	Unclear	

Study information			Quality assessment		
Number of studies	**Design**	**Description of theme or finding**	**Criteria**	**Rating**	**Overall**
		"I go to clinic, and I go in and I come out as quickly as I can." (22 year old with cystic fibrosis)	Applicability of evidence	Unclear	
			Saturation	Not saturated	
Sub-theme 3: emotional support					
2 studies (Al-Yateem 2012, Tierney 2013)	2 studies using interviews	Two studies conducted in Ireland and the UK with young adults with cystic fibrosis reported on the lack of understanding of mental state and their needs during the transition period. Transition from children to adult healthcare setting created anxiety in people with cystic fibrosis: *"I am worried about the cutbacks in health and all when we move there (the new hospital), you know that with cystic fibrosis there are some cuts that you don't know when it's going to knock off…" (young person with cystic fibrosis).* Some participants who had transferred very recently felt ill-equipped emotionally to cope with this change. *"…the doctor did ask me "what do you want to do?"…in children's they wouldn't do that, they'd just say 'you need IVs, you should come in.' So it was quite a bit, it was a bit confusing because I didn't really know what to do myself. I was like, I don't know, you tell me what should I do" (young person with cystic fibrosis).*	Limitation of evidence	Major limitations	VERY LOW QUALITY
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Saturation	Not saturated	

7.3.6 Economic evidence

No economic evaluations related to the transition in cystic fibrosis were identified in the literature search conducted for this guideline. Full details of the search and economic article selection flow chart can be found in Appendix E and F, respectively.

This review question is not relevant for economic analysis because it does not involve a decision between alternative courses of action.

7.3.7 Evidence statements

7.3.7.1 Overarching themes

Transition as natural stage

Low quality evidence from 3 qualitative studies conducted with young people and young adults with cystic fibrosis, parents and healthcare professionals, noted that transition to adult services was seen as a natural and inevitable process. Most people with cystic fibrosis reported that as they grew up, healthcare professionals started to treat them as adults, and this was perceived as positive.

Parallel changes and planning

Low quality evidence from 2 qualitative studies conducted with young people and young adults with cystic fibrosis and parents highlighted that relocating to a new healthcare system is one a of several transitions young people with a long-term condition must face (for example going to university). Hence, transfer takes place against a backdrop of additional pressures and might not always be a top priority for the person. Young people and their parents are concerned and sad about the future, and the impact the illness will have in their personal life.

Independence in decision making

Moderate quality evidence from 5 qualitative studies with young people and young adults with cystic fibrosis, parents and healthcare professionals reported on the importance of being allowed to make choices, self-advocacy and build independence gradually. Young people and healthcare professionals recognised that young people should become more involved in decision making as they become adults. Many young participants actively led this process and welcomed the opportunity to lead discussions with healthcare professionals. In some instances, young people do not want parents to be involved in consultations or decision making anymore. Parents, however, wanted to be recognised as an integral part of the young person's care and found it difficult to accept the new family dynamic.

7.3.7.2 Support before transition to adult services

Provision of information or sharing of knowledge

Very low quality evidence from 3 qualitative studies conducted with young people and young adults with cystic fibrosis and healthcare professionals, reported on the information needs during transition. Participants noted the need for information in relation to different aspects of the process, such as the new place of care, and services structure. They also noted the information has to be adapted to the age and developmental stage of the person, and it should be provided at timely intervals.

Transition planning

Low quality evidence from 5 qualitative studies conducted with young people and young adults with cystic fibrosis and healthcare professionals reported on the need of careful transition planning, especially with regards to the timing involved. Participants felt transition should happen at the right time, not just because of arbitrary criteria, such as the person turning 18. They also highlighted the process should be clearly structured, with anticipated planning and coordination between paediatric and adult care. They noted the importance of having a care coordinator during the process, which helps the person navigating between both services. Ultimately, planning and care tailored for the individual person for transition were considered important.

7.3.7.3 Support after transition to adult services

Healthcare professionals and services configuration

Very low to moderate quality from 6 qualitative studies conducted with young people and young adults with cystic fibrosis, parents and healthcare professionals discussed the challenges faced during the transition process. Participants noted it would be useful to have a familiar person in the new setting; instead, they had to face disruption in the care received during the transition from paediatric to adult care. This made people with cystic fibrosis and parents feel lost, abandoned and anxious. They attributed this to the different care culture. These negative experiences had a negative impact in the long term for some people, but most participants agreed they finally were able to adapt to the new situation. Some participants, on the contrary, highlighted there were benefits, such as feeling greater control over and more involvement in decision making. In addition, people with cystic fibrosis and their parents noted healthcare professionals should not only focus on clinical information, but also on the emotional aspects related to transition.

Healthcare professionals suggested that monitoring the process can help improve the experience of transition to adult services.

Psychosocial support

Very low to low quality evidence from 4 qualitative studies conducted with young people and young adults with cystic fibrosis, participants highlighted the importance of having psychosocial support. Family and social support networks were seen as useful and were described as reassuring. They also noted the importance of understanding the mental state and the emotional needs of the people during this process.

7.3.7.4 Economic evidence statements

No evidence on cost-effectiveness in people with cystic fibrosis was available for this review.

7.3.8 Evidence to recommendations

7.3.8.1 Relative value placed on the outcomes considered

The aim of this review was to identify elements of the transition process (for example, transition planning involvement) from paediatric to adult services from the perspectives of young people with cystic fibrosis and their family and carers.

Although themes were identified from the literature, the committee identified some expected themes they thought would be important during protocol stage. They agreed that the following themes would provide useful perspectives: transition plan, transition lead, preparation period, involvement of young people and their family or carers in planning and

implementation, clarity about the process, coordination between paediatric and adult services, timing of transition and availability of information.

7.3.8.2 Consideration of clinical benefits and harms

The committee acknowledged the evidence and they thought that the themes and sub-level themes which emerged, or were derived from the evidence, were useful and relevant. They agreed the evidence matched their clinical observations. The committee also acknowledged the recommendations by the CF Trust and the NHS service specifications for cystic fibrosis.

The committee highlighted transition is a continual and stepwise process that does not stop when the young person is transferred to adult services. With regards to when transition should start, they agreed the transition process should start at the age of 12 and they should usually have moved to adult services before they reach 18 years. This is consistent with the recommendations made by the NHS service specifications for cystic fibrosis. They noted that the NICE guideline on transition from children's to adults' services for young people using health or social care services (NICE NG43) has a section on transition planning which includes guidance on when transition should happen. For example, the NICE NG43 guideline mentions that the point of transfer should not be based on a rigid age threshold, and should take place at a time of relative stability for the young person. They agreed paediatric services are not adequate for young people over 16. However, some flexibility should be allowed, for example if the young person is very unwell or approaching end of life.

As raised in the literature, the Committed discussed young people going through a number of transitions, for example going to university, when additional support may be needed. They also agreed it is important to respect individual needs and to note that young people mature at different rates.

When reviewing the evidence, the committee discussed the role of parents. As identified in the literature, the parent's role changes during transition. It is very important to work with both the young person and parents for transition to go smooth. They agreed there is a lack of recognition of parents in adult services. It was noted, for example, that in some cases parents are not allowed to attend adult consultations but they concurred that parents may be especially needed during the initial visits. They agreed it is important to respect the family dynamics and to ask parents how they want to be involved in their child's care. However, priority should always be given to the young person when deciding who should be involved in decision making.

With regards to the healthcare professionals that should be involved, the committee underlined that transition should take account of the whole MDT and not just the cystic fibrosis paediatricians. Paediatricians should play an important role in providing information that it is adequate to the young person's needs. They also agreed it is important to have a documented coordinated pathway to handover information from paediatric to adult services. As noted in the studies, some young people are concerned about the differences between paediatric and adult services. For example, some young people may be taken off prophylactic antibiotics after transition as it is not common practice in adult treatment.

As highlighted in the evidence, the committee noted the coordination between child and adult services is challenging. The committee noted that the NICE guideline on transition from children's to adults' services for young people using health or social care services (NICE NG43) has a section on overarching principles, which provides guidance on joint responsibility and working together with other organisations.

Moreover, as noted in the evidence, the committee thought it could be useful to have a named person for point of contact to coordinate and facilitate transition. This is common practice and it is consistent with the NHS Service Specifications for cystic fibrosis. In current practice, nurses are mostly responsible for coordinating and taking the lead, but they agreed it could be done by other members of the MDT. The committee noted that the NICE guideline

on transition from children's to adults' services for young people using health or social care services (NICE NG43) has a section on named workers.

Finally, the committee agreed it is important to seek continuous feedback to evaluate the transition process. This was also highlighted in the evidence, as healthcare professionals working with people with cystic fibrosis suggested that monitoring the transition process could help to improve care during transition. In addition, assessing the progress of the transition process allows them to identify if it is going according to plan or if any further interventions are needed.

7.3.8.3 Consideration of economic benefits and harms

This review question was not relevant for economic analysis because it does not involve a decision between alternative courses of action. Even so, there may be resource implications arising from the provision of any services that facilitate the transition from paediatric to adult services.

The committee stated that identifying an accountable healthcare professional to support a person's transition is often considered as ideal practice by clinics, and consequently not in place by all centres. Following this, the committee did not think significant additional expenditure was necessary to implement this across all centres. This was on the basis that the named worker role comprises a set of tasks to be done by an existing worker, rather than the creation of a new post. Furthermore, it is likely that the worker allocated these tasks will be undertaking many of them already as there is a continual flow of transitioning young people at every clinic. Instead, the committee advised that the recommendation will formalise the process and lead to more timely and accurate records to promote a coordinated, transparent and cost-effective transition.

Following this, the committee noted that existing guides on the process to prepare for transition such as "Ready Steady Go" developed by Southampton Children's Hospital, can be adapted for people with cystic fibrosis, providing a cost-effective solution to developing de novo guides.

The committee stated that paediatric and adult clinics see many transitions throughout the year and may continue to use established methods to conduct the transition without reviewing the pathways they follow and considering the opportunity cost of resources a transition requires. As a result, the committee prioritised a recommendation to review transition pathways, as pathways could be improved by deduplicating work, removing unnecessary or inefficient aspects of work and putting those resources into aspects that increase satisfaction and care.

7.3.8.4 Quality of evidence

Very low to moderate quality evidence was presented in this review as assessed by GRADE-CERQual. The main reasons leading to downgrading the quality of the evidence included:

- Many studies did not clearly report how they selected the participants and a few studies reported a low response rate from participants. The inclusion and exclusion criteria was not reported in most studies nor were the characteristics of the population. In most studies, the relationship between researchers, interviewers and participants was not described.
- Data collection relied on interviews in most studies, but the process was not always adequately described. Few studies included the list of questions used during the interview. Data saturation was generally not discussed.
- Most studies conducted thematic analysis, although the process was not always described in detail. For example, there were no discussions about validity or robustness of data. The role of the researchers in the analysis was not described. In general, themes

were supported by quotes, but most studies did not indicate whether saturation was achieved. When considering the evidence as a whole it did not appear very saturated as many themes were identified in a study and there were few quotes to support them.

7.3.8.5 Other considerations

The committee agreed the NICE guideline on transition from children's to adult's care (NG43) provides useful guidance. However, they noted that are some aspects that are unique for young people with cystic fibrosis, their families and carers. Therefore the recommendations related to this evidence review were based on the evidence and the committee's clinical experience. In addition, an overarching recommendation pointed to the NICE guideline on transition from children's to adults' services for young people using health or social care services (NICE NG43).

The committee discussed potential equality issues. They noted that young people who live far from a specialist centre may be disadvantaged. However, they agreed no additional recommendations were needed as the use of alternative models of care had already extensively been discussed in the service delivery review. See section 7.1 on service configuration.

The committee discussed whether a research recommendation was needed for this topic. They agreed the only research recommendation would be to develop a cystic fibrosis specific transition guideline or pathway for implementation across all centres. But they agreed this is an unnecessary use of resources given the fact that funding is finite and the NICE transition guideline recently developed would apply to cystic fibrosis, albeit with minor adaptation.

7.3.8.6 Key conclusions

The committee concluded that the transition from paediatric to adult services is an ongoing, stepwise process that should start when the young person is 12 years old and continue into adult services. Having a coordinated transition pathway is a useful tool to achieve a successful transition.

7.3.9 Recommendations

34. **Begin discussing the transition process to adult services with young people with cystic fibrosis when they are 12 years old, and with their family members or carers (as appropriate).**

35. **All cystic fibrosis services should have a coordinated and documented pathway for transition from children's to adults' services that includes plans for managing all cystic-fibrosis-related aspects of care.**

36. **Ask people with cystic fibrosis and their family members or carers (as appropriate) for feedback on the quality of the transition service, taking account of the section on planning and developing transition services in the NICE guideline on transition for young people using health or social care services.**

37. **For more guidance on managing transition from children's to adults' services, see the NICE guideline on transition for young people using health or social care services. In particular, see the sections on:**
    - transition planning, for guidance on when transition should happen
    - named workers
    - overarching principles, for guidance on joint responsibility and working together with other organisations.

8 Complications of cystic fibrosis

Review question: What are the non-lower-respiratory complications of cystic fibrosis in infants, children, young people and adults?

8.1 Introduction

Cystic fibrosis is a multifaceted genetic disease with a wide range of complications which depend upon genotype, environment and disease progression. Traditionally, progressive lung disease due to chronic infection and the impairment of pancreatic function have typified cystic fibrosis, resulting in premature death. However, the success of new-born screening programmes allows earlier intervention, slowing disease progression and altering the clinical manifestation of the condition. Also, with increasing longevity come unexpected complications due to the side-effects of treatment regimens, as well as those associated with older age.

Thus, a range of other co-morbidities are becoming increasingly apparent and the traditional view of cystic fibrosis is increasingly disfavoured as other organ systems are involved and have a significant effect on the person's health. This review question aims to determine the key health problems associated with a diagnosis of cystic fibrosis. It focuses on non-lower-respiratory complications since lower airway disease is addressed in detail in the rest of the guideline.

The results are presented separately for each complication.

See study selection flow chart in Appendix F, study evidence tables in Appendix G, and list of excluded studies in Appendix H.

8.2 Malnutrition

8.2.1 Description of clinical evidence: malnutrition

The aim of this review was to determine the prevalence of malnutrition among adults with cystic fibrosis, and the prevalence of vitamin deficiency among people of all ages. This section includes studies on adult or mixed populations or studies on vitamin deficiency with people of all ages. Please see the following section on impaired growth for studies focusing on children and young people.

We requested data to the UK CF registry on the percentage of adults with body mass index (BMI) under or over the cut-offs for normal nutritional status as outlined in the consensus document on nutritional management of cystic fibrosis published by the CF Trust in 2016 (CF Trust 2016). Data from the registry should be prioritised according to the protocol. We also looked for observational studies because they would provide data on indicators not included in the registry. We aimed to prioritise prospective cohort studies, but only included a prospective cross-sectional study and 4 retrospective studies. We prioritised studies from more relevant contexts (the UK in the first instance, then countries in Western Europe, Australia or North America). We also prioritised studies with more recent data for each indicator of malnutrition. Moreover, we prioritised studies that disaggregated data between infants, children, young people and adults; as well as studies that reported prevalence at different points in time and studies that were based on registries.

For full details see review protocol in Appendix D.

We included data obtained from the UK CF registry for the year 2015. This data referred to 5701 people with cystic fibrosis aged >16 years. In addition to these data, we included 3 studies on malnutrition defined by indicators such as BMI, height percentile or BMI

percentile. One study (Moen 2011) was a prospective multicentre study conducted in Denmark, Norway and Sweden from 2003 to 2006. This study included 347 adults with cystic fibrosis. One study (Stephenson 2013) used data from the Toronto CF registry for 3 time intervals: 1985-1990, 1991-1999, and 2000-2011. This study included 909 people with cystic fibrosis attending an adult clinic. 1 study (Vieni 2013) used data from 2 centres in Italy from 2007. This study included 393 people with cystic fibrosis aged >6 years.

We included 2 retrospective studies on vitamin deficiency. One study (Chavasse 2004) used data from a CF clinic in the UK for 1999-2001. This study included 290 people with cystic fibrosis aged 1-18. One study (Rana 2014) used data from 3 paediatric centres in Australia for 2007-2010. This study included 530 people with cystic fibrosis aged ≤18 years.

8.2.2 Summary of included studies and results: malnutrition

A summary of the studies that were included in this review are presented in Table 49.

Table 49: Summary of included studies

Study	Register / Data source	Dates	Participants	Prevalence: overall results and results by age group - % (n/N)	Definitions of complication and measurement tools	Quality of the study
Data request to UK CF registry	UK CF registry	2015	5701 people with cystic fibrosis aged >16 years	Age group: >16 BMI < 20 kg/m^2: 24.5% (1398/5701) BMI > 25 kg/m2: 22.2% (1266/5701)	Cystic fibrosis care teams at every specialist centre and clinic across the UK entered data on weight, height and BMI for the registry. The following cut-offs were used: Requires additional nutritional support: • BMI <20 kg/m2 • Overweight: • >25 kg/m2	Moderate • Details on the people in the registry and on how data is collected for the registry are available in the UK Cystic Fibrosis Trust Registry 2015 Annual Data Report and on the CF Trust website. However it is unclear from these sources if weight and height were measured using objective, standard criteria or reliably.

Study	Register / Data source	Dates	Participants	Prevalence: overall results and results by age group - % (n/N)	Definitions of complication and measurement tools	Quality of the study
Moen 2011 Scandinavia (Denmark, Norway and Sweden) Prospective cross-sectional study	Multicentre study - 7 centres	September 2003-May 2006	347 adults with cystic fibrosis Age: ≥ 18 years	BMI<19.0 kg/m2: 18% (62/347) BMI<18.5 kg/m2: 13% (44/347)	• Thresholds: • BMI < 19.0 kg/m2 • BMI < 18.5 kg/m2 • Measurements: • Weight was measured in the morning wearing undergarments. • Height was measured with no stockings or shoes and the means of 3 measurements were recorded.	High
Stephenson 2013 Canada Retrospective study	Toronto CF registry	1985-1990; 1991-1999; 2000-2011	909 people with cystic fibrosis attending the Adult CF Clinic in Toronto Age not reported	Nutritional status of people attending the clinic between 2000 and 2011 (n=651), using their last recorded measurement: • Underweight: 17% • Adequate weight: 60% • Overweight: 18% • Obese: 3.8% Prevalence calculated using 1000 random measurements per time interval: Underweight • 1985-1990: 20.6% • 1991-1999: 11.6% • 2000-2011: 11.1% Overweight: • 1985-1990: 7.0% • 1991-1999: 15.8% • 2000-2011: 18.4%	• Underweight status was defined as BMI<18.5 kg/m2 • Adequate weight was defined as 18.5-24.9 kg/m2 • Overweight was defined as BMI 25-29.9 kg/m2 • Obese was defined as BMI ≥30 kg/m2 Definitions as per WHO BMI guidelines.	Low • Age not reported for each cohort • No numerators provided

Study	Register / Data source	Dates	Participants	Prevalence: overall results and results by age group - % (n/N)	Definitions of complication and measurement tools	Quality of the study
Vieni 2013 Italy Retrospective study	Regional Centre in Palermo and Satellite Centre in Messina, Italy	December 2007	393 people with cystic fibrosis Age: >6 years	Height percentile <5th: 24.4% BMI percentile <10th (paediatric) or BMI <18.5 kg/m2 (adults): 35.3%	Height percentile <5th BMI percentile <10th (paediatric) or BMI <18.5 kg/m2 (adults)	Low • Data are not disaggregated by age subgroup • No numerators provided
Vitamin deficiency						
Chavasse 2004 UK Retrospective study	Data from specialist paediatric CF clinic	August 1999-April 2001	290 people with cystic fibrosis Age: 1 to 18 years	25-hydroxyvitamin D (25-OHD) • < 15 nmol/l: 1% (4/290) • < 25 nmol/l: 6% (17/290)	25-OHD was measured by an in-house, competitive protein-binding assay following extraction and chromatography of 25-OHD on silicic acid, performed at Charing Cross Hospital.	Moderate • Data not disaggregated between infants, children, young people and adults
Rana 2014 Australia Retrospective audit	Data from 3 paediatric CF Centres	2007-2010	530 people with cystic fibrosis Age: ≤18 years • 301/470 took fat soluble-vitamin supplementation	Vitamin A deficiency: • 2007: 11.17% • 2010: 13.13% Vitamin D deficiency: • 2007: 22.11% • 2010: 20.22% Vitamin E deficiency: • 2007: 15.54% • 2010: 13.89% Deficiency of one or more fat-soluble vitamins on their first vitamin level test: 45% (240/530) Vitamin A levels: • Abnormal: 23.4% (123/526) * • Low: 15% (80/526) 25-OHD vitamin levels: • Abnormal: 19.8% (65/328) • Low: 19% (63/328)	Vitamins A and E levels were performed using protein precipitation with high-performance liquid chromatography (HPLC) and ultraviolet detection (in-house method). Vitamins A and E reference ranges varied in each laboratory due to historical reasons. The reference range at CHW was vitamin A (0.8–2.5 mmol/L), vitamin E (12–36 mmol/L); at JHCH, vitamin A (1.05–2.50 mmol/L), vitamin E (8–30 mmol/L). The reference range for vitamins	Very low • Numerators and denominators not provided for vitamin deficiency • Data not disaggregated between infants, children, young people and adults • Unclear why prevalence of low vitamin levels at first vitamin test is different from prevalence of vitamin

Study	Register / Data source	Dates	Participants	Prevalence: overall results and results by age group - % (n/N)	Definitions of complication and measurement tools	Quality of the study
				Vitamin E levels: • Abnormal: 38.4% (201/523) • Low: 20% (105/523)	A and E at SCH varied based on the child's age. 25-OHD was measured by radioimmunoassay (Diasorin, Stillwater, MN, USA). Deficiency of 25-OHD was defined as <50 nmol/L.	deficiency in 2007 • The range for normal levels of vitamins differs between the laboratories taking part in the study.

Abbreviations: BMI: Body Mass Index; CF: cystic fibrosis; HPLC: high-performance liquid chromatography; kg/m2: kilograms per square metre; mmol/l: milimoles per litre; WHO: World Health Organization; 25-OHD: 25-hydroxyvitamin D
** Percentage calculated by NGA technical team*

8.2.3 Evidence statements: malnutrition

Moderate quality evidence from the UK CF Registry with 5701 people with cystic fibrosis aged >16 found that the prevalence of those who required additional nutritional support (defined as BMI < 20 kg/m2) was 24.5% and the prevalence of overweight (defined as BMI > 25 kg/m2) was 22.2% in 2015.

High quality evidence from 1 study with 347 adults with cystic fibrosis attending 7 centres in Denmark, Norway and Sweden found that the prevalence of malnutrition defined as BMI<19.0 kg/m2 was 18% and the prevalence of malnutrition defined as BMI <18.5 kg/m2 was 13% between 2003 and 2006.

Low quality evidence from 1 study with 909 people with cystic fibrosis attending an adult clinic in Toronto found that the prevalence of underweight (defined as BMI<18.5 kg/m^2) was 17%, the prevalence of overweight (defined as BMI 25-29.9 kg/m2) was 18% and the prevalence of obesity (defined as BMI≥30 kg/m2) was 3.8%, using the last recorded measurement for each person between 2000 and 2011. Using 1000 random measurements per time interval, the prevalence of underweight was 20.6% in 1985-1990, 11.6% in 1991-1999, 11.1% in 2000-2011 and the prevalence of overweight was 7.0% in 1985-1900, 15.8% in 1991-1999, and 18.4% in 2000-2011.

Low quality evidence from 1 study with 393 people with cystic fibrosis aged >6 years from 2 centres in Italy found that the prevalence of height percentile <5th was 24.4%, and the prevalence of either BMI percentile <10th or BMI <18.5 kg/m2 (depending on the age) was 35.3% in 2007.

Moderate quality evidence from 1 study with 290 people with cystic fibrosis aged 1-18 attending a clinic in the UK found that the prevalence of 25-hydroxyvitamin D (25-OHD)< 15 nmol/l was 1% and the prevalence of 25-OHD < 25 nmol/l was 6% between 1999 and 2001.

Very low quality from 1 study with 530 people with cystic fibrosis aged ≤18 years attending 3 paediatric centres in Australia found that the prevalence of vitamin A deficiency was 11.17% in 2007 and 13.13% in 2010, the prevalence of vitamin D deficiency was 22.11% in 2007 and 20.22% in 2010, the prevalence of vitamin E deficiency was 15.54% in 2007 and 13.89% in 2010. Prevalence of deficiency of 1 or more fat-soluble vitamins was 45% on first vitamin level test. Prevalence of abnormal vitamin A levels was 23.4% and of low vitamin A levels

was 15% on first vitamin level test. Prevalence of abnormal vitamin 25-OHD levels was 19.8% and of low vitamin 25-OHD levels was 19% on first vitamin level test. Prevalence of abnormal vitamin E levels was 38.4% (201/523) and of low vitamin E levels was 20% (105/523) on first vitamin level test.

8.2.3.1 Economic evidence statements

No evidence on cost-effectiveness in people with cystic fibrosis was available for this review.

8.3 Impaired growth

8.3.1 Description of clinical evidence: impaired growth

The aim of this review was to determine the prevalence of impaired growth among infants, children and young people with cystic fibrosis.

We requested data to the UK CF registry on the percentage of children and young people with BMI percentile below the cut-off for additional nutritional support or above the cut-off for overweight as outlined in the consensus document on nutritional management of cystic fibrosis published by the CF Trust in 2016. Data from the registry should be prioritised according to the protocol. We also looked for observational studies because they would provide data on indicators not included in the registry. We aimed to prioritise prospective cohort studies, but only included 1 prospective cross-sectional study and 4 retrospective studies. We prioritised studies from more relevant contexts (the UK in the first instance, then countries in Western Europe, Australia or North America). We also prioritised studies with more recent data for each indicator of impaired growth. Moreover, we prioritised studies that disaggregated data between infants, children, young people and adults; as well as studies that reported prevalence at different points in time and studies that were based on registries.

For full details see review protocol in Appendix D.

We included data obtained from the UK CF registry for the year 2015. This data referred to 3383 people with cystic fibrosis aged 2 to 16 years. In addition to these data, we included 5 studies on impaired growth. Older studies were included because they provided data on indicators or age sub-groups not covered by more recent studies. Four studies used data from the CF Foundation National Registry in the United States. One study (Heltshe 2014) used data for 2004-2009. This study included 1992 infants and children with cystic fibrosis aged 0-24 months. One study (Zhang 2013) used data from 1994-2008 to calculate pubertal peak height velocity. This study included 1862 people with cystic fibrosis aged 10 to 18 years old. One study (Lai 2008) used data from 2002. This study included 14702 people with cystic fibrosis aged less than 20 years old. One study (Zhang 2010) used data from the CF Foundation Patient Registry in the United States from 1986 to 2005. This study included 3306 people with cystic fibrosis aged 2-18.5. This study provided the most recent data relating to Himes adjusted percentiles. One study (Lucidi 2009) was a prospective multicentre study with 10 Italian CF centres from 2005 to 2006. It included 892 people with cystic fibrosis aged 1 month to 18 years.

8.3.2 Summary of included studies and results: impaired growth

A summary of the studies that were included in this review are presented in Table 50.

Table 50: Summary of included studies

Study	Register / Data source	Dates	Participants	Prevalence: overall results and results by age group - % (n/N)	Definitions of complication and measurement tools	Quality of the study
Data request to UK CF registry	UK CF registry	2015	3383 people with cystic fibrosis aged 2 to 16 years	• Age 2-11: • BMIp < 25th: 17.3% (432/2498) • BMIp>91st: 10.1% (253/2498) • Age 12-16: • BMIp < 25th: 27.5% (243/885) • BMIp>91st: 5.9% (52/885) Age 2-16: • BMIp < 25th: 20.0% (675/3383) • BMIp>91st: 9.0% (305/3383)	Cystic fibrosis care teams at every specialist centre and clinic across the UK entered data on weight, height and BMI for the registry. The following cut-offs were used: Requires additional nutritional support: • <25th BMIp • Overweight: • > 91st BMIp	Moderate • Details on the people in the registry and on how data is collected for the registry are available in the UK CF Registry 2015 Annual Data Report and on the CF Trust website. However it is unclear from these sources if weight and height were measured using objective, standard criteria or reliably.
Heltshe 2014 United States Retrospective study	US CF Foundation National Registry	January 2004-December 2009	1992 infants and children with cystic fibrosis Age: 0 to 24 months	Age 12 months (N=374): • weight for age <10th: 11% • weight for age <5th: 8.3% • weight for age <2.5th: 3.7% • weight velocity (GUO-US) <50th: 48.1% • weight velocity (WHO)<50th: 30.5% • weight velocity <10th (WHO): 6.4%	Thresholds: • WHO standardized 2.5th, 5th, and 10th percentiles for weight and length for age • Guo et. al. US (Guo-US) 50th percentile for weight velocity and length velocity (as recommended by the CFF infant care guidelines) • WHO standardized 2.5th, 5th, 10th,	Moderate. • Numerators are not provided

Study	Register / Data source	Dates	Participants	Prevalence: overall results and results by age group - % (n/N)	Definitions of complication and measurement tools	Quality of the study
				• weight velocity<5th (WHO): 4.5% • weight velocity<2.5th (WHO): 3.5% • length for age <10th: 26.8% • length for age <5th: 17.7% • length for age <2.5th: 10.4% • length velocity (GUO-US) <50th: 45.7% • length velocity <50th (WHO): 38.4% • length velocity <10th (WHO): 20.7% • length velocity<5th (WHO): 13.4% • length velocity<2.5th (WHO): 13.4% Age 24 months (N=317): • weight for age <10th: 6.9% • weight for age <5th: 2.8% • weight for age <2.5th: 1.9% • weight velocity (GUO-US) <50th: 59.3% • weight velocity (WHO)<50th: 51.1% • weight velocity <10th (WHO): 18.3% • weight velocity<5th (WHO): 12.6% • weight velocity<2.5th (WHO): 8.2%	and 50th percentiles for weight and length velocity	

Study	Register / Data source	Dates	Participants	Prevalence: overall results and results by age group - % (n/N)	Definitions of complication and measurement tools	Quality of the study
				• length for age <10th: 24.9% • length for age <5th: 17% • length for age <2.5th: 11.4% • length velocity (GUO-US) <50th: 57.4% • length velocity <50th (WHO): 58.7% • length velocity <10th (WHO): 30.3% • length velocity<5th (WHO): 24.3% • length velocity<2.5th (WHO): 19.9%		
Lai 2008 United States Retrospective cross-sectional study	US CF Foundation Patient Registry	2002	14702 people with cystic fibrosis Age: <20 years	2002 CFF definition of underweight (Height percentile<5th or BMIp<10th or % Ideal Body Weight<90): 33.0% Corrected classification of underweight ((Height percentile <5th or BMIp<10th): 26.8% BMIp<50th: 56.8%	2002 CFF definition: • Age <2 y old: Height percentile <5th, % Ideal Body Weight <90%, or weight for height percentile <10th. • Ages 2–20 y: Height percentile <5th, % Ideal Body Weight <90%, or BMIp <10th • Corrected classification: elimination of % Ideal Body Weight <90% as an indicator of underweight Below BMI goal: • Age<2 y old: Weight for height percentile <50th.	Very low • Unclear why different definitions for infants were not taken into account in the results • Unclear how many infants, children, young people and adults • Results not disaggregated by age subgroup • Unclear if weight and height were measured consistently

Study	Register / Data source	Dates	Participants	Prevalence: overall results and results by age group - % (n/N)	Definitions of complication and measurement tools	Quality of the study
					• Ages 2-20 y old: BMIp <50th.	
Lucidi 2009 Italy Prospective cross-sectional study	Multicentre study – 10 Italian CF centres	January 2005-December 2006	892 people with cystic fibrosis Age range: 1 month to 18 years Mean age: 9.2	0-2 years (Height for age percentile: n=104; Weight for length percentile: n=101): Height for age percentile<5th: 15.4% Height for age percentile 5th-25th: 18.3% Weight for length percentile<10th: 12.9% Weight for length percentile 10th - 25th: 22.7% 2-18 years (n=788): Height for age percentile <5th: 11.8% Height for age percentile 5th-25th: 29.3% BMIp<15th: 20.9% BMIp 15th-25th: 9.6% BMIp<50th: 54.4% 10-14 years (n=179): Height for age percentile<5th: 11.7% BMIp<15th: 20.1% 14-18 years (n=183): Height for age percentile <5th: 21.9% BMIp<15th: 27.9% 0-18 years (n=892): Height for age percentile <5th: 12.2% Height for age percentile 5th-25th: 28%	Nutritional failure was defined as Height for age percentile <5th (all ages), Weight for length percentile <10th (<2 years), BMIp<15th (2-18 years) Risk of malnutrition: Height for age percentile 5th-25th (all ages), Weight for length percentile 10th-25th (<2 years), BMIp 15th-25th (2-18 years) Height and weight were measured (when the patient was in a stable clinical condition) by specifically trained personnel. Reproducibility in anthropometric measurement was evaluated by comparing measures obtained with standard instruments in all centres with those obtained with reference instruments in a sample of patients.	Moderate: • No numerators • Some age subgroups included less than 250 people

Study	Register / Data source	Dates	Participants	Prevalence: overall results and results by age group - % (n/N)	Definitions of complication and measurement tools	Quality of the study
Zhang 2010 United States Retrospective study	CFF Patient Registry	1986-2005	3306 people with cystic fibrosis Age: 2 to 18.5 years	• Unadjusted height percentile <5th: 16% • Unadjusted height percentile <10th: 26% • Himes adjusted height percentile <5th: 18% • Himes adjusted height percentile: <10th: 31% • CFF lower bound method: 24%	Procedure to calculate CFF target height and range (lower bound method): 1. Average 2 parental heights to obtain mid-parental height. Calculate the child's target adult height by adding 6.5 cm to mid-parental height for a boy, or subtracting 6.5 cm for a girl. Apply ±10 cm for a boy or ±9 cm for a girl to define the target height range. 2. Plot target height and range at age 20 years on the 2000 CDC growth chart and estimate their respective percentiles. 3. Extrapolate the percentiles of target height and range at age 20 to the child's current age. 4. Plot the child's height on the 2000 CDC growth chart; if his/her height percentile is below the target height lower bound, he/she is considered to be below genetic potential. Procedure to calculate Himes adjusted height 1. Calculate mid-parental height. 2. Based on the child's sex, age,	Moderate • Self-reported parental heights

Study	Register / Data source	Dates	Participants	Prevalence: overall results and results by age group - % (n/N)	Definitions of complication and measurement tools	Quality of the study
					height and mid-parent height, find the adjustment value from the reference tables. 3. Apply the adjustment value to the child's height to obtain adjusted height. 4. Plot adjusted height on the 2000 CDC growth chart to obtain adjusted height percentile.	
Zhang 2013 Unites States Retrospective study	US CF Foundation Registry	PHV was calculated in relation to time interval 1994-2008. Registry records from 1986-2008 were used to identify participants.	1862 people with cystic fibrosis born in 1984-87. Age: 10 to 18 years.	Pubertal peak height velocity (PHV) • Normal: 60.3% (1123/1862) • Delayed: 9.4% (175/1862) • Attenuated: 20.8% (387/1862) • Delayed and attenuated: 5.3% (98/1862) • Unknown: 4.2% (79/1862)	Longitudinal standard for peak height velocity for North American children developed by Tanner and Davies were used to define normal PHV. PHV was classified either as normal, delayed (PHV age at 2 SD later than average), attenuated (magnitude<5th percentile), or both delayed and attenuated.	High

Abbreviations: BMIp: BMI percentile; BMI: Body Mass Index; CDC: Centre for Disease Control and Prevention; CF: Cystic Fibrosis; CFF: Cystic Fibrosis Foundation; PHV: Peak Height Velocity; WHO: World Health Organization

8.3.3 Evidence statements: impaired growth

Moderate quality evidence from the UK CF Registry found that the prevalence of children who required additional nutritional support (defined as BMIp<25th) was 17.3% and the prevalence of overweight (defined as BMIp>91st) was 10.1% in 2015. The same evidence found that the prevalence of young people aged 12-16 who required additional nutritional support (defined as BMIp<25th) was 27.5% and the prevalence of overweight (defined as BMIp>91st) was 5.9% in 2015. The same evidence found that the prevalence of children and young people aged 2-16 requiring additional nutritional support (defined as BMIp<25th) was 20.0% and the prevalence of overweight (defined as BMIp>91st) was 9.0%.

Moderate quality evidence from 1 study with infants and children with cystic fibrosis aged 0-24 months in the US CF Foundation Registry found that the prevalence of impaired growth at 12 months was the following between 2004 and 2009, depending on the definition used:

- weight for age <10th: 11%
- weight for age <5th: 8.3%
- weight for age <2.5th: 3.7%
- weight velocity (GUO-US) <50th: 48.1%
- weight velocity (WHO)<50th: 30.5%
- weight velocity <10th (WHO): 6.4%
- weight velocity<5th (WHO): 4.5%
- weight velocity<2.5th (WHO): 3.5%
- length for age <10th: 26.8%
- length for age <5th: 17.7%
- length for age <2.5th: 10.4%
- length velocity (GUO-US) <50th: 45.7%
- length velocity <50th (WHO): 38.4%
- length velocity <10th (WHO): 20.7%
- length velocity<5th (WHO): 13.4%
- length velocity<2.5th (WHO): 13.4%
- The same study found that the prevalence of impaired growth at 24 months was the following between 2004 and 2009, depending on the definition used:
- weight for age <10th: 6.9%
- weight for age <5th: 2.8%
- weight for age <2.5th: 1.9%
- weight velocity (GUO-US) <50th: 59.3%
- weight velocity (WHO)<50th: 51.1%
- weight velocity <10th (WHO): 18.3%
- weight velocity<5th (WHO): 12.6%
- weight velocity<2.5th (WHO): 8.2%
- length for age <10th: 24.9%
- length for age <5th: 17%
- length for age <2.5th: 11.4%
- length velocity (GUO-US) <50th: 57.4%
- length velocity <50th (WHO): 58.7%
- length velocity <10th (WHO): 30.3%
- length velocity<5th (WHO): 24.3%
- length velocity<2.5th (WHO): 19.9%

Very low quality evidence from 1 study with 14702 people aged less than 20 years old registered in the US CF Foundation Patient Registry found that the prevalence of underweight defined as either height percentile <5th or BMIp<10th or %IBW<90 was 33.0%, the prevalence of underweight defined as height percentile <5th or BMIp < 10th was 26.8%, and the prevalence of people below BMI goal defined as BMIp<50th was 56.8% in 2002.

Moderate quality evidence from 1 study with 892 people with cystic fibrosis aged 1 month to 18 years from 10 Italian centres found that between 2005 and 2006 the prevalence of malnutrition defined as HAP<5th was 15.4% and the prevalence of malnutrition defined as

WLP<10th was 12.9% among infants and children aged 0-2 years. The prevalence of the risk of malnutrition defined as HAP 5th-25th was 18.3% and the prevalence of the risk of malnutrition defined as WLP 10th -25th was 22.7% in the same age group. Among people aged 2-18 years, the prevalence of malnutrition defined as HAP<5th was 11.8% and the prevalence of malnutrition defined as BMIp<15th was 20.9%. The prevalence of the risk of malnutrition defined as HAP 5th-25th was 29.3% and the prevalence of the risk of malnutrition defined as BMIp 15th-25th was 9.6% in the same age group. The prevalence of BMIp<50th was 54.4% in the same age group. Among people aged 10-14, the prevalence of malnutrition defined as HAP<5th was 11.7% and the prevalence of malnutrition defined as BMIp<15th was 20.1%. Among people aged 14-18 years, the prevalence of malnutrition defined as HAP<5th was 21.9% and the prevalence of malnutrition defined as BMIp<15th was 27.9%. Among people aged 0-18 years old, the prevalence of malnutrition defined as HAP<5th was 12.2% and the prevalence of the risk of malnutrition defined as HAP 5th-25th was 28%.

Moderate quality evidence from a study with 3306 people with cystic fibrosis aged 2-18.5 from the CF Foundation Patient Registry of the United States found that the prevalence of impaired growth was the following between 1986 and 2005, depending on the definition used: Unadjusted height percentile <5th: 16%; unadjusted height percentile <10th: 26%; Himes adjusted height percentile <5th: 18%; Himes adjusted height percentile: <10th: 31%; CFF lower bound method: 24%.

High quality evidence from a study with 1862 people with cystic fibrosis aged 10-18 registered in the CF Foundation Patient Registry of the United States found that the prevalence of attenuated but not delayed pubertal peak velocity (magnitude <5th percentile) was 20.8%, the prevalence of attenuated and delayed pubertal peak velocity (PHV age at 2SD later than average and magnitude <5th percentile) was 5.3% between 1994 and 2008.

8.4 Cystic fibrosis related renal disease

8.4.1 Description of clinical evidence: cystic fibrosis related renal disease

The aim of this review was to determine the prevalence of cystic fibrosis related renal disease among infants, children and young people with cystic fibrosis.

We extracted data from the UK CF Registry on renal failure and kidney stones. Data from the UK CF Registry should be prioritised according to the protocol, however the committee believed that the registry was likely to underreport the prevalence of renal failure because routine measurements of renal function are not very reliable; moreover it does not provide prevalence data for chronic kidney disease and acute kidney injury; therefore we also looked for observational studies on these complications. We aimed to prioritise prospective cohort studies, but only included 2 retrospective studies. We aimed to prioritise studies from more relevant contexts (the UK in the first instance, then countries in Western Europe, Australia or North America) and more recent studies.

For full details see review protocol in Appendix D.

We included data from the UK CF Registry for the year 2015 on 9587 people with cystic fibrosis. In addition to these data, we included 2 studies. One study (Quon 2011) used data from the CF Foundation Registry in the United States for 2001-2008. This study included 11912 adults with cystic fibrosis. One study (Wilcock 2015) used data from a database of an adult CF centre in the UK for 1969-2009. This study included 1532 people with cystic fibrosis.

8.4.2 Summary of included studies and results: cystic fibrosis related renal disease

A summary of the studies that were included in this review are presented in Table 51.

Table 51: Summary of included studies

Study	Register / Data source	Dates	Participants	Prevalence: overall results and results by age group - % (n/N)	Definitions of complication and measurement tools	Quality of the study
Cystic Fibrosis Trust UK, 2016 Registry annual data report	UK CF Registry	2015	9587 people with cystic fibrosis • <16 years: 3845 • ≥16 years: 5742	Kidney stones: • <16 years: 0.3% (12/3845) • ≥16 years: 1.5% (84/5742) • Overall: 1.0% (96/9587) • Renal failure: • <16 years: 0% (<5) • ≥16 years: 1.0% (55/5742) • Overall: 0.6% (57/9587)	Cystic fibrosis care teams at every specialist centre and clinic across the UK filled in forms where they selected what complications (if any) each person with cystic fibrosis had. No definition of complications is provided in the form.	Moderate • Criteria used to diagnose the complication and consistency of diagnosis across centres were unclear
Quon 2011 United States Retrospective study	CF Foundation Registry	2001-2008	11912 adults with cystic fibrosis Age ≥18 years	Mean annual prevalence of chronic kidney disease (stage 3 or greater): • 18-25 years old: 0.6% • Older than 55 years old: 19.2% • All ages: 2.3% Mean annual prevalence of stage 4 or greater CKD: 0.7% Mean annual prevalence of stage 5 CKD: 0.6%	CKD was defined by eGFR measured less than 60 ml/min/1.73 m2 in 2 consecutive registry years. Based on National Kidney Foundation KDOQI guidelines, this corresponds to stage 3 CKD severity and is the earliest stage that can be diagnosed using serum creatinine alone. More advanced stages of CKD were defined as follows: stage 4, eGFR less than 30 ml/min/1.73 m2; and stage 5, eGFR less than 15 ml/min/1.73 m2 or need for haemodialysis.	Moderate • No numerators or denominators
Wilcock 2015 UK	Database of adult CF department at the	1969-2009	1532 people with cystic fibrosis	• Renal problem: 5.1% (78/1532) • Acute kidney injury: 1.1% * (17/1532) (9	• AKI was defined as an acute rise in creatinine above the person's	Moderate • Percentage not provided for some conditions

Study	Register / Data source	Dates	Participants	Prevalence: overall results and results by age group - % (n/N)	Definitions of complication and measurement tools	Quality of the study
Retrospective study	Royal Brompton Hospital		• Age: Not reported	cases were presumed to be drug-induced) • Chronic kidney disease: 0.9% * (13/1532) (4 cases were presumed to be drug-induced) • Renal stone disease: 2.0% (30/1532) • Isolated proteinuria: 0.1% * (2/1532) • Isolated haematuria: 0.5% * (8/1532) • Nephrotic syndrome: 0.1%* (2/1532) • Miscellaneous disease: 0.5% * (8/1532)	established baseline; • CKD as an abnormal creatinine level for greater than 3 months; • Nephrotic syndrome as proteinuria (>3g/l), hypoalbuminaemia and peripheral oedema. Cases were excluded if: • isolated rise in plasma urea which resolved with no other evidence of renal impairment • impaired renal function in the last few weeks of life • nephrotoxic immunosuppressant therapy before any episode of renal disease	(calculated by the NGA technical team) • Study subjects were not described in detail

Abbreviations: AKI: Acute Kidney; CF: cystic fibrosis; CKD: Chronic Kidney Disease; Injury
** Percentage calculated by the NGA technical team*

8.4.3 Evidence statements: cystic fibrosis related renal disease

Moderate quality evidence from a report on 9587 people with cystic fibrosis from the UK CF Registry found that in 2015 the prevalence of kidney stones was 0.3% amongst children and young people aged <16, 1.5% amongst young people and adults aged 16 years and over, and 1.0% amongst people of all ages.

Moderate quality evidence from a report on 9587 people with cystic fibrosis from the UK CF Registry found that in 2015 the prevalence of renal failure was 0% amongst children and young people aged 10-15, 1.0% amongst young people and adults aged 16 years and over, and 0.6% amongst people of all ages.

Moderate quality evidence from a study on 11912 people with cystic fibrosis aged 18 years and over registered in the CF Foundation Registry in the United States found that between 2001 and 2008 the mean annual prevalence of chronic kidney disease (stage 3 or greater) was 0.6% among people aged 18-25, 19.2% among people older than 55 years old, and

2.3% among people of all ages. The mean annual prevalence of stage 4 or greater CKD was 0.7% and the mean annual prevalence of stage 5 CKD was 0.6%.

Moderate quality evidence from a study on 1532 people with cystic fibrosis from the adult department of a centre in the UK found that between 1969 and 2009 the prevalence of renal problems was 5.1%; the prevalence of acute kidney injury was 1.1%; the prevalence of CKD was 0.9%.

8.4.3.1 Economic evidence statements

No evidence on cost-effectiveness in people with cystic fibrosis was available for this review.

8.5 Delayed puberty

8.5.1 Description of clinical evidence: delayed puberty

The aim of this review was to determine the prevalence of delayed puberty among people with cystic fibrosis.

The UK CF Registry did not provide prevalence data on this complication; therefore we looked for observational studies. We only identified 1 study eligible for inclusion.

For full details see review protocol in Appendix D.

One study (Zhang 2013) used data from the CF Foundation Registry in the United States for 1994-2008. This study included 1862 people with cystic fibrosis aged 10-18 years old.

8.5.2 Summary of included studies and results: delayed puberty

A summary of the studies that were included in this review are presented in Table 52.

Table 52: Summary of included studies

Study	Register / Data source	Dates	Participants	Prevalence: overall results and results by age group - % (n/N)	Definitions of complication and measurement tools	Quality of the study
Zhang 2013 Unites States Retrospective study	US CF Foundation Registry	PHV was calculated in relation to time interval 1994-2008. Registry records from 1986-2008 were used to identify	1862 people with cystic fibrosis born in 1984-87. Age: 10 to 18 years.	Pubertal peak height velocity (PHV) • Normal: 60.3% (1123/1862) * • Delayed: 9.4% (175/1862) * • Attenuated: 20.8% (387/1862) * • D&A: 5.3% (98/1862) * • Unknown: 4.2% (79/1862) *	Longitudinal standard for peak height velocity for North American children developed by Tanner and Davies were used to define normal PHV. PHV was classified either as normal, delayed (PHV age at 2 SD later than average), attenuated (magnitude<5th percentile), or both delayed and attenuated (D&A).	High

Study	Register / Data source	Dates	Participants	Prevalence: overall results and results by age group - % (n/N)	Definitions of complication and measurement tools	Quality of the study
		partici pants.				

Abbreviations: CF: cystic fibrosis; D&A – Delayed and Attenuated; PHV: Peak Height Velocity
**Numerator calculated by NGA technical team*

8.5.3 Evidence statements: delayed puberty

High quality evidence from a study with 1862 people with cystic fibrosis aged 10-18 from the CF Foundation Patient Registry of the United States found that the prevalence of delayed but not attenuated pubertal peak velocity (PHV age at 2SD later than average) was 9.4% and the prevalence of attenuated and delayed pubertal peak velocity (PHV age at 2SD later than average and magnitude <5th percentile) was 5.3% between 1994 and 2008.

8.5.3.1 Economic evidence statements

No evidence on cost-effectiveness in people with cystic fibrosis was available for this review.

8.6 Abdominal pain

8.6.1 Description of clinical evidence: abdominal pain

The aim of this review was to determine the prevalence of abdominal pain among infants, children and young people with cystic fibrosis.

The UK CF Registry does not provide prevalence data on this complication. Therefore, we looked for relevant observational studies. However, we found no evidence for this complication.

For full details see review protocol in Appendix D.

8.6.2 Summary of included studies and results: abdominal pain

No evidence was found on the prevalence of this complication among people with cystic fibrosis.

8.6.3 Evidence statements: abdominal pain

No clinical or cost-effectiveness evidence was found on the prevalence of this complication among people with cystic fibrosis.

8.7 Cystic Fibrosis related diabetes

8.7.1 Description of clinical evidence: cystic fibrosis related diabetes

The aim of this review was to determine the prevalence of Cystic Fibrosis Related Diabetes (CFRD) amongst people with cystic fibrosis. We looked for data in the UK CF Registry 2015. This provided the prevalence of people on treatment for CFRD. This data was included because data from the UK CF Registry was prioritised according to the protocol. However only considering people on treatment would underestimate the prevalence of CFRD. Therefore we also looked for observational studies, excluding studies where CFRD was defined based on treatment use only. We aimed to prioritise prospective cohort studies, but

only included retrospective studies. We prioritised studies from more relevant contexts (the UK in the first instance, then countries in Western Europe, Australia or North America). We also prioritised studies with more recent data and studies that disaggregated data between infants, children, young people and adults; as well as studies that reported prevalence at different points in time and studies that were based on registries.

We included data from the UK CF Registry for the year 2015 on 6970 people with cystic fibrosis aged ≥10 years. In addition to data from the UK CF Registry, we included 3 studies. One study (Lewis 2015) used data from the Minnesota Cystic Fibrosis database (United States) from 2008 to 2012. This study included 462 people with cystic fibrosis. One study (Moran 2009) used the same database to calculate prevalence at different points in time (1992-97, 1998-2000, 2003-2008) based on 872 people. Another study (Bell 2011) used the Australian CF registry data from 2009. This study included 2986 people with cystic fibrosis.

8.7.2 Summary of included studies and results: cystic fibrosis related diabetes

A summary of the studies that were included in this review are presented in Table 53.

Table 53: Summary of included studies

Study	Register / Data source	Dates	Participants	Prevalence: overall results and results by age subgroups - % (n/N)	Definition of complication and measurement tools	Quality of the study
Cystic Fibrosis Trust UK, 2016 Registry annual data report	UK CF Registry	2015	6970 people with cystic fibrosis aged ≥10 years	Treatment for CFRD: • 10-16 years: 10.0% (134/1624) • ≥16 years: 32.2% (1848/5346) • ≥10 years: 28.0% (1982/6970)	Cystic fibrosis care teams at every specialist centre and clinic across the UK filled in forms where they selected what complications (if any) each person with cystic fibrosis had. No definition of complications is provided in the form.	Moderate • Criteria used to diagnose the complication and consistency of diagnosis across centres were unclear
Bell 2011 Australia Retrospective study	Australian CF Registry	2009	2986 people with cystic fibrosis Median age: 17.6 years	Insulin-dependent diabetes (chronic): • 0-11 years: 0.5% (5/951) • 12-17 years: 13.6% (61/448) • ≥18 years: 20.7% (144/697) • All age groups: 10.0% (210/2096) Insulin-dependent diabetes (intermittent): • 0-11 years: 0% (0/951) • 12-17 years: 1.1% (5/448)	Not reported	Moderate • Unclear criteria for measuring the condition • Unclear if different centres across Australia would measure the condition consistently

Study	Register / Data source	Dates	Participants	Prevalence: overall results and results by age subgroups - % (n/N)	Definition of complication and measurement tools	Quality of the study
				• ≥18 years: 2.3% (16/697) • All age groups: 1.0% (21)		
Lewis 2015 United States Retrospective study	Data from people seen at the UNM CF centre	September 2008-December 2012	462 people Age: ≥ 20 years	CFRD: 48% (221/462)	Diabetes diagnosed by "standard criteria".	Moderate • Criteria to diagnose CFRD not reported • Unclear if there was consistency to diagnose CFRD across the centre
Moran 2009 United States Retrospective study	Minnesota Cystic Fibrosis Database	Prevalence at the end of 3 consecutive intervals: 1992-1997, 1998-2002, 2003-2008	872 people with cystic fibrosis followed at the University of Minnesota Cystic Fibrosis Centre Age: not reported	CFRD prevalence at the end of the interval: (%): • 1992-97: 20% +-2% • 1998-2000: 30% +-2% • 2003-2008: 33% +-2% Prevalence of CFRD in September 2008: • Children < 11 years: 2% (2/93) (both without fasting hyperglycaemia). • Young people aged 11-17, 19% (14/75) (4 with fasting hyperglycaemia). • Adults aged ≥18: 43%* (155/359)	CFRD was diagnosed by standard criteria including persistent random glucose levels>200mg/dl (11.1 mmol/l) and persistent fasting glucose levels >126 mg/dl (7.0 mmol/l) or by OGTT. People with a fasting glucose ≥126 mg/dl (7.0 mmol/l) were diagnosed with CFRD with fasting hyperglycaemia. People with a fasting glucose 126 mg/dl (7.0 mmol/l) and a 2-h glucose ≥200 mg/dl (11.1 mmol/l) were diagnosed with CFRD without fasting hyperglycaemia. Routine annual OGTT screening has been recommended at the University of	Moderate • No numerator or denominator provided for prevalence calculated at the end of the interval

Study	Register / Data source	Dates	Participants	Prevalence: overall results and results by age subgroups - % (n/N)	Definition of complication and measurement tools	Quality of the study
					Minnesota since the early 1990s for patients aged ≥6 years (1.75 g/kg glucose [maximum 75g]). OGTTs are performed when patients are in their usual baseline state of health.	

Abbreviations: CF: cystic fibrosis; CFRD: Cystic Fibrosis Related Diabetes; g: grams; kg: kilograms; mmol/ l: milimoles per litre; OGTT: Oral Glucose Tolerance Test; SD: Standard deviation.
** Percentage calculated by NGA technical team*

8.7.3 Evidence statements: cystic fibrosis related diabetes

Moderate quality evidence from a report on from on 9587 people with cystic fibrosis from the UK CF Registry found that in 2015 the prevalence of people on treatment for CFRD was 10.0% among children and young people aged 10-16, 32.2% among young people and adults aged 16 years and over, and 28.0% among all people aged 10 years and over.

Moderate quality evidence from 1 study with 2986 people with cystic fibrosis from the Australian CF Registry found that om 2009 the prevalence of chronic insulin-dependent diabetes was 0.5% among infants and children aged 0-11, 13.6% among young people aged 12-17, 20.7% among adults aged 18 and over, and 10.0% among all age groups. The prevalence of intermittent insulin-dependent diabetes was 0% among infants and children aged 0-11, 1.1% among children aged 12-17, 2.3% among adults aged 18 years and over, 1.0% among all age groups.

Low quality evidence from 1 study with 462 people attending a CF centre in the United States found that the prevalence of CFRD was 48% among adults aged 20 years and over between 2008 and 2012.

Moderate quality evidence from 1 study with 872 people attending a CF centre in the United States found that the prevalence of CFRD was 20%+-2% at the end of the interval 1992-1997, 30%+-2% at the end of the interval 1998-2000, 33%+-2% at the end of the interval 2003-2008. The prevalence of CFRD in 2008 was 2% among infants and children aged less than 11 years, 19% amongst children and young people aged 11-17 and 43% among adults aged 18 years and over.

8.7.3.1 Economic evidence statements

No evidence on cost-effectiveness in people with cystic fibrosis was available for this review.

8.8 Upper airways disease

8.8.1 Description of clinical evidence: upper airways disease

The aim of this review was to determine the prevalence of upper airways disease among people with cystic fibrosis. We included data from the UK CF Registry for the year 2015 on 9587 people with cystic fibrosis. Data provided by the registry was prioritised therefore we did not include any studies from the published literature.

For full details see review protocol in Appendix D.

8.8.2 Summary of included studies and results: upper airways disease

A summary of the studies that were included in this review are presented in Table 54.

Table 54: Summary of included studies

Study	Register / Data source	Dates	Participants	Prevalence: overall results and results by age subgroups - % (n/N)	Definition of complication and measurement tools	Quality of the study
Cystic Fibrosis Trust UK, 2016 Registry annual data report	UK CF Registry	2015	9587 people with cystic fibrosis • <16 years: 3845 • ≥16 years: 5742	Nasal polyps requiring surgery: • <16 years: 1.1% (44/3845) • ≥16 years: 3.1% (177/5742) • Overall: 2.3% (221/9587) • Sinus disease • <16 years: 1.4% (53/3845) • ≥16 years: 15.4% (886/5742) • Overall: 9.8% (939/9587)	Cystic fibrosis care teams at every specialist centre and clinic across the UK filled in forms where they selected what complications (if any) each person with cystic fibrosis had. No definition of complications is provided in the form.	Moderate • Criteria used to diagnose the complication and consistency of diagnosis across centres were unclear

Abbreviations: ABPA: Allergic bronchopulmonary aspergillosis; CF: cystic fibrosis

8.8.3 Evidence statements: Upper airways disease

Moderate quality evidence from a report on 9587 people with cystic fibrosis from the UK CF Registry found that in 2015 the prevalence of nasal polyps requiring surgery was 1.1% among children and young people aged <16, 3.1% among young people and adults aged 16 years and over, and 2.3% among people of all ages.

Moderate quality evidence from a report on 9587 people with cystic fibrosis from the UK CF Registry found that in 2015 the prevalence of sinus disease was 1.4% among children and young people aged <16, 15.4% among young people and adults aged 16 years and over, and 9.8% among people of all ages.

8.8.3.1 Economic evidence statements

No evidence on cost-effectiveness in people with cystic fibrosis was available for this review.

8.9 Cystic fibrosis related musculoskeletal disorders

8.9.1 Description of clinical evidence: cystic fibrosis related musculoskeletal disorders

The aim of this review was to determine the prevalence of cystic fibrosis related musculoskeletal disorders among people with cystic fibrosis.

We extracted data from the UK CF Registry on the prevalence of arthritis and arthropathy. Data from the UK CF Registry should be prioritised according to the protocol, however, the committee believed that the registry was likely to underreport the prevalence of these complications as they are common in the general population and centres may not regard them as a cystic fibrosis specific complication. Therefore we also looked for observational studies. We aimed to prioritise prospective cohort studies but only found 1 retrospective study eligible for inclusion.

For full details see review protocol in Appendix D.

We included data from the UK CF Registry for the year 2015 on 9587 people with cystic fibrosis. In addition to these data, the included study (Watts 2009) used data from the CFF Patient Registry in the United States from 2004. This study included 22714 people with cystic fibrosis.

8.9.2 Summary of included studies and results: Cystic fibrosis related musculoskeletal disorders

A summary of the studies that were included in this review are presented in Table 55.

Table 55: Summary of included studies

Study	Register / Data source	Dates	Participants	Prevalence: overall results and results by age subgroups - % (n/N)	Definition of complication and measurement tools	Quality of the study
Cystic Fibrosis Trust UK, 2016 Registry annual data report	UK CF registry	2015	9587 people with cystic fibrosis • <16 years: 3845 • ≥16 years: 5742	Arthritis: • <16 years: 0.2% (7/3845) • ≥16 years: 2.6% (151/5742) • Overall: 1.6% (158/9587) Arthropathy: • <16 years: 0.5% (18/3845) • ≥16 years: 8.7% (499/5742) • Overall: 5.4% (517/9587) •	Cystic fibrosis care teams at every specialist centre and clinic across the UK filled in forms where they selected what complications (if any) each person with cystic fibrosis had. No definition of complications is provided in the form.	Moderate • Criteria used to diagnose the complication and consistency of diagnosis across centres were unclear
Watts 2009 United States	CFF Patient Registry	2004	22714 people with cystic fibrosis Age: not reported for the	Bone and joint complications: 6.7% (1510/22714) *	Bone and joint complications include arthritis/arthropathy, bone fractures, osteopenia, osteoporosis	Very low • No separate data for each complication

Study	Register / Data source	Dates	Participants	Prevalence: overall results and results by age subgroups - % (n/N)	Definition of complication and measurement tools	Quality of the study
Retrospective study			overall cohort			• Unclear how complications were diagnosed and whether they were diagnosed consistently • Data not disaggregated by age subgroup

Abbreviations: CF: cystic fibrosis
**Prevalence calculated by the NGA technical team*

8.9.3 Evidence statements: cystic fibrosis related musculoskeletal disorders

Moderate quality evidence from a report on 9587 people with cystic fibrosis from the UK CF Registry found that in 2015 the prevalence of arthritis was 0.2% among children and young people aged <16, 2.6% among young people and adults aged 16 years and over, and 1.6% among people of all ages.

Moderate quality evidence from a report on 9587 people with cystic fibrosis from the UK CF Registry found that in 2015 the prevalence of arthropathy was 0.5% among children and young people aged <16, 8.7% among young people and adults aged 16 years and over, and 5.4% among people of all ages.

Very low quality from 1 study on 22714 people with cystic fibrosis from the CF Foundation Patient Registry in the United States found that the prevalence of bone and joint complications was 6.7% in 2004.

8.9.3.1 Economic evidence statements

No evidence on cost-effectiveness in people with cystic fibrosis was available for this review.

8.10 Urinary stress incontinence

8.10.1 Description of clinical evidence: urinary stress incontinence

The aim of this review was to determine the prevalence of urinary stress incontinence among people with cystic fibrosis.

The UK CF Registry 2015 Annual Data Report did not provide prevalence data on this complication. Therefore, we looked for relevant observational studies. However, we found no evidence for this complication.

For full details see review protocol in Appendix D.

8.10.2 Summary of included studies and results: urinary stress incontinence

No evidence was found on the prevalence of this complication among people with cystic fibrosis.

8.10.3 Evidence statements: urinary stress incontinence

No evidence was found on the prevalence of this complication among people with cystic fibrosis.

8.11 Reduced bone mineral density

8.11.1 Description of clinical evidence: reduced bone mineral density

The aim of this review was to determine the prevalence of reduced bone mineral density among people with cystic fibrosis.

We extracted data from the UK CF Registry on the prevalence of osteopenia, osteoporosis and bone fractures. Data from the UK CF Registry should be prioritised according to the protocol, however, the committee believed that the registry was likely to underreport the prevalence of reduced bone mineral density as these complications can only be diagnosed by DXA scan for which the take-up of these is not good, so many cases will be undiscovered. Therefore we also looked for observational studies on this complication. We aimed to prioritise prospective cohort studies, but only included 2 retrospective studies. We aimed to prioritise studies from more relevant contexts (the UK in the first instance, then countries in Western Europe, Australia or North America) and more recent studies but only 2 studies, both on data from 2009, were eligible for inclusion.

For full details see review protocol in Appendix D.

We included data from the UK CF Registry for the year 2015 on 9587 people with cystic fibrosis. In addition to this data, we included 2 studies. One study (Bell 2011) used data from the Australian CF registry for 2009. It included 2986 people with cystic fibrosis. One study (Somerville 2013) used data from the CF Registry of Ireland. It included 859 people with cystic fibrosis.

8.11.2 Summary of included studies and results: reduced bone mineral density

A summary of the studies that were included in this review are presented in Table 56.

Table 56: Summary of included studies

Study	Register / Data source	Dates	Participants	Prevalence: overall results and results by age subgroups - % (n/N)	Definition of complication and measurement tools	Quality of the study
Cystic Fibrosis Trust UK, 2016 Registry annual data report	UK CF Registry	2015	9587 people with cystic fibrosis • <16 years: 3845 • ≥16 years: 5742	Osteopenia: • <16 years: 0.9% (36/3845) • ≥16 years: 22.0% (1261/5742) • Overall: 13.5% (1297/9587) Osteoporosis: • <16 years: 0% (<5/3845)	Cystic fibrosis care teams at every specialist centre and clinic across the UK filled in forms where they selected what complications (if any) each person with cystic fibrosis	Moderate • Criteria used to diagnose the complication and consistency of diagnosis across

Study	Register / Data source	Dates	Participants	Prevalence: overall results and results by age subgroups - % (n/N)	Definition of complication and measurement tools	Quality of the study
				• ≥16 years: 8.8% (507/5742) • Overall: 5.3% (511/9587) Bone fracture: • <16 years: 0.4% (14/3845) • ≥16 years: 0.6% (32/5742) • Overall: 0.5% (46/9587)	had. No definition of complications is provided in the form.	centres were unclear
Bell 2011 Retrospective study	Australian CF Registry	2009	2986 people with cystic fibrosis Median age: 17.6 years	Osteopenia: • 0-11 years: 0.3% (3/951) • 12-17 years: 3.3% (15/448) • ≥18 years: 25.0% (174/697) • All age groups: 9.2% (192/2096) Osteoporosis: • 0-11 years: 0.2% (2/951) • 12-17 years: 1.3% (6/448) • ≥18 years: 9.5% (66/697) • All age groups: 3.7% (77/2096) Fractures in 2009: • 0-11 years: 0% (0/951) • 12-17 years: 0.4% (2/448) • ≥18 years: 1.3% (9/697) • All age groups: 0.5% (10/2096)	Not reported	Moderate • Unclear criteria for measuring the condition • Unclear if different centres across Australia would measure the condition consistently
Somerville 2013 Ireland Retrospective study	CF Registry of Ireland	All people alive on 31/12/2009. Data recorded from 2001	859 people with cystic fibrosis*	Osteopenia or osteoporosis: • <18 years: 5.5% (25/454) ¥ • ≥18 years: 42.7% (173/405)	Considered present if documented in the in the medical notes in the last year	Low • N used in the analysis was different from reported N but this was not mentioned by the authors

Study	Register / Data source	Dates	Participants	Prevalence: overall results and results by age subgroups - % (n/N)	Definition of complication and measurement tools	Quality of the study
						• No denominator was provided for one age subgroup • No baseline characteristics were provided for people younger than 18

Abbreviations: CF: cystic fibrosis
** N calculated by NGA technical team*
¥Denominator calculated by NGA technical team

8.11.3 Evidence statements: reduced bone mineral density

- Moderate quality evidence from a report on 9587 people with cystic fibrosis from the UK CF Registry found that in 2015 the prevalence of osteopenia was 0.9% among children and young people aged <16, 22.0% among young people and adults aged 16 years and over, and 13.5% among people of all ages.
- Moderate quality evidence from a report on 9587 people with cystic fibrosis from the UK CF Registry found that in 2015 the prevalence of osteoporosis was 0% among children and young people aged <16, 8.8% among young people and adults aged 16 years and over, and 5.3% among people of all ages.
- Moderate quality evidence from a report on 9587 people with cystic fibrosis from the UK CF Registry found that in 2015 the prevalence of bone fractures was 0.4% among children and young people aged <16, 0.6% among young people and adults aged 16 years and over, and 0.5% among people of all ages.
- Moderate quality evidence from a study on 2986 people with cystic fibrosis from the Australian CF registry found that in 2009 the prevalence of osteopenia was 0.3% among infants and children aged 0-11, 3.3% among young people aged 12-17, 25.0% among adults, 9.2% among people of all ages. The prevalence of osteoporosis was 0.2% among infants and children aged 0-11, 1.3% among young people aged 12-17, 9.5% among adults, 3.7% among people of all ages. The prevalence of fractures was 0% among infants and children aged 0-11, 0.4% among young people aged 12-17, 1.3% among adults, 0.5% among people of all ages.
- Low quality evidence from a study on 859 people with cystic fibrosis from the CF Registry of Ireland found that in 2009 the prevalence of osteopenia or osteoporosis was 5.5% among people aged <18 years, and 42.7% among people aged ≥18 years.

8.11.3.1 Economic evidence statements

No evidence on cost-effectiveness in people with cystic fibrosis was available for this review.

8.12 Cystic fibrosis related liver disease

8.12.1 Description of clinical evidence: cystic fibrosis related liver disease

The aim of this review was to determine the prevalence of cystic fibrosis related liver disease among people with cystic fibrosis. We included data from the UK CF Registry for the year 2015 on 9587 people with cystic fibrosis. The data provided by the registry was prioritised therefore we did not include any studies from the published literature.

For full details see review protocol in Appendix D.

8.12.2 Summary of included studies and results: cystic fibrosis related liver disease

A summary of the studies that were included in this review are presented in Table 57.

Table 57: Summary of included studies

Study	Register / Data source	Dates	Participants	Prevalence: overall results and results by age subgroups - % (n/N)	Definition of complication and measurement tools	Quality of the study
Cystic Fibrosis Trust UK, 2016 Registry annual data report	UK CF registry	2015	9587 people with cystic fibrosis • <16 years: 3845 • ≥16 years: 5742	Raised liver enzymes: • <16 years: 6.9% (264/3845) • ≥16 years: 14.8% (852/5742) • Overall: 11.6% (1116/9587) Liver disease: • <16 years: 8.8% (340/3845) • ≥16 years: 18.0% (1031/5742) • Overall: 14.3% (1371/9587) Cirrhosis with no portal hypertension: • <16 years: 0.7% (26/3845) • ≥16 years: 1.6% (90/5742) • Overall: 1.2% (116/9587) Cirrhosis with portal hypertension: • <16 years: 0.7% (26/3845) • ≥16 years: 2.4% (138/5742) • Overall: 1.7% (164/9587)	Cystic fibrosis care teams at every specialist centre and clinic across the UK filled in forms where they selected what complications (if any) each person with cystic fibrosis had. No definition of complications is provided in the form.	Moderate • Criteria used to diagnose the complication and consistency of diagnosis across centres were unclear

Abbreviations: CF: cystic fibrosis

8.12.3 Evidence statements: cystic fibrosis related liver disease

Moderate quality evidence from a report on 9587 people with cystic fibrosis from the UK CF Registry found that in 2015 the prevalence of raised liver enzymes was 6.9% among children and young people aged <16, 14.8% among young people and adults aged 16 years and over, and 11.6% among people of all ages.

Moderate quality evidence from a report on 9587 people with cystic fibrosis from the UK CF Registry found that in 2015 the prevalence of liver disease was 8.8% among children and young people aged <16, 18.0% among young people and adults aged 16 years and over, and 14.3% among people of all ages.

Moderate quality evidence from a report on 9587 people with cystic fibrosis from the UK CF Registry found that in 2015 the prevalence of cirrhosis with no portal hypertension was 0.7% among children and young people aged <16, 1.6% among young people and adults aged 16 years and over, and 1.2% among people of all ages.

Moderate quality evidence from a report on 9587 people with cystic fibrosis from the UK CF Registry found that in 2015 the prevalence of cirrhosis with portal hypertension was 0.7% among children and young people aged <16, 2.4% among young people and adults aged 16 years and over, and 1.7% among people of all ages.

8.12.3.1 Economic evidence statements

No evidence on cost-effectiveness in people with cystic fibrosis was available for this review.

8.13 Infertility

8.13.1 Description of clinical evidence: infertility

The aim of this review was to determine the prevalence of infertility among people with cystic fibrosis.

The UK CF Registry does not provide prevalence data on this complication. Therefore, we looked for relevant observational studies. However, we found no evidence for this complication.

For full details see review protocol in Appendix D.

8.13.2 Summary of included studies and results: infertility

No evidence was found on the prevalence of this complication among people with cystic fibrosis.

8.13.3 Evidence statements: infertility

No evidence was found on the prevalence of this complication among people with cystic fibrosis.

8.14 Distal Intestinal Obstruction Syndrome (DIOS)

8.14.1 Description of clinical evidence: Distal Intestinal Obstruction Syndrome (DIOS)

The aim of this review was to determine the prevalence of distal intestinal obstruction syndrome among people with cystic fibrosis.

The UK CF Registry provided data on intestinal obstruction, rather than on distal intestinal obstruction syndrome; therefore we also looked for observational studies on this complication. We aimed to prioritise prospective cohort studies, but only included 1 retrospective study. We prioritised studies from more relevant contexts (the UK in the first instance, then countries in Western Europe, Australia or North America). We also requested data to the registry on intestinal obstruction disaggregated by a history of meconium ileus, because the committee agreed that prevalence may vary considerably between people with or without a history of meconium ileus.

For full details see review protocol in Appendix D.

We included data from the UK CF Registry for the year 2015 on 9587 people with cystic fibrosis. In addition to these data, we included 1 study. This study (Wiedemann 2001) used data from the CF Quality Assurance Project Registry for 1997. This study included 3448 people with cystic fibrosis.

8.14.2 Summary of included studies and results: Distal Intestinal Obstruction Syndrome (DIOS)

A summary of the studies that were included in this review are presented in Table 58.

Table 58: Summary of included studies

Study	Register / Data source	Dates	Participants	Prevalence: overall results and results by age subgroups - % (n/N)	Definition of complication and measurement tools	Quality of the study
Cystic Fibrosis Trust UK, 2016 Registry annual data report	UK CF Registry	2015	9587 people with cystic fibrosis • <16 years: 3845 • ≥16 years: 5742	Intestinal obstruction: • <16 years: 3.0% (116/3845) • ≥16 years: 7.4% (423/5742) • Overall: 5.6% (539/9587)	Cystic fibrosis care teams at every specialist centre and clinic across the UK filled in forms where they selected what complications (if any) each person with cystic fibrosis had. No definition of complications is provided in the form.	Moderate • Criteria used to diagnose the complication and consistency of diagnosis across centres were unclear
Data request to UK CF registry	UK CF Registry	2015	9587 people with cystic fibrosis • Age <16: 3845 • Age≥16: 5742	Intestinal obstruction in age group <16: • Diagnosis of meconium ileus: • 6.4% (41/643) • No diagnosis of meconium ileus: 2.3% (75/3202) Intestinal obstruction in age group ≥16: • Diagnosis of meconium ileus: 13.9% (113/815)	Cystic fibrosis care teams at every specialist centre and clinic across the UK entered data on meconium ileus and intestinal obstruction for the registry.	Moderate • Details from the people in the registry are available in the UK Cystic Fibrosis Trust Registry 2015 Annual Data Report and

Study	Register / Data source	Dates	Participants	Prevalence: overall results and results by age subgroups - % (n/N)	Definition of complication and measurement tools	Quality of the study
				• No diagnosis of meconium ileus: 6.3% (310/4927)		on the CF Trust website. However criteria used to diagnose the complication and consistency of diagnosis across centres were unclear from these sources
Wiedemann 2001 Germany Retrospective study	CF Quality Assurance Project registry	1997	3448 people with cystic fibrosis Age range: 0-58	DIOS • Children and young people (age not reported): 3.0% • Adults (age not reported): 3.5% • All ages: 3.2%	Criteria used to diagnose DIOS not reported. Centres reported data for each person once a year from a routine visit near the person's birthday when the person was in a stable clinical condition.	Low • Unclear how DIOS was diagnosed and whether it was diagnosed consistently across centres. • Age cut-off to define age subgroups was unclear • Numerators and denominators not provided. • Data was not disaggregated between children and young people

Abbreviations: CF: cystic fibrosis; DIOS: Distal Intestinal Obstruction Syndrome

8.14.3 Evidence statements: Distal Intestinal Obstruction Syndrome (DIOS)

Moderate quality evidence from a report on 9587 people with cystic fibrosis from the UK CF Registry found that in 2015 the prevalence of intestinal obstruction was 3.0% among children and young people aged <16, 7.4% amongst young people and adults aged 16 years and over, and 5.6% amongst people of all ages.

Moderate quality evidence from the UK CF Registry with 9587 people found that in 2015 the prevalence of intestinal obstruction was 6.4% among children and young people aged <16 with a diagnosis of meconium ileus, and 2.3% among children and young people aged <16 without a diagnosis of meconium ileus. The same evidence found that the prevalence of intestinal obstruction was 13.9% among people aged ≥16 with a diagnosis of meconium ileus and 6.3% among people aged ≥16 without a diagnosis of meconium ileus.

Low quality evidence from a study on 3448 people with cystic fibrosis from the Quality Assurance Project registry in Germany found that in 1997 prevalence of DIOS was 3.0% among children and young people, 3.5% among adults, and 3.2% among all ages.

8.14.3.1 Economic evidence statements

No evidence on cost-effectiveness in people with cystic fibrosis was available for this review.

8.15 Meconium ileus

8.15.1 Description of clinical evidence: meconium ileus

The aim of this review was to determine the prevalence of meconium ileus among people with cystic fibrosis. We included data from the UK CF Registry for the year 2015 on 9587 people with cystic fibrosis. The data provided by the registry was prioritised therefore we did not include any studies from the published literature.

For full details see review protocol in Appendix D.

8.15.2 Summary of included studies and results: meconium ileus

A summary of the studies that were included in this review are presented in Table 59.

Table 59: Summary of included studies

Study	Register / Data source	Dates	Participants	Prevalence: overall results and results by age subgroups - % (n/N)	Definition of complication and measurement tools	Quality of the study
Cystic Fibrosis Trust UK, 2016 Registry annual data report	UK CF registry	2015	9587 people with cystic fibrosis • <16 years: 3845 • ≥16 years: 5742	Meconium ileus: • <16 years: 16.7% (643/3845) • ≥16 years: 14.2% (815/5742) • Overall: 15.2% (1458/9587)	Cystic fibrosis care teams at every specialist centre and clinic across the UK filled in forms where they selected what complications (if any) each person with cystic fibrosis had. No definition of complications	Moderate • Criteria used to diagnose the complication and consistency of diagnosis across centres were unclear

Study	Register / Data source	Dates	Participants	Prevalence: overall results and results by age subgroups - % (n/N)	Definition of complication and measurement tools	Quality of the study
					is provided in the form.	

Abbreviations: CF: cystic fibrosis

8.15.3 Evidence statements: meconium ileus

Moderate quality evidence from a report on 9587 people with cystic fibrosis from the UK CF Registry (year 2015) found that meconium ileus had occurred in 16.7% of children and young people aged <16, 14.2% of young people and adults aged 16 years and over, and 15.2% of people of all ages.

8.15.3.1 Economic evidence statements

No evidence on cost-effectiveness in people with cystic fibrosis was available for this review.

8.16 Economic evidence

No economic evaluations related to the complications of cystic fibrosis were identified in the literature search conducted for this guideline. Full details of the search and economic article selection flow chart can be found in Appendix E and F, respectively.

This review question is not relevant for economic analysis because it does not involve a decision between alternative courses of action.

8.17 Evidence to recommendations

8.17.1 Relative value placed on the outcomes considered

The committee agreed that the prevalence of complications of cystic fibrosis was a critical outcome.

8.17.2 Consideration of clinical benefits and harms

8.17.2.1 Malnutrition and impaired growth

The committee noted that the evidence on prevalence of vitamin deficiency was of very low quality in relation to vitamins A and E; there was no evidence in relation to vitamin K. However, based on their clinical expertise the committee agreed that vitamin K deficiency may occur. The quality of the evidence in relation to vitamin D ranged between very low and moderate. The committee agreed that pancreatic insufficiency (common in cystic fibrosis) hinders the body's inability to digest fat hence fat-soluble vitamins are poorly absorbed. The committee noted that prevalence of vitamin deficiency would depend on whether people take vitamin supplements. Moreover the prevalence of vitamin D deficiency would change depending on the time of the year with changes in hours of daylight. Therefore, the committee decided not to specify a numerical estimate of prevalence of vitamin deficiency in the recommendations. They recommended to be aware that fat-soluble vitamin deficiencies (including vitamins A, D, E and K) are common in people with cystic fibrosis.

The committee noted that a multitude of anthropometric indicators of malnutrition and impaired growth was used in the studies and agreed that in the future, consistency in indicators is needed across studies in order to meaningfully compare results. The committee

decided to prioritise the data from the UK registry on BMI (recorded as percentile until age 16 and in units of kg/m^2 for people older than 16) in order to formulate recommendations because this data was the most recent and older studies were likely to show higher prevalence due to treatment regimens that would not correspond to the current ones. However, the committee noted that the registry data indicated that children with cystic fibrosis have better BMI compared to the non-cystic fibrosis population (17% of children <25th percentile) and young people with cystic fibrosis have similar BMI compared to the non-cystic fibrosis population (27.5% of young people <25th percentile) and this was in contrast with their experience in clinical practice. Therefore the committee decided not to give a numerical estimate of the prevalence of reduced BMI and prioritised a recommendation to be aware that underweight is common in people with cystic fibrosis.

8.17.2.2 Meconium ileus

The committee used the data from the UK CF Registry to formulate a recommendation on meconium ileus. The prevalence in the overall population corresponds to 1 in 7 people. Therefore they recommended to be aware that meconium ileus is common in people with cystic fibrosis (affects 1 in 7 newborn babies).

8.17.2.3 Abdominal pain

There was no evidence on abdominal pain. Abdominal pain is common in school-age children. The cause is often uncertain and most do not require investigation. Abdominal pain may also occur in adults, for example, due to irritable bowel syndrome. Against this clinical background, people with cystic fibrosis might also experience abdominal pain and in some cases this might be due to cystic fibrosis. The committee agreed that the gastrointestinal complications of cystic fibrosis can cause abdominal pain. For example, pancreatic insufficiency requires treatment with pancreatic enzyme replacement therapy and getting the dosage right can be difficult in some patients and constipation or diarrhoea can be common when titrating doses (which may cause abdominal pain). Other causes of abdominal pain are: distal intestinal obstruction syndrome, constant coughing, inflammatory bowel disease or gastro-oesophageal reflux disease. Less common causes of abdominal pain in children with cystic fibrosis include recurrent intussusception, volvulus, fibrosing colonopathy and appendiceal disease. The committee agreed that abdominal pain can be disabling, however it is difficult to give an estimate of prevalence. For example, some people with cystic fibrosis are continuously asked if they have abdominal pain, which may lead to over reporting. Moreover, many people present with non-specific abdominal pain (generalised abdominal pain with no specific focal point and no definable cause). The committee did not include abdominal pain as a specific complication of cystic fibrosis because in each case the underlying likely explanation might differ and the cause would need consideration.

8.17.2.4 Distal intestinal obstruction syndrome

The committee prioritised the data from the UK CF Registry because it was more recent than the data from the included study from the published literature. The data from the registry was on intestinal obstruction rather than on distal intestinal obstruction syndrome. However the committee agreed that intestinal obstruction would mostly be due to distal intestinal obstruction syndrome in people with cystic fibrosis. The committee noted that the data provided by the UK CF Registry showed an important difference in prevalence between those who have a history of meconium ileus and those without a history of meconium ileus, as well as between children and adults. However, the committee agreed that the recommendations should not go into too much detail in terms of numerical estimates of prevalence because the risk of complications would vary considerably from person to person. Therefore the committee decided to keep the recommendation general and recommended to be aware that distal intestinal obstruction syndrome is common in people with cystic fibrosis.

8.17.2.5 Cystic fibrosis related musculoskeletal disorders

The committee noted that in their clinical experience people with cystic fibrosis often have muscle pains and arthralgia. There was no evidence on these complications, therefore the committee decided to make a recommendation based on their expertise to be aware that muscle pains and arthralgia are common in people with cystic fibrosis.

The committee noted that evidence from the UK CF Registry showed that arthritis was rare. They noted that the prevalence varies considerably between the age groups used in the registry (younger than 16 years or 16 years and over) and reasoned that if additional age cut-offs were used, prevalence would most likely vary between the smaller age sub-groups. Therefore the committee decided not to specify numerical estimates of prevalence and decided to recommend to be aware that cystic fibrosis-related arthritis is less common than other complications in people with cystic fibrosis.

8.17.2.6 Delayed puberty

There was some evidence on the prevalence of delayed puberty, however, the committee believed that the evidence was too old to be relevant because puberty occurs earlier nowadays. Delayed puberty is related to malnutrition and it occurs in people with severe disease. Therefore, the committee used their clinical experience to recommend to be aware that delayed puberty is less common than other complications in people with cystic fibrosis and is associated with severe cystic fibrosis.

8.17.2.7 Infertility

There was no evidence on the prevalence of infertility. The committee used their clinical experience and expertise to recommend to be aware that male infertility caused by obstructive azoospermia and reduced female fertility are common in people with cystic fibrosis. The committee agreed that almost all males with cystic fibrosis are infertile as a result of congenital absence of the vas deferens. As the vas deferens is lined by mucus in order to lubricate the passage of sperm along the tube, the cystic fibrosis pathological process interrupts the development of the vas deferens in the foetus. Thus, most males with cystic fibrosis are born with an absent vas deferens. However, this process is not absolute and a very small proportion of males have a functioning vas deferens, especially in those who have a lesser expression of the cystic fibrosis condition (a very mild phenotype). Indeed, there are a group of males with cystic fibrosis in which the condition is only suspected when they are found to have an absent vas deferens as part of investigations for infertility when they are adults. The committee noted that it was important to take into account the small proportion of males with a functioning vas deferens, especially considering the risk of unwanted pregnancies. Thus, the committee agreed that the statement “almost all males” was appropriate to use in the recommendations.

8.17.2.8 Upper airways disease

The committee noted that the evidence from the UK CF Registry showed that both the prevalence of nasal polyps requiring surgery and the prevalence of sinus disease increase with age. This age trend reflected their clinical experience. However, the committee also noted that the prevalence of sinus disease and nasal polyps seemed low compared to their clinical experience and agreed that the data was likely to be based on symptomatic disease only. The committee also noted that underestimating the prevalence of nasal polyps in the recommendations would lead to dismissal of this complication as minor and rare when in fact early recognition and management can improve quality of life significantly. Therefore they decided not to mention a numerical estimate of prevalence of sinus disease and nasal polyps in the recommendations. The committee recommended to be aware that upper airway complications, including nasal polyps and sinusitis are common complications of cystic fibrosis (prevalence increases with age).

8.17.2.9 Cystic-fibrosis related diabetes

The committee noted that the included studies from the published literature were not from the UK and prioritised the data from the UK Registry to people on treatment for CFRD because this data was based on the context where NICE guidelines are implemented. The committee noted that the registry did not have data on people under 10 years of age on CFRD treatment because it is uncommon in this age group. The committee noted that the prevalence was lower in the group of people aged 10 to 16 years (10%) compared to the prevalence among people aged 16 or older (32%). The committee agreed that the prevalence of people on CFRD treatment was likely to underestimate the prevalence of people with CFRD because many centres do not know how to accurately test for it. Therefore, based on their clinical experience and expertise, the committee recommended to be aware that cystic fibrosis-related diabetes is common in people with cystic fibrosis (uncommon in children under 10 years, but the prevalence increases with age and it affects up to 1 in 2 adults).

8.17.2.10 Chronic liver disease

The evidence from the UK CF Registry showed that 9% of people younger than 16 years and 18% of people aged 16 years and over have liver disease. The committee noted that liver disease is a chronic condition that develops slowly and, for many it, does not majorly impact on overall health. Only a small number of people develop liver failure requiring transplant. The committee noted that it is rare to diagnose liver disease in adulthood. Most people present with abnormal liver function or abnormal ultrasound scan (AUSS) in childhood or early teens. Therefore, the committee recommended to be aware that chronic liver disease is common in people with cystic fibrosis, the prevalence increases with age until early adulthood.

8.17.2.11 Cystic fibrosis related renal disease

The committee noted that the evidence from the UK CF Registry was likely to underreport prevalence of renal failure because routine measurements of renal function are not very reliable. Moreover, the committee decided not to include a recommendation on acute renal failure because this is likely to be related to drug use (aminoglycosides; immunosuppressant medications) and therefore it is debatable whether it is a complication of cystic fibrosis rather than a complication of specific drugs. The committee noted that there was some evidence from the published literature on the prevalence of chronic kidney disease. However, the evidence from 1 study was only on chronic kidney disease of stage 3 or greater and the evidence from another study was based on records from 1969 to 2009 therefore unlikely to be up to date. Therefore, the committee decided not to include a recommendation about the prevalence of chronic kidney disease.

The committee noted that the UK CF Registry data showed that the prevalence of kidney stones was higher among people aged 16 years or older (1.5%) compared to people aged less than 16 years (0.3%). The committee noted that this age trend reflected their clinical expertise. However, they agreed that the registry data on kidney stones (1% prevalence for the overall population) was likely to underreport the prevalence because they are often asymptomatic and are only discovered when they cause problems. Based on the committee's clinical expertise and experience prevalence of kidney stones in adults was about 5%. Therefore, the committee recommended to be aware that although renal calculi are less common than other complications in people with cystic fibrosis, the incidence increases with age and 1 in 20 adults are affected.

8.17.2.12 Urinary stress incontinence

There was no evidence on the prevalence of urinary stress incontinence. Therefore the committee decided not to include a numerical estimate of prevalence in the

recommendations and based on their clinical expertise recommended to be aware that urinary stress incontinence is common in people with cystic fibrosis.

8.17.2.13 Reduced bone mineral density

There was evidence from the UK CF Registry on the prevalence of osteopenia, osteoporosis and bone fracture. The committee agreed that given the low prevalence of bone fractures there was no need to mention these in the recommendations. The committee noted that the registry was likely to underreport prevalence of osteopenia and osteoporosis as these complications can only be diagnosed by DXA scan for which the take-up is not good and as a result many cases will be undiscovered. There was some evidence from the published literature on the prevalence of osteopenia or osteoporosis in Ireland and Australia. This evidence was based on registries and did not specify how the conditions were diagnosed. However, diagnosing practices in these countries are likely to mirror UK practice, with the same limitations leading to underreporting. Given the limitations in the evidence the committee decided not to include a numerical estimate of prevalence in the recommendations and only recommended to be aware that reduced bone mineral density and osteoporosis are common in people with cystic fibrosis.

8.17.3 Consideration of economic benefits and harms

This was an epidemiological review question and economic analysis to assess cost-effectiveness is not applicable as it does not involve a comparison of competing alternatives. Even so, the assessment, monitoring, referral and management of the comorbidities all have cost implications.

The committee recognised that if complications are not identified and management appropriately they can negatively impact on wellbeing, function and participation and increase their risk of further complications leading to additional treatment costs and reductions in quality of life. Therefore, knowing the prevalence of important complications may lead to increased vigilance and thus more timely management and has therefore, indirectly, potentially important resource implications. Estimating the costs to manage those complications would go beyond the scope of the guideline, but it was clear from the committee that such costs would offset the potential downstream costs from delayed or inappropriate management.

8.17.4 Quality of evidence

This was a prevalence review, therefore the quality assessment with GRADE was not performed. The quality of the studies was assessed with the checklist by Munn et al. 2014. It was often unclear from the evidence how a condition was diagnosed whether objective, standard criteria were used for the measurement of the condition or whether the condition was measured reliably. Moreover, some of the evidence did not disaggregate data by age groups.

8.17.5 Other considerations

The committee discussed whether people with cystic fibrosis may feel overwhelmed if presented with a long list of complications they are at risk of. However they agreed that people with cystic fibrosis have the right to receive all the available information on their condition. Moreover, the committee noted that the risk for each individual largely depends on management, this should be made clear in conversations with people with cystic fibrosis.

No equality issues were identified by the committee for this review question.

The committee agreed a research recommendation was not needed. They noted that there was sufficient awareness of both common and rarer complications of cystic fibrosis. It was

also felt that there are robust reporting mechanisms (UK CF Registry) should the prevalence of certain complications change in the future. As people with cystic fibrosis survive longer they are more likely to present with problems associated with organ damage such as retinopathy or kidney problems in those who have diabetes. However, these are complications that are well established in the wider health-care setting and there are no specific cystic fibrosis-related treatments.

8.17.6 Key conclusions

The guideline developers concluded that health care professionals should explain to each person with cystic fibrosis and their family members or carers, as appropriate, what complications they are at risk of, taking into account each individual's clinical risk factors. Depending on the evidence available for each complication and the individual risk factors, it may be appropriate to either use the terms common or less common, or provide a numerical estimate.

8.18 Recommendations

38. Be aware that people with cystic fibrosis are at risk of the following common complications:

- being underweight
- meconium ileus (affects 1 in 7 newborn babies)
- fat-soluble vitamin deficiencies (including vitamins A, D, E and K)
- distal intestinal obstruction syndrome
- muscle pains and arthralgia
- male infertility caused by obstructive azoospermia (almost all males with cystic fibrosis are infertile)
- reduced female fertility
- upper airway complications, including nasal polyps and sinusitis (prevalence increases with age)
- chronic liver disease (the prevalence increases with age until early adulthood)
- urinary stress incontinence
- cystic-fibrosis-related diabetes (uncommon in children under 10 years, but the prevalence increases with age and it affects up to 1 in 2 adults)
- reduced bone mineral density (including osteoporosis).

39. Be aware that people with cystic fibrosis are at risk of the following less common complications:

- cystic-fibrosis-related arthritis
- delayed puberty (associated with severe cystic fibrosis)
- renal calculi (incidence increases with age and 1 in 20 adults are affected).

9 Pulmonary monitoring, assessment and management

9.1 Pulmonary monitoring

Review questions:

1) What is the value of the following investigative strategies in monitoring the onset of pulmonary disease in people with cystic fibrosis without clinical signs or symptoms of lung disease?

- Non-invasive microbiological investigation- induced sputum samples, cough swab, throat swab, and nasopharyngeal aspiration
- Invasive microbiological investigation- broncho-alveolar lavage
- Lung physiological function tests- Cardiopulmonary exercise testing, Spirometry and Lung Clearance Index (LCI)
- Imaging techniques- Chest x-ray and CT scan

2) What is the value of the following investigative strategies in monitoring evolving pulmonary disease in people with established lung disease?

- Non-invasive microbiological investigation- induced sputum samples, cough swab, throat swab, and nasopharyngeal aspiration
- Invasive microbiological investigation- broncho-alveolar lavage
- Lung physiological function tests- Cardiopulmonary exercise testing, Spirometry and LCI
- Imaging techniques- Chest x-ray and CT scan.

3) What is the added value of imaging and invasive microbiological testing in addition to non-invasive microbiological testing and lung function tests in monitoring the response to treatment following an acute exacerbation?

9.1.1 Introduction

Treatment for cystic fibrosis lung disease is based on the prevention of lung infection and subsequent colonisation by pathogenic organisms, long term maintenance therapies to ensure clinical stability and prevent progressive loss of lung function and treatment of infective exacerbations. It is a condition which requires constant vigilance to monitor disease state with aggressive, early intervention to treat infection.

Infective exacerbations are associated with considerable morbidity and some episodes can lead to permanent reduction in lung function. Treatment response for pulmonary exacerbation is measured by a number of outcome measures, including analysis of non-invasive microbiological specimens, improvement in symptoms, oxygenation, inflammatory markers and pulmonary function. The treatment of an acute exacerbation is closely monitored by cystic fibrosis teams and therapy may be changed depending on the assessment of treatment response.

9.1.2 Description of clinical evidence

The aim of this review was to examine different monitoring strategies for pulmonary disease in people with cystic fibrosis and to determine their impact on improving subsequent intervention and clinical outcomes, therefore the diagnostic accuracy of the different tests was not prioritised for this review. Monitoring techniques were split into 4 categories:

- Monitoring technique 1: non-invasive microbiological investigation of respiratory tract samples (including induced sputum samples, cough swabs, throat swabs and nasopharyngeal aspiration);
- Monitoring technique 2: invasive microbiological investigation (i.e. bronchoalveolar lavage - BAL);
- Monitoring technique 3: pulmonary function tests (including cardiopulmonary exercise testing, spirometry and LCI);
- Monitoring technique 4: imaging techniques (including chest X-ray and CT scanning).

The committee considered the effects of monitoring considering three clinical scenarios associated with lung disease and corresponding review questions and protocols were drafted for people with cystic fibrosis:

- Protocol 1: without clinical signs or symptoms of lung disease
- Protocol 2: with established pulmonary disease
- Protocol 3: following an acute pulmonary exacerbation

The committee recognised that those with no pulmonary disease would principally, but not exclusively be young children and that this review would inform investigative strategies to identify the onset of pulmonary disease, as opposed to identifying evolving pulmonary disease in the second population. The committee were interested in comparisons of individual techniques within categories, individual techniques across categories and in combinations of techniques within or across categories. Of particular interest was the effectiveness of imaging techniques in addition to non-invasive microbiological techniques and spirometry.

The committee were specifically interested in the value of adding invasive microbiological investigations and/or imaging techniques to non-invasive microbiological testing and lung function tests to evaluate treatment response in those with an acute pulmonary exacerbation.

We aimed to include systematic reviews, test and treat RCTs and prospective and retrospective observational studies.

For full details see review protocols in Appendix D.

One single literature search was run for the 3 protocols, and 2 studies were included. Neither of these studies absolutely adhered to the clinical scenarios of the protocols.

9.1.2.1 Review 1. Monitoring for pulmonary disease onset in people with cystic fibrosis without clinical signs or symptoms of lung disease

One study (Sanders 2015) was identified for this protocol. The authors used registry data to follow up 60 children who were initially recruited to a RCT of pulmozyme. The authors investigated whether chest CT and pulmonary function test scores (taken at the start and end of the RCT) were associated with the rate of pulmonary exacerbations over the subsequent 10 year period.

9.1.2.2 Review 2. Monitoring for evolving pulmonary disease in people with cystic fibrosis with established lung disease

No studies were identified for this protocol.

9.1.2.3 Review 3. Monitoring for evolving pulmonary disease in people with cystic fibrosis following an acute pulmonary exacerbation

One study (Wainwright 2011) was identified for this protocol. This study was a multicentre RCT (ACFBAL) which recruited 170 participants to determine whether monitoring using BAL

to direct therapy for pulmonary exacerbations in the first five years of life reduced *P aeruginosa* infection and structural lung injury at age 5 years compared with standard management based on clinical features and oropharyngeal culture results.

A summary of the studies included in the reviews is presented in Table 60 and Table 61. See also study selection flow chart in Appendix F, study evidence tables in Appendix G, list of excluded studies in Appendix H, and full GRADE profiles in Appendix J.

9.1.3 Summary of included studies

9.1.3.1 Review 1. Monitoring for pulmonary disease onset in people with cystic fibrosis without clinical signs or symptoms of lung disease

A summary of the studies that were included in this review is presented in Table 60.

Table 60: Summary of included studies

Study	Intervention/ Comparison	Population	Outcomes	Comments
Sanders 2015 (USA) Cohort study	Chest CT (Brody score) • Baseline data: For this study the authors used data obtained at the baseline and at end of the PEIT study (1997-1999) • Follow-up data: Data from the time of chest CT in 1999 through 2009 were obtained from the CFFPR and linked to the original chest CT data FEV_1% predicted • PFTs were obtained on the same day as the chest CT	N=60 children with CF who participated in the PEIT trial Age: 6 to 10 years	• Pulmonary exacerbations • (proxy outcome for time to next exacerbation)* • (pulmonary exacerbation defined as hospitalizations treated with IV AB and/ or if the "pulmonary exacerbation" box was checked in the CFFPR form • FEV_1% predicted** * multivariate Poisson model adjusted for sex, genotype, and FEV_1 and mucoid *P aeruginosa* status at the time of the chest CT **multivariate linear regression model adjusted for sex, genotype, and FEV_1 and mucoid *P aeruginosa* status at the time of the chest CT	No adjustments for the confounder of concurrent treatment with immunomodulatory and/or mucolytic agents

BAL: bronchoalveolar lavage; CFFPR: cystic fibrosis Foundation Patient Registry; MD: mean difference; SD: standard deviation

9.1.3.2 Review 2. Monitoring for evolving pulmonary disease in people with cystic fibrosis with established lung disease

No studies were identified for this protocol.

9.1.3.3 Review 3. Monitoring for evolving pulmonary disease in people with cystic fibrosis following an acute pulmonary exacerbation

A summary of the studies that were included in this review is presented in Table 61.

Table 61: Summary of included studies

Study	Intervention/ Comparison	Population	Outcomes	Comments
Wainwright 2011 (Australia & New Zealand) Multicentre RCT	Standard monitoring group Used clinical features and oropharyngeal cultures to direct therapy. BAL monitoring group standard monitoring + BAL performed before 6 months when well, when hospitalised for exacerbations, if *P aeruginosa* cultured from oropharyngeal specimen and following *P aeruginosa* eradication therapy. Culture results from the BAL fluid informed treatment decisions	N=168 infants with CF <6 months Mean age (SD): 3.6 (1.6) months • Standard therapy: n=84 • BAL therapy: n=86 • Children were followed until age 5 years	• FEV_1 z scores • Weight z scores • Height z scores • BMI z scores	Indirectness: intervention in BAL monitoring group does not reflect that of current clinical practice

BAL: bronchoalveolar lavage; CFFPR: cystic fibrosis Foundation Patient Registry; MD: mean difference; SD: standard deviation

9.1.4 Clinical evidence profiles

9.1.4.1 Review 1. Monitoring for pulmonary disease onset in people with cystic fibrosis without clinical signs or symptoms of lung disease

The clinical evidence profiles for this review question are presented in Table 62, Table 63 and Table 64.

Table 62: Summary clinical evidence profile: Monitoring technique 3. Lung physiological function tests (FEV_1% predicted at baseline) for prognosis of pulmonary exacerbations and FEV_1 percent predicted at 10 years

Prognostic factors	Included studies	Study design	Setting	n	Result (adjRR, MD)	Quality	Notes
Pulmonary exacerbations (defined as hospitalizations treated with IV AB), 10 year follow-up							
FEV_1 % predicted, 5-point decrease	1 (Sanders 2015)	Cohort study	CF centres in Europe	60	adjRR: 1.19 (95% CI: 1.10 – 1.30)	Moderate[1]	Multiple Poisson model adjusted for sex, genotype, FEV_1 and mucoid *P aeruginosa* status at time of chest CT. p value = < 0.001
Difference in FEV_1 % predicted							
FEV_1 % predicted, 5-point decrease	1 (Sanders 2015)	Cohort study	CF centres in	60	MD: -4.47 (95% CI:	Moderate[1]	Multiple linear model adjusted for sex, genotype, FEV_1 and mucoid *P aeruginosa* status

Prognostic factors	Included studies	Study design	Setting	n	Result (adjRR, MD)	Quality	Notes
			Europe		-6.48 to -2.76)		at time of chest CT. p value = < 0.001

Abbreviations: adjRR: adjusted rate ratio; CF: cystic fibrosis; CI: confidence interval; CT: computerised tomography; FEV_1: forced expiratory volume in 1 second; MD: mean difference adjRR: adjusted rate ratio 1 The quality of the evidence was downgraded by 1 due to no adjustments for the confounder of concurrent treatment with immunomodulatory and/or mucolytic agents.

Table 63: Summary clinical evidence profile: Monitoring technique 4. Chest CT scan for prognosis of pulmonary exacerbations and FEV_1% predicted at 10 years

Prognostic factors	Included studies	Study design	Setting	n	Result (adjRR, MD)	Quality	Notes
Pulmonary exacerbations (defined as hospitalizations treated with IV AB), 10 year follow-up							
Brody chest CT score, 1-point increase	1 (Sanders 2015)	Cohort study	CF centres in Europe	60	adjRR: 1.39 (95% CI: 1.15 – 1.67)	Moderate[1]	Multiple Poisson model adjusted for sex, genotype, FEV_1 and mucoid *P aeruginosa* status at time of chest CT. p value = < 0.001
Difference in FEV_1 % predicted, 10 year follow-up							
Brody chest CT score, 1-point increase	1 (Sanders 2015)	Cohort study	CF centres in Europe	60	MD: -4.76 (95% CI: -7.80 to -1.72)	Moderate[1]	Multiple linear model adjusted for sex, genotype, FEV_1 and mucoid *P aeruginosa* status at time of chest CT. p value = 0.003

Abbreviations: adjRR: adjusted rate ratio; CF: cystic fibrosis; CI: confidence interval; CT: computerised tomography; FEV_1: forced expiratory volume in 1 second; MD: mean difference
1 The quality of the evidence was downgraded by 1 due to no adjustments for the confounder of concurrent treatment with immunomodulatory and/or mucolytic agents

Table 64: Summary clinical evidence profile: Comparison 1. FEV_1% predicted versus chest CT scan for prognosis of pulmonary exacerbations and FEV_1% predicted at 10 years

Comparison 1. FEV_1% predicted versus chest CT scan for prognosis of pulmonary exacerbations and FEV_1% predicted at 10 years						
Outcomes	Illustrative comparative risks* (95% CI)		Difference between tests p-value	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	FEV_1% **predicted, 5% decrease**	**Brody chest CT score, 1-point decrease**				
Pulmonary exacerbations, defined as hospitalization treated with IV AB Follow-up: 10 years	adjRR = 1.19 (95% CI: 1.10 – 1.30)2	adjRR = 1.39 (95% CI: 1.15 – 1.67)2	RR = 0.86*, p-value =0.037 By Chi-Square test2	60 (Sanders 2015)	⊕⊕⊕⊖ moderate[1]	Multiple Poisson model adjusted for sex, genotype, FEV_1 and mucoid *P aeruginosa* status at time of chest CT.
Change/ decline in	Mean difference:	Mean difference: -4.76 (95%	MD: 0.29*,	60	⊕⊕⊕⊖	Multiple linear model adjusted for

Comparison 1. FEV_1% predicted versus chest CT scan for prognosis of pulmonary exacerbations and FEV_1% predicted at 10 years						
FEV_1% predicted Follow-up: 10 years	-4.47 (95% CI: -6.48 to -2.76)	CI: -7.80 to -1.72)	p-value = 0.4 By F test2	(Sanders 2015)	moderate[1]	sex, genotype, FEV_1 and mucoid *P aeruginosa* status at time of chest CT.
**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).* *Abbreviations: AB: antibiotics; adjRR: adjusted rate ratio; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; IV: intravenous; MD: mean difference*						

** Calculated by NGA technical team*
adjRR: adjusted rate ratio
1 The quality of the evidence was downgraded by 1 due to no adjustments for the confounder of concurrent treatment with immunomodulatory and/or mucolytic agents
2 This result was reported narratively only

9.1.4.2 Review 2. Monitoring for evolving pulmonary disease in people with cystic fibrosis with established lung disease

Not applicable, as no studies were included for this review.

9.1.4.3 Review 3. Monitoring for evolving pulmonary disease in people with cystic fibrosis following an acute pulmonary exacerbation

The clinical evidence profile for this review question is presented in Table 65.

Table 65: Summary clinical evidence profile: Comparison 1. BAL monitoring versus standard monitoring

Comparison 1. BAL monitoring versus standard monitoring						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Standard monitoring risk	**BAL monitoring**				
FEV_1 z score Better indicated by higher values Follow-up: 5 years	The mean FEV_1 in the control group was -0.41	The mean FEV_1 in the intervention group was 0.15 lower (0.58 lower to 0.28 higher)		157 (Wainwright 2011)	⊕⊕⊕⊖ moderate[1]	
Clearance of *P aeruginosa* following 1 or 2 courses of eradication therapy Better indicated by higher values Follow up: 5 years	907 per 1000	970 per 1000 (871 to 1000)	RR 1.07 (0.96 to 1.2)	82 (Wainwright 2011)	⊕⊕⊕⊖ moderate[1]	

Comparison 1. BAL monitoring versus standard monitoring						
Weight z scores Better indicated by higher values Follow-up: 5 years	The mean weight in the control group was -0.21	The mean weight in the intervention group was 0.06 higher (0.21 lower to 0.32 higher)		157 (Wainwright 2011)	⊕⊕⊖⊖ low[1,2]	
Height z scores Better indicated by higher values Follow-up: 5 years	The mean height in the control group was -0.19	The mean height in the intervention group was 0.06 higher (0.23 to 0.35 lower)		157 (Wainwright 2011)	⊕⊕⊕⊖ moderate[1]	
BMI z scores, BMI calculated as weight in kg divided by height in meters squared. Better indicated by higher values Follow-up: 5 years	The mean BMI in the control group was 0.01	The mean BMI in the intervention group was 0.02 higher (0.25 lower to 0.3 higher)		157 (Wainwright 2011)	⊕⊕⊕⊖ moderate[1]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: BAL: bronchoalveolar lavage; BMI: body mass index; FEV_1: forced expiratory volume in 1 second; MD: mean difference; RR: risk ratio

1 The quality of the evidence was downgraded by 1 due to serious indirectness as intervention in BAL monitoring group does not reflect that of current clinical practice.
2 The quality of the evidence was downgraded by 1 due to serious imprecision as 95% CI crossed 1 default MID.

9.1.5 Economic evidence

One economic evaluation relevant to the protocol was identified in the literature search conducted for this guideline. This study was a prospective cost-benefit analysis undertaken on the RCT by Wainwright (2011) (Section 9.1.2.3). A second study has also been included to aid consideration on the frequency of testing for people with established pulmonary disease. Data extraction tables and quality assessments of included studies can be found in Appendix L and M, respectively. Full details of the search and economic article selection flow chart can be found in Appendix E and F, respectively.

This review question was not prioritised for de novo economic modelling. To aid consideration of cost-effectiveness relevant resource and cost use data are presented in Appendix K.

9.1.6 Evidence statements

9.1.6.1 Review 1. Monitoring for pulmonary disease onset in people with cystic fibrosis without clinical signs or symptoms of lung disease

9.1.6.1.1 Monitoring technique 1. Non-invasive microbiological investigation

No evidence was found.

9.1.6.1.2 Monitoring technique 2. Invasive microbiological investigation

No evidence was found.

9.1.6.1.3 Monitoring technique 3. Lung physiological function tests

Lung function

Moderate quality evidence from 1 cohort study with 60 children with cystic fibrosis showed that a 5-point decrease in FEV_1% predicted was associated with a reduction in FEV_1% predicted at 10 years follow-up.

Clearance of the organism from the cultures

No evidence was found for this important outcome.

Pulmonary exacerbations

Moderate quality evidence from 1 cohort study with 60 children with cystic fibrosis showed that a 5-point decrease in FEV_1% predicted was associated with a higher rate of pulmonary exacerbations during the 10-year follow-up period.

Nutritional parameters

No evidence was found for this important outcome.

Quality of life

No evidence was found for this important outcome.

9.1.6.1.4 Monitoring technique 4. Imaging tests

Lung function

Moderate quality evidence from 1 cohort study with 60 children with cystic fibrosis showed that a 1-point increase in Brody chest CT score was associated with a reduction in FEV_1% predicted at 10-year follow-up.

Clearance of the organism from the cultures

No evidence was found for this important outcome.

Pulmonary exacerbations

Moderate quality evidence from 1 cohort study with 60 children with cystic fibrosis showed that a 1-point increase in Brody chest CT score was associated with a higher rate of pulmonary exacerbations during the 10-year follow-up period.

Nutritional parameters

No evidence was found for this important outcome.

Quality of life

No evidence was found for this important outcome.

9.1.6.1.5 Comparison 1. Lung function tests versus imaging tests

Lung function

Moderate quality evidence from 1 cohort study with 60 children with cystic fibrosis showed that there were no differences in the strengths of the association between the Brody chest CT score and FEV_1% predicted in 1999 with FEV_1% predicted in 2009. This result was reported narratively only.

Clearance of the organism from the cultures

No evidence was found for this important outcome.

Pulmonary exacerbations (proxy outcome for time to chronic infection)

Moderate quality evidence from 1 cohort study with 60 children with cystic fibrosis showed that a 1-point difference in the Brody chest CT score was more strongly associated with the rate of pulmonary exacerbations between 1999 and 2009 than a 5% predicted difference in FEV_1% predicted at the time of the chest CT. This result was reported narratively only.

Nutritional parameters

No evidence was found for this important outcome.

Quality of life

No evidence was found for this important outcome.

9.1.6.2 Review 2. Monitoring for evolving pulmonary disease in people with cystic fibrosis with established lung disease

No evidence was found for this review.

9.1.6.3 Review 3. Monitoring for evolving pulmonary disease in people with cystic fibrosis following an acute pulmonary exacerbation

9.1.6.3.1 Monitoring strategy 1. Invasive microbiological investigations and/or imaging techniques in addition to non-invasive microbiological investigations and/or lung function test VERSUS non-invasive microbiological investigations

Comparison 1. Monitoring using bronchoalveolar lavage (BAL) versus standard monitoring

Lung function

Moderate quality evidence from 1 RCT with 157 infants with cystic fibrosis <6 months showed no clinically significant difference between monitoring using BAL and standard monitoring for FEV_1 z scores at 5 years follow-up.

Clearance of the organism from the cultures

Moderate quality evidence from 1 RCT with 157 infants with cystic fibrosis <6 months showed no clinically significant difference between monitoring using BAL and standard monitoring for clearance of *P aeruginosa* following 1 or 2 courses of eradication therapy at 5 years follow-up.

Time to chronic infection

No evidence was found for this important outcome

Nutritional parameters

Low to moderate quality evidence from 1 RCT with 157 infants with cystic fibrosis <6 months showed no clinically significant difference in weight, height and BMI (measured as final z-scores) between monitoring using BAL and standard monitoring at 5 years follow-up.

Quality of life

No evidence was found for this important outcome

9.1.6.3.2 Monitoring strategy 2. Invasive microbiological investigations and/or imaging techniques in addition to non-invasive microbiological investigations and/or lung function test VERSUS lung function test

No evidence was found for this strategy.

9.1.6.3.3 Monitoring strategy 3. Invasive microbiological investigations and/or imaging techniques in addition to non-invasive microbiological investigations and/or lung function test VERSUS non-invasive microbiological investigations and lung function test

No evidence was found for this strategy.

9.1.6.4 Economic evidence statements

One cost-benefit analysis (Moodie 2014) on people with cystic fibrosis in Australia and New Zealand found that the additional cost of BAL therapy compared to standard therapy was not offset by reductions in other healthcare expenditure over 5 years. This analysis has minor limitations and is directly applicable given that the type of economic evaluation is unlikely to change the conclusions about cost-effectiveness and all other applicability criteria are met.

One cost-consequence analysis (Etherington 2008) on people with cystic fibrosis in the UK over 6 months, found that the number of routine susceptibility tests conducted on *P aeruginosa* isolates can be reduced to provide cost savings without adversely affecting clinical outcomes. This analysis will be used as indirect evidence as the frequency of testing was not a comparator included in the protocol. This evidence is characterised by potentially serious limitations, including the before and after type study design and lack of detail regarding the costs included and their sources.

9.1.7 Evidence to recommendations

9.1.7.1 Relative value placed on the outcomes considered

The aim of this review was to examine different monitoring strategies for pulmonary disease in people with cystic fibrosis and determine their impact on improving subsequent intervention and clinical outcomes. The outcomes selected were different for each clinical scenario:

- For monitoring for onset of pulmonary disease in people with cystic fibrosis without clinical signs or symptoms of lung disease (review 1), the committee chose lung function and

clearance of the organism from the cultures as critical outcomes for decision making. Time to chronic infection, nutritional parameters and quality of life were rated as important. Given that no evidence was found for time to chronic infection, pulmonary exacerbations were considered a proxy outcome.

- For monitoring for evolving pulmonary disease in people with cystic fibrosis with established lung disease (review 2), the committee chose lung function and time to next exacerbation as critical outcomes for decision making. Time to chronic infection, mortality, nutritional parameters and quality of life were rated as important
- For monitoring for evolving pulmonary disease in people with cystic fibrosis following an acute pulmonary exacerbation (review 3), the committee chose lung function, time to next exacerbation and clearance of the organism as critical outcomes for decision making. Time to chronic infection, inflammatory markers, nutritional parameters and quality of life were rated as important.

9.1.7.2 Consideration of clinical benefits and harms

The committee acknowledged the scarcity of the evidence and, therefore, most of the recommendations were based on their clinical expertise and experience and good practice recommendations.

The committee discussed the recommendations for asymptomatic and symptomatic people to reflect the different scenarios associated with lung disease; people without clinical signs or symptoms of lung disease and people with established lung disease or people presenting an acute pulmonary exacerbation. A distinction was also made between children and adults, were appropriate.

Asymptomatic people

The committee noted that asymptomatic adults should have an annual review including clinical examination, oxygen saturation test, spirometry, chest X-ray, microbiological investigations with sampling and culture of respiratory tract secretions for early asymptomatic infection with cystic fibrosis pathogens and blood testing to include white cell count and markers or aspergillus, including aspergillus serology and serum IgE.

The committee considered annual chest X-rays to be justified due to the low radiation dose, particularly compared with CT scan, and the benefit of comparing serial films, which may pick up changes representing development or progression of lung disease before symptoms develop. This aligned with the CF Trust consensus recommendations that recommends a regular (annual) chest radiograph.

The committee agreed that conducting microbiological tests was also very useful. This was because detection of early infection is of key importance in cystic fibrosis. It ensures that, where indicated, eradication therapy can be instituted promptly to prevent chronic infection. Problematic pathogens may be found even in asymptomatic patients and the committee consider knowledge of infection status essential for infection control purposes.

The committee considered blood tests for aspergillus, specifically IgE and precipitins, necessary to investigate for the presence of allergic broncho-pulmonary aspergillosis (ABPA), a common complication of cystic fibrosis lung disease.

The usefulness of CT scan in this population was also discussed by the committee. The committee agreed that chest x-rays are poorly sensitive for milder lung disease. They argued that the scan is a much more sensitive way of showing bronchiectasis than a plain film from a plain chest radiograph, which can only show bronchiectasis when it is developed. So in asymptomatic children where the lungs are thought to be healthy, a CT scan may find early bronchiectasis allowing escalation of treatment and, therefore, preventing further deterioration. In addition, a CT scan gives a better idea of the structure of the lungs and will

show other changes for example, mucus plugging to allow for targeting of physiotherapy. Given the increased dose of radiation exposure associated to CT scans (compared with X-ray, for example), the committee agreed that the chest CT scan for children should be a low-dose scan and a baseline CT scan in asymptomatic children should only be performed when this has not previously been carried out. The committee noted that people with cystic fibrosis may require many CT scans during their life with associated radiation dose. Moreover, modern CT techniques provide high quality long CT at a much lower dose than previously required. Many patients with CF are thin and, therefore, low-dose CT is particularly appropriate. The committee noted that the recommendation to think about a low-dose CT scan is a weak recommendation which indicates that the decision to perform or not perform the low-dose CT scan would be made based on clinical judgement based on individual circumstances.

Finally the committee agreed that lung function testing should also be part of the annual review, due to the usefulness in detecting any deterioration in the lung function.

Symptomatic people

They noted that symptomatic adults should be reviewed at least every 3 months and should have microbiological cultures, spirometry and measurement of oxygen saturation at each encounter. The rationale for recommending these tests at each encounter in those with lung disease is that the objective of the routine reviews (from the lung perspective) is to prevent deterioration in lung function. Obtaining microbiological cultures helps to ensure that if the cause of any such deterioration is an infection, treatment can be tailored accordingly. This aligned with the CF Trust consensus recommendations, which state that frequent (at every clinic visit) microbiological surveillance of respiratory secretions should be undertaken (for example, cough swab, sputum culture and induced sputum). Moreover, the committee agreed that each routine review should include a review of adherence to therapies as many people with cystic fibrosis are on several long term medications and need to perform daily treatments. Treatment adherence is a major determinant of clinical outcomes. The committee noted that lung function testing with spirometry could only be performed in children and young people who can do this.

The committee recommended that for people with cystic fibrosis with lung disease who have symptoms that are concerning them, or their family members or carers, assessments should be considered on an individualised basis. Depending on the assessments that are needed, it can be decided whether to use telemedicine or face-to-face assessments. The committee noted that some people have devices which allow them to measure oxygen saturation, FEV_1, and take respiratory secretion samples at home. Many people would be able to measure weight and length or height at home, and clinical history could be reviewed using telemedicine.

No evidence was found on LCI. The committee noted that LCI can be a useful tool to assess disease progression as it could provide additional respiratory information to spirometry. However, the committee added that LCI is currently in its infancy in the UK. As a result, the committee made recommendations to consider the use of LCI for those clinics that have access to the equipment and ability to interpret the results. To enable stronger recommendations in the future, a research recommendation to assess if LCI is a useful and cost-effective tool for the routine assessment and monitoring of changes in pulmonary status in people with cystic fibrosis was made by the committee.

Additionally, the committee agreed that the annual review should include the same investigations as for asymptomatic adults.

The committee noted that more frequent assessment of symptomatic children may be necessary to ensure resolution of symptoms.

It was noted that, in people who are responding poorly to treatment, and in the absence of identification of pathogens from cough swabs and induced sputum, more invasive procedures including bronchoalveolar lavage (BAL) or CT scanning can be considered.

Although the included study did not show clinically significant differences between the BAL-directed therapy group and the standard group, BAL is still considered the gold standard. The committee discussed that it is likely that children allocated to the standard group did actually receive BAL when they experience an exacerbation, which could explain the lack of differences between both groups.

As evidence was found to suggest correlation between CT score and prognosis, CT may be useful to monitor disease progression. Where CT scores suggest a worsening prognosis, a more aggressive treatment approach may be required to limit or reverse deterioration and improve the prognosis. Based on this, the committee thought doing a low-dose chest CT scan for children with cystic fibrosis could be useful as it helps to monitor disease progression. The committee agreed that the CT scan could detect features that other tests, such as plain chest radiograph, would miss (for example early bronchiectasis).

Acute exacerbations

The committee noted that those with acute exacerbations need to have a separate, defined protocol for monitoring during the exacerbation. As part of this monitoring process, individuals with exacerbations should undergo clinical assessment, microbiological investigations (sputum or cough swab for cystic fibrosis pathogens including selective media) and spirometry.

The committee noted that usually, in practice, a chest X-ray is performed if FEV_1 drops by 10% or more, although treatment of an exacerbation may be provided without reference to an X-ray. The committee, therefore, recommended that performance of X-ray for acute exacerbation should be considered dependent on severity of the exacerbation, symptoms (for example, where there is suspicion of a pneumothorax) or where there is an element of treatment failure. Where new radiological abnormalities are present on X-ray, this should be repeated to confirm resolution following treatment.

The committee noted that during and following an exacerbation, response to treatment should be assessed using spirometry and microbiological investigation, time to next exacerbation and patient reported outcomes.

As for asymptomatic adults, culture of respiratory secretions for early identification of microbial pathogens is important to allow the most appropriate antibiotics to be selected in line with good antibiotic stewardship. An acute exacerbation may be the initial presentation of a newly acquired pathogen so, as for asymptomatic adults, it is important that any new organisms are detected early to allow eradication to be attempted.

They also agreed lung function tests can be useful to assess response to treatment. They noted height is necessary for accurate calculation of spirometric indices and should be confirmed when spirometry is undertaken where not recently been established.

They considered non-invasive oxygen saturation testing (pulse oximetry) to be part of the clinical assessment, justifying the recommendation without specific evidence.

The committee noted that inflammatory markers are helpful to indirectly determine lung damage and monitor response to treatment. As this is not specific to cystic fibrosis, the committee felt it was justified to include reference to this test in this section.

9.1.7.3 Consideration of economic benefits and harm

Spirometry was the cheapest lung function test under consideration and the committee noted that the accuracy of spirometry is demonstrated in both clinical practice and the study by Sanders 2015. For these reasons, the committee agreed spirometry was cost-effective and should continue to be used to monitor for pulmonary disease at each clinic visit.

The committee also considered a place for LCI investigations at the annual review given that the additional respiratory information resulting from a LCI investigation compared to spirometry justifies the additional cost of LCI. However, they noted that LCI is currently in its infancy in the UK and, although it is a promising investigative technique, its application is currently limited to research rather than routine clinical practice.

The committee noted that the intense monitoring schedules proposed during the first year of identification (4-weekly) would put a strain on cystic fibrosis clinics. Moreover, face-to-face contact at a clinic would be burdensome on the person with cystic fibrosis and subject to availability, which may be too late during an exacerbation. For these reasons, the committee advised that visits could be performed outside of the clinic, as either home-visits or telemedicine, where considered appropriate.

The committee acknowledged that a CT scan costs considerably more than a chest X-ray and involves greater exposure to radiation. However, they believed a CT scan would show subtle structural changes in the lungs that would not be evident from a chest X-ray, such as early bronchiectasis. As a result, a CT scan could allow early escalation of treatment to prevent further deterioration that could be more costly to treat. Furthermore, the committee noted that the accuracy of CT scans to predict pulmonary exacerbations was demonstrated in the study by Sanders 2015. For these reasons, the committee concluded they could justify the use of low-dose CT scans as a cost-effective use of NHS resources and made a recommendation to think about doing a low-dose chest CT scan in people who have not had one before.

The committee considered the high cost of BAL and agreed that despite the lack of clinical evidence in favour of BAL, an annual BAL in children would be more informative than several non-invasive investigations throughout the year. The committee also added that BAL is considered as the gold standard test in clinical practice. However, combined with the high cost of BAL, and the potential adverse effects, the committee agreed BAL could only be considered cost-effective in symptomatic people with cystic fibrosis when cheaper and less invasive investigations such as sputum induction had been unsuccessful.

Monitoring for multi-resistant organisms was discussed by the committee and they agreed it would not be a cost-effective use of resources to monitor for those organisms if there was not an effective treatment for the organisms that are identified.

9.1.7.4 Quality of evidence

There was very little evidence available to inform these 3 reviews. Although many studies examined monitoring techniques, only 2 studies were relevant to the protocol and presented clinical outcomes rather than diagnostic outcomes or estimates of correlation between monitoring techniques.

Only 1 prospective cohort study was available to inform the first protocol which focussed on people with cystic fibrosis without clinical signs or symptoms of lung disease. This study included children who had previously been participants in a randomised controlled trial. One of the criteria for inclusion to the trial was having a FVC of 85% predicted or greater. The participants actually had a mean FEV_1 of 99% predicted at the end of the trial, this was similar to the national (United States) average for children without cystic fibrosis. On this basis the study was included to inform the first protocol.

The GRADE quality of this prognostic data was moderate. It was downgraded from high as the adjustment of the rate ratios did not incorporate the potential confounders of concurrent treatment with immunomodulatory and mucolytic agents during the 10 year follow up period.

There was no available evidence that examined the effectiveness of different combinations of monitoring techniques in adults or children without clinical signs or symptoms of lung disease.

Additionally, there was no available evidence that examined the effectiveness of different combinations of monitoring techniques in adults or children with established pulmonary disease, or any prognostic data for this clinical scenario.

The RCT which informed the third protocol did compare monitoring strategies, however, the included population was aged from under 6 months to 5 years. The relevance of the intervention to use BAL to direct therapy is questionable as this would not reflect current clinical practice, the GRADE quality of outcomes was downgraded accordingly. Moreover, the generalisability of the results to adults is questionable.

9.1.7.5 Other considerations

The committee discussed potential equality issues. They noted that young people who live far from a specialist centre may be disadvantaged. However, they agreed no additional recommendations were needed as the use of alternative models care had already extensively been discussed in the service delivery review. See Service configuration.

The committee discussed the need to draft a research recommendation for this topic. They agreed it would be important to evaluate if LCI was a useful tool for routine assessment and monitoring for changes in pulmonary status in people with cystic fibrosis. This is because assessing the severity of lung disease is difficult in younger children, as not all children under 5 years can do spirometry tests and they are not sufficiently sensitive in people with good lung function, where CT scans can show pulmonary status changes before spirometry changes. A simple, sensitive and reproducible measurement such as LCI allows assessment of respiratory status in people with cystic fibrosis and could improve clinical decision-making.

9.1.7.6 Key conclusions

The committee concluded that monitoring for the onset and evolution of pulmonary disease is key to being able to treat early infections.

They agreed that it is important to conduct regular routine reviews with children and adults with cystic fibrosis even if they are asymptomatic, and these reviews should be more frequent in early life. The committee agreed reviews can be conducted more often if necessary based on clinical judgement. During these routine reviews, it is important to carry out a clinical assessment, conduct non-invasive microbiological investigations and pulmonary function tests. They also agreed it is useful to do a chest CT scan for all children before the age of 12 even in the absence of lung disease. Likewise, they agreed it is important to perform a baseline CT scan for cystic fibrosis people diagnosed in adulthood.

With regards to children who are symptomatic, the committee agreed on recommending the use of invasive microbiological investigations, such as BAL, when the cause of the disease cannot be found using non-invasive microbiological tests or if there is no response to treatment.

Finally, the committee also agreed that it is important to monitor the response to treatment during and after a pulmonary exacerbation by assessing whether symptoms have resolved, conducting microbiological investigations and pulmonary function tests.

9.1.8 Recommendations

40. For people with cystic fibrosis who have clinical evidence of lung disease, base the frequency of routine reviews on their clinical condition but review children and young people at least every 8 weeks and adults at least every 3 months. If appropriate, think about using the review schedules in recommendation 22.

41. Include the following at each routine review, in relation to pulmonary assessment, for people with cystic fibrosis:

- a clinical assessment, including a review of clinical history and medicines adherence, and a physical examination with measurement of weight and length or height
- measurement of oxygen saturation
- taking respiratory secretion samples for microbiological investigations, using sputum samples if possible, or a cough swab or nasal pharyngeal aspirate (NPA)
- lung function testing with spirometry (including forced expiratory volume in 1 second [FEV1], forced vital capacity [FVC], and forced expiratory flow [FEF] 25–75%) in adults, and in children and young people who can do this.

42. If spirometry is normal at a routine review, consider measuring lung clearance index.

43. Include the following at each annual review in relation to pulmonary assessment for people with cystic fibrosis:

- a clinical assessment, including a review of the clinical history and medicines adherence, and a physical examination, with measurement of weight and length or height
- a physiotherapy assessment
- measurement of oxygen saturation
- a chest X-ray
- blood tests, including white cell count, aspergillus serology and serum IgE
- taking respiratory secretion samples for microbiological investigations (including non-tuberculous mycobacteria)
- lung function testing (for example with spirometry, including FEV_1, FVC, and FEF 25–75%) in adults, and in children and young people who can do this.

44. Consider measuring lung clearance index at each annual review if spirometry is normal.

45. For people with cystic fibrosis with lung disease who have symptoms that are concerning them or their family members or carers (as appropriate), consider which of the following may be useful:

- review of clinical history
- physical examination, including measurement of weight and length or height
- measurement of oxygen saturation

- taking respiratory secretion samples for microbiological investigations, using sputum samples if possible, or a cough swab or NPA if not
- for adults, blood tests to measure white cell count and inflammatory markers such as C-reactive protein
- lung function testing, for example with spirometry (including FEV_1, FVC, and FEF 25–75%) in adults, and in children and young people who can do this
- lung clearance index for people with normal spirometry results.

Depending on the assessments that are needed, decide whether to provide a remote Telemedicine or face-to-face assessment.

46. **Think about doing a low-dose chest CT scan for children with cystic fibrosis who have not had a chest CT scan before, to detect features that other tests (such as a plain chest X-ray) would miss (for example early bronchiectasis).**

47. **Think about doing a chest X-ray for people with cystic fibrosis during or after treatment for an exacerbation of lung disease (taking account of severity), if:**
    - the exacerbation does not respond to treatment **or**
    - a chest X-ray before treatment showed new radiological abnormalities.

48. **Monitor the treatment response during and after an exacerbation of lung disease by assessing whether the symptoms and signs have resolved, and as appropriate:**
    - take respiratory secretion samples for microbiological investigations, using sputum samples if possible, or a cough swab or NPA if not
    - test lung function, for example with spirometry (including FEV_1, FVC and FEF 25–75%) in adults, and in children and young people who can do this
    - measure oxygen saturation.

49. **Think about using broncho-alveolar lavage to obtain airway samples for microbiological investigation in people with cystic fibrosis if:**
    - they have lung disease that has not responded adequately to treatment **and**
    - the cause of the disease cannot be found with non-invasive upper airway respiratory secretion sampling (including sputum induction if appropriate).

9.1.9 Research recommendations

1. **Is lung clearance index a useful and cost-effective tool for the routine assessment and monitoring of changes in pulmonary status in people with cystic fibrosis?**

Table 66: Research recommendation rationale

Research question	Is lung clearance index a useful and cost-effective tool for the routine assessment and monitoring of changes in pulmonary status in people with cystic fibrosis?
Why this is needed	
Importance to 'patients' or the population	LCI measured by multiple-breath washout (MBW) is a more sensitive test of impaired lung function compared to FEV_1, particularly in those with relatively normal pulmonary function. It may be a tool to help decisions on early intervention with treatment in children and adults with cystic fibrosis.

Research question	Is lung clearance index a useful and cost-effective tool for the routine assessment and monitoring of changes in pulmonary status in people with cystic fibrosis?
Relevance to NICE guidance	Validation of this tool for clinical care could change some recommendations for disease monitoring and treatment intervention. This is of particular relevance in pre-school children where FEV_1 is not reliably performed. High: the research is essential to inform future updates of key recommendations in the guideline
Relevance to the NHS	If validated and adopted training in Physiology labs and new equipment would be required. In pre-school children it may identify those who require increased intervention, and those who potentially need less regular monitoring and less aggressive therapy. Targeted treatment may potentially have cost savings.
National priorities	No document identified
Current evidence base	FEV_1 measurements are difficult to perform in preschool infants. FEV_1 measurements often do not become abnormal until significant lung disease is established.
Equality	This test is of particular relevance to preschool children.
Feasibility	The proposed research can be carried out within a realistic timescale and at an acceptable cost. There are no ethical or technical issues.
Other comments	None

Table 67: Research recommendation statements

Criterion	Explanation
Population	Children with cystic fibrosis, up to 6 years old (pre-school children)
Intervention	• LCI, measure by multiple breath washout (MBW) testing at regular intervals
Comparators	Alternative lung function test: FEV_1 (measured by spirometry)
Outcomes	• Change in lung function • Quality of life as measured by a validated tool, such as CF-QOL or CFQ-R) • Nutritional parameters (BMI, weight/ height) • Time to chronic infection • Resource use • Unit costs
Study design	RCT or cluster RCT
Timeframe	Within 2 years

9.2 Airway clearance techniques

Review question: What is the effectiveness of airway clearance techniques in people with cystic fibrosis?

9.2.1 Introduction

The genetic defect in cystic fibrosis results in the dehydration of mucus, causing increased viscidity and resultant difficulty in its clearance from the airways. Assisted airway clearance has, therefore, featured in the treatment routines of people with cystic fibrosis for decades. A variety of techniques have been developed; some require equipment, some rely on the assistance of others and some facilitate independence. The utility of each technique depends upon the degree and extent of the pathophysiology within the lungs.

The role of the specialist cystic fibrosis physiotherapist is to evaluate this pathophysiology and, in collaboration with the person with cystic fibrosis, select the best airway clearance

technique that will overcome these challenges. The aim of treatment is not only to improve the removal of bronchopulmonary secretions and reduce the risk of bacterial infection, but to reduce the burden of symptoms such as cough and breathlessness and ultimately slow disease progression. Airway clearance techniques are often employed as part of a wider airway treatment strategy which may also include mucolytic or anti-inflammatory drugs and exercise. As a result, measuring the impact or success of airway clearance techniques alone is not without difficulty.

Airway clearance approaches are individualised and physiologically reasoned and so need to be frequent reviewed and modified by the physiotherapist according to the evolution of lung disease. With the advent of newborn screening and the success of new medical treatments, the person with cystic fibrosis who has little or no lung disease also needs careful consideration. Airway clearance routines for the person with cystic fibrosis and their family or carers can be considered a significant commitment and burden to achieving 'normal' life. It is therefore essential that cystic fibrosis teams continue to question what is understood about these frequently used techniques.

9.2.2 Description of clinical evidence

The aim of this review was to examine the effectiveness of airway clearance techniques in people with cystic fibrosis.

The interventions reviewed were: manual physiotherapy techniques (including chest shaking or vibrations, chest percussion), positive expiratory pressure (PEP), active cycle of breathing techniques (ACBT), relaxation or breathing control forced expiration techniques (FET) which includes huffing and breathing control, thoracic expansion exercises, autogenic drainage (AD), oscillating devices (including acapella and flutter, cornet), high frequency chest wall oscillation (e.g. the Vest) and non-invasive ventilation (NIV).

We aimed to compare each airway technique with no intervention, to ascertain effectiveness. In addition, the committee prioritised for inclusion the following comparisons between techniques:

- Manual physiotherapy techniques versus oscillating devices (OD)
- Manual physiotherapy versus high frequency chest wall oscillation (HFCWO)
- Positive expiratory pressure (PEP) versus active cycle of breathing techniques (ACBT)
- Positive expiratory pressure (PEP) versus oscillating devices (OD)
- Positive expiratory pressure (PEP) versus high frequency chest wall oscillation (HFCWO)
- Active cycle breathing technique (ACBT) versus autogenic drainage (AD)
- Oscillating device (OD) versus high frequency chest wall oscillation (HFCWO).

We searched for systematic reviews of RCTs and RCTs aimed at assessing the effectiveness of airway clearance techniques in people with cystic fibrosis. Observational studies were not prioritised for inclusion in the review, as there was enough evidence from published randomised trials.

For full details see review protocol in Appendix D.

Six Cochrane systematic reviews (McIlwaine 2015, Morrison 2014, Moran 2013, McKoy 2012, Main 2005, Warnock 2013) and 5 non-Cochrane systematic reviews (Boy 1994, Bradley 2006, Flume 2009, Morgan 2015, Thomas 1995) were identified in our search for potential inclusion. The quality of all reviews was assessed with AMSTAR.

All the Cochrane reviews obtained a total score equal or higher than 10 (out of 11) in the AMSTAR quality checklist and were considered for inclusion. Each Cochrane review was then checked for relevant potential comparisons, as the definitions of the airway clearance techniques differ from the definitions proposed in our protocol.

Four Cochrane reviews were included, as they had relevant comparisons. Where possible, data and quality assessment were extracted from the Cochrane reviews, although the individual studies were retrieved full text for additional information and results.

The Cochrane reviews included were:

- McIlwaine (2015) evaluated the effectiveness and acceptability of PEP devices compared to other physiotherapy techniques to improve airway clearance. 4 trials were included from this review (McIlwaine 2013, McIlwaine 2001, Newbold 2005, Tannenbaum 2005), of which 1 (Tannenbaum 2005) was an abstract and only information provided by the Cochrane review was used as the paper could not be retrieved.
- Moran (2013) compared the effect of non-invasive ventilation versus no treatment in people with cystic fibrosis. 2 trials were included from this review (Placidi 2006 and Young 2008).
- Morrison (2014) evaluated whether oscillatory devices, oral or chest wall were effective for airway clearance and also compared them with other forms of airway clearance for the management of secretions in people with cystic fibrosis. Seven trials were included from this review (Darbee 2005, Grzincich 2008, Padman 1999, Oermann 2001, Homnick 1998, van Winden, Warwick 2004), of which 1 was an abstract (Grzincich 2008)
- Warnock (2013) evaluated the effectiveness and acceptability of chest physiotherapy compared to no treatment to improve airway clearance in people with cystic fibrosis. 1 trial was included from this review (Braggion 1995).

Three Cochrane reviews were excluded:

- McKoy (2012) evaluated the clinical effectiveness of ACBT with other airway clearance techniques, but it did not include comparisons relevant for this review. The individual studies were also checked for potential inclusion, but none of them met the criteria for inclusion.
- Main (2005) compared conventional chest physiotherapy to other airway clearance techniques for cystic fibrosis, but it did not include comparisons relevant for this review. The individual studies were also checked for potential inclusion, and only 1 was considered relevant (Homnick 1998), but it had already been included in another review (Morrison 2014).
- Robinson (2010) compared the clinical effectiveness of ACBT with other airway clearance techniques. One trial (Miller 1995) was considered for inclusion, but the intervention consisted in a combination of ACBT and postural drainage.

The quality of the non-Cochrane reviews obtained scores equal to or lower than 6 (out of 11) in the AMSTAR checklist and were therefore excluded. The lists of included studies in these reviews were checked in order to identify other studies that had not been already included, but none of them met the inclusion criteria in our protocol.

No further trials were identified in our search.

The size of the studies ranged from to 8 to 107 people with cystic fibrosis. Four studies included adults (Grzincich, Newbold 2005, Young 2008, Warwick 2004), 2 studies included young people and adults (Braggion 1995, Placidi 2006), 4 studies included children and young people (McIlwaine 2001, Padman 1999, Tannenbaum 2005, van Winden 1998), 4 studies included children, young people and adults (Darbee 2005, Homnick 1998, McIlwaine 2013, Oermann 2001)

One study was conducted in Italy (Braggion 1995), 5 studies in the USA (Darbee 2005, Homnick 1998, Oermann 2001, Padman 1999, Warwick 2004), 2 studies in Australia (Placidi 2006, Young 2008), 3 studies in Canada (McIlwaine 2001, McIlwaine 2013, Newbold 2005), 1 study in the Netherlands (van Winden 1998); the country was not reported in 2 abstracts (Grzincich 2008, Tannenbaum 2005).

The included studies assess the effectiveness and acceptability of airway clearance interventions with the following comparisons:

- manual physiotherapy techniques versus oscillating devices – 2 studies (Homnick 1998, Padman 1999)
- manual physiotherapy versus high frequency chest wall oscillation (HFCWO) – 1 study (Warwick 2004)
- positive expiratory pressure (PEP) versus no airway clearance - 2 studies (Braggion 1995, Placidi 2006)
- positive expiratory pressure (PEP) versus oscillating devices – 6 studies (McIlwaine 2001, McIlwaine 2013, Newbold 2005, Padman 1999, Tannenbaum 2005, van Winden 1998)
- positive expiratory pressure (PEP) versus high frequency chest wall oscillation (HFCWO) – 4 studies (Braggion 1995, Darbee 2005, Grzincich 2008, McIlwaine 2013)
- oscillating device versus high frequency chest wall oscillation (HFCWO) - 1 study (Oermann 2001)
- non-invasive ventilation versus no airway clearance technique – 1 study (Young 2008).

Where no evidence for sputum volume was found in the study, sputum weight (both dry and wet) was taken as a proxy outcome for sputum volume.

Evidence from these are summarised in the clinical GRADE evidence profile below (Table 62Table 69 to Table 75). See also the study selection flow chart in Appendix F, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix H.

9.2.3 Summary of included studies

A summary of the studies that were included in this review are presented in Table 68.

Table 68: Summary of included studies

Study	Intervention/Comparison	Population	Outcomes	Comments
Cochrane systematic reviews				
McIlwaine 2015 Cochrane SR	Positive Expiratory Pressure (PEP) vs High Frequency Chest Wall Oscillation (HFCWO) (McIlwaine 2013) Positive expiratory pressure (PEP) vs oscillating device (McIlwaine 2001, Newbold 2005, Tannenbaum 2005)	People with CF of any age with any degree of disease severity. People with CF post-lung transplant were excluded.	• PEP vs HFCWO • Sputum weight (dry and wet) PEP vs oscillating device: • Patient preference (self-withdrawal due to lack of effectiveness) • Hospitalisations for respiratory exacerbation • Number of participants experiencing respiratory exacerbations • Lung function • Quality of life • Not reported:	

Study	Intervention/Comparison	Population	Outcomes	Comments
			• Oxygen saturation	
Moran 2013 Cochrane SR	Overnight non-invasive ventilation (NIV) vs no airway clearance technique (room air) (Young 2008) Positive Expiratory Pressure (PEP) mask vs no airway clearance (directed cough) (Placidi 2006)*	People with CF of any age with any type of acute and chronic respiratory failure.	NIV vs no airway clearance technique: • Lung function • Oxygen saturation (nocturnal) • Quality of life PEP vs no airway clearance technique: • Sputum weight • Lung function • Oxygen saturation • Not reported: • Patient preference • Pulmonary exacerbations • Hospitalisations	*Comparison not in Cochrane SR; comparison made by the NGA technical team using data from controls in comparisons included in Cochrane SR.
Morrison 2014 Cochrane SR	Positive Expiratory Pressure (PEP) vs High Frequency Chest Wall Oscillation (HFCWO) (Braggion 1995, Derbee 2005, Grzincich 2008) Positive expiratory pressure (PEP) vs oscillating device (flutter) (Padman 1999, van Winden 1998) Oscillating device vs High Frequency Chest Wall Oscillation (Oermann 2001) Manual physiotherapy techniques vs oscillating devices (flutter) (Homnick 1998, Padman 1999) Manual physiotherapy vs	Children, young people and adults with CF with any degree of disease severity.	PEP vs HFCWO: • Sputum volume • Lung function PEP vs oscillating device: • Lung function Oscillating device vs HFCWO: • Lung function Manual techniques vs HFCWO: • Sputum weight. Manual techniques vs oscillating device: • Lung function • Not reported: • Patient preference • Pulmonary exacerbations • Hospitalisations • Oxygen saturation (nocturnal) • Quality of life	

Study	Intervention/Comparison	Population	Outcomes	Comments
	High Frequency Chest Wall Oscillation (Warwick 2004)			
Warnock 2013 Cochrane SR	Positive expiratory pressure (PEP) mask vs no airway clearance technique (Braggion 1995)	People with CF of any age.	PEP vs control: • lung function test • Not reported: • Expectorated secretions • Sputum volume • Patient preference • Pulmonary exacerbations • Hospitalisations • Oxygen saturation (nocturnal) • Quality of life	
Primary studies included in the Cochrane SR				
Braggion 1995 (Italy) RCT, crossover design	Intervention 1: Positive expiratory pressure (PEP) • 50-minute session (unclear if this included 15 mins of nebulisation) Intervention 2: High Frequency Chest Wall Oscillation (HFCWO) • 50-minute session (unclear if this included 15 mins of nebulisation) Control: no airway clearance	N=16 young people and adults with CF Mean age (SD): 20.3 (4) years. Age range: 15 to 27	• FEV_1 % predicted • FVC % predicted	Included in Morrison 2014 SR and in Warnock 2013 SR 15 minutes of saline nebulised prior to treatment. 2 treatments per day for 2 days, then rest 1 day. Next intervention for 2 days, then rest 1 day. Then the final intervention.
Darbee 2005 (USA) RCT, crossover design	Intervention 1: Positive expiratory pressure (PEP) mask • 30-minute sessions Intervention 2: High Frequency Chest Wall	N=15 children, young people and adults with CF Age ≥7 years. Mean (SD) age: 17.5 (4.2) Participants were admitted to hospital for acute exacerbation. All participants	• FEV_1 % predicted • FVC % predicted	Included in Morrison 2014 SR Both treatments were alternated within 48 hours of hospital admission and then reversed prior to discharge.

Study	Intervention/Comparison	Population	Outcomes	Comments
	Oscillation (HFCWO) • 30-minute sessions	performed HFCWO 1 - 3 times daily as outpatients before admission, but none had performed PEP		
Grzincich 2008 (Country not reported) RCT, unclear if crossover design	Intervention 1: Positive expiratory pressure (PEP) • 30-minute sessions Intervention 2: High Frequency Chest Wall Oscillation (HFCWO) • 30-minute sessions	N=23 adults with CF Mean age: 25 years. People hospitalized for an exacerbation	• Sputum volume	Included in Morrison 2014 SR Interventions and control implemented during the first 3 days of hospitalisation for an exacerbation Abstract only
Homnick 1998 (USA) RCT, crossover design	Intervention 1. Manual physiotherapy • 30-minute sessions, 4 times daily during hospitalisation Intervention 2. Oscillating device (flutter) • 15-minute sessions, 4 times daily during hospitalisation	N=22 children, young people and adults with CF (33 hospitalisations) Mean (range) age: 12 (7 to 44)	• % change from baseline in FEV_1 • % change from baseline in FVC	Included in Morrison 2014 SR
McIlwaine 2001 (Canada) RCT, parallel design	Intervention 1. Positive expiratory pressure (PEP) mask • 20-minute sessions twice daily for 1 year Intervention 2. Oscillating device (flutter) • Sessions of ≥15 minutes twice daily for 1 year	N=40 children and young people with CF Age range: 7 to 17 • Intervention 1: n=20 • Intervention 2: n=20 Participants were excluded if they had been hospitalised within the past month for a pulmonary exacerbation, or if they were not	• Patient preference: self-withdrawal due to lack of perceived effectiveness • FEV_1 (% change from baseline) • FVC (% change from baseline)	Included in McIlwaine 2015 SR

Study	Intervention/Comparison	Population	Outcomes	Comments
		stable on clinical evaluation, chest radiograph or pulmonary function		
McIlwaine 2013 (Canada) Multi-centre RCT, parallel design	Intervention 1: Positive expiratory pressure (PEP) mask • 6 cycles; treatment for 1 year Intervention 2: High Frequency Chest Wall Oscillation (HFCWO) • 6 sets of 5-minute cycles; treatment for 1 year	N=107 children, young people and adults with CF from 12 CF centres. • PEP: n=51 • HFCWO: n=56 Age range: 6 to 47 years. FEV_1>40% predicted Participants were excluded if they had been hospitalised within the past month for a pulmonary exacerbation, or if they were not stable on clinical evaluation, chest radiograph or pulmonary function.	• FEV_1 (% change from baseline) • FVC (% change from baseline) • QoL (CFQ-R: physical domain, treatment burden, respiratory domain)	Included in McIlwaine 2015 SR On entering the study, participants performed a 2-month washout period before being allocated to an intervention
Newbold 2005 (Canada) RCT, parallel design	Intervention 1: Positive expiratory pressure (PEP) mask • 20-minute session, twice daily for 13 months Intervention 2: Oscillating device (flutter) • Duration approx. 20 minutes, twice daily for 13 months	N=42 adults with CF • PEP: n=21. Mean (SD) age: 28 (8.1) • Flutter: n=21. Mean (SD) age: 31 (8.7) Participants were excluded if they had been hospitalised within the past month for a pulmonary exacerbation, had changed their medication within the past month, or did not have a daily cough or daily sputum	• FEV_1 (% change from baseline) • FVC (% change from baseline) • Hospitalizations for respiratory exacerbations	Included in McIlwaine 2015 SR
Oermann 2001 (USA)	Intervention 1: Oscillating device (flutter).	N=29 children, young people and adults with CF	• FEV_1 % predicted	Included in Morrison 2014 SR

Study	Intervention/Comparison	Population	Outcomes	Comments
RCT, crossover design	• Number of times per day not reported Intervention 2: High Frequency Chest Wall Oscillation. • Number of times per day not reported.	Mean (range) age: 23 (9 to 39) Baseline FVC range: 50 to 80 % predicted Clinically stable for 1 month prior to enrolment.	• FVC % predicted	5 participants withdrew (4 exited due to illness and 1 due to non-compliance with clinic visits) 4 weeks in each arm, 2-week lead-in/ wash out periods during which time they resumed their normal routine therapies which were not outlined
Padman 1999 (USA) RCT, crossover design	Intervention 1: Manual chest physiotherapy Intervention 2: Positive expiratory pressure (PEP) mask • 15-minute sessions, 3 times per day for 1 month Intervention 3: Oscillating device (flutter) • 15-minute sessions, 3 times per day for 1 month	N=15 children and young people with CF were randomized, 6 completed the study. Age range: 5 to 17 Participants were clinically stable and able to perform respiratory function tests; no hospitalisations in the month prior to the study	• % change from baseline in FEV_1	Included in Morrison 2014 SR 5 participants excluded due to hospital admission for acute exacerbation, 4 withdrew (no reason given)
Placidi 2006 (Australia) RCT, crossover design	Intervention: Positive expiratory pressure (PEP) mask Control: no airway clearance technique (directed cough)	N= 17 young people and adults with CF Age: >15 years. Mean (SD) age: 28 (7) People had severe lung disease and were admitted for pulmonary exacerbation.	• Sputum dry weight • Sputum wet weight • Lung function - FEV_1 • Lung function - FVC • Oxygen saturation - Spo2 %	Included in Moran 2013 SR Follow-up: mean 2 days
Tannenbaum 2005 (Country not reported) RCT, parallel design	Intervention 1: Positive expiratory pressure (PEP) mask	N = 30 children and young people with CF Age range: 6 to 15 years	• % change from baseline FEV_1	Included in McIlwaine 2015 SR Information was provided from 3 abstracts, no further

Study	Intervention/Comparison	Population	Outcomes	Comments
	Intervention 2: oscillating device (cornet)			information obtained
Young 2008 (Australia) RCT, crossover design	Intervention: Overnight non-invasive ventilation for 6 weeks Control: No airway clearance technique (room air) for 6 weeks	N=8 adults with CF Mean (SD) age: 37 (8) years Participants with moderate lung disease.	• FEV_1 % predicted • FVC % predicted • Oxygen saturation (nocturnal) (%) • Quality of life: CF QOL chest symptom score; CF QOL traditional dyspnoea index score	Included in Moran 2013 SR 2-week washout period
van Winden 1998 (The Netherlands) RCT, crossover design	Intervention 1: Positive expiratory pressure (PEP) mask • Twice daily Intervention 2: Oscillating device (flutter) • Twice daily	N=22 children and young people with CF Mean age (range): 12 years (7 to 17). People were clinically stable for 2 weeks before the study	• FEV_1 % predicted • FVC % predicted	Included in Morrison 2014 SR 2 weeks in each arm, 1 week wash-in and wash-out period
Warwick 2004 (USA) RCT, crossover design	Intervention 1: Manual physiotherapy. • 10 hand positions • Duration: approximately 45 to 50 minutes daily for 4 weeks Intervention 2: High Frequency Chest Compression • Duration: approximately 36 to 50 minutes daily for 4 weeks	N=12 adults with CF Age mean (range): 29.1 (19 to 50) Consistent sputum producers; all volunteers with no illness within 6 weeks of study	• Sputum weight (dry) • Sputum weight (wet)	Included in Morrison 2014 SR All treatments preceded by nebulisers.

CF: cystic fibrosis, HFCWO: high frequency chest wall oscillation; PEP: positive expiratory pressure; SR: systematic review

9.2.4 Clinical evidence profile

The summary clinical evidence profiles are presented in Table 68 to Table 75.

Table 69: Summary clinical evidence profile: Comparison 2. Manual physiotherapy versus oscillating devices

Comparison 2. Manual physiotherapy compared to oscillating device for CF						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	Quality of the evidence (GRADE)	Comments
	Assumed risk	**Corresponding risk**				
	Oscillating device (OD)	**Manual physiotherapy**				
Lung function Measured as FEV_1 % change from baseline Scale from: 0 to 100 Follow-up: mean 8.8 days	The mean % change from baseline in FEV_1 in the OD group was 43.7	The mean % change from baseline in FEV_1 in the manual physiotherapy groups was 7.9 lower (31.04 lower to 15.24 higher)		22 (Homnick 1998)	⊕⊖⊖⊖ very low[1,2]	
Lung function Measured as FEV_1 % change from baseline Scale from: 0 to 100 Follow-up: mean 1 months	The mean % change from baseline in FEV_1 in the OD group was 3.66	The mean % change from baseline in FEV_1 in the manual physiotherapy groups was 2.59 higher (6.3 lower to 11.48 higher)		6 (Padman 1999)	⊕⊖⊖⊖ very low[3,4]	
Lung Function - FVC % change from baseline Scale from: 0 to 100 Follow-up: mean 2 weeks	The mean % change from baseline in FVC in the OD group was 27.2	The mean % change from baseline in FVC in the manual physiotherapy group was 2.9 higher (14.21 lower to 20.01 higher)		22 (Homnick 1998)	⊕⊖⊖⊖ very low[1,4]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; MD: mean difference

1 The quality of the evidence downgraded by 2 due to selection bias and attrition bias
2 The quality of the evidence was downgraded by 1 due to serious imprecision as 95% CI crossed 1 default MID
3 The quality of the evidence was downgraded by 2 due to attrition bias and reporting bias.
4 The quality of the evidence was downgraded by 2 due to very serious imprecision as 95% CI crossed 2 default MIDs

Table 70: Summary clinical evidence profile: Comparison 3. Manual physiotherapy versus high frequency chest wall oscillation

Comparison 3. Manual physiotherapy techniques compared to high frequency chest oscillation therapy for CF						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	High frequency chest oscillation therapy (HFCWO)	**Manual physiotherapy**				
Sputum weight (dry) (grams) Follow-up: 1-2 weeks	The mean sputum weight (dry) in the HFCWO groups was 0.57	The mean sputum weight (dry) in the manual physiotherapy groups was 0.13 lower (0.42 lower to 0.16 higher)		12 (Warwick 2004)	⊕⊕⊖⊖ low[1,2]	
Sputum weight (wet) (grams) Follow-up: 1-2 weeks	The mean sputum weight (wet) in the HFCWO groups was 13.56	The mean sputum weight (wet) in the manual physiotherapy groups was 4.04 lower (10.77 lower to 2.69 higher)		12 (Warwick 2004)	⊕⊕⊖⊖ low[1,2]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; HFCWO: high frequency chest wall oscillation; MD: mean difference

1 The quality of the evidence was downgraded by 1 due to lack of blinding.
2 The quality of the evidence was downgraded by 1 due to serious imprecision as 95% CI crossed a default MID

Table 71: Summary clinical evidence profile: Comparison 4. Positive expiratory pressure (PEP) versus no airway clearance technique

Comparison 4. Positive expiratory pressure (PEP) compared to no airway clearance technique for CF						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	No airway clearance technique	**Positive expiratory pressure (PEP)**				
Sputum dry weight (grams) Follow-up:	The mean sputum dry weight in the control groups	The mean sputum dry weight in the PEP groups was		17 (Placidi 2006)	⊕⊕⊖⊖ low[1]	

Comparison 4. Positive expiratory pressure (PEP) compared to no airway clearance technique for CF						
mean 2 days	was 0.97	0.03 lower (0.48 lower to 0.42 higher)				
Sputum wet weight (grams) Follow-up: mean 2 days	The mean sputum wet weight in the control groups was 13.98	The mean sputum wet weight in the PEP groups was 1.8 higher (1.72 lower to 5.32 higher)		17 (Placidi 2006)	⊕⊕⊕⊖ moderate [2]	
Lung function - FEV_1 % predicted Scale from: 0 to 100 Follow-up: mean 2 days	The mean FEV_1% predicted in the control groups was 60.3	The mean FEV_1% predicted in the PEP groups was 2.1 higher (11.73 lower to 15.93 higher)		16 (Braggion 1995)	⊕⊖⊖⊖ very low[3,4]	
Lung function - FEV_1 (litres) Follow-up: mean 2 days	The mean FEV_1 (litres) in the control groups was 0.99	The mean FEV_1 (litres) in the PEP groups was 0.01 higher (0.18 lower to 0.2 higher)		17 (Placidi 2006)	⊕⊕⊖⊖ low[1]	
Lung Function FVC % predicted Scale from: 0 to 100 Follow-up: mean 2 days	The mean FVC % predicted in the control groups was 81.6 % predicted	The mean FVC % predicted in the PEP groups was 1.2 higher (12.88 lower to 15.28 higher)		16 (Braggion 1995)	⊕⊖⊖⊖ very low[1,3]	
Lung function - FVC (litres Follow-up: mean 2 days	The mean FVC (litres) in the control groups was 1.96	The FVC in the PEP groups was 0.05 higher (0.35 lower to 0.45 higher)		17 (Placidi 2006)	⊕⊕⊖⊖ low[1]	
Oxygen saturation - Spo2 % Scale from: 0 to 100 Follow-up: mean 2 days	The mean oxygen saturation (spo2) in the control groups was 94.6	The mean oxygen saturation (spo2) in the PEP groups was 0.3 higher (0.58 lower to 1.18 higher)		17 (Placidi 2006)	⊕⊕⊕⊖ moderate [2]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; MD: mean difference; SpO2: peripheral capillary oxygen saturation

1 The quality of the evidence was downgraded by 2 due to very serious imprecision as 95% CI crossed 2 default MIDs

2 The quality of the evidence was downgraded by 1 due to serious imprecision as 95% CI crossed a default MID
3 The quality of the evidence was downgraded by 2 due to lack of blinding, attrition bias and reporting bias
4 The quality of the evidence was downgraded by 2 due to very serious imprecision as 95% CI crossed 2 clinical MIDs

Table 72: Summary clinical evidence profile: Comparison 6. Positive expiratory pressure (PEP) versus oscillating devices

Comparison 6. Positive expiratory pressure (PEP) compared to oscillating device for CF						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	oscillating device (OD)	**Positive expiratory pressure (PEP)**				
Patient preference: self-withdrawal due to lack of perceived effectiveness Follow-up: mean 1 years	250 per 1000	22 per 1000 (2 to 385)	RR 0.09 (0.01 to 1.54)	40 (McIlwaine 2001)	⊕⊖⊖⊖ very low[1,2]	
Hospitalizations for respiratory exacerbations number per participant Follow-up: mean 13 months	The mean number of hospitalizations for respiratory exacerbations in the OD group was 0.7 per participant	The mean hospitalizations for respiratory exacerbations in the PEP groups was 0.4 lower (0.92 lower to 0.12 higher)		42 (Newbold 2005)	⊕⊕⊖⊖ low[3,4]	
Lung function - FEV_1 % change from baseline Scale from: 0 to 100 Follow-up: 2-4 weeks	The mean % change from baseline in FEV_1 in the OD group was 3.66	The mean % change from baseline in FEV_1 in the PEP groups was 4.08 higher (4.66 lower to 12.82 higher)		6 (Padman 1999)	⊕⊖⊖⊖ very low[4,5]	
Lung function - FEV_1 % change from baseline Scale from: 0 to 100 Follow-up: mean 6-12 months	The mean % change from baseline in FEV_1 in the OD groups was -10.95	The mean % change from baseline in FEV_1 in the PEP groups was 9.71 higher (2.12 lower to 21.54 higher)		30 (McIlwaine 2001)	⊕⊕⊖⊖ low[1,4]	
Lung function - FEV_1 % change from baseline Scale from: 0 to 100	The mean % change from baseline in FEV_1 in the OD groups was 2.78	The mean % change from baseline in FEV_1 in the PEP groups was 2.82 lower		160 (McIlwaine 2013, Newbold 2005, Tannenbaum 2005)	⊕⊕⊖⊖ low[4,6]	

Comparison 6. Positive expiratory pressure (PEP) compared to oscillating device for CF						
Follow-up: 1-2 years		(6.36 lower to 0.72 higher)				
Lung function - FVC % change from baseline Scale from: 0 to 100 Follow-up: mean 1 years	The mean % change from baseline in FVC in the OD groups was -0.07	The mean % change from baseline in FVC in the PEP groups was 0.44 lower (6.66 lower to 5.78 higher)		160 (McIlwaine 2001, McIlwaine 2013, Newbold 2005)	⊕⊕⊖⊖ low[6,7]	
Lung function - FVC (% predicted) Scale from: 0 to 100 Follow-up: 2-4 weeks	The mean FVC % predicted in the OD groups was 99 % predicted	The mean FVC % predicted in the PEP groups was 2 lower (4.09 lower to 0.09 higher)		22 (van Winden 1998)	⊕⊕⊕⊖ moderate [4]	
QOL – CFQ-R: physical domain Scale from: 0 to 100 Follow-up: mean 1 years	The mean CFQ-R - physical domain in the OD groups was -3.04	The mean CFQ-R - physical domain in the PEP groups was 2.2 higher (1.32 lower to 5.72 higher)		107 (McIlwaine 2013)	⊕⊕⊕⊕ high[8]	
QOL – CFQ-R: treatment burden Scale from: 0 to 100 Follow-up: mean 1 years	The mean QOL-CFQ-R: treatment burden in the OD groups was -3.6	The mean QOL – CFQ-R: treatment burden in the PEP groups was 1.05 higher (6.35 lower to 8.45 higher)		107 (McIlwaine 2013)	⊕⊕⊕⊕ high[8]	
QOL – CFQ-R: respiratory domain Scale from: 0 to 100 Follow-up: mean 1 years	The mean CFQ-R - respiratory domain in the OD groups was 0.19	The mean CFQ-R - respiratory domain in the PEP groups was 2.79 higher (3.68 lower to 9.26 higher)		107 (McIlwaine 2013)	⊕⊕⊕⊖ moderate [8,9]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; MD: mean difference; OD: oscillating device; PEP: positive expiratory pressure; RR: risk ratio

1 The quality of the evidence was downgraded by 1 due to reporting bias.
2. The quality of the evidence was downgraded by 2 due to very serious imprecision as 95% CI crossed 2 default MIDs
3 The quality of the evidence was downgraded by 1 due to differences in baseline characteristics (pulmonary function values) between both groups.
4 The quality of the evidence was downgraded by 1 due to serious imprecision as 95% CI crossed a default MID
5 The quality of the evidence was downgraded by 2 due to attrition bias and reporting bias.
6 Taking into account weighting in a meta-analysis and the likely contribution from each component, the quality of the evidence was downgraded by 1 due differences in baseline participant characteristics.

7 The quality of the evidence was downgraded by 1 due to serious heterogeneity (I-squared inconsistency statistic of 69%) and no plausible explanation was found with sensitivity analysis.
8 Clinical MID=8.5 was used to assess imprecision because the CFQ-R questionnaire (Quittner et al. 2009) was used
9 The quality of the evidence was downgraded by 1 as 95% CI crossed 1 clinical MID

Table 73: Summary clinical evidence profile: Comparison 7. Positive expiratory pressure (PEP) versus High Frequency Chest Wall Oscillation (HFCWO)

Comparison 7. Positive expiratory pressure (PEP) compared to high frequency chest wall oscillation (HFCWO) for CF						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	High frequency oscillation therapy (HFCWO)	**Positive expiratory pressure (PEP)**				
Sputum volume (ml) Follow-up: mean 1 weeks	The mean sputum volume in the HFCWO groups was 6.7	The mean sputum volume in the PEP groups was 1.8 higher (3 lower to 6.6 higher)		23 (Grzincich 2008)	⊕⊕⊖⊖ low[1,2]	
Respiratory exacerbations: number of patients Follow-up: mean 1 years	833 per 1000	608 per 1000 (458 to 792)	RR 0.73 (0.55 to 0.95)	91 (McIlwaine 2013)	⊕⊕⊕⊖ moderate[2]	
Pulmonary exacerbations (patients requiring antibiotics) Follow-up: mean 1 years	870 per 1000	615 per 1000 (348 to 824)	RR 0.71 (0.55 to 0.93)	88 (McIlwaine 2013)	⊕⊕⊕⊖ moderate[2]	
Lung function - FEV_1 % predicted Scale from: 0 to 100 Follow-up: 1 weeks	The mean FEV_1 % predicted in the HFCWO groups was 64.8	The mean FEV_1 % predicted in the PEP groups was 0.67 higher (8.04 lower to 9.38 higher)		39 (Braggion 1995; Grzincich 2008)	⊕⊖⊖⊖ very low[3,4]	
Lung Function - FEV_1 % predicted Scale from: 0 to 100 Follow-up: 1-2 weeks	The mean FEV_1 % predicted in the HFCWO groups was 69	The mean FEV_1 % predicted in the PEP groups was 3 lower (20.54 lower to 14.54 higher)		15 (Darbee 2005)	⊕⊖⊖⊖ very low[4,5]	

Comparison 7. Positive expiratory pressure (PEP) compared to high frequency chest wall oscillation (HFCWO) for CF						
Lung function - FEV_1 change from baseline in FEV_1 % predicted Scale from: 0 to 100 Follow-up: 1 years	The mean change in FEV_1 % predicted in the HFCWO groups was 9.4	The mean change in FEV_1 % predicted in the PEP groups was 3.59 lower (9.29 lower to 2.11 higher)		88 (McIlwaine 2013)	⊕⊕⊕⊖ moderate[6]	
FVC % predicted Scale from: 0 to 100 Follow-up: 1-2 weeks	The mean FVC % predicted in the HFCWO groups was 83	The mean FVC in the PEP groups was 3 lower (16.6 lower to 10.6 higher)		15 (Darbee 2005)	⊕⊖⊖⊖ very low[5,7]	
FVC % predicted Scale from: 0 to 100 Follow-up: 1 weeks	The mean FVC % predicted in the HFCWO groups was 86.4	The mean FVC % predicted in the PEP groups was 0.66 higher (7.4 lower to 8.71 higher)		39 (Braggion 1995, Grzincich 2008)	⊕⊕⊕⊖ moderate[3]	
Lung function - FVC change from baseline in % predicted Scale from: 0 to 100 Follow-up: 1 years	The mean change in FVC % predicted in the HFCWO groups was 11.39	The mean change in FVC % predicted in the PEP groups was 5 lower (10.3 lower to 0.3 higher)		88 (McIlwaine 2013)	⊕⊕⊕⊖ moderate[2]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; HFCWO: high frequency chest wall oscillation; MD: mean difference; PEP: positive expiratory pressure; RR: risk ratio

1 The quality of the evidence was downgraded by 1 as risk of bias could not be fully assessed from abstract paper which did not discuss method in detail.
2 The quality of the evidence was downgraded by 1 due to serious imprecision as 95% CI crossed a default MID.
3 Taking into account weighting in a meta-analysis and the likely contribution from each component, the quality of the evidence was downgraded by 1 as risk of bias could not be fully assessed from abstract paper which did not discuss method in detail.
4 The quality of the evidence was downgraded by 2 due to very serious imprecision as 95% CI crossed 2 clinical MIDs.
5 The quality of the evidence was downgraded by 1 due to selection bias.
6 The quality of the evidence was downgraded by 1 due to serious imprecision as 95% CI crossed a clinical MID
7 The quality of the evidence was downgraded by 2 due to very serious imprecision as 95% CI crossed 2 default MIDs

Table 74: Summary clinical evidence profile: Comparison 12. Oscillating device versus High Frequency Chest Wall Oscillation (HFCWO)

Comparison 12. Oscillating device compared to high frequency chest wall oscillation for CF					
Outcomes	**Illustrative comparative risks* (95% CI)**	**Relative**	**No of Participan**	**Quality of the**	**Comments**

Comparison 12. Oscillating device compared to high frequency chest wall oscillation for CF						
	Assumed risk	**Corresponding risk**	**effect (95% CI)**	**ts (studies)**	**evidenc e (GRADE)**	
	High frequency chest wall oscillation (HFCWO)	**Oscillating device (OD)**				
Lung function - FEV_1 % predicted Follow-up: 2-4 weeks	The mean FEV_1 % predicted in the HFCWO groups was 56.5	The mean FEV_1 % predicted in the OD groups was 1.6 lower (3.44 lower to 0.24 higher)		24 (Oermann 2001)	⊕⊕⊕⊖ moderate [1]	
Lung function - FVC % predicted Follow-up: 2-4 weeks	The mean FVC % predicted in the HFCWO groups was 74	The mean FVC% predicted in the OD groups was 1.4 lower (3.07 lower to 0.27 higher)		24 (Oermann 2001)	⊕⊕⊖⊖ low[1,2]	
**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).* *Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; HFCWO: high frequency chest wall oscillation; MD: mean difference; OD: oscillating device*						

1 The quality of the evidence was downgraded by 1 due to reporting bias.
2 The quality of the evidence was downgraded by 1 due to serious imprecision as 95% CI crossed a default MID.

Table 75: Summary clinical evidence profile: Comparison 14. Non-invasive ventilation (NIV) versus no airway clearance technique

Comparison 14. Non-invasive ventilation (NIV) compared to no airway clearance technique for CF						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relati ve effect (95% CI)**	**No of Participan ts (studies)**	**Quality of the evidenc e (GRADE)**	**Commen ts**
	Assumed risk	**Corresponding risk**				
	No airway clearance technique	**Non-invasive ventilation (NIV)**				
Lung function - FEV_1 % predicted Scale from: 0 to 100 Follow-up: 6 weeks	The mean FEV_1 % predicted in the control groups was 32	The mean FEV_1 % predicted in the NIV groups was 1 higher (8.62 lower to 10.62 higher)		8 (Young 2008)	⊕⊕⊖⊖ low[1]	
Lung function -	The mean FVC % predicted in	The FVC% predicted in the NIV groups was		8 (Young 2008)	⊕⊕⊖⊖ low[2]	

Comparison 14. Non-invasive ventilation (NIV) compared to no airway clearance technique for CF						
FVC % predicted Scale from: 0 to 100 Follow-up: 6 weeks	the control groups was 54	4 higher (10.3 lower to 18.3 higher)				
Oxygen saturation (nocturnal) % Scale from: 0 to 100 Follow-up: 6 weeks	The mean oxygen saturation (%) (nocturnal) in the control groups was 89	The mean oxygen saturation (nocturnal) (%) in the NIV groups was 3 higher (1.12 lower to 7.12 higher)		8 (Young 2008)	⊕⊕⊕⊖ moderate[3]	
Quality of life - CF QOL chest symptom score Scale from: 0 to 100 Follow-up: 6 weeks	The mean CF-QOL chest symptom score in the control groups was 64	The mean CF-QOL chest symptom score in the NIV groups was 7 higher (11.73 lower to 25.73 higher)		8 (Young 2008)	⊕⊕⊖⊖ low[1,4]	
Quality of life - CF QOL traditional dyspnoea index score Scale from: 0 to 100 Follow-up: 6 weeks	The mean CF-QOL traditional dyspnoea index score in the control groups was -1.9	The mean CF-QOL traditional dyspnoea index score in the NIV groups was 2.9 higher (0.71 to 5.09 higher)		8 (Young 2008)	⊕⊕⊕⊖ moderate[4,5]	
**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).* *Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; MD: mean difference; NIV: non-invasive ventilation*						

1 The quality of the evidence was downgraded by 2 due to very serious imprecision as 95% CI crossed 2 clinical MIDs
2 The quality of the evidence was downgraded by 2 due to very serious imprecision as 95% CI crossed 2 default MIDs
3 The quality of the evidence was downgraded by 1 due to serious imprecision as 95% CI crossed 1 default MID
4 Clinical MID=5 was used to assess imprecision for quality of life because the CF QOL questionnaire (Gee et al. 2000) was used
5 The quality of the evidence was downgraded by 1 due to serious imprecision as 95% CI crossed 1 clinical MID

9.2.5 Economic evidence

One conference abstract identified in the literature search conducted for this guideline was considered relevant to this review question. This paper undertook a cost-consequence analysis to compare positive expiratory pressure (PEP) to high frequency chest wall oscillation (HFCWO) in 107 cystic fibrosis patients in Canada (McIlwaine 2014). They concluded that PEP was less expensive and more effective (dominant) at reducing the number of exacerbations than HFCWO. The methods and results from this analysis are provided in Appendix K.

This review question was not prioritised for de novo economic modelling. To aid consideration of cost-effectiveness, relevant resource and cost use data are presented in Appendix K.

Full details of the search and economic article selection flow chart can be found in Appendix E and F, respectively. Data extraction tables and quality assessments and of included studies can be found in Appendix L and M, respectively.

9.2.6 Evidence statements

9.2.6.1 Comparison 1. Manual physiotherapy versus no airway clearance techniques

No evidence was found for this comparison.

9.2.6.2 Comparison 2. Manual physiotherapy techniques versus oscillating devices

Sputum volume

No evidence was found for this critical outcome.

Patient preference

No evidence was found for this critical outcome.

Pulmonary exacerbations

No evidence was found for this critical outcome.

Pulmonary function tests: FEV_1 and FVC

Very low quality evidence from 1 crossover RCT with 22 children, young people and adults with cystic fibrosis showed no clinically significant difference in FEV_1 percent change from baseline between manual physiotherapy techniques and oscillating device after 8.8 days follow-up.

Very low quality evidence from 1 crossover RCT with 6 children and young people with cystic fibrosis showed no clinically significant difference in FEV_1 percent change from baseline between manual physiotherapy techniques and oscillating device after 1 month follow-up.

Very low quality evidence from 1 crossover RCT with 22 children, young people and adults with cystic fibrosis showed no clinically significant difference in FVC percent change from baseline between manual physiotherapy techniques and oscillating device after 2 week follow-up.

Oxygen saturation

No evidence was found for this important outcome.

Quality of life

No evidence was found for this important outcome.

Hospitalisations

No evidence was found for this important outcome.

9.2.6.3 Comparison 3. Manual physiotherapy versus High Frequency Chest Wall Oscillation

Sputum volume

Low quality evidence from 1 crossover RCT with 12 adults with cystic fibrosis showed no clinically significant difference in sputum dry weight between manual physiotherapy and HFCWO after 1 to 2 week follow-ups.

Low quality evidence from 1 crossover RCT with 12 adults with cystic fibrosis showed no clinically significant difference in sputum wet weight between manual physiotherapy and HFCWO after 1 to 2 week follow-ups.

Patient preference

No evidence was found for this critical outcome.

Pulmonary exacerbations

No evidence was found for this critical outcome.

Pulmonary function tests

No evidence was found for this important outcome.

Oxygen saturation

No evidence was found for this important outcome.

Quality of life

No evidence was found for this important outcome.

Hospitalisations

No evidence was found for this important outcome.

9.2.6.4 Comparison 4. Positive expiratory pressure (PEP) versus no airway clearance technique

Sputum volume

Low quality evidence from 1 crossover RCT with 17 young people and adults with cystic fibrosis showed no clinically significant difference in sputum dry weight between PEP and control after 2 days follow-up.

Moderate quality evidence from 1 crossover RCT with 17 young people and adults with cystic fibrosis showed no clinically significant difference in sputum wet weight between PEP and control after 2 days follow-up.

Patient preference

No evidence was found for this critical outcome.

Pulmonary exacerbations

No evidence was found for this critical outcome.

Pulmonary function tests: FEV_1 and FVC

Very low quality evidence from 1 crossover RCT with 16 young people and adults with cystic fibrosis showed no clinically significant difference in percent predicted FEV_1 between PEP and control after 2 days follow-up.

Low quality evidence from 1 crossover RCT with 17 young people and adults showed no clinically significant difference in FEV_1 (L) between PEP and control after 2 days follow-up.

Very low quality evidence from 1 crossover RCT with 16 young people and adults with cystic fibrosis showed no clinically significant difference in percent predicted FVC between PEP and control after 2 days follow-up.

Low quality evidence from 1 crossover RCT with 17 young people and adults showed no clinically significant difference in FVC between PEP and control after 2 days follow-up.

Oxygen saturation

Moderate quality evidence from 1 crossover RCT with 17 young people and adults showed no clinically significant difference in oxygen saturation between PEP and control after 2 days follow-up.

Quality of life

No evidence was found for this important outcome.

Hospitalisations

No evidence was found for this important outcome.

9.2.6.5 Comparison 5. Positive expiratory pressure (PEP) versus active cycle of breathing techniques (ACBT)

No evidence was found for this comparison.

9.2.6.6 Comparison 6. Positive expiratory pressure (PEP) versus oscillating devices

Sputum volume

No evidence was found for this critical outcome.

Patient preference

Very low quality evidence from 1 parallel RCT with 40 children and young people with cystic fibrosis showed no clinically significant difference in self-withdrawal due to lack of perceived effectiveness between PEP and oscillating device after 1 month follow-up.

Pulmonary exacerbations

Low quality evidence from 1 parallel RCT with 42 adults with cystic fibrosis showed no clinically significant difference in number of hospitalisation for respiratory exacerbations per participant between PEP and oscillating device after 13 months follow-up.

Pulmonary function tests: FEV_1 and FVC

Very low quality evidence from 1 crossover RCT with 6 children and young people with cystic fibrosis showed no clinically significant difference in FEV_1 percent change from baseline between PEP and oscillating device after 2 to 4 week follow-ups.

Low quality evidence from 1 parallel RCT with 30 children and young people with cystic fibrosis showed no clinically significant difference in FEV_1 percent change from baseline between PEP and oscillating device after 6 to 12 months follow-up.

Low quality evidence from 3 parallel RCTs with 160 children, young people and adults with cystic fibrosis showed no clinically significant difference in FEV_1 percent change from baseline between PEP and oscillating device after 1 to 2 years follow-up.

Low quality evidence from 3 RCTs with 160 children, young people and adults with cystic fibrosis showed no clinically significant difference in FVC percent change from baseline between PEP and oscillating device after 1 year follow-up. Moderate inconsistency was observed between the trials, but all of them showed a no clinically significant difference between both treatment groups.

Moderate quality evidence from 1 crossover RCT with 22 children and young people with cystic fibrosis showed no clinically significant difference in percent predicted FVC between PEP and oscillating device after 2 to 4 week follow-ups.

Oxygen saturation

No evidence was found for this important outcome.

Quality of life

High quality evidence from 1 parallel RCT with 107 children, young people and adults with cystic fibrosis showed no clinically significant difference in the physical domain of the CFQ-R questionnaire between PEP and oscillating device after 1 year follow-up.

High quality evidence from 1 parallel RCT with 107 children, young people and adults with cystic fibrosis showed no clinically significant difference in the treatment burden domain of the CFQ-R questionnaire between PEP and oscillating device after 1 year follow-up.

Moderate quality evidence from 1 parallel RCT with 107 children, young people and adults with cystic fibrosis showed no clinically significant difference in the respiratory domain of the CFQ-R questionnaire between PEP and oscillating device after 1 year follow-up.

Hospitalisations

No evidence was found for this important outcome.

9.2.6.7 Comparison 7. Positive expiratory pressure (PEP) versus High Frequency Chest Wall Oscillation (HFCWO)

Sputum volume

Low quality evidence from 1 RCT with 23 adults with cystic fibrosis showed no clinically significant difference in sputum volume between PEP and HFCWO after 1 week follow-up.

Patient preference

No evidence was found for this critical outcome.

Pulmonary exacerbations

Moderate quality evidence from 1 parallel RCT with 91 children, young people and adults with cystic fibrosis showed a clinically significant beneficial effect of PEP compared to HFCWO in number of patients with respiratory exacerbation after 1 year follow-up.

Moderate quality evidence from 1 parallel RCT with 88 children, young people and adults with cystic fibrosis showed a clinically significant beneficial effect of PEP compared to HFCWO in number of patients requiring antibiotics for respiratory exacerbation after 1 year follow-up.

Pulmonary function tests: FEV_1 and FVC

Very low quality evidence from a 2 RCTs with 39 young people and adults with cystic fibrosis showed no clinically significant difference in percent predicted FEV_1 between PEP and HFCWO after 1 week follow-up.

Very low quality evidence from 1 crossover RCT with 15 children, young people and adults with cystic fibrosis showed no clinically significant difference in percent predicted FEV_1 between PEP and HFCWO after 1 to 2 week follow-ups.

Moderate quality evidence from 1 parallel RCT with 88 children, young people and adults with cystic fibrosis showed no clinically significant difference in change from baseline percent predicted FEV_1 between PEP and HFCWO after 1 year follow-up.

Very low quality evidence from 1 crossover RCT with 15 children, young people and adults with cystic fibrosis showed no clinically significant difference in percent predicted FVC between PEP and HFCWO after 1 to 2 week follow-ups.

Moderate quality evidence from a 2 RCTs with 39 young people and adults with cystic fibrosis showed no clinically significant difference in percent predicted FVC between PEP and HFCWO after 1 week follow-up.

Moderate quality evidence from 1 parallel RCT with 88 children, young people and adults with cystic fibrosis showed no clinically significant difference in change from baseline percent predicted FVC between PEP and HFCWO after 1 year follow-up.

Oxygen saturation

No evidence was found for this important outcome.

Quality of life

No evidence was found for this important outcome.

Hospitalisations

No evidence was found for this important outcome.

9.2.6.8 Comparison 8. Active cycle of breathing technique (ACBT) versus no airway clearance technique

No evidence was retrieved for this comparison.

9.2.6.9 Comparison 9. Active cycle breathing technique (ACBT) versus autogenic drainage (AD)

No evidence was retrieved for this comparison.

9.2.6.10 Comparison 10. Autogenic drainage (AD) versus no airway clearance technique

No evidence was retrieved for this comparison.

9.2.6.11 Comparison 11. Oscillating device versus no airway clearance technique

No evidence was retrieved for this comparison.

9.2.6.12 Comparison 12. Oscillating device versus High Frequency Chest Wall Oscillation (HFCWO)

Sputum volume

No evidence was found for this critical outcome.

Patient preference

No evidence was found for this critical outcome.

Pulmonary exacerbations

No evidence was found for this critical outcome.

Pulmonary function tests: FEV_1 and FVC

Moderate quality evidence from 1 crossover RCT with 24 children, young people and adults with cystic fibrosis showed no clinically significant difference in percent predicted FEV_1 between oscillating device and HFCWO after 2 to 4 week follow-ups.

Low quality evidence from 1 crossover RCT with 24 participants showed no clinically significant difference in percent predicted FVC between oscillating device and HFCWO after 2 to 4 week follow-ups.

Oxygen saturation

No evidence was found for this important outcome.

Quality of life

No evidence was found for this important outcome.

Hospitalisations

No evidence was found for this important outcome.

9.2.6.13 Comparison 13. High Frequency Chest Wall Oscillation (HFCWO) versus no clearance technique

No evidence was retrieved for this comparison.

9.2.6.14 Comparison 14. Non-invasive ventilation (NIV) versus no airway clearance technique

Sputum volume

No evidence was found for this critical outcome.

Patient preference

No evidence was found for this critical outcome.

Pulmonary exacerbations

No evidence was found for this critical outcome.

Pulmonary function tests: FEV_1 and FVC

Low quality evidence from 1 crossover RCT with 8 adults with cystic fibrosis showed no clinically significant difference in percent predicted FEV_1 between NIV and control after 6 week follow-up.

Low quality evidence from 1 crossover RCT with 8 adults with cystic fibrosis showed no clinically significant difference in percent predicted FVC between NIV and control after 6 week follow-up.

Oxygen saturation

Moderate quality evidence from 1 crossover RCT with 8 adults with cystic fibrosis showed no clinically significant difference in nocturnal oxygen saturation between NIV and control after 6 week follow-up.

Quality of life

Low quality evidence from 1 crossover RCT with 8 adults with cystic fibrosis showed no clinically significant difference in quality of life chest symptom score using the CF-QOL questionnaire between NIV and control after 6 week follow-up.

Moderate quality evidence from 1 crossover RCT with 8 adults with cystic fibrosis showed no clinically significant difference in quality of life traditional dyspnoea index score using the CF-QOL questionnaire between NIV and control after 6 week follow-up.

Hospitalisations

No evidence was found for this important outcome.

9.2.6.15 Economic evidence statements

One cost-benefit analysis on people with cystic fibrosis in Canada found that PEP was less expensive and more effective at reducing exacerbations than HFCWO over 1 year. This analysis is partially applicable with serious limitations, given the limited details reported in the conference abstract.

9.2.7 Evidence to recommendations

9.2.7.1 Relative value placed on the outcomes considered

The aim of this review was to examine the effectiveness of airway clearance techniques in people with cystic fibrosis.

The committee chose sputum volume, pulmonary exacerbations and patient preference as critical outcomes for decision making. Pulmonary function (FEV_1, FVC), oxygen saturation, hospitalisations and quality of life were rated as important outcomes.

9.2.7.2 Consideration of clinical benefits and harms

The committee acknowledged the evidence, but they showed some concerns regarding the quality of the studies and its usefulness to make recommendations. They noted that the studies included in the clinical review had a low number of participants and were conducted over a short time frame. Moreover, none of the studies included children under the age of 6

and several studies excluded patients who were unstable or recovering from an exacerbation. The committee also stressed that RCTs would not reflect clinical practice as techniques are normally individualised because they do not treat the same physiological causes. Given that, the committee noted that it would be difficult for the benefits from an airway clearance technique to be demonstrated in randomised trials.

Based on the review, the committee acknowledged that there was limited evidence either in favour or against the use of routine airway clearance techniques in people with cystic fibrosis. Apart from a clinically significant beneficial effect which favoured the use of PEP over high frequency chest wall oscillation (HFCWO) in the number of pulmonary exacerbations (moderate quality evidence), there were no other clinically significant findings. The committee noted that there was low to moderate quality evidence that showed that using PEP was no better than no airway clearance technique in sputum volume, lung function or oxygen saturation. With regards to the comparisons between different techniques, very low quality evidence showed no clinically significant differences between manual physiotherapy techniques and oscillating devices in lung function. Likewise, very low to high quality evidence showed no clinically significant differences between PEP and oscillatory devices in patient preference, pulmonary exacerbations, lung function, or quality of life.

It was also noted, by the committee, that the effectiveness of airway clearance in other conditions is not generalisable to those with cystic fibrosis as cystic fibrosis is a condition with specific clinical manifestations.

However, the committee discussed that, despite the lack of evidence showing effectiveness, there was a strong rationale (physiological) that airway clearance techniques are useful in children and adults who produce sputum. This is based on the knowledge that in cystic fibrosis the normal mucociliary transport system is impaired and ineffective. Therefore, airway clearance techniques are used to make up for the defects in this system and promote the mobilisation of sputum from the airways to allow expectoration. Due to the dehydrated mucus and airway damage, airway clearance techniques may reduce the risk of infection by assisting the removal of bacteria in the sputum. The committee suggested that the number of trials comparing combinations of airway clearance techniques infers there is underlying knowledge and experience that individual airway clearance techniques are useful.

Moreover, the committee argued that the benefits of airway clearance may not be demonstrated by the amount of sputum produced. In other words, the benefits of airway clearance techniques are not always measurable because the person may just feel better. The committee noted that there are no gold standard outcome measures to evaluate effectiveness of airway clearance techniques. For these reasons the committee agreed not to make a “do not do recommendation” despite the lack of favourable evidence.

The committee also discussed which patients would benefit the most from airway clearance techniques depending on their disease trajectory. The committee noted that paediatric practice has considerably changed in the last few years. Some centres are more comfortable not instigating routine airway clearance with children that are asymptomatic. The focus has been on teaching airway clearance techniques for use when needed, using more structured exercise to promote airflow in the lungs and encouraging close parental assessment of symptoms. It was recognised that some clinicians believe that learning airway clearance techniques at a young age helps to establish a daily routine to carry forward during adulthood. Based on this, the committee agreed it is important to discuss the use of airway clearance techniques with people with cystic fibrosis who do not have clinical evidence of lung disease, and, in the case of children or young people, with their parents or carers (as appropriate) and provide them with training on airway clearance techniques and when to use them. The committee noted that given the lack of evidence of benefit, people without clinical evidence of lung disease (such as CT changes or chronic sputum production) may not have to use airway clearance techniques on a regular basis. However, training on airway clearance techniques should include how to identify the need for performing these

techniques. This would allow people with cystic fibrosis to start independently when appropriate rather than delaying the use of these techniques until a health care professional has identified the need.

On the other hand, the committee agreed that when a patient has clinical evidence of lung disease, or has received a treatment that produces sputum, such as mucolytic treatment, performing airway clearance techniques on a regular basis has a strong rationale and is often helpful in relieving symptoms of cough and breathlessness. The committee agreed that there are a number of factors that should be taken into account when choosing an airway clearance technique.

First, they noted it was important to assess the person's symptoms, including stage of lung disease and current health, and their ability to clear mucus from their lungs. In addition, they highlighted the difficulties of understanding the impact of other treatments and lifestyle choices in people with cystic fibrosis on airway clearance outcomes. They noted it is very important to take into account the individual preferences of the person and their parents or carers, as these may influence adherence.

The committee agreed it is important to assess the effectiveness of the airway clearance technique and choose a different one if needed.

The committee discussed HFCWO, which is becoming more recognised in the UK, at length. This technique is popular among patients in the USA but has a high associated cost. They noted that an increasing number of people with cystic fibrosis and carers are buying HFCWO privately because it is only funded by the NHS in exceptional circumstances, specifically when all other techniques have been exhausted. However, the evidence retrieved for this review did not support the use of HFCWO. No clinically significant differences was found between manual physiotherapy techniques and high frequency chest wall oscillation in sputum volume (low quality evidence). No clinically significant differences were found either between using oscillating devices and HFCWO in lung function (low to moderate quality). Likewise, no clinically significant differences were found between PEP and high frequency chest wall oscillation in sputum volume (low quality evidence) or lung function (very low to moderate). In fact, moderate quality evidence from 2 trials showed that PEP was better at reducing pulmonary exacerbations. Based on this, the committee agreed that, given the current evidence, HFCWO should not be recommended as part of this guideline. However, the committee added that healthcare professionals should consider HFCWO as a last resort in people with cystic fibrosis who have exceptional clinical circumstances. The specialist cystic fibrosis team should decide whether these circumstances apply, and their decision would then be subject to the NHS England policy on Individual Funding Requests. To meet NHS England definition of "exceptional clinical circumstances" the patient must demonstrate that they are both: "Significantly different clinically to the group of patients with the condition in question and at the same stage of progression of the condition" AND "Likely to gain significantly more clinical benefit than others in the group of patients with the condition in question and at the same stage of progression of the condition. Note: Non-clinical factors cannot be taken into account" (NHS England Individual Funding Request Form). In those people, such as those with a neuro-disability, the benefits from other airway clearance techniques may not be achievable given the obstacles to perform them manually. Following this, if HFCWO is the only technique that can maintain or improve their lung function it is an option to consider.

Low to moderate quality evidence from one trial showed no clinically significant beneficial effect of NIV over control in lung function, oxygen saturation and quality of life. Based on their experience and expertise, the committee noted that NIV could be used in people with cystic fibrosis who have moderate or severe lung disease and cannot clear their lungs using standard airway clearance techniques. This is because it is known that NIV unloads the respiratory muscles, therefore, reducing the symptoms associated with respiratory muscle fatigue, in moderate and severe lung disease, such as reduced oxygen and breathlessness.

The committee agreed that NIV can be beneficial as short-term option in moderate disease, when people have difficulty clearing their airways using other clearance techniques, by unloading the respiratory muscles and reducing fatigue.

9.2.7.3 Consideration of economic benefits and harms

Techniques including ACBT, oscillating devices and PEP can be performed at home after an initial visit with a physiotherapist to issue the device and teach the techniques. Therefore, the cost of performing combinations would be similar to single techniques. Moreover, there is no increase in cost if those techniques are performed more frequently as no additional resources are required. In current clinical practice, the person with cystic fibrosis, and their parents or carers, are offered training in airway clearance techniques before there is evidence of lung disease. This early training will prevent the downstream costs from delayed management. Following this, the committee agreed training was relatively cheap to provide and made a recommendation to reinforce best practice, to offer training.

The committee noted that those relatively inexpensive techniques should not be performed if they are ineffective, particularly when the opportunity cost of the person's time is considered. Performing long, regular periods of airway clearance could reduce adherence to other treatments which could potentially reduce the effects of those treatments. However, the committee agreed that lack of evidence does not mean lack of effect, and hence, lack of cost-effectiveness. Therefore, they made a recommendation to discuss the use of airway clearance techniques.

The committee agreed there was clinical and cost-effectiveness evidence to suggest HFCWO was dominated (more expensive and less effective) by PEP. Subsequently, the committee made a recommendation against its routine use, to prevent a cost ineffective use of NHS resources. However, the committee added that healthcare professionals should consider HFCWO as a last resort in people with cystic fibrosis who have exceptional clinical circumstances, as explained above in the clinical benefits and harms section. However, without knowing the benefits of HFCWO in people with exceptional clinical circumstances, we cannot know if HFCWO will be cost-effective.

Based on their experience and expertise the committee stated that NIV is considered as a cost-effective intervention in clinical practice as it can reduce fatigue (breathlessness) caused by moderate to severe lung disease, unlike cheaper airway clearance techniques.. The committee also agreed that NIV can be beneficial in the short-term, during exacerbations, when people have difficulty clearing their airways using other airway clearance techniques. However, the committee added that the high cost of NIV could not be justified in people with mild disease as any improvements in their outcomes would be negligible and result in a cost-ineffective use of resources.

9.2.7.4 Quality of evidence

The quality of the evidence presented in this report ranged from very low to high as assessed by GRADE. The main reasons that led to downgrading the quality of the evidence were:

- For the domain risk of bias, the studies were assigned the same risk of bias as in the Cochrane reviews and were not individually reviewed. The main biases that lead to downgrading the quality of the evidence were selection, attrition, and reporting bias.
- Another reason that lead to downgrading the quality of the evidence was the imprecision, as confidence intervals crossed 1 or 2 MIDs. The committee noted that many trials were underpowered to detect a clinically important difference.

No serious issues were found regarding inconsistency (heterogeneity) and the directness of the population (generability of the results).

9.2.7.5 Other considerations

No equality issues were identified by the committee for this review question.

The committee discussed the need to draft a research recommendation for this topic. Since the advent of newborn screening for cystic fibrosis there has been international debate about the level of physiotherapy intervention required from diagnosis to preserve lung health. Some clinical teams opt to teach and recommend daily airway clearance techniques, whereas others use parental respiratory assessment tools with structured exercise. Routine airway clearance from diagnosis places considerable responsibility and time burden on the parents and carers at a time when such techniques are challenging to perform and negotiate with the infant and child. It is important that we fully understand if routine practice is providing benefit to maintain lung health or, in fact, creating unnecessary burden. Future research must seek to understand the impact, not only on long term clinical outcomes, but on the lives of parents, families and carers of infants and children with cystic fibrosis.

9.2.7.6 Key conclusions

The committee concluded that there was limited evidence in favour or against the use of airway clearance techniques in patients with cystic fibrosis. However, there is a strong physiological rationale for airway clearance techniques and they continue to be used routinely in the patient with clinical evidence of lung disease. The use of manual physiotherapy techniques, PEP, ACBT and AD were prioritised by the committee. But they agreed HFCWO should not be recommended due to its cost and the evidence that is inferior to other airway clearance techniques. HFCWO should only be considered as an option of last resort in people with exceptional clinical circumstances. The specialist cystic fibrosis team should decide whether these circumstances apply, and their decision would then be subject to the NHS England policy on Individual Funding Requests. The decision to choose one technique over another would be based on individual factors and the physiological problem or circumstances at the time, rather than one technique being superior to another. Individual preferences should be taken into account when deciding an airway clearance technique as this may impact adherence. NIV could be used in people who are limited by symptoms such as breathlessness and fatigue due to moderate or severe lung disease and cannot clear their lungs using standard airway clearance techniques.

9.2.8 Recommendations

50. Discuss the use of airway clearance techniques with people with cystic fibrosis who do not have clinical evidence of lung disease and their parents or carers (as appropriate). Provide them with training in airway clearance techniques and explain when to use them.

51. Offer training in airway clearance techniques to people with cystic fibrosis who have clinical evidence of lung disease and their parents or carers (as appropriate).

52. When choosing an airway clearance technique for people with cystic fibrosis:

- assess their ability to clear mucus from their lungs, and offer an individualised plan to optimise this
- take account of their preferences and (if appropriate) those of their parents and carers
- take account of any factors that may influence adherence.

53. Regularly assess the effectiveness of airway clearance techniques, and modify the technique or use a different one if needed.

54. **Do not offer high-frequency chest wall oscillation as an airway clearance technique for people with cystic fibrosis except in exceptional clinical circumstances. The specialist cystic fibrosis team will decide whether these circumstances apply, and their decision would then be subject to the NHS England policy on Individual Funding Requests. Be aware that the evidence shows high-frequency chest wall oscillation is not as effective as other airway clearance techniques.**

55. **Consider using non-invasive ventilation in people with cystic fibrosis who have moderate or severe lung disease and cannot clear their lungs using standard airway clearance techniques.**

9.2.9 Research recommendations

2. **How effective are daily airway clearance techniques in maintaining lung function in infants and children with cystic fibrosis?**

Table 76: Research Recommendation justification

Research question	How effective are daily airway clearance techniques in maintaining lung function in infants and children with cystic fibrosis?
Why this is needed	
Importance to 'patients' or the population	Performing daily airway clearance techniques places considerable responsibility and time burden on parents and carers at a time when such techniques are challenging to perform and negotiate with the infant and child with cystic fibrosis. It is essential that parents, carers and people with CF are reassured that this level of input is based on proven clinical benefit. Parent, carers and people with CF frequently report in the literature that daily airway clearance routines are difficult to adhere to and incorporate into daily life. If routine airway clearance is not deemed necessary until a certain time point, this could have a significant impact on the quality of life of parents, carers and people with CF.
Relevance to NICE guidance	High: With this evidence, definitive recommendations could be made regarding 'routine' vs 'when required' use of airway clearance techniques – at present there is varied clinical practice throughout the UK
Relevance to the NHS	CF services need to be able to direct and plan the physiotherapy input to people with CF and their families/carers to ensure that the resources are placed where there is proven clinical benefit rather than basing service delivery on historical behaviours. Further evidence in this area will eliminate the need to provide an intervention 'just in case' it preserves lung health but in fact physiotherapists will be able to use the evidence to target the right patients with the right intervention based on evidence of the likelihood of improved health outcomes. There will be a financial advantage if less airway clearance devices are required in the future due to a reduction in routine airway clearance approaches in the UK. There may be a small financial disadvantage if more airway clearance devices are required if routine airway clearance is proven from diagnosis to benefit health outcomes. There is unlikely to be any change in the physiotherapy input required as interventions will continue to include exercise guidance, advice on assessment/monitoring of lung health and teaching of airway clearance techniques for when they are required.
National priorities	This research question is similar to one of the top 10 research priorities published by the James Lind Alliance in January 2017 – 'Can exercise replace chest physiotherapy for people with CF'

Research question	How effective are daily airway clearance techniques in maintaining lung function in infants and children with cystic fibrosis?
	The comparative group to 'routine airway clearance' is likely to include structured exercise so could help answer the above question for infants and children.
Current evidence base	The current evidence base includes mostly small, short term studies with limited methodological rigour and are unable to draw conclusions regarding the long-term impact of airway clearance techniques on lung health in people with CF. Most of the studies include people with respiratory symptoms and established lung disease and therefore it is also not possible to apply this knowledge to the asymptomatic person without evidence of lung disease. The current evidence base compares the different types of airway clearance techniques but has yet to answer the question whether airway clearance as an intervention provides any long term clinical benefit to lung health either in the symptomatic or indeed the asymptomatic person with CF.
Equality	CF centres across the UK have different approaches to routine airway clearance – further evidence will help direct care and potentially improve equity of access of evidence based physiotherapy interventions.
Feasibility	The research could be carried out within a realistic timescale and with realistic funding
Other comments	None

Table 77: Research Recommendation Statements

Criterion	Explanation
Population	Infants and children with a diagnosis of cystic fibrosis – to be confirmed by specified criteria
Intervention	○ Daily airway clearance techniques
Comparators	Airway clearance techniques only when specified criteria met. For example, based on: - Disease severity - Asymptomatic/ symptomatic
Outcomes	• Expectorated secretions (mucus, sputum, phlegm) • Sputum volume • Hospitalisations, change in frequency • Pulmonary exacerbations, change in frequency • Lung function (FEV_1, FVC) • o forced vital capacity (FVC) • Oxygen saturation measured by pulse or transcutaneous oximetry • Quality of Life (using a validated tool, such CFQ-R or CF-QOL) • Patient preference • Resource use • Unit costs
Study design	Multicentre RCT
Timeframe	2-6 years

9.3 Mucoactive agents

Review question: What is the effectiveness of mucoactive or mucolytic agents, including dornase alfa, nebulised sodium chloride (isotonic and hypertonic) and mannitol?

9.3.1 Introduction

The underlying lung defects in people with cystic fibrosis leads to an increase in water absorption from the epithelial surface. This results in a reduced airway surface liquid layer and a more viscous mucus layer on the surface of the airways. This mucus accumulates due to reduced clearance and supports the retention of micro-organisms. This, in turn, leads to infection and the destructive inflammatory processes which lead to bronchiectasis.

The primary aim of pulmonary disease management in people with cystic fibrosis is to stabilise, or prevent decline in, pulmonary function and prevent the occurrence of acute pulmonary exacerbations. Therefore, people with cystic fibrosis who have evidence of pulmonary disease commonly employ airway clearance techniques to reduce the burden of viscid mucus and break the destructive cycle of mucus stasis, infection and inflammation.

Mucoactive agents are often employed as adjuncts to airway clearance techniques. These agents change the properties of mucus, through a number of mechanisms, rendering it easier to expectorate: dornase alfa is a recombinant human enzyme which acts by cleaving extracellular DNA (a by-product of neutrophil degeneration) in the mucus; osmotic agents such as mannitol and hypertonic sodium chloride draw water onto the airway surface to rehydrate the airway surface liquid layer; solutions of hypertonic sodium chloride disrupt ionic bonds within the mucus gel.

With a number of mucoactive agents available, this review question aims to determine the effectiveness of mucoactive or mucolytic agents – including dornase alfa, inhaled sodium chloride solutions (both isotonic and hypertonic) and inhaled mannitol – in order to determine their place in the management of cystic fibrosis pulmonary disease.

9.3.2 Description of clinical evidence

The aim of this review was to establish the clinical and cost effectiveness of mucoactive or mucolytic agents in improving airway clearance in children, young people and adults with cystic fibrosis.

The nebulised and inhaled mucoactive and mucolytic agents reviewed were: acetylcysteine, dornase alfa, nebulised sodium chloride (hypertonic and isotonic) and mannitol (only in children and young people up to the age of 18 years as Technology Appraisal (TA) in adults will be included).

NICE TA266 has been published to provide guidance on the use of mannitol dry powder for inhalation for the treatment of cystic fibrosis in adults. The following comparisons were considered:

- Mannitol versus placebo
  - 2 trials (DPM-CF-301, DPM-CF-302) were included in the TA to assess the effectiveness of mannitol
  - another 4 trials were excluded from the TA because of their short duration (DPM-CF-201, DPM-CF-202), population (children only) (DPM-CF-203), and low dose of mannitol and short duration of treatment (Robinson 1999); these trials have been retrieved for potential inclusion in this review.
- Mannitol versus other treatments

- no trials were included
  - 1 trial (Robinson 1999) was identified in the TA for the comparison mannitol versus hypertonic sodium chloride, but was excluded due to low dosage, short treatment duration and small population
  - 2 trials (CF-301, Jaques 2008) compared mannitol to control (control = low dose mannitol) and 8 trials (Button 1996, Chadwick 1997, Elkins 2006, Eng 1996, Riedler 1996, Robinson 1996, Robinson 1997, Robinson 1999) compared hypertonic sodium chloride to control; however, the Technology Assessment Group (TAG, Riemsma 2011) agreed that the results were not comparable due to the difference in duration (26 weeks versus < 2 weeks).

A report from the National Horizon Scanning Centre (NHSC 2008) was also identified. This report included 4 trials that have been retrieved for assessment.

Systematic reviews of RCTs and RCTs, including cross-over trials were considered for this review. Systematic reviews were assessed for inclusion against the protocol, and if relevant, their quality was assessed using AMSTAR. High-quality systematic reviews were included in our review, and where possible, data was taken directly from the review. Individual studies were also retrieved for completeness and accuracy. Low-quality systematic reviews were excluded from the review, but the list of included studies was checked to identify relevant trials.

Three Cochrane reviews were identified and included in this review:

- Yang 2016 evaluated the effectiveness of dornase alfa compared to placebo and other mucoactive or mucolytic agents. Twelve trials were included from this review (Amin 2011; the trial reported in both Ballmann 1998 and Ballmann 2002; Fuchs 1994, Laube 1996, McCoy 1996, Minasian 2010; Quan 2011; Ramsey 1993a; Ranasinha 1993, Shah 1995; the trial reported in Suri 2001, Suri 2002a and Suri 2002b; Wilmott 1996).
- Nolan 2015 evaluated the effectiveness and safety of inhaled mannitol in people with cystic fibrosis. Four trials have been included from this review (Aitken 2012, Bilton 2011, Jaques 2008, Minasian 2010). Two of the trials had already been included in the TA report (Aitken 2012, Bilton 2011) and were used to retrieve additional outcomes.
- Wark 2010 evaluated the effectiveness of nebulised hypertonic sodium chloride compared to placebo and other mucoactive or mucolytic agents. Three trials have been included from this review (the trial reported in both Ballmann 1998 and Ballmann 2002; Elkins 2006; and the trial reported in Suri 2001, Suri 2002a and Suri 2002b).

Four (non-Cochrane) systematic reviews were also identified (Christopher 1999, Cramer 1996, Duijvestijn 1999, Taylor 200). All of them were excluded due to their low methodological quality, and the list of included studies checked for their potential inclusion.

In addition, 9 trials were identified for inclusion (Amin 2010, Conrad 2015, Dentice 2016, Gupta 2012, Mainz 2016, Ratjen 1985, Rosenfeld 2012, Shah 1996, Skov 2015).

The size of the trials ranged from 14 to 968 participants. Twelve trials included children, young people and adults (Aitken 2012, Bilton 2011, Conrad 2015, Elkins 2006, Fuchs 1994, Jaques 2008, Mainz 2016, McCoy 1996; Ramsey 1993a; Ratjen 1985, Shah 1995a, Wilmott 1996), 1 trial included infants and children (Rosenfeld 2012), 1 trial included children only (Quan 2001), 2 studies included children and young people (Gupta 2012; and the trial reported in Suri 2001, Suri 2002a and Suri 2002b), 3 trials included children and young people and adults aged 18 only (Amin 2010, Amin 2011, Minasian 2010), 2 trials included adults only (Laube 1996, Skov 2015), 3 trials included young people and adults (Dentice 2016, Ranasinha 1993, Shah 1996). The age range was not reported for 1 trial (reported in both Ballmann 1998 and Ballmann 2002 – mean age 13.3).

Five trials were conducted in the United States (Conrad 2015, Fuchs 1994, Laube 1996, McCoy 1996, Wilmott 1996), 3 in the UK (Minasian 2010; the trial reported in Suri 2001, Suri

2002a and Suri 2002b; and Shah 1996), 2 in Canada (Amin 2010, Amin 2011), 2 in Australia (Dentice 2016, Elkins 2006), 1 in India (Gupta 2012), 1 in Denmark (Skov 2015) and 3 in Germany (Mainz 2016, Ratjen 1985; and the trial reported in both Ballmann 1998 and Ballmann 2002). The following 6 studies were conducted in multiple countries: 1 in the United States, Canada, Argentina and Europe (Aitken 2012), 1 in Australia, New Zealand, UK and Ireland (Bilton 2011), 1 in Australia and New Zealand (Jaques 2008), 1 in the United States, Canada and the UK (Shah 1995a), 1 in the United States and Canada (Rosenfeld 2012), 1 in Australia, Belgium, Canada, Denmark, Germany, Ireland, Israel, Netherlands, Norway, Spain, Switzerland and the United States (Quan 2001). For 2 trials the country was not reported (Ramsey 1993a and Ranasinha 1993).

The included studies assessed the effectiveness of mucoactive or mucolytic agents based on the following comparisons:

- mannitol versus placebo – 3 trials (Aitken 2012, Bilton 2011, Jaques 2008)
- mannitol versus dornase alfa – 1 trial (Minasian 2010)
- mannitol plus dornase alfa versus dornase alfa – 1 trial (Minasian 2010)
- dornase alfa versus placebo – 10 trials (Amin 2011, Fuchs 1994, Laube 1996, McCoy 1996, Ramsey 1993a, Ranasinha 1993, Quan 2001, Shah 1995, Shah 1996, Wilmott 1996)
- dornase alfa versus nebulised sodium chloride – 2 trials (trial reported in both Ballman 1998 and Ballmannn 2002; and trial reported in Suri 2001, Suri 2002a and Suri 2002b)
- nebulised sodium chloride (>3% concentration) versus placebo (0.9% to 0.12%) or low concentration (≤3%)
  - nebulised sodium chloride (7% concentration) versus placebo (0.9% sodium chloride concentration) – 3 trials (Amin 2010, Elkins 2006, Rosenfeld 2012)
  - nebulised sodium chloride (7% concentration) versus placebo (0.12% sodium chloride concentration) – 1 trial (Dentice 2016)
  - nebulised sodium chloride (7% concentration) versus low concentration (3%) – 1 trial (Gupta 2016)
  - nebulised sodium chloride (6% concentration) versus placebo (0.9% sodium chloride concentration – 1 trial (Mainz 2016)
- acetylcysteine versus placebo – 3 trials (Conrad 2015, Ratjen 1985, Skov 2015)

A summary of the studies included in this review are presented in Table 78. See study selection flow chart in Appendix F, study evidence tables in Appendix G, list of excluded studies in Appendix H, forest plots in Appendix I, and full GRADE profiles in Appendix J.

9.3.3 Summary of included studies

A summary of the studies that were included in this review are presented in Table 78.

Table 78: Summary of included studies

Study	Intervention/ Comparison	Population	Outcomes	Comments
NICE Technology Appraisal				
NICE Technical Appraisal (TA Mannitol 2012)	Comparison 1: Mannitol versus placebo • CF-301 • CF-302 Comparison 2:	Adults with CF.	Comparison 1: Mannitol versus placebo • Change in FEV_1 • Reduction in pulmonary exacerbations	CF-301: Bilton 2011 CF-302: Aitken 2012 This TA was reviewed in Riemsma et al., Mannitol dry

Study	Intervention/ Comparison	Population	Outcomes	Comments
	Mannitol versus other treatments No studies were included.		• Reduction of AB and hospitalization days • Quality of life • Safety Comparison 2: Mannitol versus other treatments n/a	powder for inhalation for the treatment of cystic fibrosis. Klejnen Systematic Reviews Ltd., 2011
Cochrane systematic reviews				
Yang 2016 Cochrane SR	Comparison 1: Dornase Alfa versus placebo • Amin 2011 • Ballmann 1998 and Ballmann 2002 • Fuchs 1994 • Laube 1996 • McCoy 1996 • Minasian 2010 • Quan 2001 • Ramsey 1993a • Ranasinha 1993 • Shah 1995a • Wilmott 1996 (non-NMA) Comparison 2: Dornase alfa versus hypertonic sodium chloride • Suri 2001, Suri 2002 and Suri 2002a	Children and adults with CF (diagnosed clinically and by sweat or genetic testing) and with all stages of lung disease were included.	Comparison 1: Dornase Alfa versus placebo • FEV_1 change • People experiencing exacerbations • Use of antibiotics • Adverse events • Change in quality of life Comparison 2: Dornase alfa versus hypertonic sodium chloride • FEV_1 change • Quality of life • Days of inpatient treatment	AMSTAR: 10/ 11
Nolan 2015 Cochrane SR	Comparison 1: Mannitol versus placebo • Aitken 2012 • Bilten 2011 Comparison 2: Mannitol versus Dornase Alfa • Minasian 2010 Comparison 3: Mannitol + Dornase Alfa versus Dornase Alfa • Jaques 2008	Children and adults with CF (diagnosed clinically and by sweat or genetic testing) and including all degrees of disease severity.	Comparison 1: Mannitol versus placebo • FEV_1 ml, % predicted • Pulmonary exacerbations • Time to first pulmonary exacerbation • Number of patients needing AB/ hospitalisation • HRQOL – 11 domains • Adverse events	AMSTAR: 11/ 11

Study	Intervention/ Comparison	Population	Outcomes	Comments
			Comparison 2: Mannitol versus Dornase Alfa • FEV_1% change Comparison 3: Mannitol + Dornase Alfa versus Dornase Alfa • FEV_1% change	
Wark 2010 Cochrane SR	Comparison 1: Nebulised hypertonic sodium chloride versus isotonic sodium chloride • Elkins 2006 Comparison 2: hypertonic sodium chloride versus dornase alfa (dornase alfa) • Ballmann 1998 and Ballmann 2002 • Suri 2001, Suri 2002a and Suri 2002b	Children and adults with CF (diagnosed clinically and by sweat or genetic testing) and including all degrees of disease severity.	Comparison 1: Nebulised hypertonic sodium chloride versus isotonic sodium chloride • FEV_1 • Inflammatory markers • Quality of life • Hospital admissions • Adverse events Comparison 2: hypertonic sodium chloride versus dornase alfa (dornase alfa) • FEV_1 • Quality of life • Hospital admissions	AMSTAR: 9/11 The update for this review was not yet published when we carried out our review. Cochrane kindly provided us with a copy of the update. We concluded that the relevant studies included in the update were also included in Wark 2010.
Individual studies included in the TA or the Cochrane SR				
CF-301: Bilton 2011 (Australia, New Zealand, UK, Ireland) Multi-centre RCT, parallel design	Intervention: Inhaled dry powder mannitol, 400 mg BD for 26 weeks Comparison: Subtherapeutic mannitol (mannitol 50 mg)	N=295 people with CF were randomized Mean (SD) age: 23 (11.3) years. Age ≥6 years. Participants were clinically stable at start of study.	• Change in FEV_1 % predicted • Time to first protocol defined pulmonary exacerbation • Number of patients needing additional IV antibiotics • Change in quality of life (HRQOL – CFQOL) • Adverse events: ○ bronchospasm (mild, moderate and severe) ○ haemoptysis (mild, moderate and severe)	In NICE TA on Mannitol & in Cochrane SR Nolan 2015 Participants receiving hypertonic saline were excluded. High dropout rate, however sensitivity analysis showed a consistent treatment effect with no change to conclusions.
CF-302: Aitken 2012	Intervention: Inhaled dry mannitol, 400 mg	N= 305 people with CF from 53	• Change in FEV_1 % predicted	In NICE TA on Mannitol & in

Study	Intervention/ Comparison	Population	Outcomes	Comments
(USA, Canada, Argentina, Europe) Multi-centre RCT, parallel design	BD for 26 weeks Comparison: Subtherapeutic mannitol (mannitol 50 mg)	sites were randomized Mean age: 20 years. Age range: 6 to 53. Participants were clinically stable at start of study.	• Time to first protocol defined pulmonary exacerbation • Number of patients needing additional IV antibiotics • Change in quality of life (HRQOL – CFQOL) • Adverse events: ○ haemoptysis (mild, moderate and severe)	Cochrane SR Nolan 2015 Participants receiving hypertonic saline were excluded. High dropout rate, however sensitivity analysis showed a consistent treatment effect with no change to conclusions.
Amin 2011 (Canada) RCT, crossover design	Intervention: Dornase alfa, 2.5 mg OD for 4 weeks intervention/comparison, 4-week washout period Comparison: Placebo	N=19 people with CF were randomized. Age range: 6 to 18years Baseline FEV_1 ≥ 80% predicted	• Change in FEV_1 % predicted • Change in quality of life (measured with CFQ-R questionnaires)	In Cochrane SR Yang 2016 Data only reported on 17 people who completed the trial.
Ballmann 1998 and Ballmann 2002 (Germany) RCT, crossover design	Intervention 1: Nebulization of 2.5 mg dornase alfa OD 3 weeks intervention, 3-week washout period Intervention 2: Nebulization of 10 ml 5.85% sodium chloride OD	N=14 people with CF Mean age: 13.3. Age range not reported. With mild to moderate pulmonary involvement.	• % change in FEV_1	In Wark 2010 and Yang 2016 Withdrawals were not discussed within the paper. Both interventions preceded by 2 puffs salbutamol via a spacer
Elkins 2006 (Australia) RCT, parallel design	Intervention: 7% sodium chloride BD 48 weeks Comparison: 0.9% sodium chloride BD	N=164 people with CF from 16 hospitals were randomized. Age ≥6 years Participants were in clinically stable condition.	• % change in FEV_1 • Change in quality of life (measured with CFQ-R questionnaires)	In Wark 2010 2 people were excluded from the analysis: 1 person in each group voluntarily withdrew before first dose. 17 people were lost to follow-up. 15 people stopped inhalation but continued visits.

Study	Intervention/ Comparison	Population	Outcomes	Comments
Fuchs 1994 (USA) RCT, parallel design	Intervention: Nebulized dornase alfa 2.5 mg OD or BD 24 weeks Comparison: Placebo	N= 968 people with CF were randomized. Age: Over 5. FVC: > 40% predicted Clinically stable	• Relative mean % change in FEV_1 • Number of people experiencing exacerbations • Adverse events: haemoptysis, voice alteration	In Cochrane SR Yang 2016 25 people withdrew from the study, 8 in the placebo group and once-daily group and 9 in the twice-daily group. All participants were included in the analysis.
Jaques 2008 (Australia and New Zealand) Multi-centre RCT, crossover design	Intervention: Inhaled dry powder mannitol 420mg BD for 2 weeks, 2-week washout period Comparison: Non-respirable Mannitol	39 people with CF from 7 sites were randomized. Mean (range)age: 19.1 (range 8 to 48) years Participants were clinically stable at start of study	• Change in FEV_1 % predicted • Adverse events: haemoptysis (mild and severe)	In Cochrane SR Nolan 2015 No hypertonic saline within 2 weeks of start of study. 4 withdrawals.
Laube 1996 (USA) RCT, parallel design	Intervention: 2.5 mg nebulized dornase alfa BD for 6 days Comparison: placebo	N= 20 adults with CF Age: Over 18 With stable stage CF. FVC: 35%-75% predicted No withdrawals.	• Relative mean % change in FEV_1 (overall and for subgroup with moderate disease)	In Cochrane SR Yang 2016 There were no withdrawals.
McCoy 1996 (USA) RCT, parallel design	Intervention: Nebulized dornase alfa 2.5 mg OD for 12 weeks Comparison: Placebo	N= 320 people with CF Age: 7 to 57 FVC: < 40% predicted.	• Relative mean % change in FEV_1 • Number of days of IV antibiotic use • Adverse events: voice alteration	In Cochrane SR Yang 2016 40 participants withdrew from the trial.
Minasian 2010 (UK) RCT, crossover design	Intervention1: Mannitol 400mg BD Intervention 2: Dornase alfa alone: 2.5 mg BD Intervention 3: Mannitol (as above) plus dornase alfa (dose unclear) For 12 weeks	N=28 people with CF randomised Mean (SD) age: 13.3 (2.24) years. Age for eligibility was between 8 and 18 years. Participants were clinically stable at start of study. Currently receiving dornase alfa or	• FEV_1 % change from baseline	In Cochrane SR Nolan 2015 and Cochrane SR Yang 2016 Participants using hypertonic saline were excluded. 45 were recruited but only 28 were randomised. 8 participants withdrew.

Study	Intervention/ Comparison	Population	Outcomes	Comments
		having an FEV_1 >40% and <70% predicted (and therefore eligible to receive dornase alfa).		
Quan 2001 (Australia, Belgium, Canada, Denmark, Germany, Ireland, Israel, Netherlands, Norway, Spain, Switzerland and the United States) Multi-centre RCT, parallel design	Intervention: 2.5 mg dornase alfa OD for 96 weeks Comparison: Placebo	N=474 children with CF randomized from 49 centres Age: 6 to 10 (mean age 8.4) FVC>85% predicted	• Absolute mean % change in FEV_1 • Number of people experiencing exacerbations • Adverse events: voice alteration	In Cochrane SR Yang 2016 • 410 completed the study. 60 participants withdrew from the study. The ITT population was 470.
Ramsey 1993a (Country not reported) RCT, parallel design	Intervention: Nebulized dornase alfa 0.6 mg, 2.5 mg or 10 mg BD for 10 days Comparison: placebo	N= 181 people with CF Age: 8 to 65 Stable stage CF FVC>= 40% predicted	• Relative mean % change in FEV_1 (overall results and subgroup analysis for people with moderate disease severity) • Adverse events: voice alteration	In Cochrane SR Yang 2016 No withdrawals.
Ranasinha 1993 (Country not reported) RCT, parallel design	Intervention: Nebulized dornase alfa 2.5 mg BD for 10 days Comparison: placebo	N= 71 people with CF Age range: 16 to 55 All participants had stable disease FVC > 40% predicted	• Relative mean % change in FEV_1 (overall results and subgroup analysis for people with moderate disease severity) • Adverse events: haemoptysis, voice alteration	In Cochrane SR Yang 2016
Shah 1995a (USA, Canada, UK) Multi-centre RCT, parallel design	Intervention: 2.5 mg nebulised dornase alfa BD for 14 days Comparison: Placebo	N: 70 people with CF randomized from 3 sites. Age: ≥5 years Severe (FVC < 40% predicted) lung disease	• Relative mean % change in FEV_1 (Overall results and subgroup analysis for people with severe disease) • Adverse events: haemoptysis, voice alteration	In Cochrane SR Yang 2016 5 dropouts (2 died, 2 withdrew consent, 1 had a heart lung transplant)
Suri 2001, Suri 2002a and Suri 2002b	Intervention 1: 2.5 mg dornase alfa OD;	N= 48 children and young people with CF	• Mean % change in FEV_1 • Number of days of inpatient treatment	In Wark 2010 and Yang 2016 45 completed first treatment

Study	Intervention/ Comparison	Population	Outcomes	Comments
(UK) RCT, crossover design	Intervention 2: alternate day 2.5 mg dornase alfa; Intervention 3: 5 mL 7%hypertonic saline BD 12-week treatment periods with a 2-week washout period between each period	were randomised. Age range: 7.3 to 17.		period, 44 completed the second treatment period and 40 completed the third treatment period.
Wilmott 1996 (USA) RCT, parallel design	Intervention: Dornase alfa 2.5 mg nebulised BD over 15 days Comparison: Placebo	N= 80 people with CF from 11 CF centres Age: Over 5 Admitted to hospital for at least 1 night for treatment of a chest exacerbation (protocol defined) with FVC > 35% predicted Participants in both groups had a moderate clinical degree of dyspnoea.	• Mean % change in FEV_1	In Cochrane SR Yang 2016 No withdrawals mentioned in the paper
Additional primary studies				
Amin 2010 (Canada) RCT, crossover design	Intervention: 7% sodium chloride BD for 4 weeks, 4-week washout period Comparison: 0.9% sodium chloride	N=20 people with CF randomized. Mean (SD) age: 10.5 (3.1). Age range for eligibility: 6 to 18 years. Baseline FEV_1% predicted ≥80%	• Quality of life (Measured with CFQ-R questionnaire)	1 person was excluded from the analysis.
Conrad 2015 (USA) RCT, parallel design	Intervention: Acetylcysteine 3 times daily for 24 weeks Comparison: Placebo	N0=70 people with CF were randomized. Age range: 9 to 59 years. Stable mild-moderate lung disease; FEV_1 ≥40% and ≤85% predicted	• Change in FEV_1 • Change in sputum IL-8 (log10) • Incidence of pulmonary exacerbations • Quality of life (Measured with CFQ-R)	6 in the acetylcysteine group and 2 in the placebo group were withdrawn or lost to follow-up. Of these, 1 in the placebo group was excluded from the analysis.

Study	Intervention/ Comparison	Population	Outcomes	Comments
Dentice 2016 (Australia) RCT, parallel design	Intervention: 7% sodium chloride 4ml 3 times daily throughout hospital admission Control: 0.12% sodium chloride Both groups received usual care.	N=132 people with CF admitted for management of a pulmonary exacerbation. Mean age (SD), range: • Intervention: 28 (9), 17 to 62 years • Control: 27 (9), 18 to 63 years	• Failed to regain pre-exacerbation FEV_1% predicted • Change in quality of life • Time to first pulmonary exacerbation	All participants were included in the analysis related to relevant outcomes. On average, hospital admission lasted 12 days in intervention group and 13 in control group
Gupta 2012 (India) RCT, parallel design	Intervention: 7% sodium chloride BD for 28 days (high dose) Comparison: 3% sodium chloride	N=31 children and young people with CF were randomized. Age range: 6 to 16 years Able to perform reproducible pulmonary function test was among inclusion criteria. No inclusion criteria relating to severity of lung disease.	• % change in FEV_1	30 people completed the study and were included in the analysis.
Mainz 2016 (Germany) RCT, crossover design	Intervention: 6% sodium chloride OD for 28 days, 28-day washout period Comparison: 0.9% sodium chloride	N=69 people with CF with chronic rhinosinusitis Age ≥6 years. Mean age (SD): 22.8 (12).	• FEV_1 % predicted	5 people were excluded from the analysis.
Ratjen 1985 (Germany) RCT, parallel design	Intervention: Acetylcysteine 3 times daily for 12 weeks Comparison: Placebo	N=21 people with CF were included in the analysis. Mean (range) age: 13.9 (6 to 21) People with mild to moderate lung disease.	• Change in FEV_1	Total N in the study was 36 people who were randomized to 3 interventions (1 not relevant to this review). There were 4 withdrawals out of 36 people; 1 in placebo group, 3 unclear.

Study	Intervention/ Comparison	Population	Outcomes	Comments
Rosenfeld 2012 (USA and Canada) Multicentre RCT, parallel design	Intervention: 7% sodium chloride BD for 48 weeks Comparison: 0.9% sodium chloride	N=321 infants and children with CF were randomized. Age: < 6 years	• Time to first pulmonary exacerbation • Number of days of treatment for a pulmonary exacerbation • Change in quality of life (Measured with CFQ-R)	29 withdrew (15 in intervention group and 14 in comparison group) but everyone was included in the analysis.
Shah 1996 (UK) RCT, parallel design	Intervention 1: 2.5 mg dornase alfa bd BD for 10 days Placebo: 150 mmol sodium chloride, 1.5 mmol calcium chloride	N: 71 people with CF randomized. Age: >15 years Stable condition prior for 14 days prior to enrolment	• Relative mean % change in FEV_1	30 people were excluded from the analysis due to inadequate sputum samples.
Skov 2015 (Denmark) Open trial, parallel design	Intervention: Acetylcysteine 2400 mg/day for 4 weeks Comparison: Placebo	N=21 people with CF n=11 in the NAC group and n=10 in the placebo group Median age: 39 years (range 25 to 61)	• Change in FEV_1 % predicted	There were 2 withdrawals, 1 in the intervention and 1 in the placebo group.

Abbreviations: BD: twice daily; CF: cystic fibrosis; FEV: forced expiratory volume; N: number; OD: once daily; RCT: randomised controlled trial; SR: systematic review

9.3.4 Clinical evidence profile

The clinical evidence profiles for this review question are presented in Table 79 to Table 85.

9.3.4.1 Mannitol

Table 79: Summary clinical evidence profile: Comparison 1.1. Mannitol versus placebo

Comparison 1.1. Mannitol versus placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Mannitol				
FEV_1 % predicted (repeated measures, change from baseline) Range of scores: 0 to 100	Not reported	The mean FEV_1 % predicted (repeated measures, change from baseline) in the mannitol groups was		36 (Jaques 2008)[1]	⊕⊕⊖⊖ low[2,3]	

Comparison 1.1. Mannitol versus placebo						
Follow-up: 2 weeks		3.95 higher (0.96 to 6.94 higher)				
FEV_1 % predicted (repeated measures, change from baseline) Range of scores: 0 to 100 Follow-up: 2 months	Not reported	The mean FEV_1 % predicted (repeated measures, change from baseline) in the mannitol groups was 2.98 higher (1.04 to 4.92 higher)		600 (Aitken 2012, Bilton 2011)	⊕⊕⊕⊖ moderate [2]	
FEV_1 % predicted (repeated measures, change from baseline) Range of scores: 0 to 100 Follow-up: 4 months	Not reported	The mean FEV_1 % predicted (repeated measures, change from baseline) in the mannitol groups was 3.26 higher (1.16 to 5.35 higher)		600 (Aitken 2012, Bilton 2011)	⊕⊕⊖⊖ low[2,3]	
FEV_1 % predicted (repeated measures, change from baseline) Range of scores: 0 to 100 Follow-up: 6 months	Not reported	The mean FEV_1 % predicted (repeated measures, change from baseline) in the mannitol groups was 3.89 higher (1.69 to 6.08 higher)		600 (Aitken 2012, Bilton 2011)	⊕⊕⊖⊖ low[2,3]	
FEV_1 % predicted in children and young people (repeated measures, change from baseline) Range of scores: 0 to 100 Follow-up: 2 months	Not reported	The mean FEV_1 % predicted (repeated measures, change from baseline) in the mannitol groups was 2.64 higher (0.73 lower to 6.02 higher)		258 (Aitken 2012, Bilton 2011)	⊕⊕⊖⊖ low[2,3]	
FEV_1 % predicted in children and young people (repeated measures, change from	Not reported	The mean FEV_1 % predicted (repeated measures, change from baseline) in		258 (Aitken 2012, Bilton 2011)	⊕⊕⊖⊖ low[2,3]	

Comparison 1.1. Mannitol versus placebo						
baseline) Range of scores: 0 to 100 Follow-up: 4 months		the mannitol groups was 1.34 higher (2.42 lower to 5.10 higher)				
FEV_1 % predicted in children and young people (repeated measures, change from baseline) Range of scores: 0 to 100 Follow-up: 6 months	Not reported	The mean FEV_1 % predicted (repeated measures, change from baseline) in the mannitol groups was 3.03 higher (0.78 lower to 6.84 higher)		258 (Aitken 2012, Bilton 2011)	⊕⊕⊖⊖ low[2,3]	
FEV_1 % predicted in adults (repeated measures, change from baseline) Range of scores: 0 to 100 Follow-up: 2 months	Not reported	The mean FEV_1 % predicted (repeated measures, change from baseline) in the mannitol groups was 3.72 higher (0.82 to 6.64 higher)		317 (Aitken 2012, Bilton 2011)	⊕⊕⊖⊖ low[2,3]	
FEV_1 % predicted in adults (repeated measures, change from baseline) Range of scores: 0 to 100 Follow-up: 4 months	Not reported	The mean FEV_1 % predicted (repeated measures, change from baseline) in the mannitol groups was 4.23 higher (0.98 to 7.48 higher)		317 (Aitken 2012, Bilton 2011)	⊕⊕⊖⊖ low[2,3]	
FEV_1 % predicted in adults (repeated measures, change from baseline) Range of scores: 0 to 100 Follow-up: 6 months	Not reported	The mean FEV_1 % predicted (repeated measures, change from baseline) in the mannitol groups was 5.74 higher (2.36 to 9.13 higher)		317 (Aitken 2012, Bilton 2011)	⊕⊕⊖⊖ low[2,3]	

Comparison 1.1. Mannitol versus placebo						
Time to first protocol defined pulmonary exacerbation Follow-up: 6 months	Not reported	Not reported	HR 0.7 (0.48 to 1.02)	600 (Aitken 2012, Bilton 2011)	⊕⊕⊖⊖ low[2,4]	
Number of children and young people with protocol defined exacerbations (proxy for time to next exacerbation) Follow-up: 6 months	Not calculable (events per group not reported)	Not calculable (events per group not reported)	RR 0.62 (0.35 to 1.09)	259 (Aitken 2012, Bilton 2011)	⊕⊕⊖⊖ low[2,5]	
Number of adults with protocol defined exacerbations (proxy for time to next exacerbation) Follow-up: 6 months	Not calculable (events per group not reported)	Not calculable (events per group not reported)	RR 0.76 (0.52 to 1.13)	341 (Aitken 2012, Bilton 2011)	⊕⊕⊖⊖ low[2,5]	
Number of patients needing additional IV antibiotics Follow-up: 6 months	Study population		RR 0.81 (0.7 to 0.95)	600 (Aitken 2012, Bilton 2011)	⊕⊖⊖⊖ very low[2,5,6]	
	561 per 1000	454 per 1000 (392 to 533)				
	Moderate					
	560 per 1000	454 per 1000 (392 to 532)				
Quality of life - CFQOL respiratory domain (change from baseline) Range of scores: 0 to 100 Follow-up: 4 months	The mean change in CFQOL respiratory in the placebo group was 3.8 in 1 study, 0.1 in the other study	The mean change in CFQOL respiratory domain in the mannitol groups was 1.54 lower (4.69 lower to 1.61 higher)		507 (Aitken 2012, Bilton 2011)	⊕⊖⊖⊖ very low[2,3,7]	
Quality of life – CFQOL respiratory domain (change from baseline) Range of scores: 0 to 100 Follow-up: 6 months	The mean change in CFQOL respiratory in the placebo group was 5.6 in 1 study, -2.5 in the other study	The mean change in CFQOL respiratory in the mannitol groups was 0.99 lower (4.5 lower to 2.52 higher)		465 (Aitken 2012, Bilton 2011)	⊕⊖⊖⊖ very low[2,8,9]	
Quality of life - CFQOL vitality domain (change	The mean change in CFQOL	The mean change in CFQOL vitality		361 (Aitken 2012,	⊕⊕⊖⊖ low[2,3]	

Comparison 1.1. Mannitol versus placebo						
from baseline) Range of scores: 0 to 100 Follow-up: 4 months	vitality in the placebo group was -5.4 in 1 study, -3.5 in the other study	in the mannitol groups was 3.42 higher (0.21 lower to 7.04 higher)		Bilton 2011)		
Quality of life - CFQOL vitality domain (change from baseline) Range of scores: 0 to 100 Follow-up: 6 months	The mean change in CFQOL change in CFQOL vitality in the placebo group was -4.2 in 1 study, -5.1 in the other study	The mean change in CFQOL vitality in the mannitol groups was 4.84 higher (0.86 to 8.82 higher)		325 (Aitken 2012, Bilton 2011)	⊕⊕⊖⊖ low[2,3]	
Quality of life - CFQOL physical domain (change from baseline) Range of scores: 0 to 100 Follow-up: 4 months	The mean change in CFQOL physical in the placebo group was 2.3 in 1 study, -1.5 in the other study	The mean change in CFQOL physical in the mannitol groups was 1.8 lower (4.72 lower to 1.11 higher)		505 (Aitken 2012, Bilton 2011)	⊕⊕⊕⊖ moderate[2]	
Quality of life - CFQOL physical domain (change from baseline) Range of scores: 0 to 100 Follow-up: 6 months	The mean change in CFQOL physical in the placebo group was 1.1 in 1 study, -4.7 in the other study	The mean change in CFQOL physical in the mannitol groups was 0.52 higher (2.75 lower to 3.79 higher)		465 (Aitken 2012, Bilton 2011)	⊕⊖⊖⊖ very low[2,9,10]	
Quality of life - CFQOL emotion domain (change from baseline) Range of scores: 0 to 100 Follow-up: 4 months	The mean change in CFQOL emotion in the placebo group was 2.9 in 1 study, -0.1 in the other study	The mean change in CFQOL emotion in the mannitol groups was 2.11 lower (4.56 lower to 0.34 higher)		506 (Aitken 2012, Bilton 2011)	⊕⊕⊕⊖ moderate[2]	
Quality of life - CFQOL emotion domain (change from baseline) Range of scores: 0 to 100 Follow-up: 6 months	The mean change in CFQOL emotion in the placebo group was 2.1 in 1 study, 0.5 in	The mean change in CFQOL emotion in the mannitol groups was 1.27 lower		465 (Aitken 2012, Bilton 2011)	⊕⊕⊕⊖ moderate[2]	

Comparison 1.1. Mannitol versus placebo						
	the other study	(3.74 lower to 1.2 higher)				
Quality of life - CFQOL eating domain (change from baseline) Range of scores: 0 to 100 Follow-up: 4 months	The mean change in CFQOL eating in the placebo group was -3.3 in 1 study, 0.6 in the other study	The mean change in CFQOL eating in the mannitol groups was 0.81 higher (1.96 lower to 3.58 higher)		505 (Aitken 2012, Bilton 2011)	⊕⊕⊕⊖ moderate [2]	
Quality of life - CFQOL eating domain (change from baseline) Range of scores: 0 to 100 Follow-up: 6 months	The mean change in CFQOL eating in the placebo group was -1.4 in 1 study, 1.9 in the other study	The mean change in CFQOL eating in the mannitol groups was 0.68 higher (2.29 lower to 3.65 higher)		466 (Aitken 2012, Bilton 2011)	⊕⊕⊕⊖ moderate [2]	
Quality of life - CFQOL health domain (change from baseline) Range of scores: 0 to 100 Follow-up: 4 months	The mean change in CFQOL health in the placebo group was -1 in 1 study, 2.3 in the other study	The mean change in CFQOL health in the mannitol groups was 0.43 lower (4.18 lower to 3.32 higher)		360 (Aitken 2012, Bilton 2011)	⊕⊕⊕⊖ moderate [2]	
Quality of life - CFQOL health domain (change from baseline) Range of scores: 0 to 100 Follow-up: 6 months	The mean change in CFQOL health in the placebo group was -0.9 in 1 study, 1.1 in the other study	The mean change in CFQOL health in the mannitol groups was 0.21 lower (4.14 lower to 3.72 higher)		325 (Aitken 2012, Bilton 2011)	⊕⊕⊕⊖ moderate [2]	
Quality of life - CFQOL social domain (change from baseline) Range of scores: 0 to 100 Follow-up: 4 months	The mean change in CFQOL social in the placebo group was 0.2 in 1 study, -0.8 in the other study	The mean change in CFQOL social (change from baseline) in the mannitol groups was 1.2 lower (3.7 lower to 1.3 higher)		504 (Aitken 2012, Bilton 2011)	⊕⊕⊕⊖ moderate [2]	
Quality of life - CFQOL social domain (change from baseline) Range of scores:	The mean change in CFQOL social in the placebo	The mean change in CFQOL social in the mannitol groups was		465 (Aitken 2012, Bilton 2011)	⊕⊖⊖⊖ very low [2,3,11]	

Comparison 1.1. Mannitol versus placebo						
0 to 100 Follow-up: 6 months	group was 0.9 in 1 study, -0.7 in the other study	1.47 lower (4.25 lower to 1.32 higher)				
Quality of life - CFQOL body domain (change from baseline) Range of scores: 0 to 100 Follow-up: 4 months	The mean change in CFQOL body in the placebo group was 1.5 in 1 study, 1.6 in the other study	The mean change in CFQOL body in the mannitol groups was 3.1 lower (6.49 lower to 0.29 higher)		500 (Aitken 2012, Bilton 2011)	⊕⊕⊖⊖ low[2,3]	
Quality of life - CFQOL body domain (change from baseline) Range of scores: 0 to 100 Follow-up: 6 months	The mean change in CFQOL body in the placebo group was 2.9 in 1 study, 1.8 in the other study	The mean change in CFQOL body in the mannitol groups was 1.19 lower (4.51 lower to 2.13 higher)		461 (Aitken 2012, Bilton 2011)	⊕⊕⊕⊖ moderate [2]	
Quality of life - CFQOL role domain (change from baseline) Range of scores: 0 to 100 Follow-up: 4 months	The mean change in CFQOL role in the placebo group was -0.8 in 1 study, -2.4 in the other study	The mean change in CFQOL role in the mannitol groups was 1.22 higher (2.21 lower to 4.66 higher)		358 (Aitken 2012, Bilton 2011)	⊕⊕⊕⊖ moderate [2]	
Quality of life - CFQOL role domain (change from baseline) Range of scores: 0 to 100 Follow-up: 6 months	The mean change in CFQOL role in the placebo group was 1.1 in 1 study, -1.6 in the other study	The mean change in CFQOL role in the mannitol groups was 1.43 lower (4.87 lower to 2 higher)		324 (Aitken 2012, Bilton 2011)	⊕⊖⊖⊖ very low[2,3,12]	
Quality of life - CFQOL digestion domain (change from baseline) Range of scores: 0 to 100 Follow-up: 4 months	The mean change in CFQOL digestion in the placebo group was 2.1 in 1 study, 0.2 in the other study	The mean change in CFQOL digestion in the mannitol groups was 1.49 lower (4.77 lower to 1.78 higher)		505 (Aitken 2012, Bilton 2011)	⊕⊕⊕⊖ moderate [2]	
Quality of life - CFQOL digestion domain (change	The mean change in CFQOL	The mean change in CFQOL		465 (Aitken 2012,	⊕⊕⊖⊖ low[2,3]	

Comparison 1.1. Mannitol versus placebo						
from baseline) Range of scores: 0 to 100 Follow-up: 6 months	digestion in the placebo group was 2.8 in 1 study, 0 in the other study	digestion in the mannitol groups was 1.07 lower (5.04 lower to 2.9 higher)		Bilton 2011)		
Quality of life - CFQOL weight domain (change from baseline) Range of scores: 0 to 100 Follow-up: 4 months	The mean change in CFQOL weight in the placebo group was 4.6 in 1 study, 7.3 in the other study	The mean change in CFQOL weight in the mannitol groups was 4.23 lower (10.28 lower to 1.83 higher)		360 (Aitken 2012, Bilton 2011)	⊕⊕⊖⊖ low[2,3]	
Quality of life - CFQOL weight domain (change from baseline) Range of scores: 0 to 100 Follow-up: 6 months	The mean change in CFQOL weight in the placebo group was 7.8 in 1 study, 6.5 in the other study	The mean change in CFQOL weight in the mannitol groups was 3.27 lower (9.84 lower to 3.31 higher)		325 (Aitken 2012, Bilton 2011)	⊕⊕⊖⊖ low[2,3]	
Adverse events: haemoptysis (mild) Follow-up: 2 weeks	0%	0%	Not estimable	36 (Jaques 2008)1	⊕⊕⊕⊖ moderate [2,a,b]	
Adverse events: haemoptysis (severe) Follow-up: 2 weeks	53 per 1000	53 per 1000 (8 to 355)	RR 1 (0.15 to 6.74)	(Jaques 2008)1	⊕⊖⊖⊖ very low[2,9]	
Adverse events: Bronchospasm (mild) Follow-up: 6 months	0 events in each group	0 events in each group	Not estimable	295 (Bilton 2011)	⊕⊕⊕⊖ moderate [2,a,b]	
Adverse events: Haemoptysis (mild) Follow-up: 6 months	Study population		RR 1.73 (0.26 to 11.62)	600 (Aitken 2012, Bilton 2011)	⊕⊖⊖⊖ very low[2,9]	
	8 per 1000	14 per 1000 (2 to 97)				
	Moderate					
	9 per 1000	16 per 1000 (2 to 105)				
Adverse events: Bronchospasm (moderate) Follow-up: 6 months	0 per 1000	0 per 1000 (0 to 0)	RR 2.01 (0.03 to 133.11)	295 (Bilton 2011)	⊕⊖⊖⊖ very low[2,9]	
Adverse events: Haemoptysis (moderate)	Study population		RR 4.66 (0.5 to 43.49)	600 (Aitken 2012,	⊕⊖⊖⊖ very low[2,9]	
	4 per 1000	19 per 1000 (2 to 182)				

Comparison 1.1. Mannitol versus placebo						
Follow-up: 6 months	Moderate			Bilton 2011)		
	4 per 1000	19 per 1000 (2 to 174)				
Adverse events: Bronchospasm (severe) Follow-up: 6 months	0 per 1000	0 per 1000 (0 to 0)	RR 2.01 (0.03 to 133.11)	295 (Bilton 2011)	⊕⊖⊖⊖ very low[2,9]	
Adverse events: Haemoptysis (severe) Follow-up: 6 months	Study population		RR 1.55 (0.13 to 18.99)	600 (Aitken 2012, Bilton 2011)	⊕⊖⊖⊖ very low[2,9]	
	4 per 1000	6 per 1000 (1 to 79)				
	Moderate					
	4 per 1000	6 per 1000 (1 to 76)				
Adverse events: bronchospasm in children and young people	0 events	0 events	Not estimable (0 events in either group)	105 (Bilton 2011)	⊕⊕⊕⊖ moderate [2,a,b]	
Adverse events: bronchospasm in adults	Not calculable (events per group not reported)	Not calculable (events per group not reported)	RR 3.35 (0.16 to 71.50)	190 (Bilton 2011)	⊕⊖⊖⊖ very low[2,9]	
Adverse events: haemoptysis in children and young people	Not calculable (events per group not reported)	Not calculable (events per group not reported)	RR 5.48 (0.69 to 43.50)	259 (Aitken 2012, Bilton 2011)	⊕⊖⊖⊖ very low[2,9]	
Adverse events: haemoptysis in adults	Not calculable (events per group not reported)	Not calculable (events per group not reported)	RR 1.83 (0.64 to 5.23)	341 (Aitken 2012, Bilton 2011)	⊕⊖⊖⊖ very low[2,9]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

*Abbreviations: CFQOL: cystic fibrosis quality of life questionnaire; CI: confidence interval; **FEV_1**: forced expiratory volume in 1 second; HR: hazard ratio; MD: mean difference; RR: risk ratio*

1 Cross-over design
2 The quality of the evidence was downgraded by 1 as the participants in the trial underwent a tolerance test at screening. Those who failed were not entered in the study, and this limits the generalisability of the results to the general CF population.
3 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 clinical MID
4 The quality of the evidence was downgraded by 1, as the 95% CI crossed the null effect
5 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 default MID
6 The quality of the evidence was downgraded by 1 due to moderate heterogeneity (I2=59%)
7 The quality of the evidence was downgraded by 1 due to moderate heterogeneity (I2=37%).
8 The quality of the evidence was downgraded by 2 due to high heterogeneity (I2=89%)
9 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 default MIDs
10 The quality of the evidence was downgraded by 1 due to high heterogeneity (I2=77%). It was not downgraded further as both studies showed no differences between groups.
11 The quality of the evidence was downgraded by 2 due to high heterogeneity (I2=70%). Studies show conflicting results.
12 The quality of the evidence was downgraded by 1 due to moderate heterogeneity (I2=41%)
a Imprecision not calculable because risk ratio could not be estimated as there were 0 events in each group
b Risk ratio not estimable because there were 0 events in each group

Table 80: Summary clinical evidence profile: Comparison 1.2.1. Mannitol versus dornase alfa

Comparison 1.2.1. Mannitol versus dornase alfa						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Dornase alfa	Mannitol				
FEV_1 (% change from baseline) - Range of scores: 0 to 100 Follow-up: 3 months	Not reported	The mean FEV_1 (% change from baseline) in the intervention mannitol was 2.8 higher (4.8 lower to 10.4 higher)		20 (Minasian 2010)1	⊕⊖⊖⊖ very low[2,3,4]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; MD: mean difference

1 Cross-over design
2 The quality of the evidence was downgraded by 1 because this is an open trial, and there is high risk of incomplete reporting
3 The quality of the evidence was downgraded by 1 as the participants in the trial underwent a tolerance test at screening. Those who fail were not entered in the study, and this limits the generalisability of the results to the general CF population
4 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 clinical MIDs

Table 81: Summary clinical evidence profile: Comparison 1.2.2. Mannitol plus dornase alfa versus dornase alfa

Comparison 1.2.2. Mannitol plus dornase alfa versus dornase alfa						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Dornase alfa alone	Mannitol + Dornase alfa				
FEV_1 (% change from baseline) - Range of scores: 0 to 100 Follow-up: 3 months	Not reported	The mean FEV_1 (% change from baseline) in the mannitol + dornase alfa groups was 4.3 lower (14.1 lower to 5.5 higher)		20 (Minasian 2010)1	⊕⊖⊖⊖ very low[2,3,4]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; MD: mean difference

1 Cross-over design
2 The quality of the evidence was downgraded by 1 because this is an open trial, and there is high risk of incomplete reporting
3 The quality of the evidence was downgraded by 1 as the participants in the trial underwent a tolerance test at screening. Those who fail were not entered in the study, and this limits the generalisability of the results to the general CF population

4 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 clinical MIDs

9.3.4.2 Dornase alfa

Table 82: Summary clinical evidence profile: Comparison 2.1. Dornase alfa versus placebo

Comparison 2.1. Dornase alfa versus placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Dornase alfa				
Lung function: relative mean % change in FEV_1 Range of scores: 0 to 100 Follow-up: 10 days	The relative mean % change in FEV_1 in the placebo group was 0.15	The relative mean % change in FEV_1 the dornase alfa group was 13.17 higher (0.70 to 25.64 higher)		41 (Shah 1996)	⊕⊖⊖⊖ very low[1,7]	
Lung function: relative mean % change in FEV_1 Range of scores: 0 to 100 Follow-up: 1 months	The relative mean % change in FEV_1 in the placebo group was -1.9 in the first study, -1.6 in the second study, -1.5 in the third study, 4.2 in the fourth study	The relative mean % change in FEV_1 in the dornase alfa groups was 9.52 higher (0.59 to 18.46 higher)		248 (Laube 1996, Ramsey 1993a, Ranasinha 1993, Shah 1995)	⊕⊖⊖⊖ very low[3,4,7]	
Lung function: relative mean % change in FEV_1 Range of scores: 0 to 100 Follow-up: 3 months	The relative mean % change in FEV_1 in the placebo group was 0.76 in 1 study, 2.1 in the other study	The relative mean % change in FEV_1 in the dornase alfa groups was 6.7 higher (3.72 to 9.67 higher)		319 (Amin 2011, McCoy 1996)[5]	⊕⊖⊖⊖ very low[5,6,7]	
Lung function: relative mean % change in FEV_1 Range of scores: 0 to 100 Follow-up: 6 months	The relative mean % change in FEV_1 in the placebo group was 0	The relative % mean change in FEV_1 in the dornase alfa groups was 5.8 higher (4.41 to 7.19 higher)		647 (Fuchs 1994)	⊕⊕⊖⊖ low[7,8]	
subgroup analysis based on disease	The relative mean % change in	The mean % change in FEV_1 in the		183 (Laube 1996,	⊕⊕⊕⊖ low[9]	

Comparison 2.1. Dornase alfa versus placebo						
severity: moderate relative mean % change in FEV_1 – Range of scores: 0 to 100 Follow-up: 1 months	FEV_1 in the placebo group was -1.8 in the first study, -1.6 in the second study, -1.5 in the third study	dornase alfa groups was 14.32 higher (10.81 to 17.83 higher)		Ramsey 1993a, Ranasinha 1993)		
subgroup analysis based on disease severity: severe FEV_1 relative mean % change in FEV_1 - Range of scores: 0 to 100 Follow-up: 1 months	The relative mean % change in FEV_1 in the placebo group was 4.2	The mean % change in FEV_1 in the dornase alfa groups was 2.8 lower (8.76 lower to 3.16 higher)		65 (Shah 1995)	⊕⊖⊖⊖ very low[7]	
subgroup analysis based on disease severity: acute pulmonary exacerbation mean % change in FEV_1 Range of scores: 0 to 100 Follow-up: 1 months	The mean % change in FEV_1 in the placebo group was 19	The mean % change in FEV_1 in the dornase alfa groups was 1 higher (13.93 lower to 15.93 higher)		80 (Wilmott 1996)	⊕⊖⊖⊖ very low[2,11]	
Lung function: absolute mean % change in FEV_1 Range of scores: 0 to 100 Follow-up: 2 years	The absolute mean % change in FEV_1 in the placebo group was -3.2	The mean % change in FEV_1 in the dornase alfa groups was 3.24 higher (1.03 to 5.45 higher)		410 (Quan 2001)	⊕⊕⊕⊖ moderate[7]	
Number of people experiencing exacerbations Follow-up: 6 months	274 per 1000	222 per 1000 (167 to 290)	RR 0.81 (0.61 to 1.06)	647 (Fuchs 1994)	⊕⊕⊖⊖ low[8,12]	
Number of people experiencing exacerbations Follow-up: 2 years	239 per 1000	170 per 1000 (117 to 244)	RR 0.71 (0.49 to 1.02)	470 (Quan 2001)	⊕⊕⊕⊖ moderate[12]	
Number of days of IV antibiotics use Follow-up: 3 months	The mean number of days of IV antibiotics use in the	The mean number of days of IV antibiotics use in the dornase		320 (McCoy 1996)	⊕⊖⊖⊖ very low[13,14]	

Comparison 2.1. Dornase alfa versus placebo						
	placebo group was 28.31	alfa groups was 2.96 lower (7.29 lower to 1.37 higher)				
Adverse events: haemoptysis Follow-up: 1 months	Study population 43 per 1000 Moderate 43 per 1000	53 per 1000 (9 to 327) 53 per 1000 (9 to 328)	RR 1.23 (0.20 to 7.64)	141 (Ranasinha 1993, Shah 1995)	⊕⊖⊖⊖ very low[14,15]	
Adverse events: haemoptysis Follow-up: 6 months	Study population 65 per 1000	53 per 1000 (28 to 98)	RR 0.82 (0.44 to 1.52)	647 (Fuchs 1996)	⊕⊖⊖⊖ very low[8,14]	
Adverse events: voice alteration Follow-up: 1 months	Study population 25 per 1000 Moderate 0 per 1000	71 per 1000 (1 to 1000) 0 per 1000 (0 to 0)	RR 2.79 (0.03 to 278.07)	233 (Ramsey 1993a, Ranasinha 1993, Shah 1995)	⊕⊖⊖⊖ very low[14,16,17]	
Adverse events: voice alteration Follow-up: 3 months	62 per 1000	177 per 1000 (89 to 352)	RR 2.87 (1.44 to 5.71)	320 (McCoy 1996)	⊕⊕⊕⊖ moderate[13]	
Adverse events: voice alteration Follow-up: 6 months	22 per 1000	37 per 1000 (15 to 93)	RR 1.73 (0.69 to 4.34)	647 (Fuchs 1994)	⊕⊖⊖⊖ very low[8,14]	
Adverse events: voice alteration Follow-up: 2 years	115 per 1000	110 per 1000 (66 to 183)	RR 0.95 (0.57 to 1.59)	470 (Quan 2001)	⊕⊕⊖⊖ low[14]	
Quality of life: change in CFQ-R (CFQ-R parents) Range of scores: 0 to 100 Follow-up: 3 months	The change in CFQ-R parents in the placebo group was 0.89	The mean change in CFQ-R parents in the dornase alfa groups was 5.45 lower (15.23 lower to 4.33 higher)		17 (Amin 2011)[5]	⊕⊕⊕⊖ moderate[7]	
Quality of life: change in CFQ-R - CFQ-R 14+ Range of scores: 0 to 100 Follow-up: 3 months	The change in CFQ-R 14+ in the placebo group was -5.28	The mean change in CFQ-R 14+ in the dornase alfa groups was 5.21 lower (15.5 lower to 5.08 higher)		17 (Amin 2011)[5]	⊕⊕⊕⊖ moderate[7]	

Comparison 2.1. Dornase alfa versus placebo
**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).* *Abbreviations: CFQ-R: cystic fibrosis questionnaire revised; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; IV: intravenous; MD: mean difference; RR: risk ratio*

1 The quality of the evidence was downgraded by due to unclear sequence generation, allocation concealment, blinding and reporting
2 The quality of the evidence was downgraded by 2 as the CI crossed 2 clinical MIDs
3 The quality of the evidence was downgraded by 2 due to unclear sequence generation, blinding, allocation concealment and reporting in 3 of the trials, and unclear blinding and reporting in the fourth trial
4 The quality of the evidence was downgraded by 1 due to high heterogeneity (I2=88%). See sensitivity analysis.
5 Amin 2011: cross-over trial
6 The quality of the evidence was downgraded by 1 due to unclear sequence generation, blinding, allocation concealment and reporting in the 1 of the trial
7 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 clinical MID
8 The quality of the evidence was downgraded by 1 due to unclear blinding, allocation, concealment and reporting
9 The quality of the evidence was downgraded by 2 due to unclear sequence generation, blinding, allocation concealment and reporting in 2 of the trials, and unclear blinding and reporting in the third trial
10 The quality of the evidence was downgraded by 2 due to unclear sequence generation, blinding, allocation concealment and reporting
11 The quality of the evidence was downgraded by 2 due to unclear sequence generation, blinding, allocation concealment and reporting
12 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 default MID
13 The quality of the evidence was downgraded by 2 due to unclear randomisation, blinding, allocation concealment and reporting
14 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 default MIDs
15 The quality of the evidence was downgraded by 2 due to unclear sequence generation, blinding, allocation concealment and reporting in both trials
16 The quality of the evidence was downgraded by 2 due to unclear blinding, allocation concealment and reporting in 2 of the trials, and unclear blinding and reporting in the third trial
17 The quality of the evidence was downgraded by 1 due to high heterogeneity (I2=85%)

Table 83: Summary clinical evidence profile: Comparison 2.2. Dornase alfa versus nebulised sodium chloride

Comparison 2.2. Dornase alfa versus nebulised sodium chloride						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Nebulised sodium chloride	Dornase alfa				
Lung function: mean % change in FEV_1 Range of scores: 0 to 100 Follow-up: 3 weeks	The mean % change in FEV_1 in the nebulised sodium chloride group was 7.7	The mean % change in FEV_1 in the dornase alfa groups was 1.6 higher (7.96 lower to 11.16 higher)		48 (Ballmann 1998)[1]	⊕⊖⊖⊖ very low[2,3]	
Lung function: mean % change in FEV_1 Range of scores: 0 to	Not reported	The mean % change in FEV_1 in the dornase alfa groups was 8 higher (2 to 14 higher)		14 (Suri 2001)[1]	⊕⊕⊖⊖ low[2,4]	

Comparison 2.2. Dornase alfa versus nebulised sodium chloride						
100 Follow-up: 3 months						
Number of days inpatient treatment Follow-up: 3 months	Not reported	The mean number of days inpatient treatment in the dornase alfa groups was 0.4 lower (2.32 lower to 1.52 higher)		14 (Suri 2001)[1]	⊕⊕⊕⊖ moderate[2]	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; MD: mean difference						

1 Cross-over study
2 The quality of the evidence was downgraded by 1 due to unclear blinding, allocation, concealment and reporting
3 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 clinical MIDs
4 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 clinical MID

9.3.4.3 Nebulised sodium chloride

Table 84: Summary clinical evidence profile: Comparison 3.1. Nebulised sodium chloride (> 3% concentration) versus placebo (0.9% to 0.12%) or low-concentration (≤ 3%)

Comparison 3.1. Nebulised sodium chloride (> 3% concentration) versus placebo (0.9% to 0.12%) or low-concentration (≤ 3%)						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Low concentration(≤ 3% sodium chloride)	High concentration (>3% sodium chloride)				
Failed to regain pre-exacerbation FEV_1% predicted Range of scores: 0 to 100 Follow-up: at hospital discharge	431 per 1000	254 per 1000 (155 to 418)	RR 0.59 (0.36 to 0.97)	132 (Dentice 2016)	⊕⊕⊕⊖ moderate [1]	
Lung function: % change in FEV_1 Range of scores: 0 to 100	The mean % change in FEV_1 in the ≤3% sodium chloride group was 13.81	The mean % change in FEV_1 in the >3% sodium chloride groups was 14.35 lower		30 (Gupta 2012)	⊕⊕⊕⊖ moderate [1]	

Follow-up: 2 weeks		(27.8 to 0.9 lower)				
Lung function: % change in FEV_1 Range of scores: 0 to 100 Follow-up: 4 weeks	The mean % change in FEV_1 in the ≤3% sodium chloride group was 12.53 in 1 study, -0.3 in the other study	The mean % change in FEV_1 in the >3% sodium chloride groups was 4.92 lower (17.69 lower to 7.86 higher)		93 (Gupta 2012, Mainz 2016)[2]	⊕⊖⊖ very low[3,4,5]	
Lung function: % change in FEV_1 Range of scores: 0 to 100 Follow-up: 12 weeks	The mean % change in FEV_1 in the ≤3% sodium chloride group was 3.96	The mean % change in FEV_1 in the >3% sodium chloride groups was 4.1 higher (0.08 lower to 8.28 higher)		149 (Elkins 2006)	⊕⊕⊕⊖ moderate[1]	
Lung function: % change in FEV_1 Range of scores: 0 to 100 Follow-up: 24 weeks	The mean: % change in FEV_1 in the ≤3% sodium chloride group was 4.46	The mean % change in FEV_1 in the >3% sodium chloride groups was 5.37 higher (1.03 to 9.71 higher)		140 (Elkins 2006)	⊕⊕⊕⊖ moderate[1]	
Lung function: % change in FEV_1 Range of scores: 0 to 100 Follow-up: 36 weeks	The mean % change in FEV_1 in the ≤3% sodium chloride group was 5	The mean % change in FEV_1 in the >3% sodium chloride groups was 3.63 higher (1.56 lower to 8.82 higher)		134 (Elkins 2006)	⊕⊕⊕⊖ moderate[1]	
Lung function: % change in FEV_1 Range of scores: 0 to 100 Follow-up: 48 weeks	The mean% change in FEV_1 in the ≤3% sodium chloride group was 4.75	The mean % change in FEV_1 in the >3% sodium chloride groups was 2.31 higher (2.72 lower to 7.34 higher)		134 (Elkins 2006)	⊕⊕⊕⊖ moderate[1]	
Time to first pulmonary exacerbation Follow-up: mean 1 years	Not reported	Not reported	HR 0.92 (0.74 to 1.14)	453 (Dentice 2016, Rosenfeld 2012)	⊕⊕⊕⊖ moderate[6]	
Number of days of treatment for a pulmonary exacerbation	The mean number of days of treatment for a pulmonary exacerbation in the ≤3%	The mean number of days of treatment for a pulmonary exacerbation in		321 (Rosenfeld 2012)	⊕⊕⊕⊕ high	

Follow-up: 48 weeks	sodium chloride group was 52	the >3% sodium chloride groups was 1.11 higher (0.89 to 1.33 higher)				
Change in quality of life following treatment - CFQOL - physical domain Range of scores: 0 to 100 Follow-up: 7 days	The mean change CFQOL physical domain in the ≤3% sodium chloride groups was 9	The mean change in CFQOL - physical domain in the >3% sodium chloride groups was 2.00 higher (3.12 lower to 7.12 higher)		132 (Dentice 2016)	⊕⊕⊕⊖ moderate [1]	
Change in quality of life following treatment - CFQOL - burden domain Range of scores: 0 to 100 Follow-up: 7 days	The mean change CFQOL burden domain in the ≤3% sodium chloride groups was 9	The mean change in CFQOL - burden domain in the >3% sodium chloride groups was 0.00 higher (4.78 lower to 4.78 higher)		132 (Dentice 2016)	⊕⊕⊕⊕ high	
Change in quality of life following treatment - CFQOL - health domain Range of scores: 0 to 100 Follow-up: 7 days	The mean change in CFQOL health domain in the ≤3% sodium chloride groups was 14	The mean change in CFQOL - health domain in the >3% sodium chloride groups was 2.00 lower (8.15 lower to 4.15 higher)		132 (Dentice 2016)	⊕⊕⊕⊖ moderate [1]	
Change in quality of life following treatment - CFQOL - respiratory domain Range of scores: 0 to 100 Follow-up: 7 days	The mean change in CFQOL - respiratory domain in the ≤3% sodium chloride groups was 12	The mean change in CFQOL - respiratory domain in the >3% sodium chloride groups was 1.00 higher (4.99 lower to 6.99 higher)		132 (Dentice 2016)	⊕⊕⊕⊖ moderate [1]	
Change in quality of life following treatment - CFQOL - physical	The mean change in CFQOL- physical domain in the ≤3% sodium	The mean change in CFQOL - physical domain in the >3% sodium		132 (Dentice 2016)	⊕⊕⊕⊖ moderate [1]	

domain Range of scores: 0 to 100 Follow-up: 7 days	chloride groups was 14	chloride groups was 2.00 higher (4.15 lower to 8.15 higher)				
Change in quality of life following treatment - CFQOL - burden domain Range of scores: 0 to 100 Follow-up: 7 days	The mean change CFQOL - burden domain in the ≤3% sodium chloride groups was -1	The mean change in CFQOL - burden domain in the >3% sodium chloride groups was 2.00 higher (4.04 lower to 8.04 higher)		132 (Dentice 2016)	⊕⊕⊕⊖ moderate [1]	
Change in quality of life following treatment - CFQOL - health domain Range of scores: 0 to 100 Follow-up: 7 days	The mean change in CFQOL - health domain in the ≤3% sodium chloride groups was 18	The mean change in CFQOL - health domain in the >3% sodium chloride groups was 2.00 higher (4.99 lower to 8.99 higher)		132 (Dentice 2016)	⊕⊕⊕⊖ moderate [1]	
Change in quality of life following treatment - CFQOL - respiratory domain Range of scores: 0 to 100 Follow-up: 7 days	The mean change in CFQOL - respiratory domain in the ≤3% sodium chloride groups was 21	The mean change in CFQOL - respiratory domain in the >3% sodium chloride groups was 2.00 lower (8.67 lower to 4.67 higher)		132 (Dentice 2016)	⊕⊕⊕⊖ moderate [1]	
Quality of life: CFQ-R respiratory: CFQ parent Range of scores: 0 to 100 Follow-up: 4 weeks	Not reported	The mean CFQ-R respiratory, CFQ parent in the >3% sodium chloride group was 5.9 higher (3.1 lower to 14.9 higher)		20 (Amin 2010)[7]	⊕⊕⊕⊖ moderate [1]	
Quality of life: CFQ-R respiratory 14+ Range of scores: 0 to 100	Not reported	The mean CFQ-R respiratory, CFQ 14+ in the >3% sodium chloride groups was 5.2 higher (7		20 (Amin 2010)[7]	⊕⊕⊖⊖ low[5]	

Follow-up: 4 weeks		lower to 17.4 higher)				
Change in quality of life: CFQ - CFQ-R parents Range of scores: 0 to 100 Follow-up: 48 weeks	The mean change in CFQ-R parents in the ≤3% sodium chloride group was 0.9	The mean change in CFQ-R parents in the >3% sodium chloride groups was 1.13 lower (7.49 lower to 5.23 higher)		67 (Elkins 2006)	⊕⊕⊖⊖ low[5]	
Change in quality of life: CFQ-R 14+ Range of scores: 0 to 100 Follow-up: 48 weeks	The mean change in CFQ-R 14+ in the ≤3% sodium chloride group was 1.09	The mean change in CFQ-R 14+ in the >3% sodium chloride groups was 7.77 higher (1.86 to 13.68 higher)		92 (Elkins 2006)	⊕⊕⊕⊖ moderate [1]	
Change in quality of life: CFQ-R respiratory domain Range of scores: 0 to 100 Follow-up: 48 weeks	The mean change in CFQ-R respiratory domain in the ≤3% sodium chloride group was -3.2	The mean change in CFQ-R respiratory domain in the >3% sodium chloride groups was 3.3 higher (0 to 6.6 higher)		321 (Rosenfeld 2012)	⊕⊕⊕⊖ moderate [1]	

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Abbreviations: CFQ-R: cystic fibrosis questionnaire revised; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; HR: hazard ratio, MD: mean difference; RR: risk ratio

1 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 clinical MID
2 Mainz 2016: Cross-over study
3 The quality of the study was downgraded by 1 due to unclear risk of bias in relation to random sequence generation, allocation concealment and selective reporting in 1 study
4 The quality of the evidence was downgrade by 2 due to serious inconsistency (I2=77%)
5 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 clinical MIDs
6 The quality of the evidence was downgraded by 1 as the 95% CI crossed the null effect
7 Amin 2010: cross-over study

9.3.4.4 Acetylcysteine

Table 85: Summary clinical evidence profile: Comparison 4. Acetylcysteine versus placebo

Comparison 4. Acetylcysteine versus placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Acetylcysteine				

Comparison 4. Acetylcysteine versus placebo						
Lung function: change in FEV_1 % predicted Range of scores: 0 to 100 Follow-up: 4 weeks	The mean change in FEV_1 in the placebo group was -1.41	The mean change in FEV_1 % predicted in the acetylcysteine groups was 3.51 higher (0.65 lower to 7.67 higher)		21 (Skov 2015)	⊕⊖⊖⊖ very low[1,2]	
Lung function: change in FEV_1 % predicted Range of scores: 0 to 100 Follow-up: 12 weeks	The mean change in FEV_1 in the placebo group was -8.6	The mean change in FEV_1 % predicted in the acetylcysteine groups was 5 higher (10.84 lower to 20.84 higher)		21 (Ratjen 1985)	⊕⊕⊖⊖ low[3]	
Lung function: change in FEV_1 % predicted Range of scores: 0 to 100 Follow-up: 24 weeks	Not reported	The mean change in FEV_1 % predicted in the acetylcysteine groups was 4.4 higher (0.83 to 7.97 higher)		70 (Conrad 2015)	⊕⊕⊕⊖ moderate[2]	
Inflammatory markers: change in sputum IL-8 (log10) Follow-up: 24 weeks	Not reported	The mean change in sputum IL-8 (log10) in the acetylcysteine groups was MD 0.19 higher (0.03 lower to 0.42 higher)		70 (Conrad 2015)	⊕⊕⊕⊕ high[4]	
Incidence of pulmonary exacerbations Follow-up: 24 weeks	500 per 1000	415 per 1000 (250 to 695)	RR 0.83 (0.5 to 1.39)	70 (Conrad 2015)	⊕⊕⊖⊖ low[3]	
Quality of life: CFQ-R respiratory Follow-up: 24 weeks	Not reported	The mean CFQ-R respiratory in the acetylcysteine groups was 0.34 lower (6.3 lower to 5.62 higher)		70 (Conrad 2015)	⊕⊕⊖⊖ low[3]	

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Abbreviations: CFQ-R: cystic fibrosis questionnaire revised; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; IL-8: interleukin 8; MD: mean difference; RR: risk ratio

1 The quality of the evidence was downgraded by 1 as this is an open trial, and there was unclear randomisation and allocation concealment.
2 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 clinical MID
3 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 clinical MIDs
4 Imprecision not calculable, as SD for the control group was not available in the study

9.3.5 Economic evidence

Six economic evaluations of mucoactive or mucolytic agents to manage cystic fibrosis were identified in the literature search conducted for this guideline. Five of those 6 studies included dornase alfa as an intervention compared with either no dornase alfa or hypertonic sodium chloride, the remaining economic evaluation assessed mannitol (with and without dornase alfa) against best supportive care (control). No economic evaluations were identified that included acetylcysteine. A description of the methods and results of those economics evaluations can be found in Appendix K.

Full details of the search and economic article selection flow chart can be found in Appendix E and F, respectively. Data extraction tables and quality assessments of included studies can be found in Appendix L and M, respectively.

Based on the available evidence, the committee agreed additional economic analysis would be superfluous. Instead, a cost description of the interventions was undertaken in Appendix K.

9.3.6 Evidence statements

9.3.6.1 Mannitol

9.3.6.1.1 Comparison 1.1 Mannitol versus placebo

Lung function: FEV_1

Low quality evidence from 1 cross-over trial with 36 people with cystic fibrosis aged ≥8 years showed no clinically significant difference in the lung function (measured as change in FEV_1 % predicted) between the group of participants receiving mannitol (420 mg twice daily) and those in the control group (non-respirable mannitol <2%) at 2 week follow-up.

Moderate quality evidence from 2 RCTs with 600 people with cystic fibrosis aged ≥6 years showed no clinically significant difference in the lung function (measured as change in FEV_1 % predicted) between the group of participants receiving mannitol (400 mg twice daily) and those in the control group (mannitol 50 mg twice daily) at 2, 4 and 6 months follow-up. Data from these 2 RCTs was also available stratified by age subgroups and is presented below.

- Children and young people: Low quality evidence from 2 RCTs with 258 children and young people with cystic fibrosis aged ≥6 years showed no clinically significant difference in the lung function (measured as change in FEV_1 % predicted) between the group of participants receiving mannitol (400 mg twice daily) and those in the control group (mannitol 50 mg twice daily) at 2, 4 and 6 months follow-up.
- Adults: Low quality evidence from 2 RCTs with 317 adults with cystic fibrosis showed no clinically significant difference in the lung function (measured as change in FEV1 % predicted) between the group of participants receiving mannitol (400 mg twice daily) and those in the control group (mannitol 50 mg twice daily) at 2 and 4 months follow-up. However low quality evidence from the same studies showed a clinically significant increase in FEV_1 % predicted in the group of adults receiving mannitol compared to the control group at 6 months follow-up.

Time to next exacerbation

Low quality evidence from 2 RCTs with 600 people with cystic fibrosis aged ≥6 years showed no clinically significant difference in the time to first pulmonary exacerbation (protocol defined exacerbation) between the participants receiving mannitol (400 mg twice daily) and those in the control group (mannitol 50 mg twice daily) at 6 months follow-up.

Number of people with protocol defined pulmonary exacerbations (proxy for time to next exacerbation)

Data from the 2 RCTs mentioned under the outcome “time to next exacerbation” did not provide data on time to next exacerbation stratified by age subgroups however data on the proxy outcome “number of people with protocol defined pulmonary exacerbations” was available stratified by age subgroups and is presented below.

- Children and young people: Low quality evidence from 2 RCTs with 259 children and young people with cystic fibrosis aged ≥6 years showed no clinically significant difference in the number of participants with protocol defined pulmonary exacerbations between those receiving mannitol (400 mg twice daily) and those in the control group (mannitol 50 mg twice daily) at 6 months follow-up.
- Adults: Low quality evidence from 2 RCTs with 341 adults with cystic fibrosis showed no clinically significant difference in the number of participants with protocol defined pulmonary exacerbations between those receiving mannitol (400 mg twice daily) and those in the control group (mannitol 50 mg twice daily) at 6 months follow-up.

Need for additional intravenous antibiotics for pulmonary exacerbation

Very low quality evidence from 2 RCTs with 600 people with cystic fibrosis ≥6 years showed no clinically significant difference in the number of people requiring intravenous antibiotics between the group of participants receiving mannitol (400 mg twice daily) and those in the control group (mannitol 50 mg twice daily) at 6 months follow-up. Moderate heterogeneity was observed between both trials. One trial (n=305) showed no clinically significant differences, whereas the other trial (n=295) showed that there was a clinically significant lower number of people who needed additional intravenous antibiotics in the mannitol group.

Inflammatory markers

No evidence was found for this outcome.

Quality of life

Very low to moderate quality evidence from 2 RCTs with 600 people with cystic fibrosis ≥6 years showed no clinically significant difference in the quality of life (measured with CF-QOL respiratory, vitality, physical, emotion, eating, health, social, body, role, digestion and weight domains) between the participants receiving mannitol (400 mg twice daily) and those in the control group (mannitol 50 mg twice daily) at 4 and 6 months follow-up.

Moderate to high heterogeneity was observed for the respiratory domain at 4 and 6 months, and for the physical, social and role domains at 6 months. In spite of the heterogeneity, both trials showed that the differences between groups were not clinically significant in either trial for the respiratory domain at 4 months, and for the physical and social domains at 6 months.

However, for the respiratory domain, 1 trial (n=278) showed a clinically significant improvement in the control group compared to the mannitol group, whereas the other trial (n=229) showed no clinically significant differences at 6 months follow-up.

Adverse events

Moderate quality evidence from 1 cross-over trial with 36 people with cystic fibrosis aged ≥8 years reported that none of the participants in the intervention group (Mannitol 420 mg twice daily) or the control group (non-respirable mannitol <2%) experienced mild haemoptysis at 2 week follow-up.

Very low quality evidence from the same trial with 36 people with cystic fibrosis aged ≥8 years showed no clinically significant difference in the occurrence of severe haemoptysis

between the participants receiving Mannitol (420 mg twice daily) and those in the control group (non-respirable mannitol <2%) at 2 week follow-up.

Moderate quality evidence from 1 trial with 295 people with cystic fibrosis ≥6 years reported that none of the participants in the intervention group (Mannitol 400 mg twice daily) or in the control group (50 mg twice daily) experienced mild bronchospasm at 6 months follow-up.

Moderate quality evidence from the same 1 trial with 295 people with cystic fibrosis ≥6 years reported that 1 participant in the mannitol group experienced moderate bronchospasm, and 1 participant experienced severe bronchospasm in the mannitol group. No events of moderate or severe bronchospasm were observed in the control group at 6 months follow-up. These differences were not clinically significant. Data from this 1 RCT was also available stratified by age subgroups and is presented below.

- Children and young people: Moderate quality evidence from 1 RCT with 105 children and young people with cystic fibrosis showed that that none of the participants in the intervention group (Mannitol 400 mg twice daily) or in the control group (50 mg twice daily) experienced bronchospasm at 6 months follow-up.
- Adults: Very low quality evidence from 1 RCT with 190 adults with cystic fibrosis showed no clinically significant difference in the occurrence of bronchospasm between the participants receiving mannitol (400 mg twice daily) and those in the control group (mannitol 50 mg twice daily) at 6 months follow-up.

Very low quality evidence from 2 trials with 600 people with cystic fibrosis ≥6 years showed no clinically significant differences in the occurrence of mild, moderate or severe haemoptysis between the participants receiving mannitol (420 mg twice daily) and those in the control group (mannitol 50 mg twice daily) at 6 months follow-up. Data from these 2 RCTs was available stratified by age subgroups and is presented below.

- Children and young people: Very low quality evidence from 2 RCTs with 259 children and young people with cystic fibrosis aged ≥6 years showed no clinically significant difference in the occurrence of haemoptysis between the group of participants receiving mannitol (400 mg twice daily) and those in the control group (mannitol 50 mg twice daily) at 6 months follow-up.
- Adults: Very low quality evidence from 2 RCTs with 341 adults with cystic fibrosis showed no clinically significant difference in the occurrence of haemoptysis between the group of participants receiving mannitol (400 mg twice daily) and those in the control group (mannitol 50 mg twice daily) at 6 months follow-up.

9.3.6.1.2 Comparison 1.2.1. Mannitol versus dornase alfa

Lung function: FEV_1

Very low quality evidence from 1 cross-over trial with 20 children and young people with cystic fibrosis (mean age 13.2 years) showed no clinically significant difference in the lung function (measured as FEV_1 % change from baseline) between the group of participants receiving mannitol (400 mg twice daily) and the participants receiving dornase alfa (2.5 mg twice daily).

Time to next exacerbation

No evidence was found for this outcome.

Need for additional intravenous antibiotics for pulmonary exacerbation

No evidence was found for this outcome.

Inflammatory markers

No evidence was found for this outcome.

Quality of life

No evidence was found for this outcome.

Adverse events

No evidence was found for this outcome.

9.3.6.1.3 Comparison 1.2.1. Mannitol plus dornase alfa versus dornase alfa

Lung function: FEV_1

Very low quality evidence from 1 cross-over trial with 20 children and young people with cystic fibrosis (mean age 13.2 years) showed no clinically significant difference in the lung function (measured as FEV_1 % change from baseline) between the group of participants receiving a combination of mannitol (400 mg mannitol twice daily) and dornase alfa (2.5 mg twice daily) and the participants receiving dornase alfa alone (2.5 mg twice daily).

Time to next exacerbation

No evidence was found for this outcome.

Need for additional intravenous antibiotics for pulmonary exacerbation

No evidence was found for this outcome.

Inflammatory markers

No evidence was found for this outcome.

Quality of life

No evidence was found for this outcome.

Adverse events

No evidence was found for this outcome.

9.3.6.1.4 Comparison 1.3: Mannitol versus nebulised sodium chloride

No evidence was found for this comparison.

9.3.6.1.5 Comparison 1.4. Mannitol versus acetylcysteine

No evidence was found for this comparison.

9.3.6.2 Dornase alfa

9.3.6.2.1 Comparison 2.1: Dornase alfa versus placebo

Lung function: FEV_1

Very low quality evidence from 1 RCT with 41 people with cystic fibrosis aged >15 years showed a clinically significant improvement in lung function (measured as relative mean %

change in FEV_1) in the group of participants receiving dornase alfa (2.5 mg twice daily) compared to those who were receiving placebo at 10 days follow-up.

Very low quality evidence from 4 RCTs with 248 people with cystic fibrosis >5 years showed a clinically significant improvement in lung function (measured as relative mean % change in FEV_1) in the group of participants receiving dornase alfa (2.5 mg once daily or twice daily) compared to those who were receiving placebo at 1 month follow-up. However, a high level of heterogeneity was found. A subgroup analysis showed that that this improvement in lung function was significant in people with moderate lung disease (3 RCTs, n=183, low quality), whereas no differences were found in the group of participants with severe lung disease (1 RCT, n=65, very low quality).

Very low quality evidence from 1 RCT with 80 people with cystic fibrosis and acute pulmonary exacerbation >5 years showed no clinically significant difference in lung function (measured as % mean change in FEV_1) between the group of participants receiving dornase alfa (2.5 mg) and those who were receiving placebo at 1 month follow-up.

Very low quality evidence from 2 RCTs with 319 people with cystic fibrosis >6 years showed a clinically significant improvement in lung function (measured as relative mean % change in FEV_1) in the group of participants receiving dornase alfa (2.5 mg twice daily) compared to those who were receiving placebo at 3 months follow-up.

Low quality evidence from 1 RCT with 647 people with cystic fibrosis >6 years showed a clinically significant improvement in lung function (measured as relative mean % change in FEV_1) in the group of participants receiving dornase alfa (2.5 mg once daily or twice daily) compared to those who were receiving placebo at 6 months follow-up.

Moderate quality evidence from 1 RCT with 410 children with cystic fibrosis aged 6 to 10 years showed no clinically significant difference in lung function (measured as absolute mean % change in FEV_1) between the group of participants receiving dornase alfa (2.5 mg) and those who were receiving placebo at 2 years follow-up.

People experiencing exacerbations (proxy outcome for time to next exacerbation)

Low quality evidence from 1 RCT with 647 people with cystic fibrosis ≥5 years showed no clinically significant difference in the number of people experiencing pulmonary exacerbations between the group of participants receiving dornase alfa (2.5 mg once daily or twice daily) and those who were receiving placebo at 6 months follow-up.

Moderate quality evidence from 1 RCT with 470 children with cystic fibrosis aged 6 to 10 years showed no clinically significant difference in the number of children experiencing pulmonary exacerbations between the group of participants receiving dornase alfa (2.5 mg) and those who were receiving placebo at 6 months follow-up.

Number of days of intravenous antibiotics use (proxy outcome for need for additional intravenous antibiotics for pulmonary exacerbation)

Very low quality evidence from 1 RCT with 320 people with cystic fibrosis ≥7 years showed no clinically significant difference in the number of days of intravenous antibiotic use between the group of participants receiving dornase alfa (2.5 mg once daily or twice daily) and those who were receiving placebo at 3 months follow-up.

Inflammatory markers

No evidence was found for this outcome.

Quality of life

Moderate quality evidence from 1 cross-over RCT with 17 children and young people with cystic fibrosis aged 6 to 18 years showed no clinically significant difference in the quality of life (CFQ-R parents and CFQ-R 14+) between the group of participants receiving dornase alfa (2.5 mg) and those who were receiving placebo at 3 months follow-up.

Adverse events

Very low quality evidence from 2 RCTs with 141 people with cystic fibrosis >5 years showed no clinically significant difference in the occurrence of haemoptysis between the group of participants receiving dornase alfa (2.5 mg) and those who were receiving placebo at 1 month follow-up.

Likewise, very low quality evidence from another RCT with 647 people with cystic fibrosis ≥5 years showed no clinically significant difference in the occurrence of haemoptysis between the group of participants receiving dornase alfa (2.5 mg) and those who were receiving placebo at 6 months follow-up.

Very low quality evidence from 3 RCTs with 233 people with cystic fibrosis >5 years showed a clinically significant higher occurrence of voice alteration in the group of participants receiving dornase alfa (2.5 mg) compared to those who were receiving placebo at 1 month follow-up. Significant heterogeneity was noted between the 2 trials that could be pooled in the meta-analysis. One trial (n=92) noted a harmful effect of dornase alfa, whereas the other did not show any differences. The third trials reported no events in either group.

Likewise, moderate quality evidence from another RCT with 320 children with cystic fibrosis aged 6 to 10 years showed a clinically significant higher occurrence of voice alteration in the group of participants receiving dornase alfa (2.5 mg) compared to those who were receiving placebo at 3 months follow-up.

However, very low quality evidence from 1 RCT with 647 people with cystic fibrosis ≥5 years showed no clinically significant difference in the occurrence of voice alteration between the group of participants receiving dornase alfa (2.5 mg once daily or twice daily) and those who were receiving placebo at 6 months follow-up.

Similarly, low quality evidence from another RCT with 470 children with cystic fibrosis aged 6 to 10 years showed no clinically significant difference in the occurrence of voice alteration between the group of participants receiving dornase alfa (2.5 mg once daily or twice daily) and those who were receiving placebo at 2 years follow-up.

9.3.6.2.2 Comparison 2.2. Dornase alfa versus nebulised sodium chloride - hypertonic or isotonic (NaCL HS or IS)

Lung function: FEV_1%

Very low quality evidence from 1 cross-over trial with 48 children with cystic fibrosis (mean age 13.3) showed no clinically significant difference in the lung function (measured as mean % change in FEV_1) between the participants receiving dornase alfa (2.5 mg) and those receiving 5.85% sodium chloride at 3 week follow-up.

Low quality evidence from 1 cross-over trial with 14 people with cystic fibrosis >7 years showed a clinically significant improvement in the lung function (measured as mean % change in FEV_1) in the participants receiving dornase alfa (2.5 mg) compared to those receiving 7% sodium chloride at 3 months follow-up.

Time to next exacerbation

No evidence was found for this outcome.

Number of days of inpatient treatment (proxy outcome for need for additional intravenous antibiotics for pulmonary exacerbation)

Moderate quality evidence from 1 cross-over trial with 14 people with cystic fibrosis >7 years showed no clinically significant difference in the number of days of inpatient treatment between the participants receiving dornase alfa (2.5 mg) and those receiving 7% sodium chloride at 3 months follow-up.

Inflammatory markers

No evidence was found for this outcome.

Quality of life

No evidence was found for this outcome.

Adverse events

No evidence was found for this outcome.

9.3.6.2.3 Comparison 2.3. Dornase alfa versus acetylcysteine

No evidence was found for this comparison.

9.3.6.3 Nebulised sodium chloride: hypertonic or isotonic

9.3.6.3.1 Comparison 3.1. Nebulised sodium chloride (> 3% concentration) versus placebo (0.9%) or low-concentration (≤ 3%)

Lung function: FEV_1 %

Moderate quality evidence from 1 RCT with 132 adults with cystic fibrosis showed a clinically significant higher likelihood of regaining pre-exacerbation FEV_1% predicted in the group of participants receiving 7% sodium chloride compared to those who were receiving 3% sodium chloride at hospital discharge.

Moderate quality evidence from 1 RCT with 30 children and young people with cystic fibrosis aged 6 to 16 years showed a clinically significant decrease in the lung function (measured as % change in FEV_1) between the group of participants receiving 7% sodium chloride compared to those who were receiving 3% sodium chloride at 2 week follow-up.

Very low quality evidence from 2 RCTs with 93 people with cystic fibrosis aged ≥6 years showed no clinically significant difference in lung function (measured as % change in FEV_1) between the group of participants receiving 6 to 7% sodium chloride compared to those who were receiving 3% sodium chloride at 4 week follow-up. Significant heterogeneity was observed between both trials. The larger trial (n=123) showed no clinically significant difference between both groups, whereas the smallest trial (n=30) showed a clinical significant difference in favour of low-dose concentration.

Moderate quality evidence from 1 RCT with 148 people with cystic fibrosis ≥6 years showed no clinically significant difference in the lung function (measured as % change in FEV_1) between the group of participants receiving 7% sodium chloride and those who were receiving 0.9% sodium chloride at 12, 36 and 48 week follow-ups.

Moderate quality evidence from 1 RCT with 140 people with cystic fibrosis ≥5 years showed a clinically significant improvement in the lung function (measured as % change in FEV_1) in the group of participants receiving 7% sodium chloride compared to those who were receiving 0.9% sodium chloride at 24 week follow-up.

Time to next exacerbation

Moderate quality evidence from 2 RCTs with 453 infants, children, young people and adults with cystic fibrosis showed no clinically significant difference in the time to first pulmonary exacerbation between the group of participants receiving 7% sodium chloride and those who were receiving <3% sodium chloride at 48 week follow-up.

Need for additional intravenous antibiotics for pulmonary exacerbation

High quality evidence from 1 RCT with 321 children with cystic fibrosis ≤6 years showed a clinically significant increase in the number of days of treatment 7% sodium chloride -dose NaCl (7% HS) compared to those who were receiving 0.9% sodium chloride at 48 week follow-up.

Inflammatory markers

No evidence was found for this outcome.

Quality of life

Moderate to high quality evidence from 1 RCT with 132 adults with cystic fibrosis showed no clinically significant difference in the quality of life (measured with CF-QOL physical, burden, health and respiratory domains) between the group of participants receiving 7% sodium chloride and those who were receiving 3% sodium chloride at hospital discharge and at 7 week follow-up.

Low to moderate quality evidence from 1 cross-over trial with 20 children and young people with cystic fibrosis aged 6 to 18 years showed no clinically significant difference in the quality of life (measured with CFQ-R 14+ or CFQ-R parent respiratory domain) between the group of participants receiving 7% sodium chloride and those who were receiving 0.9% sodium chloride at 4 week follow-up.

High quality evidence from 1 RCT with 67 people with cystic fibrosis ≥6 years showed no clinically significant difference in the quality of life (measured as change in CFQ-R parents) between the group of participants receiving 7% sodium chloride and those who were receiving 0.9% sodium chloride at 48 week follow-up.

Moderate quality evidence from 1 RCT with 92 people with cystic fibrosis ≥6 years showed a clinically significant beneficial effect in the quality of life (measured as change in CFQ-R 14+) in the group of participants receiving 7% sodium chloride compared to those who were receiving 0.9% sodium chloride at 48 week follow-up.

Moderate quality evidence from 1 RCT with 321 children with cystic fibrosis ≤6 years showed no clinically difference in the quality of life (measured as change in CFQ-R respiratory) between the group of participants receiving 7% sodium chloride compared and those who were receiving 0.9% sodium chloride at 48 week follow-up.

Adverse events

No evidence was found for this outcome.

9.3.6.3.2 Comparison 3.2. Nebulised sodium chloride versus acetylcysteine

No evidence was found for this comparison.

9.3.6.4 Acetylcysteine

9.3.6.4.1 Comparison 4. Acetylcysteine versus placebo

Lung function: FEV_1

Very low quality evidence from 1 RCT with 21 adults with cystic fibrosis showed no clinically significant difference in the lung function (measured as change in FEV_1 % predicted) between the participants receiving acetylcysteine (2400 mg per day) and those receiving placebo at 4 week follow-up

Low quality evidence from 1 RCT with 22 children and young people with cystic fibrosis aged 6 to 21 years showed no clinically significant difference in the lung function (measured as change in FEV_1 % predicted) between the participants receiving acetylcysteine (200 mg x 3 times per day) and those receiving placebo at 12 week follow-up.

Similarly, moderate quality evidence from 1 RCT with 70 people with cystic fibrosis >9 years showed no clinically significant difference in the lung function (measured as change in FEV_1 % predicted) between the participants receiving acetylcysteine (900mg/ 3 times per day) and those receiving placebo at 24 week follow-up.

Time to next exacerbation

No evidence was found for this outcome.

Incidence of exacerbations (proxy outcome for need for additional intravenous antibiotics for pulmonary exacerbation)

Low quality evidence from 1 RCT with 70 people with cystic fibrosis >9 years showed no clinically significant difference in the incidence of pulmonary exacerbations between the participants receiving acetylcysteine (900mg/ 3 times per day) and those receiving placebo at 24 week follow-up.

Inflammatory markers

High quality evidence from 1 RCT with 70 people with cystic fibrosis >9 years showed no significant difference in the inflammatory markers (measured as sputum IL-8 log10) between the participants receiving acetylcysteine (900mg/ 3 times per day) and those receiving placebo at 24 week follow-up. The uncertainty for this outcome could not be calculated.

Quality of life

Low quality evidence from 1 RCT with 70 people with cystic fibrosis >9 years showed no clinically significant difference in the quality of life (measured with CFQ-R respiratory domain) between the participants receiving acetylcysteine (900mg/ 3 times per day) and those receiving placebo at 24 week follow-up.

Adverse events

No evidence was found for this outcome.

9.3.6.5 Economic evidence statements

One cost-benefit analysis (Menzin 1996) undertaken in the UK, on people with cystic fibrosis, found that daily dornase alfa may reduce the cost of respiratory tract infection related care compared to placebo, over 24 weeks. This analysis is partially applicable as clinical effectiveness data was taken from an old US trial that may reflect outdated practices and

practices that may not be generalisable to the UK. The evidence was also associated with very serious limitations including the omission of dornase alfa in their costs.

One cost-effectiveness analysis (Christopher 1999) undertaken in the UK, on people with cystic fibrosis, using a lifetime horizon, found that the cost per life year gained for daily dornase alfa compared to placebo was £52,550 for all participants and £16,110 for the subgroup of participants with FEV1≤70%. This analysis is partially applicable with very serious limitations, namely as clinical effectiveness data was taken from an old US trial that may reflect outdated practices and practices that may not be generalisable to the UK.

One cost-benefit analysis (McIntyre 1996) undertaken in the UK, on people with cystic fibrosis, using a lifetime horizon, found that the cost per life year gained for daily dornase alfa compared to placebo could range from £10,311 to £45,234. This analysis is partially applicable with very serious limitations, namely as clinical effectiveness data was taken from an old US trial that may reflect outdated practices and practices that may not be generalisable to the UK.

One cost-benefit analysis (Suri 2002) on people with cystic fibrosis in the UK, over 12 weeks, found that daily dornase alfa was more effective than hypertonic saline, but significantly increased health care costs. Administering dornase alfa on alternate days, rather than daily, was as effective, with a potential for cost savings. This analysis is partially applicable with minor limitations.

One cost-effectiveness analysis (Grieve 2003) on people with cystic fibrosis in the UK found that the cost per 1% gain in FEV1% over 12 weeks, for daily dornase alpha compared to hypertonic saline was £110; for daily dornase alfa compared to alternate day dornase alfa £214 and for alternate day dornase alfa compared to hypertonic saline £89. This analysis has minor limitations and is directly applicable given that the type of economic evaluation is unlikely to change the conclusions about cost-effectiveness and all other applicability criteria are met.

One cost-utility analysis (NICE TA266) on people with cystic fibrosis in the UK using a lifetime horizon, found that the ICER for mannitol compared to best supportive care was £41,074 and for mannitol plus dornase alfa compared to best supportive care plus dornase alfa £47,095. Amendments to the original analysis found that mannitol plus dornase alfa compared dornase alfa plus best supportive care for people with cystic fibrosis using dornase alfa (i.e. mannitol as add-on therapy) produced an ICER of £80,098. For mannitol compared to best supportive care for people with cystic fibrosis who are ineligible, intolerant or inadequately responsive to rhDNase (i.e. mannitol as second-line therapy) the ICER was £29,883. This analysis is directly applicable. The initial analysis is associated with serious limitations as both comparisons use clinical effectiveness data taken from the whole adult population, irrespective of dornase alfa use which underestimates the effectiveness of dornase alfa use.

9.3.7 Evidence to recommendations

9.3.7.1 Relative value placed on the outcomes considered

The aim of this review was to establish the clinical and cost effectiveness of mucoactive or mucolytic agents in improving airway clearance in children, young people and adults with cystic fibrosis.

The committee identified lung function (FEV_1% predicted), time to pulmonary exacerbation and the need for intravenous antibiotics for pulmonary exacerbation as critical outcomes for this evidence review. Where no evidence was found for time to pulmonary exacerbation, the number of people experiencing a pulmonary exacerbation was taken as a proxy outcome. Inflammatory markers, quality of life and adverse events were rated as important outcomes.

9.3.7.2 Consideration of clinical benefits and harms

The committee discussed whether a mucoactive or mucolytic agent should be prescribed to everyone who has cystic fibrosis. However, taking into account the potential adverse effects, as well as the inconvenience and the cost of treatment, it was agreed not to recommend it to everyone. Instead, the committee agreed that it should be offered to people with cystic fibrosis who have clinical evidence of lung disease based on radiological imaging or lung function testing.

The committee reviewed the evidence comparing dornase alfa to placebo, which shows significant differences in FEV_1 in favour of dornase alfa at 1, 3, 6 and 24 month follow-ups, but also a lack of significant differences in FEV_1 in people with severe lung disease at 1 month follow-up.

The committee discussed the evidence comparing nebulised sodium chloride with control (0.9%) or low-concentration (< 3%). After reviewing the conflicting evidence comparing 7% sodium chloride to 0.9% sodium chloride, the committee relied on their expertise and experience to recommend hypertonic sodium chloride instead of isotonic sodium chloride. The committee also reviewed the evidence comparing 7% sodium chloride to 3% sodium chloride. A moderate quality RCT found a clinically significant improvement in FEV_1 in the group of participants receiving 7% sodium chloride compared to those who were receiving 3% sodium chloride at 2 and 4 week follow-ups. It was discussed whether a specific concentration of hypertonic sodium chloride should be specified in the recommendations. The committee concluded that it was appropriate not to mention a specific concentration because the highest concentration tolerable for the individual patient should be used (to maximum 7%).

The committee reviewed the evidence comparing acetylcysteine to placebo. Very low to moderate quality evidence showed no clinically significant differences in FEV_1 between acetylcysteine and placebo at 4, 12 and 24 week follow-ups. Likewise, low quality evidence showed no differences in need for additional intravenous antibiotics for pulmonary exacerbation at 24 week follow-up. No clinically significant differences were found in inflammatory markers or quality of life either. The committee also noted that acetylcysteine was not commonly used in clinical practice because of the unpleasant smell and taste. Moreover, acetylcysteine needs to be taken up to 4 times a day, so overall it is less tolerable and more burdensome than other mucoactive agents. Based on this, the committee agreed not to make a recommendation in favour of acetylcysteine.

The committee was aware of the NICE TA266 that provides guidance on the use of mannitol dry powder for inhalation for the treatment of cystic fibrosis in adults. Therefore data on mannitol was stratified by age to allow the committee to consider the evidence on children and young people separately from the evidence on adults. The committee discussed the recommendations from NICE TA266 and agreed that mannitol could be recommended as an option in adults who cannot use dornase alfa because of ineligibility, intolerance or inadequate response, and in those whose lung function is rapidly declining (FEV_1 decline greater than 2% annually) for whom other osmotic agents are not considered appropriate. They agreed that people currently receiving mannitol whose cystic fibrosis does not meet the cited criteria should be able to continue treatment until they, and their clinician, consider it appropriate to stop. Therefore, the committee adopted these recommendations from NICE TA266.

The committee discussed the use of mannitol in children and young people. Overall the evidence did not show mannitol to have significant clinical benefit nor harm. The committee noted that mannitol is rarely used in clinical practice in children and young people. They were aware of issues of poor tolerability and difficulties with the inhaler device in children and young people. The committee agreed that mannitol may be an option for children and young people when rhDNase and hypertonic sodium chloride have failed or are not tolerated and so made a recommendation to this effect.

The committee reviewed the evidence comparing nebulised dornase alfa to hypertonic sodium chloride, which showed significant differences in FEV_1 in favour of dornase alfa at 3 month follow-up but not at 3 week follow-up. The evidence was low or very low quality. Due to the limited evidence, the committee relied on their expertise and experience to guide their decision as to whether dornase alfa or hypertonic sodium chloride should be the first-line treatment. On balance, they agreed that dornase alfa was more effective and tolerable, and insufficient evidence was presented to change currently accepted practice. Therefore, the committee recommended dornase alfa as first choice treatment and hypertonic sodium chloride as second choice treatment.

The committee recommended using hypertonic sodium chloride (alone or in combination with dornase alfa) if there is an inadequate response to dornase alfa, based on clinical assessment or lung function testing. The committee noted that treatment should be tailored to the individual, taking into account their previous experience of mucoactive agents and any previously demonstrated efficacy.

The committee discussed whether separate recommendations on dornase alfa and hypertonic sodium chloride were needed for different age groups. However, they concluded that the choice of mucoactive agent would not differ based on age group in current practice and noted that some studies did not present data disaggregated by age subgroups.

No evidence was found for children under 5 years in the evidence review. The committee noted that dornase alfa is not licensed for this age group, however, it is current practice to prescribe dornase alfa to children under 5.

9.3.7.3 Consideration of economic benefits and harms

The economic evidence found that dornase alfa was more expensive and more effective than placebo. Although those subjective measures of cost-effectiveness cannot be compared to NICE's threshold, the committee concluded that the evidence did not infer dornase alfa was cost-ineffective in order to warrant a change in current clinical practice. Furthermore, the clinical evidence showed clinically significant improvements in participants receiving dornase alfa compared to those receiving placebo, providing evidence that the benefits of dornase alfa could justify the costs. The committee also added that there is some evidence that early use of dornase alfa is associated with better survival rates. Therefore, despite the high acquisition cost of dornase alfa, the committee believed, based on the evidence, their knowledge and expertise, that a recommendation in favour of dornase alfa as the first-line treatment would be a cost-effective use of resources.

In light of the economic evidence from Suri 2002 and Grieve 2003, the committee agreed that substantial cost savings could be made by reducing dornase alfa from once daily (current practice in England) to alternate day use. However, the committee noted that the trial by Suri 2002 aimed to identify a change in FEV_1% and was not powered to measure a change in exacerbations, which have a greater treatment cost and impact on health-related quality of life. The committee noted that alternate day use is encouraged in Wales based on the findings in those studies, but agreed that additional research was needed to justify a deviation to the licensed dose.

For these reasons, the committee agreed that a research recommendation should be made to analyse the clinical and cost-effectiveness of once daily dornase alfa compared to alternate day dornase alfa. To acknowledge this uncertainty, the committee did not state whether dornase alfa should be offered daily or on alternate days in their recommendation, given that potential cost savings from alternate day use should not be discouraged, where they are considered effective.

It was noted that a high proportion of the participants in the trial by Suri 2002 were already receiving dornase alfa at enrolment. When questioned if hypertonic sodium chloride should be used as a first-line treatment, the committee stated that dornase alfa and hypertonic

sodium chloride have different mechanisms of action and there was clinical and cost-effective evidence to suggest that the former should be targeted first. The committee also highlighted that the unpleasant taste and experience of hypertonic saline can lead to poor adherence, subsequently reducing the potential benefits of treatment.

However, the committee agreed that when dornase alfa begins to stabilise respiratory symptoms, there was a role for hypertonic sodium chloride as an add-on, or second-line therapy to dornase alfa, to improve their symptoms, before more costly treatment (mannitol) is considered. The committee stated higher concentrations of hypertonic sodium chloride are more effective than lower concentrations; although higher concentrations are less well tolerated. Given the unit cost of hypertonic sodium chloride (£0.45 per 4ml, NHS Electronic Drug Tariff November 2016) is equivalent regardless of concentration (7%, 6% or 3%) the committee wanted to recommend the highest tolerable concentration, before mannitol is considered.

When presented with the HTA on mannitol (NICE TA266) in adults, the committee acknowledged that the appraisal committee did not find mannitol to be cost-effective as add-on therapy to dornase alfa in all adults with cystic fibrosis. However, the committee accepted the population identified by the appraisal committee (adults with cystic fibrosis for whom hypertonic saline is not considered appropriate, who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase and whose lung function is rapidly declining) as a cost-effective use of resources. Following this, the committee agreed a recommendation in favour of dornase alfa as first-line therapy and hypertonic as the subsequent add-on, or second line therapy, would reflect the sequence of treatments inferred from the HTA.

The committee noted that the cost-effectiveness of mucoactive agents would not differ between children and adults, referring to the clinical evidence did not find any important differences between age groups. However, given that the HTA (NICE TA266) on mannitol was explicitly for adults, the committee agreed a recommendation in children and young people should be considered to prevent potentially cost-ineffective practices from a relatively expensive treatment. Subsequently, the committee noted there was no significant clinical evidence in favour of mannitol over control in children and young people with cystic fibrosis. Combined with the committee's experience that mannitol is poorly tolerated and unlikely to provide additional benefits compared to nebulised treatments such as hypertonic saline that are cheaper and easier to administer, the committee concluded that mannitol would only be considered as a cost-effective option in children and young people when all other options have failed. As a result, the committee included a recommendation to consider mannitol in children and young people when other options provide an inadequate response or are not tolerated, to reflect current practice.

The committee advised that unlike dornase alfa, acetylcysteine is not as well tolerated and is more burdensome to take which may reduce its effects. Moreover, despite the low acquisition cost of acetylcysteine, the clinical evidence review found no significant benefits compared to placebo to make a recommendation in favour of acetylcysteine. As a result, the committee agreed that the use of acetylcysteine would depend on clinical judgement and did not make a recommendation on its use.

Following the review of the clinical and economic evidence, the committee concluded that additional economic analysis in this area would have limited value to influence their recommendations given that current practice, inferred largely by NICE TA266, was followed. Following this, the committee iterated the importance of a research recommendation to identify the most clinical and cost effectiveness dose of dornase alfa in people with cystic fibrosis.

9.3.7.4 Quality of evidence

The quality of the evidence presented in this report ranged from very low to high as assessed by GRADE. The main reasons that led to downgrading the quality of the evidence were:

- For the domain risk of bias, the studies were assigned the same risk of bias as in the Cochrane reviews and were not individually reviewed. The main biases that lead to downgrading the quality of the evidence were selection, attrition, and reporting bias.
- Another reason that lead to downgrading the quality of the evidence was the imprecision, as confidence intervals crossed 1 or 2 clinical or default MIDs.
- High heterogeneity was also a reason to downgrade the quality of the evidence. The committee noted some studies were underpowered to detect differences between groups.

With regards to indirectness, the committee noted that the participants in the trials comparing mannitol versus placebo, mannitol versus dornase alfa and mannitol + dornase alfa versus dornase alfa alone had undergone a tolerance test at screening. Those who failed were not entered in the studies and this limits the generalisability of the results to the general cystic fibrosis population. No serious issues were found regarding the directness of the population or intervention for the other comparisons.

9.3.7.5 Other considerations

No equality issues were identified by the committee for this review question.

The committee agreed to draft a research recommendation for this topic. They noted the trial by Suri 2002 (comparing daily dornase alfa, alternate day dornase alfa and hypertonic saline) was underpowered to detect a difference in the number of exacerbations. They discussed that reducing the dose, for example from once daily to alternate day dornase alfa, would reduce the burden of treatment and potentially increase adherence. In addition, substantial cost savings are also anticipated.

In certain circumstances medicines are prescribed outside their licensed indications (off-label use) to children and young people because the clinical need cannot be met by licensed medicines, for example, for an indication not specified in the marketing authorisation, or administration of a different dose. At the time of publication (October 2017), rhDNase did not have a UK marketing authorisation for use in children with cystic fibrosis for this indication. However, the Standing Committee on Medicines has issued a policy statement on the use of unlicensed medicines and the use of licensed medicines for unlicensed indications in children and young people. This states clearly that such use is necessary in paediatric practice and that doctors are legally allowed to prescribe medicines outside their licensed indications where there are no suitable alternatives and where use is justified by a responsible body of professional opinion.

It was noted that in the management of chronic infections a smaller pack size of drug may be available to assess the initial effects of the treatment (test dose), so as to minimise the potential for waste. Where a test pack is not available, the manufacturer may be able to offer alternative solutions to prevent waste in the event of a failed test dose. Without this test pack healthcare professionals may need to open a month’s treatment to assess the effects and tolerance in each patient. However, the aim to reduce pharmacy waste is not exclusive to cystic fibrosis and should be considered as good practice in all disease areas.

The role of CFTR modulators were not included in the scope as current clinical practice in this area was considered to be consistent and effective, relative to the other areas under consideration. For completeness, a recommendation referring to the NICE technology appraisal on lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation was added.

9.3.7.6 Key conclusions

The committee concluded that a mucoactive agent should be given to everyone who has respiratory symptoms or other evidence of lung disease. They agreed rhDNase should be recommended as first-line treatment and hypertonic sodium chloride as second-line treatment. The guideline should recommend hypertonic sodium chloride instead of isotonic sodium chloride, but should not mention the concentration of hypertonic sodium chloride. They agreed that Mannitol dry powder should be recommended to adults that fulfil the criteria outlined by the HTA (NICE TA266) and should be considered as third line treatment only for children and young people if inadequate response or intolerability to rhDNase and hypertonic sodium chloride.

9.3.8 Recommendations

56. **Offer a mucoactive agent to people with cystic fibrosis who have clinical evidence of lung disease.**

57. **Offer rhDNase (dornase alfa; recombinant human deoxyribonuclease)[1] as the first choice of mucoactive agent.**

58. **If clinical evaluation or lung function testing indicates an inadequate response to rhDNase, consider both rhDNase[2] and hypertonic sodium chloride or hypertonic sodium chloride alone.**

59. **Consider mannitol dry powder for inhalation[3] for children and young people who cannot use rhDNase and hypertonic sodium chloride because of ineligibility, intolerance or inadequate response.**

60. **Mannitol dry powder for inhalation is recommended as an option for treating cystic fibrosis in adults:**
    - who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase and
    - whose lung function is rapidly declining (forced expiratory volume in 1 second [FEV1] decline greater than 2% annually) and
    - for whom other osmotic agents are not considered appropriate.

    [This recommendation is from Mannitol dry powder for inhalation for treating cystic fibrosis (NICE technology appraisal 266).]

61. **People currently receiving mannitol whose cystic fibrosis does not meet the criteria in recommendation 56 should be able to continue treatment until they and their clinician consider it appropriate to stop.**

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[1] At the time of publication (October 2017), rhDNase did not have a UK marketing authorisation for use in children under 5 years of age with cystic fibrosis. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[2] At the time of publication (October 2017), rhDNase did not have a UK marketing authorisation for use in children under 5 years of age with cystic fibrosis for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information

[3] At the time of publication (October 2017), rhDNase did not have a UK marketing authorisation for use in children with cystic fibrosis for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information

[This recommendation is from Mannitol dry powder for inhalation for treating cystic fibrosis (NICE technology appraisal 266).]

62. **For guidance on using lumacaftor–ivacaftor, see the NICE technology appraisal on lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation.**

9.3.9 Research recommendations

3. **What is the most clinically and cost-effective dose of rhDNase (dornase alfa; recombinant human deoxyribonuclease) for people with cystic fibrosis?**

Table 86: Research Recommendation justification

Research question	**What is the most clinical and cost effective dose of rhDNase (dornase alfa; recombinant human deoxyribonuclease) for people with cystic fibrosis?**
Why this is needed	
Importance to 'patients' or the population	Taking daily dornase alfa increases the treatment burden on people with cystic fibrosis who already have complex treatment schedules, including multiple nebulised treatments. It is essential that parents, carers and people with cystic fibrosis are reassured that this dosing frequency is necessary to provide clinical benefit. Parents, carers and people with cystic fibrosis frequently report that reducing the treatment frequency burden increases overall adherence and this will improve the treatment effect. There is some evidence that alternate day dornase alfa is as effective as daily administration, if this is confirmed then overall treatment adherence may improve and moreover cost savings would be made. There is also some evidence that early use of dornase alfa is associated with better survival rates; hence, if alternate day dornase alfa was an option this would potentially lower the threshold for its use.
Relevance to NICE guidance	With this evidence, a definitive recommendation could be made regarding dosing frequency – at present there is varied clinical practice between England and Wales.
Relevance to the NHS	Further evidence in this area will eliminate the need to provide an intense treatment schedule 'just in case' it improves respiratory symptoms. There will be a financial advantage if administration frequency can be reduced in the future.
National priorities	Research priorities from the James Lind Alliance highlighted reducing treatment burden as a priority which would fit with this, in addition to its economic advantages.
Current evidence base	The current evidence base includes mostly small, underpowered, short-term trials with limited methodological rigour and are unable to draw conclusions regarding the long-term impact of dornase alfa in people with cystic fibrosis. Most of the studies assess the licensed dose in people who are not naïve to treatment. There is insufficient evidence as yet to answer the question whether reduced dosing frequency of dornase alfa as a first-line treatment is cost-effective, in people with cystic fibrosis who have respiratory symptoms.
Equality	None
Feasibility	The proposed research can be carried out within a realistic timescale and at an acceptable cost. There are no ethical or technical issues.

Research question	**What is the most clinical and cost effective dose of rhDNase (dornase alfa; recombinant human deoxyribonuclease) for people with cystic fibrosis?**
Other comments	If improvements on alternate day dornase alfa are similar to that given daily, it may be cost-effective to titrate the dose further.

Table 87: Research Recommendation Statements

Criterion	Explanation
Population	People with a diagnosis of cystic fibrosis with respiratory symptoms
Intervention	Once daily dornase alfa (2.5 mg)
Comparators	Reduced dosing frequency of dornase alfa, including alternate day dornase alfa (2.5 mg)
Outcomes	• Hospitalisations, change in frequency • Pulmonary exacerbations, change in frequency and severity • Lung function (FEV_1, FVC) • Quality of Life (using a validated tool, such CFQ-R or CF-QOL) • Patient preference • Adverse events • Resource use • Unit costs
Study design	Multicentre RCT
Timeframe	Five years of randomisation and 5 year of follow up, providing recruitment numbers are sufficient to achieve population numbers of sufficient size to answer the research question.

9.4 Pulmonary Infection

Pulmonary infection is the cause of much of the morbidity and mortality associated with cystic fibrosis.

Antimicrobial treatment strategies aim to prevent acquisition of infection, eradicate early infection and suppress chronic respiratory infections where chronic infection ensues from organisms with known or suspected pathogenicity. There is a low threshold to treat respiratory infection. To minimise the risk of antimicrobial resistance, treatment is guided and informed by known or expected microbiological results, based on local surveillance data where necessary.

Chronic infection with *P aeruginosa* and *B cepacia* complex leads to a worsening clinical picture, a reduction in respiratory function, more hospital admissions and increased treatment costs. Prompt and aggressive treatment of these organisms is therefore imperative for first and recurrent isolates following a period free from infection.

The scope of these review questions is to review the evidence in people with cystic fibrosis for the prevention of *S aureus* infection and the treatment of respiratory exacerbations and chronic infection caused by *S aureus*, *P aeruginosa*, *B cepacia* complex and *Aspergillus* species.

This chapter will also review evidence for the use of antifungal treatments. The use of antifungal agents is increasing in the management of cystic fibrosis with recognition that fungi such as *Aspergillus* spp may lead to infection as well as a damaging immune response associated with allergic bronchopulmonary aspergillosis.

Other organisms such as *Achromobacter xylosoxidans* and *Stenotrophomonas maltophilia* are encountered in people with cystic fibrosis. These have a relatively lower prevalence and are beyond the scope of this current guideline.

9.4.1 Prophylaxis

Review question: What is the effectiveness of long-term antimicrobial prophylaxis to prevent pulmonary bacterial colonisation with *S aureus* in people with CF?

9.4.1.1 Description of clinical evidence

The aim of this review was to compare the clinical and cost effectiveness of various antimicrobials given as long-term prophylaxis (for more than 3 months) against bacterial infection in people with cystic fibrosis.

We searched for systematic reviews of RCTs and RCTs aimed at assessing the effectiveness of long-term antimicrobial prophylaxis to prevent pulmonary bacterial infection with *S aureus* in people with cystic fibrosis. Cross-over trials were not considered for inclusion, as this study design does not allow evaluation of the effects of prophylaxis on long-term outcomes measures.

For full details see review protocol in Appendix D.

Two systematic reviews were identified for potential inclusion in this review (McCaffery 1999, Smyth 2014).

One systematic review (McCaffery 1999) was finally excluded as the quality was assessed as low according to AMSTAR checklist (score of 5 out of 11). The individual studies included in this review were checked for potential inclusion.

One Cochrane systematic review (Smyth 2014) was included as the quality was assessed as high according to AMSTAR checklist (score of 10 out of 11). This systematic review included 4 RCTs (Chatfield 1991, Schlesinger 1984, Stutman 2002, Weaver 1994, Beardsmore 1995). One study (Schlesinger 1984) was excluded from our review as it included treatments that were not specified in the evidence review protocol and it did not report on any outcomes of interest.

The data and risk of bias assessment from the systematic review were used where possible. The individual studies were also retrieved full copy for completeness. Data for other outcomes of interests included in the protocol, but not included in the Cochrane SR, was directly extracted from the individual studies.

No further studies were identified in our search.

With regards to the population, the studies included in the Cochrane review included infants or small children (under 2 years) with confirmed cystic fibrosis.

The trials compared the effectiveness of long-term prophylactic antibiotic treatment with placebo and treatment “as required”. The treatments evaluated included continuous oral Flucloxacillin and continuous oral Cephalexin.

In relation to the outcomes, evidence was found for number of children who *S aureus* was identified at least once; lung function, measured as FEV_1, minor adverse events and identification of *P aeruginosa*. Where no evidence was retrieved for time to next pulmonary exacerbation, number of children experiencing a pulmonary exacerbations and number of children requiring hospitalisation due to infection was taken as a proxy outcome.

No results were identified for time to identification of *S aureus*, major adverse events and emergence of the resistant organisms.

Evidence from these are summarised in the clinical GRADE evidence profile below (Table 89 and Table 90). See also the study selection flow chart in Appendix F, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix H.

9.4.1.2 Summary of included studies

A summary of the studies that were included in this review are presented in Table 88.

Table 88: Summary of included studies

Study	Intervention/ Comparison	Population	Outcomes	Comments
Cochrane systematic reviews				
Smyth 2014 Cochrane SR	Intervention Prophylactic anti-staphylococcal antibiotic + antibiotic 'as required' Comparison Placebo + antibiotic 'as required'	People with a confirmed diagnosis of cystic fibrosis, of any age.	• Number of positive pathogen cultures (*S aureus*) identified during study period - measured as number of children from whom *S aureus* was isolated at least once by year of age (n/N) • Lung function measured as FEV_1 • Evidence of inflammation in CT scan - Proxy outcome, X-ray scores (Crispin-Norman score at 1.3 years) • Pulmonary exacerbation - Proxy outcome, number of children requiring admission • Adherence to treatment • Adverse events, minor events • Number of children in whom *P aeruginosa* was identified	SR AMSTAR score: 10/11
Primary studies included in the Cochrane SR				
Chatfield 1991 (UK) RCT	Intervention • Continuous oral Flucloxacillin Comparison Placebo + antibiotic 'as required'	Infants with a confirmed diagnosis of cystic fibrosis. Age: not reported •	• Number of positive pathogen cultures (*S aureus*) identified during study period - measured as number of children from whom *S aureus* was isolated at least once by year of age (n/N) • Evidence of inflammation in CT scan (only for < 5 yrs) - Proxy outcome, X-ray scores (Crispin-Norman score at 1.3 years) • Pulmonary exacerbation - Proxy outcome,	Included in Smyth 2014

Study	Intervention/ Comparison	Population	Outcomes	Comments
			number of children requiring admission (annualised rates) • Number of children in whom *P aeruginosa* was identified	
Stutman 2002 (USA) RCT	Intervention • Continuous cephalexin Comparison Placebo + antibiotic 'as required'	Infants and children with a confirmed diagnosis of cystic fibrosis. Age: 4 to 24 months •	• Number of positive pathogen cultures (*S aureus*) identified during study period - measured as number of children from whom *S aureus* was isolated at least once by year of age (n/N) • Lung function - measured as FEV_1 at 6 years • Pulmonary exacerbation - Proxy outcome, number of children requiring admission (annualised rates) • Minor adverse events, including generalised rash, nappy rash, increased stool frequency • Number of children in whom *P aeruginosa* was identified	Included in Smyth 2014
Weaver 1994 (UK) RCT	Intervention • continuous oral Flucloxacillin Comparison Placebo + antibiotic 'as required'	Infants with a confirmed diagnosis of cystic fibrosis, of any age. Age: not reported •	• Number of positive pathogen cultures (*S aureus*) identified during study period - measured as number of children from whom *S aureus* was isolated at least once by year of age (n/N) • Pulmonary exacerbation - Proxy outcome, number of children requiring admission (annualised rates) • Number of children in whom *P aeruginosa* was identified	Included in Smyth 2014 Additional data obtained from Beardsmore 1995

AB: antibiotics; SR: systematic review

9.4.1.3 Clinical evidence profile

The summary clinical evidence profiles for this review question are presented in Table 89 and Table 90.

Table 89: Summary clinical evidence profile: Comparison 1. Continuous oral Flucloxacillin versus antibiotics 'as required'

Comparison 1. Continuous oral Flucloxacillin versus antibiotics 'as required'						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Control	**Continuous oral Flucloxacillin, antibiotic prophylaxis**				
Number of children from whom *S aureus* isolated at least once Follow-up: mean 1 year	373 per 1000	201 per 1000 (101 to 395)	RR 0.54 (0.27 to 1.06)	96 (Chatfield 1991)	⊕⊖⊖⊖ very low[1,2]	
Number of children from whom *S aureus* isolated at least once Follow-up: mean 2 years	Study population		RR 0.44 (0.25 to 0.77)	149 (Chatfield 1991, Weaver 1994)	⊕⊕⊖⊖ low[3]	
	425 per 1000	187 per 1000 (106 to 327)				
	Moderate					
	483 per 1000	213 per 1000 (121 to 372)				
Number of children from whom *S aureus* isolated at least once Follow-up: mean 3 years	431 per 1000	224 per 1000 (125 to 392)	RR 0.52 (0.29 to 0.91)	119 (Chatfield 1991)	⊕⊖⊖⊖ very low[1,2]	
Number of children from whom *P aeruginosa* isolated at least once Follow-up: mean 1 year	59 per 1000	136 per 1000 (36 to 514)	RR 2.32 (0.62 to 8.73)	95 (Chatfield 1991)	⊕⊖⊖⊖ very low[1,4]	
Number of children from whom *P aeruginosa* isolated at least once Follow-up: mean 2 years	Study population		RR 0.74 (0.34 to 1.61)	149 (Chatfield 1991, Weaver 1994)	⊕⊖⊖⊖ very low[3,4]	
	175 per 1000	129 per 1000 (60 to 282)				
	Moderate					
	217 per 1000	161 per 1000 (74 to 349)				
Number of children from whom *P aeruginosa* isolated at least once Follow-up: mean 3 years	212 per 1000	168 per 1000 (78 to 354)	RR 0.79 (0.37 to 1.67)	120 (Chatfield 1991)	⊕⊖⊖⊖ very low[1,4]	
Number of children requiring admission due to pulmonary exacerbations	333 per 1000	327 per 1000 (197 to 540)	RR 0.98 (0.59	124 (Chatfield 1991,	⊕⊖⊖⊖ very low[3,4]	

Comparison 1. Continuous oral Flucloxacillin versus antibiotics 'as required'						
(annualised rates) Follow-up: mean 3 years			to 1.62)	Weaver 1994)		
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio						

1 The quality of the evidence was downgraded by 2 as this study was rated as high risk of bias (Cochrane review Smyth 2014)
2 The quality of the evidence was downgraded by 1 as the 95% CI crosses 1 default MID
3 The quality of the evidence was downgraded by 2 as these studies was rated as high and moderate risk of bias (Cochrane review Smyth 2014)
4 The quality of the evidence was downgraded by 2 as the 95% CI crosses 2 default MIDs

Table 90: Summary clinical evidence profile: Comparison 2. Continuous oral Cephalexin versus antibiotics 'as required'

Comparison 2. Continuous oral Cephalexin versus antibiotics 'as required'						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Antibiotics 'as required'	**Continuous oral Cephalexin, antibiotic prophylaxis**				
Number of children from whom *S aureus* isolated at least once Respiratory cultures Follow-up: mean 1 years	468 per 1000	145 per 1000 (79 to 266)	RR 0.31 (0.17 to 0.57)	152 (Stutman 2002)	⊕⊕⊕⊖ moderate[1]	
Number of children from whom *S aureus* isolated at least once Respiratory cultures Follow-up: mean 2 years	658 per 1000	217 per 1000 (145 to 336)	RR 0.33 (0.22 to 0.51)	166 (Stutman 2002)	⊕⊕⊕⊖ moderate[2]	
Number of children from whom *S aureus* isolated at least once Respiratory cultures Follow-up: mean 3 years	688 per 1000	289 per 1000 (199 to 406)	RR 0.42 (0.29 to 0.59)	141 (Stutman 2002)	⊕⊕⊕⊖ moderate[3]	
Number of children from whom *S aureus*	839 per 1000	352 per 1000 (252 to 495)	RR 0.42	127	⊕⊕⊕⊖ moderate[4]	

Comparison 2. Continuous oral Cephalexin versus antibiotics 'as required'						
isolated at least once Respiratory cultures Follow-up: mean 4 years			(0.3 to 0.59)	(Stutman 2002)		
Number of children from whom *S aureus* isolated at least once Respiratory cultures Follow-up: mean 5 years	850 per 1000	348 per 1000 (238 to 501)	RR 0.41 (0.28 to 0.59)	98 (Stutman 2002)	⊕⊕⊖⊖ low[5]	
Number of children from whom *S aureus* isolated at least once Respiratory cultures Follow-up: mean 6 years	778 per 1000	280 per 1000 (140 to 552)	RR 0.36 (0.18 to 0.71)	43 (Stutman 2002)	⊕⊕⊖⊖ low[6]	
Lung function FEV_1 Follow-up: mean 6 years	The mean lung function in the control group was 115.8	The mean lung function in the intervention groups was 2.3 lower (13.59 lower to 8.99 higher)		119 (Stutman 2002)	⊕⊖⊖⊖ very low[7,8]	
Any pulmonary exacerbations % Follow-up: mean 6 years	The mean number of pulmonary exacerbation in the control group was 66.8	The mean number of pulmonary exacerbations in the intervention groups was 4.9 lower (22.24 lower to 12.44 higher)		119 (Stutman 2002)	⊕⊖⊖⊖ very low[7,9]	
Number of children requiring admission due to pulmonary exacerbations (annualised rates) not reported Follow-up: mean 6 years	78 per 1000	74 per 1000 (20 to 260)	RR 0.94 (0.26 to 3.32)	119 (Stutman 2002)	⊕⊖⊖⊖ very low[7,9]	
Adherence to treatment Parents self-report Follow-up: mean 6 years	The mean adherence to treatment in the control groups	The mean adherence to treatment in the intervention groups was 5 higher (0 to 0 higher)		119 (Stutman 2002)	⊕⊕⊕⊖ moderate[7,10]	

Comparison 2. Continuous oral Cephalexin versus antibiotics 'as required'						
	was 85 %					
Minor adverse events - generalised rash Parents self-report Follow-up: mean 6 years	The mean number of generalised rash events in the control group was 0.2	The mean – number of generalised rash events in the intervention groups was 0.4 higher (0.07 lower to 0.87 higher)		119 (Stutman 2002)	⊕⊕⊕⊖ moderate[7]	
Minor adverse events - nappy rash Parents self-report Follow-up: mean 6 years	The mean number of nappy rash events in the control group was 3.1	The mean – number of nappy rash events in the intervention groups was 0.9 higher (1.06 lower to 2.86 higher)		119 (Stutman 2002)	⊕⊕⊕⊖ moderate[7]	
Minor adverse events - increased stool frequency Parents self-report Follow-up: mean 6 years	The mean number of increased stool frequency events in the control group was 4.1	The mean minor increased stool frequency events in the intervention groups was 0.2 higher (2.18 lower to 2.58 higher)		119 (Stutman 2002)	⊕⊕⊕⊖ moderate[7]	
Number of children from whom *P aeruginosa* identified at least once Follow-up: mean 1 years	312 per 1000	358 per 1000 (231 to 564)	RR 1.15 (0.74 to 1.81)	152 (Stutman 2002)	⊕⊖⊖⊖ very low[1,9]	
Number of children from whom *P aeruginosa* identified at least once Follow-up: mean 2 years	506 per 1000	435 per 1000 (314 to 603)	RR 0.86 (0.62 to 1.19)	166 (Stutman 2002)	⊕⊕⊖⊖ low[2,11]	
Number of children from whom *P aeruginosa* identified at least once Follow-up: mean 3 years	594 per 1000	582 per 1000 (445 to 772)	RR 0.98 (0.75 to 1.3)	141 (Stutman 2002)	⊕⊖⊖⊖ very low[3,9]	
Number of children from whom *P*	Study population		RR 1.1 (0.83	127 (Stutman 2002)	⊕⊕⊖⊖ low[4,11]	
	589 per 1000	648 per 1000 (489 to 854)				

Comparison 2. Continuous oral Cephalexin versus antibiotics 'as required'						
aeruginosa identified at least once Follow-up: mean 4 years	Moderate 589 per 1000	648 per 1000 (489 to 854)	to 1.45)			
Number of children from whom *P aeruginosa* identified at least once Follow-up: mean 5 years	550 per 1000	709 per 1000 (512 to 979)	RR 1.29 (0.93 to 1.78)	98 (Stutman 2002)	⊕⊖⊖⊖ very low[5,11]	
Number of children from whom *P aeruginosa* identified at least once Follow-up: mean 6 years	667 per 1000	880 per 1000 (613 to 1000)	RR 1.32 (0.92 to 1.89)	43 (Stutman 2002)	⊕⊖⊖⊖ very low[6,11]	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; MD: mean difference; RR: risk ratio						

1 This study was assessed by the Cochrane review Smyth 2014 as low risk of bias. However, the quality of the evidence was downgraded by 1 for this outcome, as the losses to follow up are over 20% (n=152; N=209).
2 This study was assessed by the Cochrane review Smyth 2014 as low risk of bias. However, the quality of the evidence was downgraded by 1 for this outcome, as the losses to follow up are over 20% (n=166; N=209).
3 This study was assessed by the Cochrane review Smyth 2014 as low risk of bias. However, the quality of the evidence was downgraded by 1 for this outcome, as the losses to follow up are over 20% (n=141; N=209).
4 This study was assessed by the Cochrane review Smyth 2014 as low risk of bias. However, the quality of the evidence was downgraded by 1 for this outcome, as the losses to follow up are over 20% (n=127; N=209).
5 This study was assessed by the Cochrane review Smyth 2014 as low risk of bias. However, the quality of the evidence was downgraded by 2 for this outcome, as the losses to follow up are over 50% (n=98; N=209).
6 This study was assessed by the Cochrane review Smyth 2014 as low risk of bias. However, the quality of the evidence was downgraded by 2 for this outcome, as the losses to follow up are over 50% (n=43; N=209).
7 This study was assessed by the Cochrane review Smyth 2014 as low risk of bias. However, the quality of the evidence was downgraded by 1 for this outcome, as the losses to follow up are over 20% (n=119; N=209).
8 The quality of the evidence was downgraded by 2, as the 95% CI crossed 2 clinical MIDs
9 The quality of the evidence was downgraded by 2, as the 95% CI crossed 2 default MIDs
10 Imprecision is not calculable with the data reported
11 The quality of the evidence was downgraded by 1, as the 95% CI crossed 1 default MID for dichotomous outcomes

9.4.1.4 Economic evidence

No economic evaluations of prophylaxis treatment were identified in the literature search conducted for this guideline. Full details of the search and economic article selection flow chart can be found in Appendix E and F, respectively.

This review question was not prioritised for de novo economic modelling. To aid consideration of cost-effectiveness relevant resource and cost use data are presented in Appendix K.

9.4.1.5 Evidence statements

9.4.1.5.1 Comparison 1. Continuous oral Flucloxacillin versus antibiotics 'as required'

Time to identification of the pathogen (*S aureus*) in sputum culture

No evidence was found for this critical outcome.

Number of positive pathogen cultures (*S aureus*) identified

Very low quality evidence from 1 RCT with 96 infants with cystic fibrosis showed no clinically significant difference in the number of children in whom *S aureus* was identified between the group who were receiving continuous oral Flucloxacillin prophylaxis and the group who were receiving antibiotics 'as required' during the first year of follow-up.

Low quality evidence from 2 RCTs with 149 infants with cystic fibrosis showed that there was a clinically significant lower number of children in whom *S aureus* was identified in the group who were receiving continuous oral Flucloxacillin prophylaxis compared to the group who were receiving antibiotics 'as required' during the first 2 years of follow-up.

Very low quality evidence from 1 RCT with 119 infants with cystic fibrosis showed that there was a clinically significant lower number of children in whom *S aureus* was identified between the group who were receiving continuous oral Flucloxacillin prophylaxis and the group who were receiving antibiotics 'as required' during the first 3 years of follow-up.

Lung function

No evidence was found for this important outcome.

Pulmonary exacerbation

Very low quality evidence from 2 RCTs with 124 infants with cystic fibrosis showed no clinically significant difference in the number of annual hospital admissions due to pulmonary exacerbations between the children who were receiving continuous oral Flucloxacillin prophylaxis and the children who were receiving antibiotics 'as required' during the 3 years follow-up.

Quality of life

No evidence was found for this important outcome.

Minor adverse events

No evidence was found for this important outcome.

Major adverse events

No evidence was found for this important outcome.

Identification of *P aeruginosa*

Very low quality evidence from 1 RCT with 95 infants with cystic fibrosis showed no clinically significant difference in the number of children in whom *P aeruginosa* was identified between the group who were receiving continuous oral Flucloxacillin prophylaxis and the group who were receiving antibiotics 'as required' during the first year of follow-up.

Very low quality evidence from 2 RCTs with 149 infants with cystic fibrosis showed no clinically significant difference in the number of children in whom *P aeruginosa* was identified

between the group who were receiving continuous oral Flucloxacillin prophylaxis and the group who were receiving antibiotics 'as required' during the first 2 years of follow-up.

Very low quality evidence from 1 RCT with 120 infants with cystic fibrosis showed no clinically significant difference in the number of children in whom *P aeruginosa* was identified between the group who were receiving continuous oral Flucloxacillin prophylaxis and the group who were receiving antibiotics 'as required' during the first 3 years of follow-up.

Adherence to treatment

No evidence was found for this important outcome.

Emergence of resistant organisms

No evidence was found for this important outcome.

9.4.1.5.2 Comparison 2. Continuous oral Cephalexin versus antibiotics 'as required'

Time to identification of the pathogen (*S aureus*) in sputum culture

No evidence was found for this critical outcome.

Number of positive pathogen cultures (*S aureus*) identified

Moderate quality evidence from 1 RCT with 152 children with cystic fibrosis < 2 years (n=152) showed that there was a clinically significant lower number of children in whom *S aureus* was identified in the group who were receiving continuous oral Cephalexin prophylaxis compared to the group who were receiving antibiotics 'as required' during the first year of follow-up.

Moderate quality evidence from 1 RCT (n=166) showed that there was a clinically significant lower number of children in whom *S aureus* was identified in the group who were receiving continuous oral Cephalexin prophylaxis compared to the group who were receiving antibiotics 'as required' during the first 2 years of follow-up.

Moderate quality evidence from 1 RCT (n=141) showed that there was a clinically significant lower number of children in whom *S aureus* was identified in the group who were receiving continuous oral Cephalexin prophylaxis compared to the group who were receiving antibiotics 'as required' during the first 3 years of follow-up.

Moderate quality evidence from 1 RCT (n=127) showed that there was a clinically significant lower number of children in whom *S aureus* was identified in the group who were receiving continuous oral Cephalexin prophylaxis compared to the group who were receiving antibiotics 'as required' during the first 4 years of follow-up.

Low quality evidence from 1 RCT (n=98) showed that there was a clinically significant lower number of children in whom *S aureus* was identified in the group who were receiving continuous oral Cephalexin prophylaxis compared to the group who were receiving antibiotics 'as required' during the first 5 years of follow-up.

Low quality evidence from 1 RCT (n=43) showed that there was a clinically significant lower number of children in whom *S aureus* was identified in the group who were receiving continuous oral Cephalexin prophylaxis compared to the group who were receiving antibiotics 'as required' during the 6 years of follow-up.

Lung function: FEV_1

Very low quality evidence from 1 RCT (n=119) showed no clinically significant difference in lung function, measured as FEV_1, between the children who were receiving continuous oral Cephalexin prophylaxis and the children who were receiving antibiotics 'as required' at 6 years follow-up.

Pulmonary exacerbation

Very low quality evidence from 1 RCT (n=119) showed no clinically significant difference in the percentage of pulmonary exacerbations between the children who were receiving continuous oral Cephalexin prophylaxis and the children who were receiving antibiotics 'as required' during the six years follow-up.

Very low quality evidence from 1 RCT (n=119) showed no clinically significant difference in the number of annual hospital admissions due to pulmonary exacerbations between the children who were receiving continuous oral Cephalexin prophylaxis and the children who were receiving antibiotics 'as required' during the 6 years follow-up.

Quality of life

No evidence was found for this important outcome.

Minor adverse events

Moderate quality evidence from 1 RCT (n=119) showed no clinically significant difference in the report of generalised rash, nappy rash and stool frequency between the children who were receiving continuous oral Cephalexin prophylaxis and the children who were receiving antibiotics 'as required' during the 6 year study duration.

Major adverse events

No evidence was found for this important outcome.

Identification of *P aeruginosa*

Very low quality evidence from 1 RCT (n=152) showed no clinically significant difference in the number of children in whom *P aeruginosa* was identified between the group who were receiving continuous oral Cephalexin prophylaxis and the group who were receiving antibiotics 'as required' during the first year of follow-up.

Low quality evidence from 1 RCT (n=166) showed no clinically significant difference in the number of children in whom *P aeruginosa* was identified between the group who were receiving continuous oral Cephalexin prophylaxis and the group who were receiving antibiotics 'as required' during the first 2 years of follow-up.

Very low quality evidence from 1 RCT (n=141) showed no clinically significant difference in the number of children in whom *P aeruginosa* was identified between the group who were receiving continuous oral Cephalexin prophylaxis and the group who were receiving antibiotics 'as required' during the first 3 years of follow-up.

Low quality evidence from 1 RCT (n=127) showed no clinically significant difference in the number of children in whom *P aeruginosa* was identified between the group who were receiving continuous oral Cephalexin prophylaxis and the group who were receiving antibiotics 'as required' during the first 4 years of follow-up.

Very low quality evidence from 1 RCT (n=98) showed no clinically significant difference in the number of children in whom *P aeruginosa* was identified between the group who were

receiving continuous oral Cephalexin prophylaxis and the group who were receiving antibiotics 'as required' during the first 5 years of follow-up.

Very low quality evidence from 1 RCT (n=43) showed no clinically significant difference in the number of children in whom *P aeruginosa* was identified between the group who were receiving continuous oral Cephalexin prophylaxis and the group who were receiving antibiotics 'as required' during the 6 years of follow-up.

Adherence to treatment

Moderate quality evidence from 1 RCT (n=119) showed a higher level of adherence to treatment in the group of children who were receiving continuous oral Cephalexin prophylaxis (85% vs. 80%). The uncertainty around this could not be calculated.

Emergence of resistant organisms

No evidence was found for this important outcome.

9.4.1.5.3 Economic evidence statements

No evidence on cost-effectiveness in people with cystic fibrosis was available for this review.

9.4.1.6 Evidence to recommendations

9.4.1.6.1 Relative value placed on the outcomes considered

The aim of this review was to compare the clinical and cost effectiveness of various antimicrobials given as long-term prophylaxis (for more than 3 months) against bacterial infection in people with cystic fibrosis.

The committee identified time to identification of the pathogen (*S aureus*) in respiratory samples, the time to the next pulmonary exacerbation and the development of *P aeruginosa* infection as critical outcomes for this evidence review. If there was no evidence for time to next pulmonary exacerbation, the number of people with cystic fibrosis experiencing a pulmonary exacerbations and number of people with cystic fibrosis being admitted to hospital with to pulmonary exacerbations were taken as alternative proxy outcomes.

In addition to the critical outcomes, lung function (measured by FEV_1 or LCI), evidence of inflammation on CT scanning (in children under 5 years of age), quality of life, adherence to treatment (or patient preference), adverse events and the emergence of resistant organisms were considered important outcomes.

9.4.1.6.2 Consideration of clinical benefits and harms

The committee noted that it is accepted that *S aureus* can cause serious lung disease in cystic fibrosis. The isolation of *S aureus* from respiratory samples means that the respiratory tract is colonised or infected with this pathogen. This can lead to pulmonary inflammation and progressive lung disease.

The committee noted that the evidence showed that anti-staphylococcal prophylaxis with an antimicrobial agent (either flucloxacillin or cephalexin) led to a decreased number of children in whom *S aureus* was isolated. The quality of the evidence for this outcome ranged from very low to moderate. Despite the fact that the evidence did not show this was associated with clinical benefit, there being no improvement in lung function or reduction in exacerbations in children given prophylaxis compared with those who were not, the reduction in *S aureus* was, nevertheless, a critically important outcome. Overall, the evidence did not reveal the occurrence of adverse events with prophylaxis.

The committee were concerned about the theoretical possibility that long-term antimicrobial prophylaxis for *S aureus* might be associated with an increased risk infection with *P aeruginosa*. Although the evidence did not demonstrate this, the committee noted that the quality of the evidence for this outcome ranged from very low to low. The committee observed that, given the widespread expert consensus that this risk is a concern, they agreed that it could be mitigated by recommending that flucloxacillin be used rather than cephalexin. The fact that cephalosporins are broad spectrum is postulated to be the reason why an increase in pseudomonas isolation may be seen, but this is not known with certainty. Recommending flucloxacillin rather than a cephalosporin was in keeping with current practice. The committee discussed what age to recommend anti-staphylococcal prophylaxis until. The committee noted that a beneficial effect (decreased number of children in whom *S aureus* was isolated) was observed for the comparison oral flucloxacillin versus placebo + antibiotic "as required" at 2 and 3 years of follow-up. Therefore, the committee recommended to offer flucloxacillin up to age 3. The committee noted that the same beneficial effect was observed for the comparison between another anti-staphylococcal agent (oral cephalexin) versus placebo + antibiotic "as required" at each subsequent year of follow-up up to 6 years of follow-up. Although this evidence was on an anti-staphylococcal agent, there was no direct evidence on flucloxacillin after 3 years of follow-up. Therefore the committee decided to only make a weak recommendation to "consider" continuing flucloxacillin up to 6 years of age.

The committee noted that for children who are allergic to penicillins, an alternative oral anti-staphylococcal agent should be considered.

9.4.1.6.3 Consideration of economic benefits and harms

The committee believed, based on their knowledge and experience, that colonisation with *S aureus* was likely to be associated with an increased risk of pulmonary disease and a worse prognosis compared to no colonisation. The clinical benefits of prophylaxis, although not demonstrated by the available evidence, might well be important and, if so, prophylaxis is likely to be cost-effective.

In contrast to current recommendations in the USA, the committee did not think there were grounds to advise the non-use of prophylaxis. This was based on the low cost of prophylaxis treatment and the potentially serious consequences of *S aureus* pulmonary infection that would outweigh the cost of prophylaxis.

The committee believed cephalexin and flucloxacillin were similar in terms of efficacy, but noted that cephalexin is a broader spectrum antibiotic that could increase the risk of *P aeruginosa* infection. For this reason, the committee agreed that using the more expensive flucloxacillin would be a cost-effective choice because it is a narrower spectrum antibiotic, thus reducing the expected cost of a *P aeruginosa* infection.

The committee noted that the cost of flucloxacillin varied substantially according to the preparation used, with oral solutions costing more than capsules (NHS Electronic Drug Tariff November 2016: 250mg/5ml oral solution sugar free, £1.32/5ml versus 250mg capsules, £0.05). Prophylaxis in infants would require the use of oral solutions and the committee believed that sugar free solutions were preferable although more expensive. However, once children were old enough to take capsule preparations they believed these should be used if they are cheaper and equally effective.

The committee recognised that long-term prophylaxis could be burdensome for the person with cystic fibrosis and their parents or carers. This is particularly the case when products are unpalatable and because the need for medications for cystic fibrosis increase with age. Moreover, long-term use of flucloxacillin would be costly at approximately £67 per month (costed on a BNF recommended dose of 125 mg twice daily: 125mg/5ml oral solution sugar free; basic price, £21.97; quantity 100ml). For this reason, the committee made a recommendation to offer prophylaxis treatment up to the age of 3 years, and to consider continuing up to the age of 6 years as there was no evidence it provided benefit beyond this

age, to justify the cost and burden of treatment beyond this time. The committee added that this could reduce resource use in this area, if children who are receiving prophylactic treatment over the age of 6, discontinue treatment following the recommendation.

9.4.1.6.4 Quality of evidence

Two of the studies included in the Cochrane review (Smyth 2014) compared oral flucloxacillin versus antibiotics as required. The quality of the evidence was moderate to very low quality as assessed by GRADE. The main reasons that lead to downgrading the quality of the evidence were the moderate risk of bias found in the studies and the levels of imprecision.

One study included in the Cochrane review (Smyth 2014) compared oral cephalexin versus antibiotics as required. The quality of the evidence was moderate to very low quality as assessed by GRADE. The main reason for downgrading the quality of the evidence was the large number of losses to follow-up. It is known that the participants who leave the study do normally differ to those who remain, therefore, the results have to be interpreted with caution. The outcome about adherence to treatment was reported narratively only.

9.4.1.6.5 Other considerations

In the absence of strong evidence in favour of the use of antimicrobial prophylaxis to prevent pulmonary bacterial colonisation with *S aureus*, the committee agreed that other aspects were to be considered when deciding whether to start treatment or not. The preferences of the parents were discussed. It was acknowledged that some parents want their children to take anti-staphylococcal treatment; whereas, others are more reluctant as they cannot see a clear benefit of having treatment. The committee agreed that it was important to discuss prophylaxis with the parents and a recommendation was made to this effect.

Patient tolerance of prophylaxis was discussed by the committee. As mentioned above, clinical practice in the UK is to favour the use of flucloxacillin, but alternatives (for example cephalexin) can be considered if there are significant side effects.

An important concern raised by the committee was the duration of treatment. Currently there is considerable variation in clinical practice. It was noted that although there is a common view that prophylaxis should continue until the age of 3 (as suggested by the CF Trust), in many cases it is continued beyond that age. The study included in the review followed children up to the age of 6. There was no conclusive evidence that there was continuing benefit of prophylaxis treatment up to this age. But it was the consensus view of the committee that continuing up to age 6 was a reasonable duration of treatment. Given the lack of evidence comparing different lengths of prophylaxis treatment, and the concerns raised by patients and parents alike, the committee concluded that this should be a priority for research. However, they agreed not to draft a research recommendation as there is an ongoing trial that will address this issue (Cystic Fibrosis Trust CF START).

At the time of publication (October 2017), flucloxacillin did not have a UK marketing authorisation for use in people with cystic fibrosis for this indication. However, there are clinical situations in which the off-label use of a medicine may be judged by the prescriber to be in the best clinical interests of the patient. As a result, the committee agreed they could recommend the off-label use of flucloxacillin because the clinical need cannot be met by a licensed product and there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy to support this.

No equality issues were identified by the committee for this review question.

9.4.1.6.6 Key conclusions

The committee agreed to recommend anti-staphylococcal prophylaxis for children with cystic fibrosis up to age 3, and consider continuing up to 6 years of age. The committee agreed that the potential benefits and disadvantages of treatment should be discussed with parents or

carers before starting anti-staphylococcal prophylaxis. Flucloxacillin should be the first choice given that cephalexin may be associated with a higher rate of *P aeruginosa* growth or isolation.

9.4.2 Acute

Review question: What is the effectiveness of antimicrobial treatment for acute pulmonary infection or those with an exacerbation in children and adults with cystic fibrosis?

9.4.2.1 Description of clinical evidence

The aim of this review was to compare the clinical and cost effectiveness of different antimicrobial regimens in achieving clinical resolution of acute pulmonary infection or exacerbation in children and adults with cystic fibrosis.

We looked for studies that included children and adults with cystic fibrosis who presented with clinical manifestations suggesting development of an acute pulmonary infection or those with an exacerbation and who are already known to have a positive sputum or airway culture for one of the following pathogens at entry to the trial:

- *S aureus*
- *P aeruginosa*
- *B cepacia complex*
- *Haemophilus influenzae*
- Nontuberculous *mycobacteria* (*Mycobacterium avium* complex and *Mycobacterium abscessus*).
- We also looked for studies that included children and adults with cystic fibrosis who present with clinical manifestations suggesting development of an acute pulmonary infection or those with an exacerbation without an identified pathogen at trial entry.

Pulmonary exacerbation was defined as:

1. Fuchs definition (original form (4/16 symptoms leading to IV antibiotic treatment) or modified form (4/16 symptoms leading to any change in antibiotic therapy).
2. or
3. European Cystic Fibrosis Society Consensus definition: “need for additional antibiotic treatment as indicated by a recent change in at least 2 of 6 defined symptoms”.

However, the definition of pulmonary exacerbation used in the study was also accepted.

Additionally, acute infection was defined as a person with cystic fibrosis who is found, on routine microbiological investigation, to have a significant respiratory pathogen (newly identified infection).

We searched for systematic reviews of RCTs and RCTs. Systematic reviews were assessed for inclusion against the protocol, and if relevant, their quality was assessed using AMSTAR. High-quality systematic reviews were included in our review, and where possible, data and quality assessment was taken directly from the review. Individual studies were also retrieved for completeness and accuracy, and were also checked for additional outcomes of interest. Low-quality SR were excluded from our review, but the list of included studies was checked to identify relevant trials.

For full details see review protocol in Appendix D.

The results are presented separately for each pathogen.

9.4.2.1.1 P aeruginosa

The interventions that were included in the protocol for the treatment of infection with or exacerbation due to *P aeruginosa* were: Ciprofloxacin (oral), Aztreonam (inhaled or IV), Ceftazidime (IV), Meropenem (IV), Piperacillin-Tazobactam (IV), Fosfomycin (IV), Ticarcillin-Clavulanate (IV), Aztreonam (inhaled or IV), Chloramphenicol (oral). For first infection only we also considered sequencing antibiotics: Ciprofloxacin (oral) then either Colistin or Tobramycin (inhaled).

Four Cochrane systematic reviews were identified in the search (Elphick 2016, Hurley 2015, Hewer 2014, Remmington 2016).

Two reviews were included:

- Hurley (2015) evaluated if intravenous antibiotics for the treatment of pulmonary exacerbations in people with CYSTIC FIBROSIS improve short- and long-term clinical outcomes. 13 randomised control trials (RCTs) from this Cochrane review were included (Blumer 2005; Conway 1997; De Boeck 1989, Elborn 1992; Gold 1985; Macystis fibrosisarlane 1985; Master 2001; McCarty 1988; Richard 1997; Salh 1992; Schaad 1987; Schaad 1989; Wesley 1988). The outcome 'eradication of pathogen' was not included in this Cochrane review. Each paper was checked for this outcome and 2 RCTs (Richard 1997 and Schaad 1989) were included.
- Langton (2014) evaluated whether antibiotic treatment of early *P aeruginosa* infection in children and adults with CYSTIC FIBROSIS alters clinical and microbiological outcomes. Two RCTs from this Cochrane review were included (Proesmans 2013, Taccetti 2012). These RCTs aimed to eradicate acute infection (first positive isolate of *P aeruginosa*).

Two reviews were excluded.

- Elphick (2016): no additional RCTs were included from this Cochrane review.
- Remmington (2016): no additional RCTs were included from this Cochrane review.

No additional relevant trials were identified in our search.

- The 13 included studies from the Hurley (2015) Cochrane systematic review evaluated the effectiveness of intravenous antibiotics for the treatment of pulmonary exacerbations based on the following comparisons:
- Comparison 1. Single IV agents compared
  - Ceftazidime versus Aztreonam (Elborn 1992, Salh 1992)
- Comparison 2. Single IV antibiotic (with placebo) versus combination IV antibiotic
  - Tobramycin+placebo versus tobramycin+ceftazidime (Master 2001)
  - Tobramycin+placebo versus piperacillin + tobramycin (Macystis fibrosisarlane 1985)
- Comparison 3. Single IV antibiotic versus combination IV antibiotic
  - Piperacillin versus piperacillin+tobramycin (McCarty 1988)
  - Ceftazidime versus tobramycin + ticarcillin (Gold 1985, Wesley 1988)
  - Ceftazidime versus tobramycin + piperacillin (De Boeck 1989)
  - Colistin versus colistin + another anti-pseudomonal antibiotic (Conway 1997)
- Comparison 4. Combination IV antibiotics versus combination IV antibiotics
  - Aztreonam+IV amikacin versus IV ceftazidime+IV amikacin (Schaad 1989)
  - IV meropenem + IV tobramycin versus IV ceftazidime + IV tobramycin (Blumer 2005)
- Comparison 5. Combination of two IV antibiotics + inhaled antibiotic versus 2 IV antibiotics without inhaled antibiotic
  - IV ceftazidime + IV amikacin versus IV ceftazidime + IV amikacin + inhaled amikacin (Schaad 1987)

- Comparison 6. Combination of IV ceftazidime + IV tobramycin versus oral ciprofloxacin (Richard 1997)
- The 2 included studies from the Langton (2014) Cochane systematic review evaluated the effectiveness of antibiotic treatment for acute infection with the first positive isolate of *P aeruginosa* based on the following comparisons:
- Comparison 7. Oral ciprofloxacin + inhaled colistin versus inhaled tobramycin (Proesmans 2013)
- Comparison 8. Inhaled colistin + oral ciprofloxacin versus inhaled tobramycin + oral ciprofloxacin (Taccetti 2012)
- The size of studies ranged from 19 to 223 participants with cystis fibrosis. Five studies included children, young people and adults (Blumer 2005, Macystis fibrosisarlane 1985, Schaad 1987, Schaad 1989, Taccetti 2012), 1 study included adults only (Conway 1997), 3 studies included young people and adults (Elborn 1992, Gold 1985, Salh 1992), 4 studies included children and young people (McCarty 1988, Proesmans 2013, Richard 1997, Wesley 1988), 2 studies did not report the age range (De Boeck 1989, Master 2001).
- Three studies were conducted in the UK (Conway 1997, Elborn 1992, Salh 1992), 2 in the USA (Blumer 2005, McCarty 1988), 2 in Belgium (De Boeck 1989, Proesmans 2013), 1 in Canada (Gold 1985), 2 in Australia (Macystis fibrosisarlane 1985, Master 2001), 3 in Switzerland (Richard 1997, Schaad 1987, Schaad 1989), 1 in New Zealand (Wesley 1988), 1 in Italy (Taccetti 2012).

9.4.2.1.2 S aureus

The interventions that were included in the protocol for the treatment of infection with or exacerbation due to *S aureus* were: Flucloxacillin (oral or IV), Cotrimoxazole (oral or IV), Doxycycline (oral) (not for under 12's) and Cefradrine (oral).

One Cochrane systematic review was identified for inclusion (Lo 2015). This review examined interventions for eradicating methicillin-resistant *S aureus*, however no published RCTs were identified.

An additional Cochrane systematic review (Southern 2012) on the use of macrolide antibiotics was assessed. The RCTs included in this review have comparisons of placebo and different dosages. As these comparisons are not included in our protocol, no RCTs from this Cochrane review were included.

No relevant trials were identified in our search.

9.4.2.1.3 B cepacia complex

The interventions that were included in the protocol for the treatment of infection with or exacerbation due *B Cepacia* Complex were: Cotrimoxazole (oral or IV), Meropenem (IV or inhaled), Ceftazidime (IV or inhaled), Temocillicin (oral or IV), Imipenem (oral or IV), Trimethoprim (oral or IV) and Tobramycin (oral or IV).

Two Cochrane systematic reviews were identified for inclusion. One Cochrane review examined eradication of *B Cepacia* Complex (Regan 2016) and another Cochrane review examined treatment of exacerbations in people with *B Cepacia* Complex (Horsley 2016). Neither of these Cochrane reviews included any RCTs.

No relevant trials were identified in our search.

9.4.2.1.4 *H influenzae*

The interventions that were included in the protocol for the treatment of infection with or exacerbation due to *H influenzae* were: Co-amoxiclav (oral or IV), Cefuroxime (IV), Cefaclor, Cefixime, Doxycycline (>12 years), and Macrolide (clarithromycin/azithromycin).

No relevant systematic reviews or trials were identified in our search.

9.4.2.1.5 *Nontuberculous mycobacteria*

We considered *Mycobacterium Avium* Complex and *Mycobacterium Abscessus*.

The interventions that were included in the protocol for the treatment of infection with or exacerbation due to *M. Avium* Complex were: Clarithromycin (oral), Azithromycin (oral), Rifampicin (oral), Ethambutol (oral) and Amikacin (inhaled and potentially IV).

The interventions that were included in the protocol for the treatment of infection with or exacerbation due to *M. Abscessus* were: Cefoxitin (IV), Clarithromycin (IV), Amikacin (IV and inhaled), Meropenem (IV and inhaled), Tigecycline, Co-trimoxazole (oral), Moxifloxacin (oral), Ciprofloxain (oral), Doxycycline/minocycline (tetratcyclines) (oral), Linezolid (oral) and Clofazimine (oral).

A Cochrane SR was identified in the search (Waters 2016). This review aimed to compare antibiotic treatment *versus* non-antibiotic treatment, or different combinations of antibiotics, for non-tuberculous *mycobacteria* lung infection in people with CYSTIS FIBROSIS. No trials were identified for inclusion in this review.

No relevant trials were identified in our search.

9.4.2.1.6 *No identified pathogen*

The interventions that were included in the protocol for the treatment of infection with or exacerbation without an identified pathogen at trial entry were any of the above.

No relevant systematic reviews or trials were identified in our search.

Evidence from these are summarised in the clinical GRADE evidence profile below (Table 65 -Table 103). See also the study selection flow chart in Appendix F, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix H.

9.4.2.2 Summary of included studies

A summary of the studies that were included in this review are presented in Table 91 to Table 95.

9.4.2.2.1 *P aeruginosa*

Table 91: Summary of included studies for antimicrobials for pulmonary exacerbations with *P aeruginosa*

Study	Intervention/Comparison	Population	Outcomes	Comments
Cochrane systematic reviews				
Hurley 2015 Cochrane SR	Comparison 1. Single IV agents compared • (Elborn 1992, Salh 1992) Comparison 2. Single IV (with placebo) vs	Participants diagnosed with cystic fibrosis using the Cystic Fibrosis Foundation diagnostic consensus statement, of all ages and all levels of severity. All studies that explicitly aimed to trial	• Lung function (FEV_1) • Time to next exacerbation	AMSTAR score: 11/11

Study	Intervention/Comparison	Population	Outcomes	Comments
	combination of IV antibiotics • (Macystis fibrosisarlane 1985, Master 2001) Comparison 3. Single IV vs combination of IV antibiotics • (De Boeck 1989, Conway 1997, Gold 1985, McCarty 1988, Wesley 1988) Comparison 4. Combination of antibiotics vs combination of antibiotics • (Blumer 2005, Richard 1997, Schaad 1989)	an IV antibiotic for the treatment of pulmonary exacerbation were considered.	• Quality of life (CFQ-R) • Mortality (cystic fibrosis-related and all causes) • Adverse events	
Primary studies included in the Cochrane SR				
Blumer 2005 (USA) RCT	Intervention 1: IV meropenem 40 mg/kg up to a maximum dose of 2 g and IV tobramcyin(given for a mean of 13.5 days) Intervention 2: IV ceftazidime 50 mg/kg up to a maximum dose of 2 g and I V tobramycin(given for a mean of 14.1 days) • Tobramycin dose adjusted to give a peak serum concentration of>= 8 µg/mL and trough concentration of < 2 µg/mL	N=121 participants with a recent (usually < 1 month) culture of *P aeruginosa* or *B cepacia* complex recruited at a protocol-de fined exacerbation. • Age: ≥ 5 years of age	• Lung function (FEV_1)	Included in Cochrane SR Hurley 2015
Conway 1997 (UK) RCT	Intervention 1: IV colistin (2 MU 3x daily). Intervention 2: IV colistin (2 MU 3x daily) and a second anti-pseudomonal antibiotic	N=71 adults with cystic fibrosis and chronic *P aeruginosa* experiencing a protocol-defined exacerbation. • Mean age (SD): 21 (4.2) years.	• FEV_1 • Mortality • Adverse effects	Included in Cochrane SR Hurley 2015
De Boeck 1989 (Belgium	Intervention 1: IV ceftazidime 50 mg/kg 3x daily.	N=21 participants with cystic fibrosis and a protocol-defined pulmonary exacerbation, chronically infected with	• FEV_1 • Time to readmission • Mortality	Included in Cochrane SR Hurley 2015

Study	Intervention/Comparison	Population	Outcomes	Comments
RCT	Intervention 2: IV piperacillin 75 mg/kg 4x daily and IV tobramycin 10 mg/kg/day in3 doses	*P aeruginosa* that was sensitive to piperacillin, tobramycin and ceftazidime • Mean age 14.8 years		
Elborn 1992 (UK) RCT	Intervention 1: IV ceftazidime 2 g 3x daily. Intervention 2: IV aztreonam 2 g 3x daily.	N=24 participants with cystic fibrosis and chronic *P aeruginosa* infection experiencing exacerbations. Mean (range) age: 20 (14 to 48) years	• FEV_1	Included in Cochrane SR Hurley 2015
Gold 1985 (Canada) RCT	Intervention 1: IV ceftazidime 200 mg/kg/day in 4 doses. Intervention 2: IV ticarcillin 300 mg/kg/day in 4 doses and IV tobramycin 10 mg/kg/day in 3 doses	N=30 participants with cystic fibrosis and *P aeruginosa* infection present at the previous clinic visit, experiencing an acute respiratory exacerbation. • Age >12 years. Mean age (SD): 18.9 (1.1) in group 1; 17.8 (0.8) in group 2	• FEV_1 • Adverse effects	Included in Cochrane SR Hurley 2015
Macystis fibrosisarlane 1985 (Australia) RCT	Intervention 1: IV piperacillin 50 mg/kg 4-hourly. Intervention 2: IV placebo 5% dextrose 4-hourly Intervention 3: IV piperacillin 100 mg/kg 8-hourly. Intervention 4: IV placebo 5% dextrose 8-hourly. All participants received IV tobramycin 2.5 mg/kg 3x daily, oral flucloxacillin 25 mg/kg/day in 4 doses and oral probenecid (suggested to increase antibiotic concentrations)250 - 500 mg 3x daily Duration: 14 days.	N=19 participants aged over 8 years with cystic fibrosis with *P aeruginosa* in sputum admitted to hospital for worsening respiratory status. • Mean age: 13.7 to 15.6 years	• FEV_1 • Adverse effects	Included in Cochrane SR Hurley 2015 Pseudomonas was not eradicated from the sputum in any of the patients
Master 2001 (Australia) RCT	Intervention 1: IV ceftazidime 50 mg/kg/dose 3x daily and IV tobramycin 3 mg/kg/dose 3x daily	N=51 participants with cystic fibrosis experiencing a protocol-defined exacerbation with *P aeruginosa*	• FEV_1 • Adverse effects	Included in Cochrane SR Hurley 2015

Study	Intervention/Comparison	Population	Outcomes	Comments
	Intervention 2: IV tobramycin 9 mg/kg/day 1x daily. Duration: at least 10 days.	isolated from sputum. Participants with an FVC lower than 40% predicted were excluded. • Mean age (SD): 16 (7) years in group 1; 14 (5) years in group 2		
McCarty 1988 (USA) RCT	Intervention 1: IV piperacillin 600 mg/kg/day (regimen not detailed) Intervention 2: IV piperacillin 600 mg/kg/day and tobramycin 8 - 10 mg/kg/day(regimen not detailed Duration: at least 10 days.	N=17 children with cystic fibrosis admitted for treatment of pulmonary exacerbations with *P aeruginosa*. • Age range: 2 to 12 years.	• FEV_1 • Eradication of pseudomonas • Adverse effects	Included in Cochrane SR Hurley 2015
Richard 1997 (Switzerland) RCT	Intervention 1: oral ciprofloxacin 15 mg/kg 2x daily. Intervention 2: IV ceftazidime 50 mg/kg 3x daily and IV tobramycin 3 mg/kg 3x daily Duration: 14 days.	N=108 children with cystic fibrosis and *P aeruginosa* infection and experiencing a protocol-defined pulmonary exacerbation with *P aeruginosa*. • Mean age: 10.2 years in group 1; 11 years in group 2. Age range: 5 to <17.	• Eradication of pseudomonas • Adverse effects	Included in Cochrane SR Hurley 2015
Salh 1992 (UK) RCT	Intervention 1; IV aztreonam 8 g/day in 4 doses. Intervention 2: IV ceftazidime 8 g/day in 4 doses. Duration: 2 weeks	N=22 participants with cystic fibrosis and *P aeruginosa* sensitive to the study drugs who were admitted to hospital due to an infective exacerbation • Age range: 16 to 32 years.	• FEV_1	Included in Cochrane SR Hurley 2015
Schaad 1987 (Switzerland) RCT	Intervention 1: IV ceftazidime 250 mg/kg/day in 4 doses and IV amikacin 33 mg/kg/day in 3 doses Intervention 2: IV ceftazidime 250 mg/kg/day in 4 doses and IV amikacin 33 mg/kg/day in 3 doses and nebulised	N=62 participants with cystic fibrosis admitted with an acute pulmonary exacerbation who had *P aeruginosa* isolated on admission. Those who had been admitted to hospital in the recent 6 months were excluded	• Adverse effects	Included in Cochrane SR Hurley 2015

Study	Intervention/Comparison	Population	Outcomes	Comments
	amikacin 100 mg 2x daily Duration: 15 days	• (n=87 courses of therapy by random assignment) • Age range: 3 to 24 years.		
Schaad 1989 (Switzerland) RCT	Intervention 1: IV aztreonam 300 mg/kg/day in 4 doses and IV amikacin 36 mg/kg/day in 3 doses Intervention 2: IV ceftazidime 300 mg/kg/day in 4 doses and IV amikacin 36 mg/kg/day in 3 doses for 2 weeks followed by oral ciprofloxacin 30 mg/kg/day for 4 weeks Duration: 2 weeks IV treatment, with oral treatment extended for a further 4 weeks in1 group	N=42 participants with cystic fibrosis admitted with a protocol-defined pulmonary exacerbation and *P aeruginosa* isolated at admission. Those who had been admitted to hospital in previous 4 months were excluded • (n=56 treatment courses by random assignment) • Mean age (SD): 15.4 (6) years (range 2.3 to 25.4 years).	• Eradication of Pseudomonas • FEV_1 • Adverse effects	Included in Cochrane SR Hurley 2015
Wesley 1988 (New Zealand) RCT	Intervention 1: IV ceftazidime 150 mg/kg/day (regimen not detailed) Intervention 2: IV tobramycin 7.5 mg/kg/day and IV ticarcillin 300 mg/kg/day (regimen not detailed) Duration: 14 days	N=13 children with cystic fibrosis and severe chest disease with pseudomonas chest exacerbation. • Age range: 9 to 15 years.	• Number of admission requiring iv antibiotics or death • Adverse effects	Included in Cochrane SR Hurley 2015 Conference abstract

FEV_1: Forced Expiratory volume. Information provided in the table is adapted from Hurley 2015.

Table 92: Summary of included studies for antimicrobials for the treatment of acute infection with *P aeruginosa*

Study	Intervention/Comparison	Population	Outcomes	Comments
Cochrane systematic reviews				
Langton 2014 Cochrane SR	Comparisons of combinations of oral, inhaled or intravenous antibiotics (Proesman 2013, Tacetti 2012)	Children and adults with confirmed cystic fibrosis with a first ever positive microbiological isolate of *P aeruginosa* from a respiratory tract specimen.	• FEV_1 • Trial discontinuation due to lack of compliance (proxy outcome for treatment failure) • Adverse effects	AMSTAR score: 10/11

Study	Intervention/Comparison	Population	Outcomes	Comments
Primary studies included in the Cochrane systematic reviews				
Proesmans 2013 (Belgium) RCT	Intervention Inhaled TSI (300 mg 2x daily for 28 days), 3 months Control Combination therapy with inhaled colistin (2 MU 2x daily)+ oral ciprofloxacin (10 mg/kg 3x daily), 3 months	N=58 children with cystic fibrosis, all with new isolation of *P aeruginosa* (sputum or cough swabs) • Treatment: n=29 • Control: n=29 • Age: median age 9 years, interquartile range (4.7 - 13.1 years)	• Adverse effects	Included in Langton 2014 Cochrane SR This study did not report the outcome 'eradication of pathogen' but reported 'number of positive respiratory culture for pseudomonas. There was no difference between groups in positive pseudomonas culture 6 months and 24 months follow-up
Taccetti 2012 (Italy) RCT	Group A 28 days therapy 2 x daily inhalation of 2 MU colistin with 2 x daily doses of ciprofloxacin 15 mg/kg/dose. Group B 28 days therapy TSI (300 mg 2 x daily) with 2 x daily doses of ciprofloxacin 15 mg/kg/dose	N=223 participants with cystic fibrosis with first ever or new *P aeruginosa* infection. New infection defined as *P aeruginosa* isolation following bacterial clearance documented by 3 negative cultures within the previous 6 months • Group A: n=105 (52 male and 53 female) • Group B: n=118 (64 male and 54 female) • Age: over 1 year.	• FEV_1 • Trial discontinuation due to lack of compliance (proxy outcome for treatment failure)	Included in Langton 2014 Cochrane SR This study did not report the outcome 'eradication of pathogen' but reported 'number of positive respiratory culture for pseudomonas'. No difference was found in positive respiratory

Study	Intervention/Comparison	Population	Outcomes	Comments
				cultures of pseudomonas at end of treatment between both regimes. An increased incidence of the emerging pathogen *S maltophilia* was reported following treatment,

9.4.2.2.2 *S aureus*

Table 93: Summary of included studies for the antimicrobial treatment of infection with or exacerbation due to *S aureus*

Study	Intervention/Comparison	Population	Outcomes	Comments
Cochrane systematic reviews				
Lo 2015 Cochrane SR	Intervention Any combination of topical, inhaled, oral or intravenous antibiotics with the primary aim of eradicating MRSA Comparison • Placebo • Standard treatment • No treatment	Children and adults with confirmed diagnosis of cystic fibrosis with a confirmed positive microbiological isolate of MRSA on clinically relevant cystic fibrosis respiratory cultures.	No studies were identified for inclusion in this review	AMSTAR score:10/11

CYSTIS FIBROSIS: cystic fibrosis; SR: systematic review; MRSA: methicillin-resistant S aureus

9.4.2.2.3 *B cepacia complex*

Table 94: Summary of included studies for the antimicrobial treatment of infection with or exacerbation due *B Cepacia* Complex (BCC)

Study	Intervention/Comparison	Population	Outcomes	Comments
Cochrane systematic reviews				
Horsley 2016 Cochrane SR	Intervention Any antibiotic treatment regimen for treating an exacerbation of CF lung disease	Patients with cystic fibrosis of any age with evidence of pulmonary infection with organisms of the BCC (defined as at least 2 positive sputum or bronchoalveolar	No studies were identified for inclusion in this review	AMSTAR score:11/11

Study	Intervention/Comparison	Population	Outcomes	Comments
	Comparison • Placebo • Different antibiotic regimen	lavage specimens within the last 6 months		
Regan 2016 Cochrane SR	Intervention Any antibiotic or antibiotic adjuvant therapy used alone or in combination to eradicate BCC infection Comparison • Placebo • No treatment • Alternative antimicrobial agent (excluding the participant's usual therapeutic regimen)	Any person of any age with a confirmed clinical diagnosis of cystic fibrosis who acquires a new infection or a re-infection with BCC. People will all disease severity were included.	No studies were identified for inclusion in this review	AMSTAR score:10/11

BCC: B Cepacia Complex; CYSTIS FIBROSIS: cystic fibrosis; SR: systematic review

9.4.2.2.4 Non-tuberculous mycobacteria

Table 95: Summary of included studies for the antimicrobial treatment of infection with or exacerbation due to non-tuberculous *mycobacteria* (NTM)

Study	Intervention/Comparison	Population	Outcomes	Comments
Cochrane systematic reviews				
Waters 2016 Cochrane SR	Intervention Antibiotics to treat NTM pulmonary infection Comparison No antibiotic treatment Different NTM antibiotic regimen	Children and adults with a confirmed clinical diagnosis of cystic fibrosis, who have NMT pulmonary infection. People will all disease severity were included.	No studies were identified for inclusion in this review	AMSTAR score: 10/11 Last search September 2016

9.4.2.2.5 Non-identified pathogen

No studies were identified for inclusion.

9.4.2.3 Clinical evidence profile

The clinical evidence profiles for the review question addressing antimicrobials for pulmonary exacerbation are presented in Table 65 - Table 101. The clinical evidence profiles for the review question addressing antimicrobials for acute exacerbations are presented in Table 102 and Table 103.

9.4.2.3.1 *P aeruginosa*

Antimicrobials for pulmonary exacerbations due to *P aeruginosa*

Table 96: Summary clinical evidence profile: Comparison 1.Single IV agents compared for pulmonary exacerbations with *P aeruginosa*

Comparison 1.Single IV agents compared for pulmonary exacerbations with *P aeruginosa*						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Single IV agents	Single IV agents				
[ceftazidime *versus* aztreonam] FEV_1 (absolute change) litres Follow-up: 2 weeks	The mean absolute change in FEV_1 litres in the IV aztreonam group ranged between 0.27 and 0.54	The mean absolute change in FEV_1 litres in the IV ceftazidime group was 0.06 lower (0.44 lower to 0.32 higher)		46 (Elborn 1992, Salh 1992)	⊕⊕⊖⊖ low[1,2]	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; MD: mean difference						

1 The quality of the evidence was downgraded by 1 as 4 participants received both drugs in Salh 1992 study,
2 The quality of the evidence was downgraded by 1 due to serious heterogeneity (chi-squared p<0.1, I-squared inconsistency statistic of 50%-74.99%)

Table 97: Comparison 2. Single IV antibiotic (with placebo) *versus* combination IV antibiotic for pulmonary exacerbations with *P aeruginosa*

Comparison 2. Single IV antibiotic (with placebo) versus combination IV antibiotic for pulmonary exacerbations with *P aeruginosa*						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Combination IV antibiotics	Single IV antibiotic (with placebo)				
[tobramycin + placebo *versus* tobramycin + ceftazidime] FEV_1 % predicted (absolute change) - Follow-up: 10 days	The mean FEV_1% predicted (absolute change) in the tobramycin + ceftazidime group was 12.8	The mean FEV_1 % predicted (absolute change) in the tobramycin + placebo groups was 2.2 lower (6.63 lower to 2.23 higher)		98 (Master 2001)	⊕⊕⊖⊖ low[1,2]	

[tobramycin + placebo *versus* piperacillin + tobramycin] FEV_1% predicted (relative change) - Follow-up: 2 weeks	The mean FEV_1% predicted (relative change) in the piperacillin + tobramycin group was 12.2	The mean FEV_1% predicted (relative change) in the tobramycin + placebo groups was 4.2 lower (26.5 lower to 18.1 higher)		9 (Macystis fibrosisarlane 1985)	⊕⊖⊖⊖ very low[3,4]	
[tobramycin + placebo *versus* piperacillin + tobramycin] FEV_1% predicted (relative change) - Follow-up: 2 weeks	The mean FEV_1% predicted (relative change) in the piperacillin + tobramycin group was 1.8	The mean FEV_1% predicted (relative change) - in the tobramycin + placebo groups was 7.95 higher (8.78 lower to 24.68 higher)		9 (Macystis fibrosisarlane 1985)	⊕⊖⊖⊖ very low[3,4]	
[tobramycin + placebo *versus* piperacillin all regimens] Adverse effects - sensitivity reaction - number of participants Follow-up: 2 weeks	300 per 1000	51 per 1000 (3 to 888)	RR 0.17 (0.01 to 2.96)	18 (Macystis fibrosisarlane 1985)	⊕⊕⊖⊖ low[3,5]	
[tobramycin + placebo *versus* tobramycin + ceftazidime] Adverse effects - Number of hospital admissions due to Tinnitus Follow-up: 2 weeks	39 per 1000	43 per 1000 (6 to 290)	RR 1.09 (0.16 to 7.4)	98 (Master 2001)	⊕⊖⊖⊖ very low[1,6]	
[tobramycin + placebo *versus* tobramycin + ceftazidime] Adverse effects - serum - Creatinine Follow-up: 2 weeks	The mean serum creatinine in the tobramycin + ceftazidime groups was 0	The mean serum creatinine in the Tobramycin + placebo groups was 4 lower (9.38 lower to 1.38 higher)		44 (Master 2001)	⊕⊖⊖⊖ very low[1,6]	
[tobramycin + placebo *versus* tobramycin + ceftazidime] Adverse effects - serum - NAG Follow-up: 2 weeks	The mean serum NAG in the tobramycin + ceftazidime groups was	The mean serum NAG in the Tobramycin + placebo groups was 2.1 lower (3.46 lower to 0.74 lower)		44 (Master 2001)	⊕⊕⊕⊖ moderate[1]	

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; MD: mean difference; NAG: N-acetyl glucosamine; RR: risk ratio

1 The quality of the evidence was downgraded by 1 as each participant contributed to multiple treatment episodes.
2 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 clinical MID
3 The quality of the evidence was downgraded by 1 due to attrition bias (2 participants withdrew and did not contribute to analysis) and 1 participant received 2 treatment courses.
4 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 clinical MIDs
5 The quality of the evidence was downgraded by 1 due to very serious imprecision as 95%CI crossed 1 default MIDs
6 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 default MIDs

Table 98: Comparison 3. Single IV antibiotic *versus* combination IV antibiotic for pulmonary exacerbations with *P aeruginosa*

Comparison 3. Single IV antibiotic versus combination IV antibiotic for pulmonary exacerbations with *P aeruginosa*						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Combination IV antibiotic	Single IV antibiotic				
[piperacillin *versus* piperacillin + tobramycin] Eradication: number people in whom pseudomonas isolates were eradicated at end of course - Follow-up: 10 days	632 per 1000	265 per 1000 (114 to 600)	RR 0.42 (0.18 to 0.95)	38 (McCarty 1988)	⊕⊕⊖⊖ low[1,2]	
[ceftazidime *versus* IV tobramycin + ticarcillin] FEV_1 (relative change) - % Follow-up: 10 to 14 days	The mean FEV_1 (relative change) in the tobramycin + ticarcillin groups was 33.3	The mean FEV_1 (relative change) in the ceftazidime groups was 19.6 lower (38.26 to 0.94 lower)		30 (Gold 1985)	⊕⊕⊖⊖ low[3,4]	
[colistin *versus* colistin + "other"] FEV_1 (absolute change) ml Follow-up: 12 days	The mean FEV_1 (absolute change) in the colistin + "other" groups was 300	The mean FEV_1 (absolute change) in the colistin groups was 160 lower (309.72 to 10.28 lower)		71 (Conway 1997)	⊕⊕⊖⊖ low[5]	

Comparison 3. Single IV antibiotic versus combination IV antibiotic for pulmonary exacerbations with *P aeruginosa*						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
[ceftazidime *versus* tobramycin + piperacillin] FEV_1 % predicted (absolute change) Follow-up: 12 days	The mean FEV_1 % predicted (absolute change) in the ceftazidime groups was 1 higher (8.85 lower to 10.85 higher)	The mean FEV_1 % predicted (absolute change) in the ceftazidime groups was 1 higher (8.85 lower to 10.85 higher)		21 (De Boeck 1989)	⊕⊖⊖⊖ very low[3,6]	
[ceftazidime *versus* tobramycin + piperacillin] Time to readmission - months Follow-up: 24 to 26 months	The mean time to readmission in the tobramycin + piperacillin groups was 9 months	The mean time to readmission in the piperacillin groups was 1 month lower (5.52 lower to 3.52 higher)		19 (De Boeck 1989)	⊕⊖⊖⊖ very low[3,7]	
[ceftazidime *versus* tobramycin + ticarcillin] Number of admissions, requiring IV antibiotics or death - Follow-up: 3 months	500 per 1000	585 per 1000 (265 to 1000)	RR 1.17 (0.53 to 2.55)	22 (Wesley 1988)	⊕⊖⊖⊖ very low[7,8]	
[ceftazidime *versus* tobramycin + piperacillin] Mortality - Follow-up: 4 months	91 per 1000	100 per 1000 (7 to 1000)	RR 1.1 (0.08 to 15.36)	21 (De Boeck 1989)	⊕⊕⊖⊖ low[9,10]	
[IV colistin *versus* IV colistin + "other"] Mortality – Follow-up: 12 weeks	29 per 1000	9 per 1000 (0 to 220)	RR 0.32 (0.01 to 7.7)	71 (Conway 1997)	⊕⊕⊖⊖ low[5,10]	
[ceftazidime *versus* IV tobramycin + ticarcillin] Adverse effects: liver transaminase	87 per 1000	133 per 1000 (29 to 618)	RR 1.53 (0.33 to 7.11)	52 (Gold 1987 and Wesley 1988)a,b	⊕⊖⊖⊖ very low[7,11]	

Comparison 3. Single IV antibiotic versus combination IV antibiotic for pulmonary exacerbations with *P aeruginosa*						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
enzyme elevation Follow-up: 10-14 days						
[colistin *versus* combination anti-pseudomonal antibiotics] Adverse effects: neurological adverse effects Follow-up: 12 days	1000 per 1000	940 per 1000 (860 to 1000)	RR 0.94 (0.86 to 1.04)	17 (McCarty 1988)	⊕⊕⊖⊖ low[5]	
[piperacillin *versus* piperacillin + tobramycin] Adverse effects: rash Follow-up: 10 days	111 per 1000	41 per 1000 (2 to 888)	(McCarty 1988)	(McCarty 1988)	⊕⊖⊖⊖ very low[1,7]	
[piperacillin *versus* piperacillin + tobramycin] Adverse effects -fever Follow-up: 10 days	111 per 1000	124 per 1000 (9 to 1000)	RR 1.12 (0.08 to 15.19)	17 (McCarty 1988)	⊕⊖⊖⊖ very low[1,7]	
[ceftazidime *versus* tobramycin + ticarcillin] Adverse effects – proteinuria Follow-up: 10 - 14 days	59 per 1000	59 per 1000 (4 to 866)	RR 1 (0.07 to 14.72)	34 (Gold 1985)a	⊕⊖⊖⊖ very low[3,7]	
[colistin *versus* combination anti-pseudomonal antibiotics] Adverse effects - renal toxicity - Change in blood urea (mmol/l)	The mean renal toxicity - change in blood urea (mmol/l) in the combination anti-pseudomonal AB groups was 0.83	The mean renal toxicity - change in blood urea (mmol/l) in the colistin groups was 0.26 lower (0.93 lower to 0.41 higher)		71 (Conway 1997)	⊕⊖⊖⊖ very low[5,12]	

Comparison 3. Single IV antibiotic versus combination IV antibiotic for pulmonary exacerbations with *P aeruginosa*						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Follow-up: 12 days						
[colistin *versus* combination anti-pseudomonal antibiotics] Adverse effects: renal toxicity - Change in serum creatinine (mol/l) Follow-up: 12 days	The mean change in serum creatinine (mol/l) in the combination anti-pseudomonal AB groups was -5.85	The mean change in serum creatinine (mol/l) in the colistin groups was 8.85 higher (0.66 lower to 18.36 higher)		71 (Conway 1997)	⊕⊖⊖⊖ very low[5,7]	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; IV: intravenous; MD: mean difference; mmol/ l: millimoles per litre; RR: risk ratio						

a Gold 1985: total of 34 treatment observations in N=30
b Wesley 1988: total of 23 observations in N=13
1 The quality of the evidence was downgraded by 2 due to no blinding and 3 participants were included twice in analysis
2 Minimal important difference for this outcome (MID) = any difference is clinically significant
3 The quality of the evidence was downgraded by 1 due to no blinding.
4 The quality of the evidence was downgraded by 1 as 95% CI crossed 1 clinical MID
5 The quality of the evidence was downgraded by 2 due to single blinding and 18 participants were enrolled twice.
6 The quality of the evidence was downgraded by 2 due as 95%CI crossed 2 clinical MIDs.
7 The quality of the evidence was downgraded by 2 as 95% CI crossed 2 default MIDs
8 The quality of the evidence was downgraded by 1 as 13 participants received 23 courses of treatment.
9 The quality of the evidence was downgraded by 1 due to multiple enrolment of participants (40 participants contribute to 46 treatment episodes).
10 The quality of the evidence was downgraded by 1, as the 95% CI crossed the null effect (mortality could either decrease or increase)
11 The quality of the evidence was downgraded by 1 due lack of blinding in 1 trial, and because some participants were enrolled twice
12 The quality of the evidence was downgraded by 1 as 95% CI crossed 1 default MID

Table 99: Comparison 4. Combination IV antibiotics *versus* combination IV antibiotics for pulmonary exacerbations with *P aeruginosa*

Comparison 4. Combination IV antibiotics versus combination IV antibiotics for pulmonary exacerbations with *P aeruginosa*						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Combination IV	Combination IV				

Comparison 4. Combination IV antibiotics versus combination IV antibiotics for pulmonary exacerbations with *P aeruginosa*						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
[aztreonam + amikacin *versus* ceftazidime + amikacin] Eradication of pathogen Follow-up: 2 weeks	571 per 1000	606 per 1000 (394 to 943)	RR 1.06 (0.69 to 1.65)	56 a (Schaad 1989)	⊕⊖⊖⊖ very low[1,2]	
[aztreonam + amikacin *versus* ceftazidime + amikacin] FEV_1 % predicted (absolute change) - (combination B) Follow-up: 2 weeks	The mean FEV_1 % predicted (absolute change) in the *versus* IV ceftazidime + IV amikacin groups was 9	The mean FEV_1 % predicted (absolute change) in the Aztreonam + IV amikacin groups was 4 higher (0.25 lower to 8.25 higher)		49a (Schaad 1989)	⊕⊕⊖⊖ low[1,3]	
[meropenem + tobramycin *versus* ceftazidime + tobramycin] FEV_1 % predicted (absolute change) - Follow-up: 2 to 4 weeks[b]	The mean FEV_1 % predicted (absolute change) in the *versus* IV ceftazidime + IV tobramycin groups was 11.1	The mean FEV_1 % predicted (absolute change) in the IV meropenem + IV tobramycin groups was 2.7 higher (0.76 lower to 6.16 higher)		97 (Blumer 2005)	⊕⊕⊖⊖ low[3,4]	
[meropenem + tobramycin *versus* ceftazidime + tobramycin] FEV_1 % predicted (relative % change) - Follow-up: 2 to 4 weeks[b]	The mean FEV_1 % predicted (relative % change) in the *versus* IV ceftazidime + IV tobramycin groups was 29.4	The mean FEV_1 % predicted (relative % change) in the IV meropenem + IV tobramycin groups was 9.4 higher (8.44 lower to 27.24 higher)		97 (Blumer 2005)	⊕⊖⊖⊖ very low[4,5]	
[aztreonam + amikacin *versus* ceftazidime + amikacin] Adverse effects - Rash Follow-up: 2 weeks	71 per 1000	14 per 1000 (1 to 285)	RR 0.2 (0.01 to 3.99)	56a (Schaad 1989)	⊕⊖⊖⊖ very low[1,6]	

Comparison 4. Combination IV antibiotics versus combination IV antibiotics for pulmonary exacerbations with *P aeruginosa*						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
[aztreonam + amikacin *versus* ceftazidime + amikacin] Adverse effects - Liver transaminases - AST + ALT Follow-up: 2 weeks	71 per 1000	143 per 1000 (29 to 718)	RR 2 (0.4 to 10.05)	56a (Schaad 1989)	⊕⊖⊖⊖ very low[1,6]	
[aztreonam + amikacin *versus* ceftazidime + amikacin] Adverse effects - Thrombocytopenia Follow-up: 2 weeks	0 per 1000	0 per 1000 (0 to 0)	RR 7 (0.38 to 129.55)	56a (Schaad 1989)	⊕⊖⊖⊖ very low[1,6]	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Abbreviations: AST: aminotransferase, ALT: alanine aminotransferase; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; IV: intravenous; MD: mean difference; RR: risk ratio						

a total of 56 treatment courses were randomised, N=42 participants
b 2 to 4 weeks after discontinuation of 2 week course.
1 The quality of the evidence was downgraded by 1 due to attrition bias (clinical outcomes available for only around 50% of participants).
2 The quality of the evidence was downgraded by 2, as the 95% CI crossed the null effect and the CI was very wide
3 The quality of the evidence was downgraded by 1 as 95%CI crossed 1 clinical MID.
4 The quality of the evidence was downgraded by 1 due to attrition bias (some data missing).
5 The quality of the evidence was downgraded by 2 as 95%CI crossed 2 clinical MIDs.
6 The quality of the evidence was downgraded by 2 as 95%CI crossed 2 default MIDs.

Table 100: Comparison 5. Two IV antibiotics + inhaled antibiotic versus 2 IV without inhaled antibiotic for pulmonary exacerbations with *P aeruginosa*

Comparison 5. Two IV antibiotics + inhaled antibiotic versus 2 IV without inhaled antibiotic for pulmonary exacerbations with *P aeruginosa*						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	2 IV without inhaled antibiotic	2 IV antibiotic + inhaled antibiotic				
[IV ceftazidime + IV amikacin + inhaled amikacin *versus* IV ceftazidime + IV amikacin] Eradication of P *aeruginosa*	409 per 1000	749 per 1000 (503 to 1000)	RR 1.83 (1.23 to 2.73)	84 (Schaad 1987)	⊕⊕⊕⊖ moderate[1]	

Comparison 5. Two IV antibiotics + inhaled antibiotic versus 2 IV without inhaled antibiotic for pulmonary exacerbations with *P aeruginosa*						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Follow-up: 15 days						
[IV ceftazidime + IV amikacin + inhaled amikacin *versus* IV ceftazidime + IV amikacin] Adverse effects: raised liver transaminases Follow-up: 4 to 6 weeks	250 per 1000	168 per 1000 (58 to 480)	RR 0.67 (0.23 to 1.92)	54 (Schaad 1987)	⊕⊖⊖⊖ very low[1,2]	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio;						

1 The quality of the evidence was downgraded by 1 as 18 participants were recruited twice and 6 participants enrolled 3 times.
2 The quality of the evidence was downgraded by 2 due to serious imprecision as 95% CI crosses 2 default MIDs.

Table 101: Comparison 6. IV ceftazidime + IV tobramycin *versus* oral ciprofloxacin for pulmonary exacerbations with *P aeruginosa*

Comparison 6. IV ceftazidime + IV tobramycin versus oral ciprofloxacin for pulmonary exacerbations with *P aeruginosa*						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Oral ciprofloxacin	IV ceftazidime + IV tobramycin				
Eradication of *P aeruginosa* Follow-up: 2 weeks	245 per 1000	624 per 1000 (365 to 1000)	RR 2.55 (1.49 to 4.39)	89 (Richard 1997)	⊕⊕⊕⊖ moderate[1]	
Adverse effects - Treatment-related events Follow-up: 2 weeks	164 per 1000	188 per 1000 (83 to 427)	RR 1.15 (0.51 to 2.61)	108 (Richard 1997)	⊕⊖⊖⊖ very low[1,2]	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Abbreviations: CI: confidence interval; IV: intravenous; RR: risk ratio						

1 The quality of the evidence was downgraded by 1 due to no blinding.
2 The quality of the evidence was downgraded by 2 as 95% CI crossed 2 default MIDs.

Antimicrobials for acute infection with *P aeruginosa*

Table 102: Comparison 7. Oral ciprofloxacin + inhaled colistin *versus* inhaled tobramycin for acute infection with *P aeruginosa*

Comparison 7. Oral ciprofloxacin + inhaled colistin versus inhaled tobramycin for acute infection with *P aeruginosa*						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Inhaled tobramycin	Oral ciprofloxacin + inhaled colistin				
Adverse events - Severe cough Follow-up: 3 months	34 per 1000	11 per 1000 (0 to 271)	RR 0.33 (0.01 to 7.86)	58 (Proesmans 2013)	⊕⊖⊖⊖ very low[1,2]	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Abbreviations: CI: confidence interval; RR: risk ratio						

1 The quality of the evidence was downgraded by 1 due to no blinding. Blinding was not possible due to route of administration (oral versus inhaled).
2 The quality of the evidence was downgraded by 2 due to very serious imprecision as 95% CI crossed 2 default MIDs.

Table 103: Comparison 8. Inhaled colistin + oral ciprofloxacin *versus* inhaled tobramycin + oral ciprofloxacin for acute infection with *P aeruginosa*

Comparison 8. Inhaled colistin + oral ciprofloxacin versus inhaled tobramycin + oral ciprofloxacin for acute infection with *P aeruginosa*						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Inhaled tobramycin + oral ciprofloxacin	Inhaled colistin +oral ciprofloxacin				
Relative change in % predicted FEV_1 from baseline Follow-up: 54 days	The mean relative change in % predicted FEV_1 from baseline in the control groups was 2.15	The mean relative change in % predicted FEV_1 from baseline in the intervention groups was 2.4 lower (5.885 lower to 1.0855 higher)		128 (Taccetti 2012)	⊕⊖⊖⊖ very low[1,2]	

Treatment failure - trial discontinuation due to Lack of compliance Follow-up: 28 days	110 per 1000	105 per 1000 (50 to 224)	RR 0.95 (0.45 to 2.03)	223 (Taccetti 2012)	⊕⊖⊖⊖ very low[1,3,4]	
Adverse events - Vomiting Follow-up: 28 days	17 per 1000	9 per 1000 (1 to 104)	RR 0.56 (0.05 to 6.11)	223 (Taccetti 2012)	⊕⊖⊖⊖ very low[1,5]	
Adverse events - Photosensitivity Follow-up: 28 days	0 per 1000	0 per 1000 (0 to 0)	RR 3.37 (0.14 to 81.79)	223 (Taccetti 2012)	⊕⊖⊖⊖ very low[1,5]	
Adverse events - Wheeze Follow-up: 28 days	8 per 1000	3 per 1000 (0 to 77)	RR 0.37 (0.02 to 9.09)	223 (Taccetti 2012)	⊕⊖⊖⊖ very low[1,5]	
Adverse events leading to trial discontinuation - Pulmonary exacerbation during early eradication treatment leading to treatment failure Follow-up: 28 days	42 per 1000	38 per 1000 (11 to 138)	RR 0.9 (0.25 to 3.26)	223 (1 study)	⊕⊖⊖⊖ very low[1,4]	

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; IV: intravenous; RR: risk ratio

1 The quality of the evidence was downgraded by 1 due to serious imprecision as there was no blinding (open-label).
2 The quality of the evidence was downgraded by 2 due to serious imprecision as 95% CI crosses two clinical MIDs.
3 The quality of the evidence was downgraded due to indirect outcome for discontinuation due to adverse events. It is unclear if discontinuation is due to adverse events or other factors.
4 The quality of the evidence was downgraded by 2, as the 95% CI crossed the null effect and the CI was very wide
5 The quality of the evidence was downgraded by 2 due to serious imprecision as 95% CI crosses 2 default MIDs.

9.4.2.3.2 S aureus

No studies were identified for inclusion.

9.4.2.3.3 B cepacia complex

No studies were identified for inclusion.

9.4.2.3.4 Non-tuberculous mycobacteria

No studies were identified for inclusion.

9.4.2.3.5 Non-identified pathogen

No studies were identified for inclusion.

9.4.2.4 Economic evidence

No economic evaluations of interventions relevant to acute antimicrobial treatment were identified in the literature search conducted for this guideline. Full details of the search and economic article selection flow chart can be found in Appendix E and F, respectively.

This review question was not prioritised for de novo economic modelling. Instead additional economic analysis has been undertaken on chronic antimicrobial treatment as this was considered to have a larger impact on resources and current clinical practice.

To aid their recommendations, the committee requested a cost description on antimicrobials to manage acute pulmonary infection with *P aeruginosa.* Unlike the other pathogens under consideration*, P Aeruginosa* was considered to be one of the most prevalent pathogens that require urgent treatment.

Antimicrobials to manage pulmonary infection with *P aeruginosa* include ceftazidime, meropenem and imipenem amongst others. But for these antimicrobials, several brands are available resulting in a variety of acquisition costs. As outlined in NICE's Guide to the methods of technology appraisal 2013, the reduced price should be used in the reference-case analysis to best reflect the price relevant to the NHS. For this reason the lowest cost brand is presented in Table 104. Basic prices are taken from the NHS Electronic Drug Tariff November 2016, unless otherwise stated.

Table 104: Cost of antimicrobials to resolve acute pulmonary infection with *P aeruginosa*

Antimicrobial (quantity, basic price)	Unit cost
Ciprofloxacin (oral)	
100mg tablets (6, £1.86)	£0.31
250mg tablets (10, £0.74)	£0.07
250mg/5ml oral suspension (100ml, £19.80)	£0.99/5ml
500mg tablets (10, £0.87)	£0.09
750mg tablets (10, £8.00)	£0.80
Chloramphenicol (oral)	
250mg capsules (60, £377.00)	£6.28
Aztreonam (inhaled or oral) [a]	
Cayston 75mg powder and solvent for nebuliser solution vials with Altera Nebuliser Handset (84, £2,181.53)	£25.97
Azactam 1g powder for solution for injection vials (1, £9.40)	£9.40
Azactam 2g powder for solution for injection vials (1, £18.82)	£18.82
Meropenem IV [a]	
1g powder for solution for injection vials (10, £153.50)	£15.35
500mg powder for solution for injection vials (10, £76.90)	£7.69
Ceftazidime IV [a]	
500mg powder for solution for injection vials (1, £4.25)	£4.25
1g powder for solution for injection vials (10, £13.90)	£1.39
2g powder for solution for injection vials (10, £27.70)	£2.77
3g powder for solution for injection vials (1, £25.76)	£25.76
Piperacillin-Tazobactam IV [a]	

Antimicrobial (quantity, basic price)	Unit cost
Piperacillin 2g / Tazobactam 250mg powder for solution for injection vials (1, £7.91)	£7.91
Piperacillin 4g / Tazobactam 500mg powder for solution for injection vials (1, £12.90)	£12.90
Tazocin 4.5g powder for solution for injection vials (1, £15.17)	£15.17
Fosfomycin IV [a]	
Fomicyt 2g powder for solution for infusion vials (10, £150.00)	£15.00
Fomicyt 4g powder for solution for infusion vials (10, £300.00)	£30.00
Ticarcillin-Clavulanate IV [a]	
Timentin 3.2g powder for solution for infusion vials (4, £21.32)	£5.33

(a) Taken from the BNF November 2016

9.4.2.5 Evidence statements

9.4.2.5.1 P aeruginosa

Antimicrobial treatment for pulmonary exacerbations due to *P aeruginosa*

Comparison 1. Single IV agents compared for pulmonary exacerbations with *P aeruginosa*

Lung function: FEV_1

Low quality evidence from 2 RCTs with 46 young people and adults with cystic fibrosis experiencing a pulmonary exacerbation with *P aeruginosa* showed no clinically significant difference in absolute change of FEV_1 litres between the participants receiving 2 week courses of both ceftazidime (2g 3/day or 8g/day in 4 doses) and those receiving aztreonam (2g 3/day or 8g/day in 4 doses) at 2 week follow-up. Moderate inconsistency was observed between both trials, but both trials showed no differences between groups. In addition, the difference in the absolute change in FEV_1 litres was minimal in both groups.

Eradication

No evidence was found for this critical outcome.

Resolution of infection/exacerbation or measure of treatment failure (e.g. need for additional antibiotics)

No evidence was found for this important outcome.

Duration of the acute episode

No evidence was found for this important outcome.

Quality of life

No evidence was found for this important outcome.

Mortality

No evidence was found for this important outcome.

Adverse events

No evidence was found for this important outcome.

Comparison 2. Single IV antibiotic (with placebo) versus combination IV antibiotic for pulmonary exacerbations with *P aeruginosa*

Lung function: FEV_1

Low quality evidence from 1 RCT with 98 young people with cystic fibrosis experiencing a pulmonary exacerbation with *P aeruginosa* showed no clinically significant difference in FEV_1 % predicted (absolute change) between the participants who received a 10 day course of IV tobramycin (9mg/kg 3x daily) with placebo and those who received a 10 day course of IV ceftazidime (50mg/kg/dose 3x daily and IV tobramycin 3mg/kg 3x daily) at 10 days follow-up.

Very low quality evidence from 1 RCT with 18 young people with cystic fibrosis with *P aeruginosa* in sputum admitted to hospital for worsening respiratory status showed no clinically significant difference in FEV_1 % predicted (relative change) between the participants who received a 2 week course of both tobramycin with placebo (5% dextrose 4-hourly) and piperacillin at both 50mg/kg 4-hourly and 100mg/kg 8-hourly at 2 week follow-up. All participants received tobramycin 2.5mg/kg 3x daily, oral flucloxacillin 25 mg/kg/day in 4 doses and oral probenecid (suggested to increase antibiotic concentrations) at 250 - 500mg 3x daily.

Adverse events

Low quality evidence from 1 RCT with 18 young people with cystic fibrosis with *P aeruginosa* in sputum admitted to hospital for worsening respiratory status showed no clinically significant difference in sensitivity reactions between the participants who received a 2-week course of tobramycin with placebo (5% dextrose 4-hourly) and those who received a 2-week course of all regimens of piperacillin (both 50 mg/kg 4-hourly and 100 mg/kg 8-hourly) at 2 week follow-up. All participants received tobramycin 2.5 mg/kg 3x daily, oral flucloxacillin 25 mg/kg/day in 4 doses and oral probenecid (suggested to increase antibiotic concentrations) at 250 - 500 mg 3x daily.

Very low quality evidence from 1 RCT with 18 young people with cystic fibrosis with *P aeruginosa* in sputum admitted to hospital for worsening respiratory status showed no clinically significant difference in number of hospital admissions due to tinnitus between the participants who received a 10 day course of both tobramycin (9 mg/kg 3x daily) with placebo and those who received ceftazidime (50 mg/kg/dose 3x daily and IV tobramycin 3 mg/kg 3x daily) at 2 week follow-up.

Very low quality evidence from 1 RCT with 44 young people with cystic fibrosis experiencing an exacerbation with *P aeruginosa* showed no clinically significant difference in serum or creatinine levels between the participants who received a 10 day course of both tobramycin (9 mg/kg 3x daily) with placebo and those who received ceftazidime (50 mg/kg/dose 3x daily and IV tobramycin 3 mg/kg 3x daily) at 2 week follow-up.

However, moderate quality evidence from the same trial showed a clinically significant lower levels of NAG in the participants who received a 10 day course of tobramycin (9 mg/kg 3x daily) with placebo compared with who received a 10 day course combination of IV ceftazidime (50 mg/kg/dose 3x daily) and IV tobramycin (3 mg/kg 3x daily) at 2 week follow-up.

Comparison 3. Single IV antibiotic versus combination IV antibiotic for pulmonary exacerbations with *P aeruginosa*

Lung function: FEV_1

Low quality evidence from 1 RCT with 30 young people with cystic fibrosis experiencing an acute exacerbation due to *P aeruginosa* showed a clinically significant beneficial effect of a 10-14 day course of combination ticarcillin (300 mg/kg/day in 4 doses) and tobramycin (10

mg/kg/day in 3 doses) in FEV_1 % relative change compared with a 10-14 day course ceftazidime (200 mg/kg/day in 4 doses) at 2 week follow-up.

Low quality evidence from 1 RCT with 71 adults with cystic fibrosis experiencing a pulmonary exacerbation with *P aeruginosa* showed a clinically significant beneficial effect of a 12 day course of a combination of colistin (2 MU 3x daily) and a second anti-pseudomonal antibiotic in FEV_1 (ml) absolute change compared with colistin (2 MU 3x daily) alone at 12 days follow-up.

Very low quality evidence from 1 RCT with 21 young people with cystic fibrosis experiencing a pulmonary exacerbation with *P aeruginosa* showed no clinically significant difference in FEV_1 % predicted (absolute change) between a 2 week course of ceftazidime 50 mg/kg 3x daily and a combination of piperacillin (75 mg/kg 4x daily) and tobramycin (10 mg/kg/day in 3 doses) at 2 week follow-up.

Eradication

Low quality evidence from 1 RCT with 38 children with cystic fibrosis showed a clinically significant beneficial effect of combination of piperacillin (600 mg/kg/day) and (tobramycin 8 - 10 mg/kg/day) in eradicating *P aeruginosa* compared with piperacillin alone (600 mg/kg/day).

Resolution of infection/exacerbation or measure of treatment failure (e.g. need for additional antibiotics)

Very low quality evidence from 1 RCT with 19 children with cystic fibrosis admitted to hospital for treatment of a pulmonary exacerbation with *P aeruginosa* showed no clinically significant difference in time to readmission (months) between a 2 week course of ceftazidime (50 mg/kg 3x daily) and a 2 week course combination piperacillin (75 mg/kg 4x daily) and tobramycin (10 mg/kg/day in 3 doses) at 3 months follow-up.

Very low quality evidence from 1 RCT with 22 children and young people with cystic fibrosis and severe chest infection treated for an exacerbation with *P aeruginosa* showed no clinically significant difference in number of admissions to hospital requiring IV antibiotics or mortality between a 2 week course of ceftazidime (150 mg/kg/day) and a 2 week course of combination tobramycin (7.5 mg/kg/day) and ticarcillin (300 mg/kg/day) at 3 months follow-up.

Duration of the acute episode

No evidence was found for this important outcome.

Quality of life

No evidence was found for this important outcome.

Mortality

Low quality evidence from 1 RCT with 21 young people with cystic fibrosis experiencing a pulmonary exacerbation with *P aeruginosa* showed no clinically significant difference in mortality between a 2 week course of ceftazidime 50 mg/kg 3x daily and 2 week course combination piperacillin (75 mg/kg 4x daily) and tobramycin (10 mg/kg/day in 3 doses) at 4 months follow-up.

Low quality evidence from 1 RCT with 71 adults with cystic fibrosis experiencing a pulmonary exacerbation with *P aeruginosa* showed no clinically significant difference in mortality between a 12 day course of a combination of colistin (2 MU 3x daily) and a second anti-pseudomonal antibiotic in FEV_1 (ml) absolute change compared with 12 day course colistin (2 MU 3x daily) alone at 12 week follow-up.

Adverse events

Very low quality evidence from 2 RCTs with 52 children and young people with cystic fibrosis experiencing an exacerbation due to *P aeruginosa* showed no clinically significant difference in liver transaminase enzyme elevation between a 10-14 day course of ceftazidime and combination ticarcillin and tobramycin.

Low quality evidence from 1 RCT with 71 adults with cystic fibrosis experiencing a pulmonary exacerbation with *P aeruginosa* showed no clinically significant difference in neurological adverse effects between a 12 day course colistin (2 MU 3x daily) alone and a 12 day course combination of colistin (2 MU 3x daily) and a second anti-pseudomonal antibiotic at 12 days follow-up.

Very low quality evidence from 1 RCT with 17 children with cystic fibrosis admitted for treatment of pulmonary exacerbations showed no clinically significant difference in rash and fever between a 10 day course of piperacillin alone (600 mg/kg/day) and a 10 day course combination piperacillin (600 mg/kg/day) and tobramycin (8 - 10 mg/kg/day) at 10 days follow-up.

Very low quality from 1 RCT with 30 young people with cystic fibrosis and *P aeruginosa* infection (34 treatment observations) showed no clinically significant difference in proteinuria between a 10-14 day course of ceftazidime (200 mg/kg/day in 4 doses) and combination ticarcillin (300 mg/kg/day in 4 doses) and 10-14 day course tobramycin (10 mg/kg/day in 3 doses) in FEV_1 % relative change compared with ceftazidime.

Low and very low quality evidence from 1 RCT with 71 adults with cystic fibrosis experiencing a pulmonary exacerbation with *P aeruginosa* showed no clinically significant difference in change in blood urea (mmol/L) and change in serum creatine (mol/L) between a 12 day course of a combination of colistin (2 MU 3x daily) and a 12 day course second anti-pseudomonal antibiotic and colistin (2 MU 3x daily) alone at 12 days follow-up.

Comparison 4. Combination IV antibiotics versus combination IV antibiotics for pulmonary exacerbations with *P aeruginosa*

Lung function: FEV_1

Low quality evidence from 1 RCT including observations for 49 courses of IV combination therapy (≈42 people with cystic fibrosis aged 3 to 24 years admitted to hospital due to a pulmonary exacerbation with *P aeruginosa*) showed no clinically significant difference in FEV_1 % predicted (absolute change) between a 2 week course of combination of aztreonam (300 mg/kg/day in 4 doses) and amikacin (36 mg/kg/day in 3 doses) and a 2 week course combination of ceftazidime (300 mg/kg/day in 4 doses) and amikacin (36 mg/kg/day in 3 doses) at 2 week follow-up.

Very low to low quality evidence from 1 RCT with 97 people with cystic fibrosis ≥5 years treated for pulmonary exacerbation showed no clinically significant difference in both FEV_1 % predicted absolute change and relative change between a 2 week course of combination of meropenem (40 mg/kg up to a maximum dose of 2 g) and tobramycin and a 2 week course combination of ceftazidime (50 mg/kg) and tobramycin. Tobramycin dose adjusted to give a peak serum concentration of>= 8 µg/mL and trough concentration of < 2 µg/mL.

Eradication

Very low quality evidence from 1 RCT including observations for 49 courses of IV combination therapy (≈42 people with cystic fibrosis aged 3 to 24 years admitted to hospital due to a pulmonary exacerbation with *P aeruginosa*) showed no clinically significant difference in eradication of *P aeruginosa* between a 2 week course of combination of aztreonam (300 mg/kg/day in 4 doses) and amikacin (36 mg/kg/day in 3 doses) and a 2 week course combination of ceftazidime (300 mg/kg/day in 4 doses) and amikacin (36 mg/kg/day in 3 doses) at 2 week follow-up.

Resolution of infection/exacerbation or measure of treatment failure (e.g. need for additional antibiotics)

No evidence was found for this important outcome.

Duration of the acute episode

No evidence was found for this important outcome.

Quality of life

No evidence was found for this important outcome.

Mortality

No evidence was found for this important outcome.

Adverse events

Very low quality evidence from 1 RCT including observations for 56 courses of IV combination therapy (≈42 people with cystic fibrosis aged 3 to 24 years admitted to hospital due to a pulmonary exacerbation with *P aeruginosa*) showed no clinically significant difference in rash, liver transaminase levels and thrombocytopenia between a 2 week course of combination of aztreonam (300 mg/kg/day in 4 doses) and amikacin (36 mg/kg/day in 3 doses) compared with a 2 week course of combination of ceftazidime (300 mg/kg/day in 4 doses) and amikacin (36 mg/kg/day in 3 doses) at 2 week follow-up.

Comparison 5. Combination of 2 IV antibiotics + inhaled antibiotic versus combination of 2 IV antibiotics without inhaled antibiotic for pulmonary exacerbations with *P aeruginosa*

Lung function

No evidence was found for this critical outcome.

Eradication of pathogen

Moderate quality evidence from 1 RCT including observations for 84 courses of treatment (≈ 62 people with cystic fibrosis aged 3 to 24 years admitted to hospital due to a pulmonary exacerbation with *P aeruginosa*) showed a clinically significant beneficial effect of a 15 day course of IV ceftazidime (250 mg/kg/day in 4 doses) and IV amikacin (33 mg/kg/day in 3 doses) and nebulised amikacin (100 mg 2x daily) compared with a 15 day course IV ceftazidime and IV amikacin without nebulised amikacin at 15 days follow-up.

Duration of the acute episode

No evidence was found for this important outcome.

Quality of life

No evidence was found for this important outcome.

Mortality

No evidence was found for this important outcome.

Adverse events

Very low quality evidence from 1 RCT with including observations for 54 courses of treatment (≈62 people with cystic fibrosis aged 3 to 24 years admitted to hospital due to a pulmonary exacerbation with *P aeruginosa*) found no clinically significant difference in raised liver transaminases between a 15 day course of IV ceftazidime (250 mg/kg/day in 4 doses) and IV

amikacin (33 mg/kg/day in 3 doses) and nebulised amikacin (100 mg 2x daily) compared with IV ceftazidime and IV amikacin without nebulised amikacin.

Comparison 6. Combination IV antibiotics versus oral antibiotics for pulmonary exacerbations with *P aeruginosa*

Lung function

No evidence was found for this critical outcome.

Eradication of pathogen

Moderate quality evidence from 1 RCT with 89 children with cystic fibrosis and *P aeruginosa* infection showed a clinically significant beneficial effect of a 2 week course of combination of IV ceftazidime (50 mg/kg 3x daily) and a 2 week IV tobramycin (3 mg/kg 3x daily) in eradicating *P aeruginosa* compared with oral ciprofloxacin (15 mg/kg 2x daily) at 2 week follow-up.

Duration of the acute episode

No evidence was found for this important outcome.

Quality of life

No evidence was found for this important outcome.

Mortality

No evidence was found for this important outcome.

Adverse events

Very low quality evidence from 1 RCT with 108 children with cystic fibrosis and *P aeruginosa* infection showed no difference in treatment-related adverse events between a 2 week course of combination IV ceftazidime (50 mg/kg 3x daily) and IV tobramycin (3 mg/kg 3x daily) and oral ciprofloxacin (15 mg/kg 2x daily).

Antimicrobial treatment for acute infection with *P aeruginosa*

Comparison 7. Oral ciprofloxacin and inhaled colistin versus inhaled tobramycin for acute infection with *P aeruginosa*

Lung function

No evidence was found for this critical outcome.

Eradication of pathogen

No evidence was found for this critical outcome.

Time to next pulmonary exacerbation

No evidence was found for this important outcome.

Resolution of infection/exacerbation or measure of treatment failure

No evidence was found for this important outcome.

Quality of life

No evidence was found for this important outcome.

Adverse events

Very low quality evidence from 1 RCT with 58 children with cystic fibrosis with new isolation of *P aeruginosa* showed no clinically significant difference in adverse events (severe cough) between a 3 month course of combination inhaled colistin (2 MU 2x daily) and oral ciprofloxacin (10 mg/kg 3x daily) compared with a 3 month course of inhaled tobramycin (300 mg 2x daily for 28 days) at 3 months follow-up.

Comparison 8. Inhaled colistin and oral ciprofloxacin versus inhaled tobramycin and oral ciprofloxacin for acute infection with *P aeruginosa*

Lung function: FEV_1

Very low quality evidence from 1 RCT with 128 people with cystic fibrosis >1 year with first ever or new *P aeruginosa* infection showed no clinically significant difference in FEV_1 % predicted (relative change) between a 28 day course of combination colistin (2x daily inhalation of 2 MU) and ciprofloxacin (2x daily of 15 mg/kg/dose) compared with a 28 day course combination of tobramycin inhaled solution (300 mg 2x daily) and ciprofloxacin (2x daily doses of 15 mg/kg/dose) at 54 days follow-up.

Eradication of pathogen

No evidence was found for this critical outcome.

Time to next pulmonary exacerbation

No evidence was found reporting this important outcome.

Resolution of infection/exacerbation or measure of treatment failure

Very low quality evidence from 1 RCT with 128 people with cystic fibrosis >1 year with first ever or new *P aeruginosa* infection showed no clinically significant difference in discontinuation due to lack of compliance between a 28 day course of combination colistin (2x daily inhalation of 2 MU) and ciprofloxacin (2x daily of 15 mg/kg/dose) compared with a 28 day course of combination of tobramycin inhaled solution (300 mg 2x daily) and ciprofloxacin (2x daily doses of 15 mg/kg/dose) at 28 days follow-up.

Very low quality evidence from 1 RCT with 128 people with cystic fibrosis >1 year with first ever or new *P aeruginosa* infection showed no clinically significant difference in pulmonary exacerbation during early eradication treatment leading to treatment failure between a 28 day course of combination colistin (2x daily inhalation of 2 MU) and ciprofloxacin (2x daily of 15 mg/kg/dose) compared with a 28 day course combination of tobramycin inhaled solution (300 mg 2x daily) and ciprofloxacin (2x daily doses of 15 mg/kg/dose) at 28 days follow-up.

Quality of life (QOL)

No evidence was found for this important outcome.

Adverse events

Very low quality evidence from 1 RCT with 128 people with cystic fibrosis >1 year with first ever or new *P aeruginosa* infection showed no clinically significant difference in adverse events (vomiting, photosensitivity, wheeze) between a 28 day course of combination colistin (2x daily inhalation of 2 MU) and ciprofloxacin (2x daily of 15 mg/kg/dose) compared with a 28 day course combination of tobramycin inhaled solution (300 mg 2x daily) and ciprofloxacin (2x daily doses of 15 mg/kg/dose) at 28 days follow-up.

9.4.2.5.2 S aureus

No evidence was found.

9.4.2.5.3 B cepacia complex

No evidence was found.

9.4.2.5.4 H influenzae

No evidence was found.

9.4.2.5.5 Nontuberculous mycobacteria

No evidence was found.

9.4.2.5.6 Non-identified pathogen

No evidence was found.

9.4.2.5.7 Economic evidence statements

No evidence on cost-effectiveness in people with cystic fibrosis was available for this review.

9.4.2.6 Evidence to recommendations

9.4.2.6.1 Relative value placed on the outcomes considered

The aim of this review was to compare the clinical and cost effectiveness of different antimicrobial regimens in achieving clinical resolution of acute pulmonary infection or exacerbation in children and adults with cystic fibrosis.

The committee chose eradication of specific pathogens, where present, and improvement in lung function measured using either FEV_1 or the lung clearance index (LCI) as critical outcomes for decision making for both acute infection and pulmonary exacerbation.

In addition they chose the following as important outcomes: resolution of exacerbation or measures of treatment failure (for example, the need for additional antibiotics), duration of the episode, quality of life, adverse events and mortality for pulmonary exacerbations. For acute pulmonary infection, the important outcomes were: time to next acute infection, resolution of infection or measure of treatment failure (for example, the need for additional antibiotics), quality of life and adverse events.

9.4.2.6.2 Consideration of clinical benefits and harms

The committee discussed the recommendations for each pathogen separately.

P aeruginosa

The committee acknowledged the evidence presented to them and discussed it in the light of their clinical expertise and experience.

The committee discussed 2 different scenarios: acute infection and pulmonary exacerbation.

If a person with cystic fibrosis develops a new infection with *P aeruginosa* (meaning a positive respiratory secretion sample culture where previous cultures in the recent past have been negative) the committee agreed antibiotic treatment is needed. They emphasised early treatment of *P aeruginosa* infection is very important as it is recognised chronic infection with this pathogen has a negative impact in the quality of life.

The committee noted the management will differ depending on the severity of the symptoms.

If the person is clinically well, the committee suggested it should be treated in order to try to eradicate it using a combination of systemic antibiotics, oral or intravenous, with an inhaled antibiotic. They discussed the use, for example, of oral ciprofloxacin combined with inhaled

colistin or nebulised tobramycin. The recommendation to treat this group was based on the committee's recognition that *P aeruginosa* is an important pathogen in cystic fibrosis. In their expert opinion intensive treatment with systemic and inhaled antibiotics should improve the chances of eradication. The committee made this recommendation based on their clinical experience as the available evidence was scarce and of very low quality and, therefore, not very useful in making recommendations.

If the person is clinically unwell, for example with new respiratory symptoms and signs or a worsening of existing respiratory symptoms and signs, the approach might be different. The committee recommended that, in that situation, the initial therapy should consist of a course of intravenous antibiotics with an inhaled antibiotic. They discussed, for example, the use of 2 anti-pseudomonal antibiotics, such as ceftazidime and tobramycin, given intravenously together with the inhaled antibiotic. This recommendation is based on moderate quality evidence that showed participants who received an inhaled antibiotic in addition to a combination of 2 intravenous antibiotics were less likely to be admitted to hospital due to a pulmonary exacerbation.

In both groups, based on the consensus of the committee, they advised giving extended treatment in order to try to increase the likelihood of eradication.

In the event that eradication was unsuccessful, the committee agreed that prolonged treatment with an inhaled antibiotic should be given to try and supress it. They recommendations using colistimethate as the first-line choice for this inhalation therapy. Please see antimicrobial treatment for the management of chronic *P aeruginosa*.

For the management of pulmonary exacerbations due to *P aeruginosa* in people who are chronically infected with pseudomonas, the committee agreed to recommend oral or intravenous antibiotics, depending on the severity of the illness. The intravenous treatment should consist in a combination of 2 agents, as supported by the evidence included in this review. The committee noted that low quality evidence showed a clinically significant beneficial effect in lung function and in eradication of the organism with a combination of 2 intravenous antibiotics compared to a single antibiotic. In addition, the evidence showed no clinically significant difference in the occurrence of adverse events.

Finally, the committee recommended that if people with chronic *P aeruginosa* infection suffer from repeated pulmonary exacerbations, consideration should be given to altering the antibiotic regimen used at intervals in order to reduce the possibility of non-response due to emergence of resistance. This should take account of the individual's pseudomonas antibiotic sensitivity testing. This recommendation was based on the consensus of the committee.

S aureus

No evidence was found for the treatment of *S aureus*, therefore, recommendations were based on committee's clinical expertise.

The committee discussed 2 possible scenarios, depending on whether the child is on prophylaxis treatment.

The committee recognised that a potential reason for emergence of *S aureus* infection was non-adherence to the prophylaxis regimen, so they advised this should be reviewed with parents and carers. They also advised that following treatment-dose anti-staphylococcal antibiotics, the prophylaxis should be reinstated even if treatment was unsuccessful as they believed that suppression of the infection was likely to be clinically beneficial.

If a child is not on prophylaxis against *S aureus*, and is then found to have developed an infection with this pathogen, the committee recommended oral antibiotic treatment if they are well. They discussed flucloxacillin, co-amoxiclav or doxycycline as potentially useful antibiotic

choices for people over 12 years. If, however, they are unwell (for example, with symptoms such as cough), and have evidence of pulmonary disease (for example, reduced lung function based on testing), then either oral or intravenous antibiotic treatment, depending on disease severity, is recommended. The antibiotic used should be broad spectrum to take account of the possibility that *S aureus* might not be the cause of the illness, but the treatment should include anti-*S aureus* cover.

The committee agreed that for people with new evidence of MRSA respiratory infection (with or without pulmonary exacerbation), specialist microbiological advice should give guidance on treatment to eradicate it.

B cepacia complex

No evidence was found for the treatment of *B cepacia* complex, therefore recommendations were based on committee's clinical expertise.

The committee agreed that if a person develops a new infection with *B cepacia* complex, an attempt should be made to eradicate the infection with antibiotic therapy whether or not the person was unwell with the infection. They considered that specialist advice should be sought on this treatment. They suggested a combination of 2 or 3 appropriate intravenous antibiotics would usually be given. Examples of intravenous antibiotics that might be advised included, but are not limited to, ceftazidime, meropenem, amikacin and temocillin in addition to specialist advice on the exact regimen was required. The committee noted that it is important to treat new *B cepacia* complex infections effectively as chronic infection can cause a deterioration in lung function and, in some people, an overwhelming, and even fatal, infection called 'cepacia syndrome' may occur. Persistent isolation of *B cepacia* complex may also adversely impact on a persons' eligibility for transplantation. The committee noted that treating new infections with B cepacia complex is common practice in adult CF centres.

The committee also discussed the case of people with chronic *B cepacia* complex infection despite attempts at eradication. They did not recommend treatment for those with chronic *B cepacia* complex who are clinically well. They noted that *B cepacia* complex is very resistant to most treatments once established, therefore, treatment is unlikely to work. However, if they became unwell with a pulmonary exacerbation, the committee recommended that specialist advice be sought regarding the use of oral or intravenous antibiotics. They discussed that this would usually be with a course of intravenous antibiotics, although oral antibiotics might also be used for a less severe exacerbation.

H influenzae

No evidence was found for the treatment of *H influenzae*, therefore recommendations were based on committee's clinical expertise.

The committee agreed it is important to treat *H influenzae* in order to prevent chronic infection with this pathogen. This is because although there might not be detectable evidence of disease due to it, the belief is that it will cause lung damage and so should be eradicated. They discussed 2 possible scenarios if a person develops an infection.

If the person is clinically well (asymptomatic), the committee recommended giving an oral antibiotic agent. If the person is clinically unwell (for example, with cough or reduced lung function), they recommended the use of an oral or intravenous antibiotic treatment depending on the severity of the illness.

These recommendations are consistent with clinical practice and with the CF Trust recommendations (CF Consensus document: antibiotic treatment for Cystic Fibrosis, 2009).

Nontuberculous *mycobacteria*

No evidence was found for the treatment of nontuberculous *mycobacteria* (NTM), therefore, recommendations were based on committee's clinical knowledge and expertise. The committee noted that treatment is complex and guidelines are evolving. There is still uncertainty about the best approach to treatment.

The committee emphasised the importance of confirming the presence on nontuberculous *mycobacteria* by repeating respiratory secretion cultures. This is because nontuberculous *mycobacteria* are often just sporadic commensal organisms, that is, they just come and go without causing disease. Therefore, the first step when this pathogen is found is to ensure that it persists before actually considering whether it is causing disease. This diagnostic issue was also raised by the CF Trust Consensus document on antibiotic treatment for cystic fibrosis (CF Consensus document: antibiotic treatment for Cystic Fibrosis, 2009).

The committee noted, in a person with respiratory disease who is found to be NTM positive, it was not always easy to determine whether or not the infection was contributing to the disease. Therefore, they recommended that a chest CT scan should be performed because it may show changes that would clarify the role of nontuberculous *mycobacteria* in the disease.

The committee recommended that a discussion should take place with the person affected and, if appropriate, with parents or carers about the uncertain benefits of therapy aimed at eradication of nontuberculous *mycobacteria*. They should discuss that, when considering a decision to treat, it is important to be aware of the potential toxicities associated with the drugs used. Potential toxic effects included vomiting, nephrotoxicity and ototoxicity. This is particularly pertinent for people who are positive for nontuberculous *mycobacteria* but clinically well, where the benefits are less certain.

The committee recommended that consideration be given to treatment for those who are positive for nontuberculous *mycobacterium* respiratory infection and who have a chest CT scan showing changes consistent with it and who are unwell with pulmonary disease, despite optimisation of other treatment. The recommendation made by the committee to treat based on clinical grounds is consistent with the CF Trust recommendations (CF Consensus document: antibiotic treatment for Cystic Fibrosis, 2009).

The committee recognised that evidence regarding the optimal antibiotic regimen and duration of treatment was lacking. The committee discussed the fact that the approaches to treating *M avium* complex and *M abscessus* differ. Currently, treatment for *M avium* typically includes a combination of 3 oral anti-mycobacterial agents including a macrolide and rifampicin and ethambutol. Current eradication treatment for *M abscessus* is more intensive and may include repeated courses of triple antibiotic therapy administered intravenously, together with a combination or oral and inhaled antibiotics. Antibiotics used include, but are not limited to, cefoxitin, tigecycline, amikacin, carbapenems and macrolides. They recommended that specialist microbiological advice be sought on which antibiotics to use and on duration of treatment. The committee noted that there was existing consensus guidance on the management of non-tuberculous mycobacteria in an article by Floto, R. A., Olivier, K. N., Saiman, L., et al. (2016) titled "US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis".

Non-identified pathogen

No evidence was found for the treatment of unidentified infections, therefore recommendations were based on committee's clinical expertise.

The committee agreed that if a person presents with clinical manifestations suggesting the development of an acute pulmonary infection, or an exacerbation without an identified pathogen, it would be appropriate to treat with a broad-spectrum antibiotic while continuing to

collect respiratory secretion samples. The choice of oral or IV treatment will depend on the severity of the symptoms.

Treatment should be modified once the pathogen causing the infection or the exacerbation is identified.

9.4.2.6.3 Consideration of economic benefits and harms

The clinical evidence review demonstrated that the benefits of combination antibiotics to treat exacerbations due to *P aeruginosa* could justify their additional cost relative to single antibiotics. For example, clinically significant beneficial effects in lung function were found for combination IV antibiotics compared to single IV antibiotics. Clinically significant benefits in eradication were found for the more intensive regimen, specifically combination IV antibiotics compared to single antibiotic therapy, 2 IV antibiotics plus an inhaled antibiotic compared to IV antibiotics without an inhaled antibiotic and combination IV antibiotics compared to oral antibiotics.

No evidence was found for the other pathogens listed in the protocol, thus the committee made recommendations to reflect current clinical practice and resource use as they considered this to be a cost-effective use of resources.

The specific antibiotics administered in the trials were of less importance to the committee as antibiotics received by a person with cystic fibrosis to treat an acute infection, or exacerbation, need to be varied in accordance with cultures, sensitivities and local resistance patterns of isolated pathogens. Consequently, the committee stated it would be inappropriate to recommend specific antibiotics or a number of antibiotics as this would limit the variation in antibiotics used by healthcare professionals and, subsequently, the effectiveness and cost-effectiveness of the antibiotic over time. Instead, the committee were interested in the combination and preparation of antibiotics that were administered to infer which regimens were cost-effective.

When the same number of different combinations of antibiotics, of the same preparation (for example, two IV antibiotics vs. a different combination of two IV antibiotics) were compared, no significant difference was demonstrated for any of the proposed outcomes. However, the committee iterated that no significance difference does not infer that there was no clinical change, pre versus post treatment, as the trials included a comparator that was an antimicrobial agent that would be expected to issue a treatment effect.

In light of the findings from the clinical evidence review and their own clinical experience, the committee wanted to recommend 2 antibiotics in different classes and consider changing regimens over time when treating exacerbations associated with *P aeruginosa*. The committee added, when discussing cost implications, that ceftazidime is used more often and is less expensive than aztreonam and meropenem.

The committee agreed IV antibiotics are generally more expensive than oral preparations for many reasons regardless of the active agent, including their purchase price and, in some cases, sterile production and healthcare professional administration. Additionally, they are more invasive and have a greater potential for associated adverse effects. Consequently, the committee recommended that, where appropriate, if the person is clinically well (asymptomatic), treatment with an oral agent should be considered; whereas if the person is clinically unwell (for example presents with cough or reduced lung function) the use of an appropriate oral or IV antibiotic could also be considered depending on the severity of symptoms.

The committee noted that the experience of each clinic to manage the range of pathogens people with cystic fibrosis can become infected with can be variable. Moreover, given the limited evidence on the most effective way to treat acute infections, the committee agreed that the cost of obtaining specialist advice on how to manage rarer, and potentially

detrimental pathogens such as MRSA, *B cepacia* complex and non-tuberculous mycobacteria, would be offset by the potential downstream costs from inappropriate management. Therefore, to ensure the most effective antibiotic regimens are utilised, the committee made recommendations to seek specialist microbiological advice on which antibiotics to use and on the duration of treatment.

The committee were reluctant to recommend "no treatment" in people with cystic who have a pulmonary disease exacerbation and no clear cause (based on recent respiratory secretion samples) as the lack of evidence should not infer lack of effect. Given that the expected downstream costs from an untreated infection would outweigh the cost of treatment, the committee agreed a broad-spectrum antibiotic should be offered.

9.4.2.6.4 Quality of evidence

P aeruginosa

The quality of the evidence was rated as very low to moderate as assessed by GRADE for the antimicrobial treatment due to pulmonary exacerbations with *P aeruginosa*, and very low for the antimicrobial treatment of acute infections with *P aeruginosa*. No high quality evidence was found. The main reasons that led to downgrading the quality of the evidence were:

- For the domain risk of bias, the studies were assigned the same risk of bias as in the Cochrane reviews and were not individually reviewed. The main biases that lead to downgrading the quality of the evidence were attrition bias and lack of blinding.
- Another reason that lead to downgrading the quality of the evidence was imprecision as confidence intervals crossed 1 or 2 MIDs.

No serious issues were found regarding the directness of the population or the interventions.

S aureus

Not applicable, as no evidence was found for this pathogen.

***B cepacia* complex**

Not applicable, as no evidence was found for this pathogen.

Non-tuberculous mycobacteria

Not applicable, as no evidence was found for this pathogen.

Non-identified pathogen

Not applicable, as no evidence was found for this pathogen.

9.4.2.6.5 Other considerations

No equality issues were identified by the committee for this review question.

The committee agreed a research recommendation should not be prioritised for this topic. They noted there is sufficient evidence available on the management of acute exacerbations with *P aeruginosa*. They also noted studies on the management of acute infection with other pathogens are difficult to conduct. Recommendations are consistent with clinical practice and new research is unlikely to lead to significant changes.

9.4.2.6.6 Key conclusions

The committee concluded that:

- People with cystic fibrosis who present with a new infection with *P aeruginosa* should be treated with a combination of oral or IV antibiotics together with inhaled antibiotics, regardless of whether the person is symptomatic or not. A follow-up antibiotic treatment could be considered with the aim to eradicate the pathogen.
- People with cystic fibrosis who present with an acute exacerbation due to *P aeruginosa* should be treated with a combination of oral or IV antibiotics, depending on the severity of the illness. Agents should be changed over time.
- Children with cystic fibrosis who are on prophylactic treatment and present with a new infection with *S aureus* should start treatment-dose anti-staphylococcal antibiotics.
- People with cystic fibrosis who are not on prophylactic treatment and present with a new infection with *S aureus* and are clinically well may require treatment with an oral anti-staphylococcal antibiotic.
- People with cystic fibrosis who are not on prophylactic treatment and present with a new infection with *S aureus* and are clinically unwell may require treatment with an additional oral or intravenous anti-staphylococcal antibiotic.
- For people who have new evidence of MRSA respiratory infection (with or without pulmonary exacerbation), specialist microbiological advice should be sought on treatment to eradicate it.
- People with cystic fibrosis who present with a new infection with *B cepacia* complex should be given a combination of IV antibiotics, regardless of whether they are symptomatic or not.
- People with cystic fibrosis who present with an acute exacerbation due to *B cepacia* complex should be treated with appropriate oral or IV antibiotics, depending on the severity of the illness.
- People with cystic fibrosis who present with a new infection with *H influenzae* should be treated with appropriate oral or IV antibiotics, depending on the severity of the symptoms.
- People with cystic fibrosis who present with a new infection where non-tuberculous *mycobacteria* is suspected should have the diagnosis confirmed prior to commencing treatment. Combination anti-mycobacterial treatment should be considered. Specialist microbiologist advice should be sought.
- People with cystic fibrosis who present with an acute exacerbation due to non-tuberculous *mycobacteria* should be treated with appropriate oral or IV antibiotics, depending on the severity of the illness.
- People with cystic fibrosis who present with an exacerbation without a known pathogen should be treated with an oral or IV broad-spectrum antibiotic. Treatment should be changed accordingly, once the pathogen has been identified.

9.4.3 Chronic

Review question: What is the effectiveness of antimicrobial regimens in suppressing chronic pulmonary infection in children and adults with cystic fibrosis with any of the following pathogens: *P aeruginosa, B cepacia Complex, S aureus* and *Aspergillus Fumigatus*?

9.4.3.1 Description of clinical evidence

The aim of this review was to determine the clinical and cost-effectiveness of different antimicrobial treatment regimens to suppress chronic pulmonary infection in children and adults with cystic fibrosis and one of the following pathogens:

- *P aeruginosa*
- *S aureus*

- *B cepacia* complex
- *A fumigatus*

We searched for systematic reviews of RCTs and RCTs, including cross-over trials. Systematic reviews were assessed for inclusion against the protocol, and if relevant, their quality was assessed using AMSTAR. High-quality systematic reviews were included in our review, and where possible, data and quality assessment was taken directly from the review. Individual studies were also retrieved for completeness and accuracy, and were checked for additional outcomes of interest. Low-quality systematic reviews were excluded from our review, but their lists of included studies were checked to identify relevant trials.

For full details see review protocol in Appendix D.

The results are presented separately for each pathogen.

9.4.3.1.1 P Aeruginosa

The interventions that were included in the protocol for the treatment of chronic infection with *P aeruginosa* were Aztreonam lysine (inhaled, nebulised), Azithromycin (oral, antibiotic-dose only), Ciprofloxacin (oral), Colistimethate sodium (dry powderfor inhalation, nebulised), Fosfomycin (inhaled) and Tobramycin (dry powder for inhalation, nebulised).

One NICE TA report 276 (Tappenden 2013) has been published to provide guidance on the treatment of chronic *P Aeruginosa*. This systematic review evaluated the effectiveness and cost-effectiveness of Colistimethate sodium dry powder inhalation and Tobramycin dry powder inhalation for the treatment of chronic *P Aeruginosa* lung infection in people with cystic fibrosis over the age of 6 years. Three trials were included in the review (COLO/DPI/02/05, COLO/DPI/02/06, Konstan 2011a/ EAGER trial).

Four Cochrane systematic reviews were identified in the search.

- Two reviews were included:
  - Remmington (2016) evaluated the effectiveness of oral anti-pseudomonal antibiotics for cystic fibrosis. One trial was included from this review (Sheldon 1993).
  - Ryan (2011) evaluated the effectiveness of inhaled antibiotics for long-term therapy in cystic fibrosis. Eight trials were included from this review (Chuchalin 2007, Hodson 2002, Jensen 1987, Lenoir 2007, McCoy 2008, Murphy 2004, Ramsay 1993, Ramsey 1999).
- Two reviews were excluded:
  - Elphick (2016) evaluated the effectiveness of single versus combination IV antibiotic therapy for treating people with cystic fibrosis. One trial included people with cystic fibrosis and chronic infection with *P Aeruginosa*, but it was not included in the review as it evaluated the effectiveness of Ceftazidime, a treatment that was not prioritised by the committee in the evidence review protocol.
  - Southern (2012) evaluated the effectiveness and safety of macrolide antibiotics. All the included studies used low dose azithromycin, lower than the therapeutic range for antimicrobial action, and they were not relevant for this review.

Seven further systematic reviews were identified. Six of them (Cai 2011, Carr 2004, Florescu 2009, Littlewood 2012, Maiz 2013 and Mukhopadhyay 1996) were assessed as low quality according to AMSTAR and were, therefore, excluded from our review. The included papers were checked for inclusion. Utteley (2013) was excluded as it reported the same data as the TA report.

In addition, 8 primary studies have also been identified (Assael 2013, Flume 2016, Galeva 2013, Konstan 2011/ EVOLVE trial, Retsch-Bogart 2009, Schuster 2013, Trapnell 2012, Wainwright 2011).

The size of the studies ranged between 16 and 520 people. Thirteen studies included children, young people and adults (Assael 2013, Chuchalin 2007, COLO/DPI/02/05, COLO/DPI/02/06, Flume 2016, Galeva 2013, Jensen 1987, Konstan 2011/EVOLVE trial, Konstan 2011a/EAGER trial, Lenoir 2007, McCoy 2008, Retsch-Bogart 2009, Schuster 2013), 2 studies included children and young people (Murphy 2004, Wainwright 2011), 1 included young people and adults (Hodson 2002), 3 studies included adults only (Ramsey 1999, Sheldon 1993, Trapnell 2012). 1 study (Ramsey 1993) did not report the age range, the mean age was 17.7 years.

Two studies were conducted in the UK (COLO/DPI/02/05, Hodson 2002), 6 in the USA (Flume 2016, Murphy 2004, Retsch-Bogart 2009, Ramsey 1993, Ramsey 1999, Trapnell 2012), 1 in Canada (Sheldon 1993), 1 in Denmark (Jensen 1987), 10 studies in multiple countries; 1 in the EU, Russia and Ukraine (COLO/DPI/02/06), 1 in Europe and the United States (Assael 2013), 1 in Hungary, Poland and Russia (Chuchalin 2007), 1 in Bulgaria, Estonia, Latvia, Lithuania, Romania, Russia, Egypt, and India (Galeva 2013), 1 in Bulgaria, Lithuania, Serbia, Argentina, Brazil, Chile, Mexico and the United States (Konstan 2011/EVOLVE trial), 1 in 15 unspecified countries (Konstan 2011a/EAGER trial), 1 in France, Italy, Moldova, Ukraine (Lenoir 2007), 1 in Australia, Canada, New Zealand and the United States (McCoy 2008), 1 in Europe (Schuster 2013), 1 in Australia and the United States (Wainwright 2011).

The included studies evaluated their effectiveness based on the following comparisons.

- Aztreonam lysine vs placebo – 3 studies (McCoy 2009, Retsch-Bogart 2009, Wainwright 2011)
- Ciprofloxacin vs placebo – 1 study (Sheldon 1993)
- Colistin vs placebo – 1 study (Jensen 1987)
- Colistin inhalation powder vs colistin inhalation solution – 1 study (COLO/DPI/02/05)
- Colistin vs tobramycin – 3 studies (Hodson 2002, COLO/DPI/02/06, Schuster 2013)
- Tobramycin vs placebo – 6 studies (Chuchalin 2007, Galeva 2013, Konstan 2011/EVOLVE trial, Lenoir 2007, Ramsey 1993, Ramsey 1999)
- Tobramycin inhalation powder vs tobramycin inhalation solution – 1 study (Konstan 2011a/EAGER trial)
- Tobramycin vs Aztreonam lysine – 1 study (Assael 2013)
- Fosfomycin + tobramycin vs placebo – 1 study (Trapnell 2012)
- Tobramycin + azithromycin vs tobramycin alone (Flume 2016)
- Continuous alternating therapy vs intermittent treatment: aztreonam lysine + tobramycin or placebo + tobramycin (Flume 2016)

A report from the National Horizon Scanning Centre (NHSC 2010) was also identified. This report included 5 trials that have been retrieved for assessment.

The presentation of evidence synthesis will be divided in 2 parts based on the type of analysis which was used to produce these syntheses:

- A network meta-analysis was conducted for the treatment of chronic *P Aeruginosa.* It included the critical outcomes listed in the protocol: lung function (FEV_1) and number of people with ≥ 1 exacerbations. The results for these will be provided at a later stage.
- Pairwise comparisons have been performed for the rest of the outcomes included in the review protocol and are presented in this review.

9.4.3.1.2 S Aureus

The interventions that were included in the protocol for the treatment of chronic infection with *S aureus* were Cefradine (oral), Cotrimoxazole (oral), Doxycycline (oral) and Flucloxacillin (oral).

One Cochrane review (Lo 2015) was identified for potential inclusion. This review aimed to evaluate the effectiveness of antimicrobial treatment regimens to eradicate methicillin-resistant *S aureus* (MRSA) in people with cystic fibrosis and all disease severities. No trials were identified for inclusion. The list of excluded studies was also checked. None of the 48 excluded studies were relevant.

No other trials relevant trials were identified in our search.

9.4.3.1.3 B Cepacia Complex

The interventions that were included in the protocol for the treatment of chronic infection with *B cepacia* complex were Ceftazidime (inhaled, nebulised), Cotrimoxazole (oral), Imipenem (inhaled, nebulised), Meropenem (inhaled, nebulised), and Trimethoprim (oral).

One Cochrane review (Ryan 2011) was identified for potential inclusion. This review included trials that evaluated the effectiveness of inhaled antibiotics for long-term therapy in cystic fibrosis and included one cross-over trial that looked at people with cystic fibrosis infected with *B cepacia*. This study was not considered for inclusion in our review as it assessed the effectiveness of inhaled Taurolidine, an intervention that is not routinely used in clinical practice.

No other trials relevant trials were identified in our search.

9.4.3.1.4 A Fumigatus

The interventions that were included in the protocol for the treatment of chronic infection with *A fumigatus* were Amphotericin (inhaled, nebulised), Itraconazole (oral), Posaconaizole (oral) and Voriconazole (oral).

One Cochrane review (Elphick 2014) was identified for potential inclusion. This review evaluated the effectiveness of antifungal interventions for the treatment of allergic bronchopulmonary aspergillosis (ABPA) in people with cystic fibrosis. No trials were identified for inclusion. The list of excluded studies was also checked. One study (Aaron 2012) had already been identified in our search and it is included in the review, and the other three studies were not relevant (due to study design or intervention evaluated). This RCT included 35 people with cystic fibrosis over the age of 6 years, and chronically colonised with *A fumigatus*. It was conducted in Canada. It compared the effectiveness of oral Itraconazole versus placebo for a 24-week treatment period. In relation to the outcomes, it included lung function, pulmonary exacerbations, quality of life and adverse events.

9.4.3.2 Summary of included studies

A summary of the studies that were included in this review are presented in Table 105 to Table 107.

Table 105: Summary of included studies for antimicrobials for chronic pulmonary infection with *P aeruginosa*

Study	Intervention/ Comparison	Population	Outcomes	Comments
Technology Appraisal				
NICE TA 276 (Tappenden 2013)	Comparison 1: Tobramycin DPI vs Tobramycin nebulised (EAGER trial) Comparison 2:	People with cystic fibrosis ≥ 6 years and chronic *P aeruginosa* pulmonary colonisation.	• Lung function, FEV_1% • Frequency and severity of respiratory exacerbations	All studies are RCTs, open label EAGER trial: Konstan 2011a Other outcomes included in the

Study	Intervention/ Comparison	Population	Outcomes	Comments
	Colistimethate sodium DPI vs tobramycin nebulised (COLO/DPI/02/06) Comparison 3: Colistimethate sodium DPI vs colistimethate sodium nebulised (Davies 2004, COLO/DPI/02/05)		• *proxy for Time to next pulmonary exacerbation* • Rate and extent of microbiological response (Eradication of the specified organism from sputum/airway cultures) • Quality of life • Adverse events Not reported: • Nutritional status • Emergence of resistant organisms/ antibiotic resistance	TA: Respiratory symptoms
Cochrane systematic reviews				
Remmingt on 2016 Cochrane SR	Comparison 1: Ciprofloxacin (500 mg) vs placebo (Sheldon 1993)	People with cystic fibrosis diagnosed by clinical features and all levels of severity of lung disease.	• Comparison 1: Ciprofloxacin vs placebo • FEV_1 • Eradication of the organism • Adverse events	AMSTAR: 11/11
Ryan 2011 Cochrane SR	Comparison 1: Aztreonam lysine vs placebo (McCoy 2008) Comparison 2: Colistin vs placebo (Hodson 2002, Jensen 1987) Comparison 3: Tobramycin vs placebo (Chuchalin 2007, Hodson 2002, Lenoir 2007, Murphy 2004, Ramsay 1993, Ramsay 1999)	People with cystic fibrosis diagnosed by clinical features and all levels of severity of lung disease.	Comparison 1: Aztreonam lysine vs placebo • FEV_1%: Included in NMA • Exacerbations: Included in NMA • QoL • Adverse events Not reported: • Eradication of the organism • Nutritional status • Emergence of resistant organisms/ antibiotic resistance Comparison 2: Colistin vs placebo • FEV_1%: Included in NMA • Exacerbations: Included in NMA Not reported: • Eradication of the organisms* • Nutritional status*	AMSTAR: 11/11 *reported in individual studies

Study	Intervention/ Comparison	Population	Outcomes	Comments
			• QoL • Adverse events • Emergence of resistant organisms/ antibiotic resistance Comparison 3: Tobramycin vs placebo • FEV_1%: Included in NMA • Exacerbations: Included in NMA • Adverse events Not reported: • Eradication of the organisms* • Nutritional status* • QoL • Emergence of resistant organisms/ antibiotic resistance*	
Primary studies included in the TA or in the Cochrane SR				
Chuchalin 2007 (Hungary, Poland, Russia) RCT	Intervention Tobramycin (nebulised) 300 mg. 24 weeks: 4 weeks "on treatment", followed by 4 weeks "off treatment" Comparison Placebo	N=247 people with cystic fibrosis and *P aeruginosa* ≥6 years Age range: 6 to 45	• Lung function (FEV_1) • Exacerbations • Nutritional status • Eradication of the organism • Adverse events • Mortality • Emergence of resistant organisms	Included in Cochrane SR Ryan 2011 Included in NMA and review
COLO/DPI/02/05 (UK) Open label RCT, with cross-over	Intervention Colistin sodium DPI 125 mg, twice daily Comparison Colistin sodium solution 2 MU, twice daily Duration: 8 weeks	N=16 people with cystic fibrosis with chronic *P aeruginosa* infection ≥8 years Mean (SD) age: 20.3 (12.87) years	• Lung function (FEV_1) • Adverse events	Included in NICE TA 276 Included in the review
COLO/DPI/02/06 (EU, Russia, Ukraine) Open label RCT	Intervention Colistin sodium DPI 125 mg; twice daily Comparison Tobramycin inhalation solution 300 mg/ 5 ml; twice daily	N=380 people with cystic fibrosis and *P aeruginosa* ≥6 years Mean (SD) age: 21.3 (9.72) vs 20.9 (9.30) years	• Lung function (FEV_1) • Time to next exacerbation • Nutritional status • Quality of life • Adverse events	Included in NICE TA 276 Included in the review

Study	Intervention/ Comparison	Population	Outcomes	Comments
	Duration: 24 weeks			
Hodson 2002 (UK) Open label RCT	Intervention Tobramycin (nebulised) 300 mg daily in 5ml twice daily Comparison Colistin (nebulised) 1MU in 3ml in saline twice daily Duration: 28 days	N=126 randomised (n=115 treated) people with cystic fibrosis Age range: 17 to 50 years	• Pulmonary function (FEV_1) • Eradication of the organism • Adverse effects • Emergence of resistant organisms	Included in Cochrane SR Ryan 2011 Included in NMA and review
Jensen 1987 (Denmark) RCT	Intervention Colistin (nebulised) 1 million units, twice daily for 3 months Comparison Placebo (normal saline)	N=40 people with cystic fibrosis and chronic *P aeruginosa* infection ≥6 years Age range: 7 to 35 years	• Lung function (FEV_1) • Eradication of the organism • Emergence of resistant organisms	Included in Cochrane SR Ryan 2011 Included in NMA and review
Konstan 2011a (EAGER trial) (15 countries, not specified)	Intervention Tobramycin inhalation powder 112 mg, 4-capsules, twice daily Comparison Tobramycin (nebulised) 300mg/ 5 ml, twice daily	N=121 people with cystic fibrosis ≥ 6 years and positive cultures of *P aeruginosa* within 6 months of screening Mean age (SD): 26 (11.4) vs 25 (10.2)	• Lung function (FEV_1) • Exacerbations (hospitalization) • Eradication of the organism • Adverse events	Included in NICE TA 276 Included in NMA and the review
Lenoir 2007 (France, Italy, Moldova, Ukraine) RCT	Intervention Tobramycin (nebulised) 300 mg twice daily for 4 weeks followed by a 4-week run-out phase Comparison Placebo	N=59 with cystic fibrosis and *P aeruginosa* infection ≥6 years Age range: 6 to 30 years	• Lung function (FEV_1) • Eradication of the organism • Adverse effects	Included in Cochrane SR Ryan 2011 Included in NMA and review
McCoy 2008 (Australia, Canada, New Zealand and USA) RCT	Intervention Aztreonam lysine 75 mg, for 4 weeks, 2 or 3- times daily Comparison Placebo (5 mg lactose in 1 ml 0.17% sodium chloride)	N=246 people with cystic fibrosis and documented *P aeruginosa* infection Age range: 7 to 65 years	• FEV_1 • Time to next exacerbation • Adverse events • Note: FEV_1 was not included in the review as it was reported narratively only, and could not be meta-analysed	Included in Cochrane SR Ryan 2011 Included in NMA and review

Study	Intervention/ Comparison	Population	Outcomes	Comments
Murphy 2004 (USA) Open label RCT	Intervention Tobramycin (nebulised), 300 mg twice daily. Alternating 4-weekly cycles for 56 weeks Comparison No treatment	N=184 children and young people with cystic fibrosis with ≥2 cultures of *P aeruginosa* Age range: 6 to 15 years	• Exacerbations (hospitalization)	Included in NMA only
Ramsey 1993 (USA) Cross-over RCT	Intervention Tobramycin (nebulised) 600 mg, 3-times daily for 28 days, then cross-over for 2 28-days periods Comparison Placebo (0.5 normal saline)	N=71 people with cystic fibrosis and *P aeruginosa* sputum culture susceptible to tobramycin Mean age (SD): 17.7 years (1.25)	• Lung function (FEV_1) • Exacerbations	Included in Cochrane SR Ryan 2011 Included in NMA and review
Ramsey 1999 (USA) RCT	Intervention Tobramycin (nebulised) 300mg twice daily for three 28-day on-off cycles Comparison Placebo (0.225 normal saline and 1.25 mg quinine)	N=520 people with cystic fibrosis infected with *P aeruginosa* Age: 18 years or older	• Lung function (FEV_1) • Exacerbations (hospitalization) • Adverse events • Note: FEV_1 was not included in the review as it was reported narratively only, and could not be meta-analysed	Included in Cochrane SR Ryan 2011 Included in NMA and review
Sheldon 1993 (Canada) RCT	Intervention Ciprofloxacin 500 mg, for 10 days every 3 months for 4 courses Comparison Placebo	N=40 adults with cystic fibrosis and chronically infected with *P aeruginosa* (31 completed the trial) Age ≥ 18 years	• Weight • Adverse events • Mortality • Emergence of resistant organisms	Included in Cochrane SR Remington 2013 Included in review and review
Additional primary studies				
Assael 2013 (Europe and USA) Open label RCT	Intervention Aztreonam lysine 28-day course x 3 Comparison Tobramycin (inhaled) 28 days course, 3000 mg, 2- times/day	N=273 people with cystic fibrosis ≥6 years and PA-positive sputum culture within the previous 3 months Mean age (SD): 25.5 years (9.0)	• Pulmonary function (FEV_1) • Exacerbations (requiring IV and/or additional antibiotics for respiratory events) • Eradication of the organism • Adverse effects	Open label Included in NMA and review
Flume 2016 (USA)	Intervention Aztreonam lysine plus tobramycin (nebulised)	N=88 people with cystic fibrosis ≥ 6	• Exacerbations (requiring IV and/or additional antibiotics	Included in NMA and review

Study	Intervention/ Comparison	Population	Outcomes	Comments
RCT	Comparison Tobramycin (nebulised) Enrolled subjects received TIS 300 mg twice daily (BID) during a 28-day run-in phase This was followed by randomisation to a 24-week comparative phase. Subjects received 3 cycles of 28-days of double-blind AZLI or placebo (1:1 randomisation) alternating with 28-days of open-label TIS.	years and documented *P aeruginosa* infection Mean age (SD): 28.4 years (11.4)	for respiratory events, time to first event and rate of hospitalisations) • Adverse effects • Adjusted mean CFQ-R scores averaged from weeks 4, 12, and 20 • Adjusted mean FEV_1% predicted average from weeks 4, 12 and 20	
Galeva 2013 (EDIT trial) (Bulgaria, Estonia, Latvia, Lithuania, Romania, Russia, Egypt, and India) RCT	Intervention Tobramycin inhalation powder 112mg twice daily, as capsules administered via the T-326 dry powder inhaler Comparison Placebo	N=62 people with cystic fibrosis ≥6 years, and a positive sputum or throat culture for P.A within 6 months of screening and positive sputum culture for P.A at the screening visit Mean age (SD), years 12.9 (4.3) vs. 12.9 (4.7)	• Pulmonary function (FEV_1) • Exacerbations (hospitalization) • Adverse effects	Included in NMA and review
Konstan 2011 (EVOLVE trial) (Bulgaria, Lithuania, Serbia, Argentina, Brazil, Chile, Mexico, USA) RCT	Intervention Tobramycin inhalation powder (112 mg), 28 day cycle followed by 2 28-day cycles open-label tobramycin inhalation powder Comparison Placebo, 28-day cycle followed by 2 28-day cycles open-label tobramycin inhalation powder Total duration 24 weeks	N=95 children, young people and adults with cystic fibrosis with a positive sputum or throat culture for *P aeruginosa* within 6 months of screening and a positive sputum culture for *P aeruginosa* at the screening visit Age: 6 to 21 years	• Pulmonary function (FEV_1) • Suppression of the organism • Adverse events	Included in NMA and review
Retsch-Bogart 2009	Intervention Aztreonam lysine	N=164 people with cystic fibrosis and *P*	• Exacerbations (hospitalization)	Included in NMA and review

Study	Intervention/ Comparison	Population	Outcomes	Comments
(USA) RCT	75mg aztreonam, 52.5mg of lysine monohydrate Comparison Placebo (5mg lactulose)	*aeruginosa* documented infection ≥ 6 years Mean age (range): 31.7 (11-74); 27.4 (7-54)	• Eradication of the organism • Quality of life • Adverse effects	
Schuster 2013 (Europe - countries not specified) Open label RCT	Intervention Colistin DPI 1.6625 MU twice daily, 24 weeks Comparison Tobramycin inhalation solution 300 mg/5 ml twice-daily, three 28-day cycles	N=380 people with cystic fibrosis chronically colonised with P *aeruginosa* infection, ≥ 6 years Mean (SD) age: 21.1 (9.49) years	• FEV_1% • Adverse events	Open label Included in NMA and review
Trapnell 2012 (USA) RCT	Intervention Fosfomycin/ Tobramycin (160/ 40 mg or 80/ 20 mg) Comparison Placebo	N=119 people with cystic fibrosis ≥ 18 years and confirmed *P aeruginosa* infection • 80/ 20 mg: n=38 • 160/ 40 mg: n=41 • Placebo: n=40 Mean age: 32 years (10.1)	• FEV_1 • Exacerbations (hospitalisation)	Included in NMA and review
Wainwright 2011 (Australia, USA) RCT	Intervention Aztreonam lysine 28 days + 14 days follow-up 75 mg/ day, 3-times Comparison Placebo	N=157 people with cystic fibrosis ≥ 6 years Age range: 6 to 17 years	• Exacerbations (hospitalization) • Eradication of the organism • Adverse effects	Included in NMA and review

Cystic fibrosis: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; DPI: dry powder for inhalation; FEV_1: forced expiratory volume; ITT: intention to treat analysis: RCT: randomized controlled trial

Table 106: Summary of included studies for antimicrobials for chronic pulmonary infection with *S aureus*

Study	Intervention/ Comparison	Population	Outcomes	Comments
Cochrane systematic reviews				
Ahmed 2016	Intervention Any combination of topical, inhaled, oral	• Children and adults with confirmed	No studies were identified for inclusion in this review	AMSTAR score:10/11

Study	Intervention/ Comparison	Population	Outcomes	Comments
Cochrane SR	or IV antimicrobials used with the objective of suppressive therapy for chronic Comparison Placebo or no treatment	diagnosis of cystic fibrosis and confirmed microbiological evidence of *S aureus* (MSSA strains only).		
Lo 2015 Cochrane SR	Intervention Any combination of topical, inhaled, oral or IV antimicrobials to eradicate MRSA Comparison Placebo, standard treatment or not treatment	Children and adults with cystic fibrosis with a confirmed positive microbiological isolate of methicillin-resistant *S aureus* (MRSA).	No studies were identified for inclusion in this review	This review includes people with different disease severity.

Table 107: Summary of included studies for antimicrobials for chronic pulmonary infection with *A fumigatus*

Study	Intervention/ Comparison	Population	Outcomes	Comments
Cochrane systematic reviews				
Elphick 2014 Cochrane SR	Intervention Antifungal treatments, including major treatments such as oral azoles and nebulised amphotericin Comparison No treatment, placebo or different dosages	Children and adults with cystic fibrosis and allergic bronchopulmonary aspergillosis.	No studies were identified for inclusion in this review	
Additional primary studies				
Aaron 2012 (Canada) RCT	Intervention Itraconazole capsules daily dose of 5 mg/kg once daily; if the dose exceeded 200 mg/day it was given twice daily Comparison Placebo	N=35 People with cystic fibrosis ≥ 6 years of age and chronically colonised with *A Fumigatus* (defined as at least 2 positive sputum cultures within the last 12 months)	• Lung function, measured as FEV_1% predicted at 24 and 48 weeks • Time to next pulmonary exacerbation • *proxy outcomes:* ○ number of patients that experienced pulmonary exacerbations requiring oral or IV AB	(+) low risk of bias for sequence generation, blinding and selective reporting (+) first prospective RCT (+) ITT analysis (?) unclear risk of bias for allocation concealment

Study	Intervention/ Comparison	Population	Outcomes	Comments
			○ number of patients that experienced pulmonary exacerbations requiring hospitalization • Quality of life, measured with the tool CFQ-R at 24 weeks • Adverse events, reported during the 24-week study duration Not reported: • Eradication of the specified organism from sputum/airway cultures • Nutritional status • Emergence of resistant organisms/ antibiotic resistance	(-) pilot study small sample size, authors failed to recruit more patients to extend the study (-) Failure to achieve therapeutic levels of Itraconazole in many patients

9.4.3.3 Clinical evidence profile

The clinical evidence profiles for this review question are presented separately for each pathogen.

9.4.3.3.1 P aeruginosa

Results from the NMA and pairwise comparisons are presented separately in this section.

9.4.3.3.2 Clinical evidence profile for NMA outcomes (FEV_1 % predicted and number of participants experiencing at least one pulmonary exacerbation)

As treatment effects were found to vary over time, NMAs were conducted separately for short (4-10 weeks) and long (>10 weeks) of treatment.

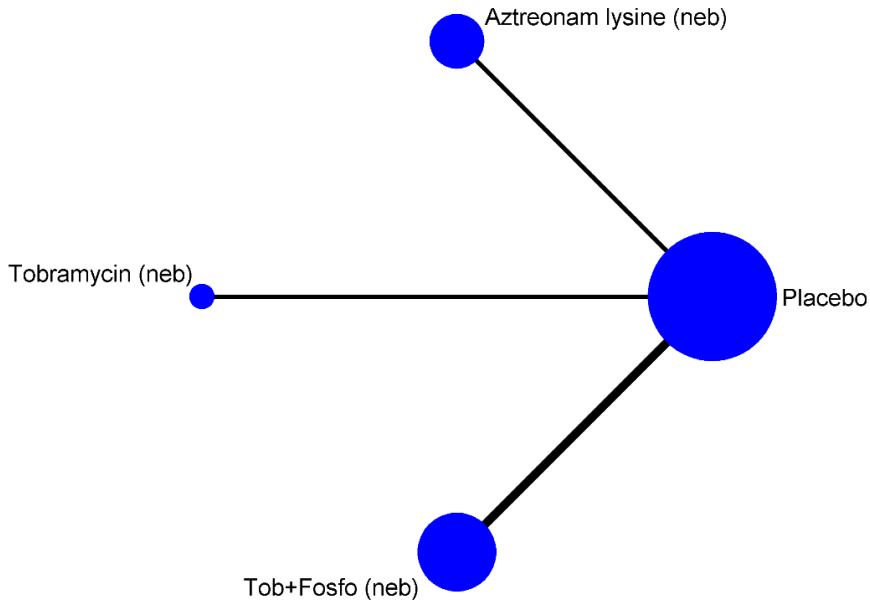
- FEV_1 % Predicted

Nine studies of 7 treatments tested in 1346 participants were included in the review. Due to very high unexplained heterogeneity between studies, it was felt that the studies should not be meta-analysed. Therefore the studies have been evaluated individually, and are reported without pooled effects (section 9.4.3.4).

- Number of patients experiencing at least one pulmonary exacerbation – Short-term treatment (4-10 weeks)

Three studies of 354 participants were included in the network of 4 interventions (placebo, aztreonam lysine (nebulised), tobramycin (nebulised), tobramycin plus fosfomycin (nebulised)) (Figure 6). The evidence for this analysis was of low quality. For all three studies the risk of bias was unclear.

Figure 6: Network for number of patients experiencing at least one exacerbation with short-term (4-10 weeks) treatment



Source/Note: Size of nodes are proportional to the number of patients in the network treated with a particular intervention. Thickness of connecting lines are proportional to the number of studies comparing two interventions.

Table 108 presents the results of the conventional pair-wise meta-analyses (head to head comparisons) (upper-right section of table), together with the results computed by the NMA for every possible treatment comparison (lower-left section of table). Both results are presented as odds ratios (95% CrI). These results were derived from a fixed effects model (see Appendix N – Model Fit).

There was considerable uncertainty throughout the network. Aztreonam lysine was found to be significantly more effective than placebo and tobramycin (nebulised) at reducing the odds of experiencing at least one exacerbation. No other significant effects were found. Inconsistency could not be assessed as there were no closed loops of treatments.

In this analysis, aztreonam lysine was found to have the highest probability (88.30%) of being the best treatment to reduce the odds of experiencing at least one exacerbation, followed by tobramycin plus fosfomycin (nebulised) (10.00%) (Table 109).

Table 108: Odds ratios (95% CrI) from conventional (white area) and network meta-analysis (grey area) for the number of people experiencing at least one exacerbation with short-term (4-10 weeks) treatment

	Placebo	Aztreonam lysine	Tobramycin (nebulised)	Tobramycin + Fosfomycin (nebulised)
Placebo		0.3 (0.08, 0.92)	3 (0.55, 24.66)	0.9 (0.25, 3.81)
Aztreonam lysine	0.3 (0.08, 0.92)			

	Placebo	Aztreonam lysine	Tobramycin (nebulised)	Tobramycin + Fosfomycin (nebulised)
Tobramycin (nebulised)	3 (0.55, 24.66)	10.43 (1.31, 122.2)		
Tobramycin + Fosfomycin (nebulised)	0.9 (0.25, 3.81)	3.11 (0.55, 21.38)	0.3 (0.03, 2.78)	

(m) Results in the top right diagonal of the table are the mean differences and 95% CrI from the conventional meta-analyses of direct evidence between the column-defined treatments compared to the row-defined treatment. Mean differences greater than 0 favour the column-defined treatment.
(n) Results in the bottom left are the mean differences and 95% CrI from the NMA model of direct and indirect evidence between the row-defined treatments compared to the column-defined treatments. Mean differences greater than 0 favour the row-defined treatment.
(o) Numbers in bold denote results for which the 95% CrI does not include the null effect of 0

Table 109: Median treatment ranking (with their 95% CrI) of all interventions in the network and the probability of being the best treatment for reducing the number of people experiencing at least one exacerbation with short-term (4-10 weeks) treatment

	Median (95% CrI) treatment rank	Probability of being the best treatment (%)
Placebo	3 (2-4)	0.70%
Aztreonam lysine	1 (1-2)	88.30%
Tobramycin (nebulised)	4 (2-4)	1.00%
Tobramycin + Fosfomycin (nebulised)	2 (1-4)	10.00%

Table 110: Quality assessment of the evidence for the NMA – number of patients with at least one exacerbation in the short-term

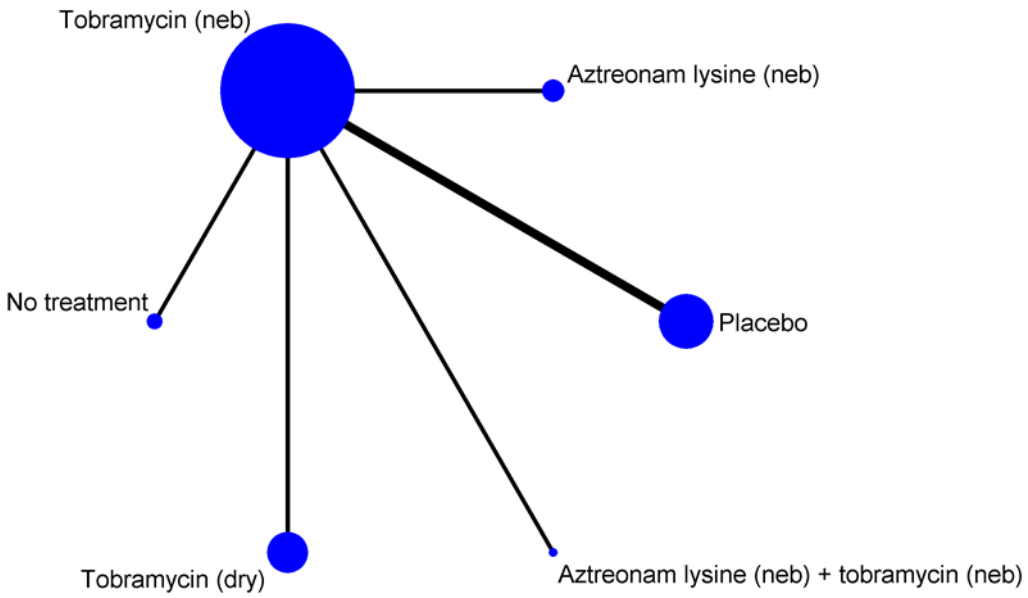
NMA	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Short-term (4-10 weeks) number of patients with at least one exacerbation (3 studies)	Serious[1]	No serious inconsistency	No serious indirectness	Serious2	None	Low

(p) 1 - For all three studies the risk of bias was unclear
(q) 2 – No intervention has rank credible intervals ≤33% of total distribution of comparators

- Number of patients experiencing at least one pulmonary exacerbation – Long-term treatment (>10 weeks)

Six studies of 1,749 participants were included in the network of 6 interventions (placebo, aztreonam lysine (nebulised), tobramycin (nebulised), no treatment, tobramycin (powder), 28 days aztreonam lysine (nebulised) alternating with 28 days tobramycin (nebulised) (Figure 7)The evidence for this analysis was of moderate quality. Two studies were at high risk of bias and for the other 4 studies the risk of bias was unclear.

Figure 7: Network for number of patients experiencing at least one exacerbation with long-term (>10 weeks) treatment



Source/Note: Size of nodes are proportional to the number of patients in the network treated with a particular intervention. Thickness of connecting lines are proportional to the number of studies comparing two interventions.

Table 111 presents the results of the conventional pair-wise meta-analyses (head to head comparisons) (upper-right section of table), together with the results computed by the NMA for every possible treatment comparison (lower-left section of table). Both results are presented as odds ratios (95% CrI). These results were derived from a fixed effects model (see Appendix G – Model Fit).

Inconsistency could not be assessed as there were no closed loops of treatments.

In this analysis, aztreonam lysine was found to have the highest probability (85.01%) of being the best treatment to reduce the odds of experiencing at least one exacerbation, followed by the combination treatment (14.83%) (Table 112).

Table 111: Odds ratios (95% CrI) from conventional (white area) and network meta-analysis (grey area) for the number of people experiencing at least one exacerbation with long-term (>10 weeks) treatment

	Placebo	Aztreonam lysine	Tobramycin (nebulised)	No treatment	Tobramycin (powder)	Combination[a]
Placebo			0.88 (0.65, 1.20)			
Aztreonam lysine	0.40 (0.22, 0.71)		2.20 (1.36, 3.61)			
Tobramycin (nebulised)	0.88 (0.65, 1.20)	2.20 (1.36, 3.61)		2.84 (1.28, 6.71)	1.14 (0.75, 1.75)	0.77 (0.33, 1.78)
No treatment	2.51 (1.07, 6.22)	6.27 (2.46, 16.81)	2.84 (1.28, 6.71)			
Tobramycin (powder)	1.01 (0.60, 1.70)	2.52 (1.33, 4.84)	1.14 (0.75, 1.75)	0.40 (0.16, 1.00)		
Combination[a]	0.67 (0.27, 1.65)	1.68 0.63, 4.48)	0.77 (0.33, 1.78)	0.27 (0.08, 0.86)	0.67 (0.26, 1.72)	

(r) Results in the top right diagonal of the table are the mean differences and 95% CrI from the conventional meta-analyses of direct evidence between the column-defined treatments compared to the row-defined treatment. Mean differences greater than 0 favour the column-defined treatment.
(s) Results in the bottom left are the mean differences and 95% CrI from the NMA model of direct and indirect evidence between the row-defined treatments compared to the column-defined treatments. Mean differences greater than 0 favour the row-defined treatment.
(t) Numbers in bold denote results for which the 95% CrI does not include the null effect of 0
(u) (a) 28 days aztreonam lysine (nebulised) alternating with 28 days tobramycin (nebulised)

Table 112: Median treatment ranking (with their 95% CrI) of all interventions in the network and the probability of being the best treatment for reducing the number of people experiencing at least one exacerbation with long-term (>10 weeks) treatment

	Median (95% CrI) treatment rank	Probability of being the best treatment (%)
Placebo	4 (2, 5)	0.03%
Aztreonam lysine	1 (1, 2)	85.01%
Tobramycin (nebulised)	3 (2, 5)	0.01%
No treatment	6 (5, 6)	0.00%
Tobramycin (powder)	4 (2, 5)	0.12%
Combination a	2 (1, 5)	14.83%

(v) 28 days aztreonam lysine (nebulised) alternating with 28 days tobramycin (nebulised)

Table 113: Quality assessment of the evidence for the NMA – number of patients with at least one exacerbation in the long-term

NMA	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Long-term (>10 weeks) number of patients with at least one exacerbation (6 studies)	Serious1	No serious inconsistency	No serious indirectness	No serious imprecision	None	Moderate

(w) 1 – For two studies the risk of bias was high and for four studies the risk of bias was unclear

9.4.3.4 Clinical evidence profile for non-NMA outcomes

The summary clinical evidence profiles for this review question are presented in Table 114 to Table 123.

Table 114: Summary clinical evidence profile: Comparison 1. Aztreonam lysine versus placebo

Comparison 1.: Aztreonam versus placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Aztreonam lysine				

Comparison 1.: Aztreonam versus placebo						
Lung function: relative change in FEV_1% predicted Scale from: 0 to 100 Follow-up: 28 days	The mean relative change in FEV_1% predicted at 28 days follow up in the placebo group was -2.5	The mean relative change in FEV_1% predicted at 28 days follow up in the aztreonam lysine groups was 2.79 higher (0.48 to 5.1 higher)		157 (Wainwright 2011)	⊕⊕⊕⊖ moderate[1]	
Number of patients with 1 or more exacerbations	NMA outcome					
Suppression of the organism: adjusted mean change sputum density log10 CFU/g Follow-up: 28 days	Not reported	The mean adjusted mean change sputum density in the aztreonam lysine groups was 1.40 lower (1.94 lower to 0.85 higher)		321 (Retsch-Bogart 2009, Wainwright 2011)	⊕⊕⊕⊕ high	
Nutritional status % weight change (kg) Follow-up: 28 days	The mean % weight change (kg) in the placebo groups ranged between 1 and 1.1	The mean % weight change (kg) in the aztreonam lysine groups was 1 higher (0.33 to 1.67 higher)		164 (Retsch-Bogart 2009)	⊕⊕⊕⊕ high	
Quality of life: change in CFQ-R body image Follow-up: 28 days	The mean change in CFQ-R body image in the placebo groups ranged between 1 and 1.1	The mean change in CFQ-R body image in the aztreonam lysine groups was 2.44 higher (0.35 lower to 5.23 higher)		320 (Retsch-Bogart 2009, Wainwright 2011)	⊕⊕⊕⊖ moderate[1]	
Quality of life: change in CFQ-R digestion Follow-up: 28 days	The mean change in CFQ-R digestion in the placebo groups ranged between 1.9 and 5.5	The mean change in CFQ-R digestion in the aztreonam lysine groups was 0.45 lower (3.53 lower to 2.63 higher)		321 (Retsch-Bogart 2009, Wainwright 2011)	⊕⊕⊕⊕ high	

Comparison 1.: Aztreonam versus placebo						
Quality of life: change in CFQ-R eating Scale from: 0 to 100 Follow-up: 28 days	The mean change in CFQ-R eating in the placebo groups ranged between -4.7 and -1.2	The mean change in CFQ-R eating in the aztreonam lysine groups was 4.99 higher (1.47 lower to 11.46 higher)		321 (Retsch-Bogart 2009, Wainwright 2011)	⊕⊖⊖⊖ very low[1,2]	
Quality of life: change in CFQ-R emotional functioning Scale from: 0 to 100 Follow-up: 28 days	The mean change in CFQ-R emotional functioning in the placebo groups ranged between -1.3 and 3.7	The mean change in CFQ-R emotional functioning in the aztreonam lysine groups was 2.36 higher (3.13 lower to 7.84 higher)		320 (Retsch-Bogart 2009, Wainwright 2011)	⊕⊖⊖⊖ very low[1,2]	
Quality of life: change in CFQ-R health perceptions Follow-up: 28 days	The mean change in CFQ-R health perceptions in the placebo groups ranged between -4.8 and -1.8	The mean change in CFQ-R health perceptions in the aztreonam lysine groups was 6.82 higher (0.75 to 12.89 higher)		272 (Retsch-Bogart 2009, Wainwright 2011)	⊕⊖⊖⊖ very low[1,2]	
Quality of life: change in CFQ-R physical functioning Follow-up: 28 days	The mean change in CFQ-Rhealth perceptions in the placebo groups ranged between -6.9 and -0.69	The mean change in CFQ-Rhealth perceptions in the aztreonam lysine groups was 5.60 higher (0.96 lower to 12.15 higher)		320 (Retsch-Bogart 2009, Wainwright 2011)	⊕⊖⊖⊖ very low[1,2]	
Quality of life: change in CFQ-Rrespiratory symptoms Follow-up: 28 days	The mean change in CFQ-Rrespiratory symptoms in the placebo groups ranged between -2.6 and 2.9	The mean change in CFQ-Rrespiratory symptoms in the aztreonam lysine groups was 4.81 higher (4.6 lower to 14.21 higher)		321 (Retsch-Bogart 2009, Wainwright 2011)	⊕⊖⊖⊖ very low[1,2]	
Quality of life: change in CFQ-Rrole/school Follow-up: 28 days	The mean change in CFQ-Rrole/school in the	The mean change in CFQ-Rrole/school in the		272 (Retsch-Bogart 2009,	⊕⊖⊖⊖ very low[1,2]	

Comparison 1.: Aztreonam versus placebo						
	placebo groups ranged between -4.2 and 0.29	aztreonam lysine groups was 2.97 higher (3.2 lower to 9.13 higher)		Wainwright 2011)		
Quality of life: change in CFQ-Rsocial functioning Follow-up: 28 days	The mean change in CFQ-Rsocial functioning in the placebo groups ranged between -3.6 and -2.6	The mean change in CFQ-Rsocial functioning in the aztreonam lysine groups was 3.54 higher (0.78 to 6.31 higher)		319 (Retsch-Bogart 2009, Wainwright 2011)	⊕⊕⊕⊖ moderate[1]	
Quality of life: change in CFQ-Rtreatment burden Follow-up: 28 days	The mean change in CFQ-Rtreatment burden in the placebo groups ranged between -3.1 and 5.1	The mean change in CFQ-Rtreatment burden in the aztreonam lysine groups was 0.36 lower (7.42 lower to 6.69 higher)		321 (Retsch-Bogart 2009, Wainwright 2011)	⊕⊖⊖⊖ very low[2,3]	
Quality of life: change in CFQ-Rvitality Follow-up: 28 days	The mean change in CFQ-Rvitality in the placebo groups ranged between -4.4 and -2.2	The mean change in CFQ-Rvitality in the aztreonam groups was 5.46 higher (0.16 to 10.76 higher)		272 (Retsch-Bogart 2009, Wainwright 2011)	⊕⊕⊖⊖ low[1,2]	
Quality of life: change in CFQ-Rweight Follow-up: 28 days	The change in CFQ-Rweight in the placebo groups ranged between 1.4 and 2.6	The change in CFQ-Rweight in the aztreonam lysine groups was 2.58 higher (2.83 lower to 7.98 higher)		272 (Retsch-Bogart 2009, Wainwright 2011)	⊕⊕⊕⊖ moderate[1]	
Minor adverse events: chest discomfort Follow-up: 28 days	48 per 1000	62 per 1000 (18 to 224)	RR 1.31 (0.37 to 4.71)	164 (Retsch-Bogart 2009)	⊕⊕⊖⊖ low[4]	
Minor adverse events: cough Follow-up: 28 days	Study population		RR 1.10 (0.87 to 1.38)	532 (Retsch-Bogart 2009, McCoy 2009 2009,	⊕⊕⊖⊖ low[4]	
	340 per 1000	374 per 1000 (296 to 470)				
	Moderate					
	342 per 1000	376 per 1000 (298 to 472)				

Comparison 1.: Aztreonam versus placebo						
				Wainwright 2011)		
Minor adverse events: headache Follow-up: 28 days	Study population		RR 0.94 (0.34 to 2.61)	321 (Retsch-Bogart 2009, Wainwright 2011)	⊕⊖⊖⊖ very low[4,6]	
	121 per 1000	114 per 1000 (41 to 316)				
	Moderate					
	121 per 1000	114 per 1000 (41 to 316)				
Major adverse events: dyspnoea Follow-up: 28 days	95 per 1000	63 per 1000 (21 to 183)	RR 0.66 (0.22 to 1.92)	164 (Retsch-Bogart 2009)	⊕⊕⊖⊖ low[4]	
Major adverse events: haemoptysis Follow-up: 28 days	Study population		RR 0.86 (0.44 to 1.7)	375 (Retsch-Bogart 2009, Mccoy 2009)	⊕⊕⊖⊖ low[4]	
	94 per 1000	81 per 1000 (41 to 159)				
	Moderate					
	94 per 1000	81 per 1000 (41 to 160)				
Mortality Follow-up: 28 days	No events	No events	-	211 (Mccoy 2009)	⊕⊕⊕⊕ High	
Emergence of resistant organisms: persistent isolation of *S aureus* Follow-up: 42 days	62 per 1000	27 per 1000 (6 to 135)	RR 0.44 (0.09 to 2.19)	155 (Retsch-Bogart 2009)	⊕⊕⊕⊖ moderate[5]	
Emergence of resistant organisms : persistent isolation of *B cepacia* Follow-up: 42 days	No events	No events	-	155 (Retsch-Bogart 2009)	⊕⊕⊕⊕ High	
Emergence of resistant organisms: persistent isolation of S. maltophilia Follow-up: 42 days	0 per 1000	0 per 1000 (0 to 0)	RR 5.47 (0.27 to 112.04)	155 (Retsch-Bogart 2009)	⊕⊕⊖⊖ low[4]	
Emergence of resistant organisms: persistent isolation of A. xilosidans Follow-up: 42 days	25 per 1000	14 per 1000 (1 to 146)	RR 0.55 (0.05 to 5.91)	155 (Retsch-Bogart 2009)	⊕⊕⊖⊖ low[4]	

Comparison 1.: Aztreonam versus placebo
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Abbreviations: cystic fibrosisQ-R: cystic fibrosis questionnaire revised; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; MD: mean difference; RR: risk ratio

1 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 clinical MID
2 The quality of the evidence was downgraded by 1 or by 2 due to the moderate of high heterogeneity in the different CFQ-Rdomains (eating I2=79%; emotional functioning I2=80%; health perceptions I2=62%; respiratory symptoms I2=85%; role/ school I2=73%; treatment burden I2=79%; vitality I2=40%)
3 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 clinical MIDs
4 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 default MIDs
5 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 default MID
6 The quality of the evidence was downgraded by 2 due to high heterogeneity (I2=62%)

Table 115: Summary clinical evidence profile: Comparison 2. Ciprofloxacin versus placebo

Comparison 2.: Ciprofloxacin versus placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Ciprofloxacin				
Lung function	Not reported					
Number of people with one or more exacerbations	NMA outcome					
Nutritional status: weight kg Follow-up: 6 to 12 months	The mean weight in the placebo group was 51.3	The mean change in weight in the ciprofloxacin groups was 4.4 higher (3.7 lower to 12.5 higher)		31 (Sheldon 1993)	⊕⊖⊖⊖ very low[1,2]	
Minor adverse events - gastrointestinal Follow-up: 12 months	0 per 1000	0 per 1000 (0 to 0)	RR 5 (0.26 to 98)	40 (Sheldon 1993)	⊕⊖⊖⊖ very low[3,4]	
Mortality Follow-up: 12 months	50 per 1000	50 per 1000 (4 to 745)	RR 1 (0.07 to 14.9)	40 (Sheldon 1993)	⊕⊕⊖⊖ low[5]	
Emergence of resistant organisms - isolation of resistant strains of *P aeruginosa* Follow-up: 12 months	312 per 1000	666 per 1000 (297 to 1000)	RR 2.13 (0.95 to 4.8)	(Sheldon 1993)	⊕⊖⊖⊖ very low[1,2]	
Emergence of resistant organisms - isolation of resistant strains of *S aureus*	375 per 1000	266 per 1000 (94 to 761)	RR 0.71 (0.25 to 2.03)	31 (Sheldon 1993)	⊕⊖⊖⊖ very low[1,4]	

Comparison 2.: Ciprofloxacin versus placebo						
Follow-up: 12 months						
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; MD: mean difference; RR: risk ratio						

1 The quality of the evidence was downgraded by 2 due to unclear blinding and reporting and high loss to follow-up
2 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 default MID
3 The quality of the evidence was downgraded by 1 due to unclear blinding and reporting
4 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 default MIDs
5 The quality of the evidence was downgraded by 2 as the 95% CI crossed the line of null effect, and the CI is very wide (trial underpowered to detect a difference)

Table 116: Summary clinical evidence profile: Comparison 3.1. Colistin versus placebo

Comparison 3.1.: Colistin versus placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Colistin				
Lung function: change in FEV_1 % predicted Follow-up: 3 months	The mean change in FEV_1 % predicted in the placebo groups was -17	The mean change in FEV_1 % predicted in the colistin groups was 6.00 higher (1.07 lower to 13.07 higher)		40 (Jensen 1987)	⊕⊕⊖⊖ low[1,2]	
Number of patients with 1 or more exacerbations	NMA outcome					
Suppression of the organism: eradication of *P aeruginosa* from the sputum Follow-up: 3 months	PA was not eradicated from the sputum of any patient during the 3-month trial		-	40 (Jensen 1987)	⊕⊕⊕⊖ moderate[1,3]	
Emergence of resistant organisms: superinfection with other colistin-resistant organisms Follow-up: 3 months	No super infection with other colistin-resistant microorganisms, including Ps. Cepacia, Serratia Macencens, Proteus mirabilis, Gram-positive organisms or funghi during the 3-month trial		-	40 (Jensen 1987)	⊕⊕⊕⊖ moderate[1,3]	
Emergence of resistant organisms: resistance to colistin Follow-up: 3 months	Resistance to colistin did no develop in any strain during the 3-month trial		-	40 (Jensen 1987)	⊕⊕⊕⊖ moderate[1,3]	

Comparison 3.1.: Colistin versus placebo					
Emergence of resistant organisms: resistance to other commonly used anti-pseudomonas treatment Follow-up: 3 months	No change in resistance pattern to other commonly used anti-pseudomonas during the 3-month trial	-	40 (Jensen 1987)	⊕⊕⊕⊖ moderate[1,3]	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval;					

1 The quality of the evidence was downgrade by 1 due to unclear randomisation, allocation and blinding methods. Poor reporting.
2 The quality of the evidence was downgraded by 1 due to serious imprecision, as the 95% CI crossed 1 clinical MID
3 Not calculable, as data reported narratively only.

Table 117: Summary clinical evidence profile: Comparison 3.2. Colistin inhalation powder versus colistin inhalation solution

Comparison 3.2. Colistin inhalation powder versus colistin inhalation solution						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Colistin inhalation solution (COLI neb)	Colistin inhalation powder (COLI DPI)				
Lung function: % mean change in FEV_1 % predicted Scale from: 0 to 100 Follow-up: 4 weeks	Not reported	The % mean change in FEV_1 % predicted in the COLI DPI groups was 3.01 lower (18.71 lower to 12.69 higher)		31 (COLO/DPI /02/05)	⊕⊖⊖⊖ very low[1,2]	
Number of patients with 1 or more exacerbations	NMA outcome					
Minor adverse events: vomiting Follow-up: 8 weeks	0 per 1000	0 per 1000 (0 to 0)	RR 4.71 (0.24 to 90.69)	31 (COLO/DPI /02/05)	⊕⊖⊖⊖ very low[1,3]	
Minor adverse events: productive cough Follow-up: 8 weeks	67 per 1000	125 per 1000 (13 to 1000)	RR 1.88 (0.19 to 18.6)	31 (COLO/DPI /02/05)	⊕⊖⊖⊖ very low[1,3]	
Minor adverse events: chest discomfort Follow-up: 8 weeks	133 per 1000	251 per 1000 (53 to 1000)	RR 1.88 (0.4 to 8.78)	31 (COLO/DPI /02/05)	⊕⊖⊖⊖ very low[1,3]	

Comparison 3.2. Colistin inhalation powder versus colistin inhalation solution						
Serious adverse events - AE: dyspnoea Follow-up: 8 weeks	267 per 1000	187 per 1000 (51 to 701)	RR 0.7 (0.19 to 2.63)	31 (COLO/DPI /02/05)	⊕⊖⊖⊖ very low[1,3]	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio;						

1 The quality of the evidence was downgraded by 1 as this is an open trial, and the randomisation is unclear
3 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 clinical MIDs
3 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 default MIDs

Table 118: Summary clinical evidence profile: Comparison 3.3. Colistin versus Tobramycin

Comparison 3.3. Colistin versus Tobramycin						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Tobramycin	Colistin				
[COLI nebulised versus TOBI nebulised] Lung function: mean % change in FEV_1 % predicted Scale from: 0 to 100 Follow-up: 1 to 3 months	The mean % change in FEV_1 % predicted in the tobramycin groups was 6.7	The mean % change in FEV_1 % predicted in the intervention groups was 6.33 lower (12.7 lower to 0.04 higher)		109 (Hodson 2002)	⊕⊖⊖⊖ very low[1,2]	
[COLI DPI versus TOBI nebulised] Lung function: mean % change in FEV_1 % predicted Scale from: 0 to 100 Follow-up: 4 weeks	Not reported	The mean % change in FEV_1 % predicted in the intervention groups was 1.67 lower (5.43 lower to 2.09 higher)		374 (COLO/DPI/02/06)	⊕⊕⊖⊖ low[2,3]	
[COLI DPI versus TOBI nebulised] Lung function: mean % change in FEV_1 % predicted Scale from: 0 to 100	Not reported	The mean % change in FEV_1 % predicted in the intervention groups was 2.63 lower (6.67 lower to 1.41 higher)		374 (COLO/DPI/02/06)	⊕⊕⊖⊖ low[2,3]	

Comparison 3.3. Colistin versus Tobramycin						
Follow-up: 12 weeks						
[COLI versus TOBI] Lung function: mean % change in FEV_1 % predicted Scale from: 0 to 100 Follow-up: 24 weeks	Not reported	The mean % change in FEV_1 % predicted in the intervention groups was 0.99 higher (0.95 to 1.03 higher)		658 (COLO/DPI/02/06, Schuster 2013)	⊕⊕⊖⊖ low[4]	
Number of patients with 1 or more exacerbations	NMA outcome					
[COLI DPI versus TOBI nebulised] Time to next pulmonary exacerbation: time to first additional anti *P aeruginosa* treatment (days)	The mean time to first additional anti *P aeruginosa* treatment in the tobramycin groups was 51.79 days	The mean time to first additional anti *P aeruginosa* treatment in the colistin groups was 3.49 higher (5.14 lower to 12.12 higher)		374 (COLO/DPI/02/06)	⊕⊖⊖⊖ very low[3,5]	
[COLI DPI versus TOBI nebulised] Suppression of the organism: change in sputum PA density Log10 CFU/ml Follow-up: 4 weeks	The mean change in sputum pa density log10 CFU/ML in the tobramycin groups was -0.79	The mean change in sputum pa density log10 CFU/ML in the colistin groups was 0.32 higher (0.32 lower to 0.96 higher)		79 (COLO/DPI/02/06)	⊕⊕⊖⊖ low[1]	
[COLI DPI versus TOBI nebulised] Nutritional status: BMI change kg Follow-up: 24 weeks	The mean BMI change in the colistin groups was 0.17	The mean BMI change in the colistin groups was 0.09 lower (0.26 lower to 0.88 higher)		374 (COLO/DPI/02/06)	⊕⊕⊖⊖ low[3,6]	
[COLI DPI versus TOBI nebulised] Quality of life: change in CFQ-R physical Scale from: 0 to 100.	The mean change in quality of life CFQ-R physical in the tobramycin groups was -1.56	The mean change in quality of life: CFQ-R physical in the colistin groups was 1.82 higher	P=0.353	374 (COLO/DPI/02/06)	⊕⊕⊕⊖ moderate [3,7]	

Comparison 3.3. Colistin versus Tobramycin						
Follow-up: 24 weeks						
[COLI DPI versus TOBI nebulised] Quality of life: change in CFQ-R vitality Scale from: 0 to 100. Follow-up: 24 weeks	The mean change in quality of life: CFQ-R vitality in the tobramycin groups was -1.40	The mean change in quality of life: CFQ-R vitality in the colistin groups was 2.27 higher	P=0.293	374 (COLO/DPI/02/06)	⊕⊕⊕⊖ moderate [3,7]	
[COLI DPI versus TOBI nebulised] Quality of life: change in CFQ-R emotion Scale from: 0 to 100. Follow-up: 24 weeks	The mean change in quality of life: CFQ-R emotion in the tobramycin groups was 0.47	The mean change in quality of life: CFQ-R emotion in the colistin groups was 1.75 higher	P=0.244	374 (COLO/DPI/02/06)	⊕⊕⊕⊖ moderate [3,7]	
[COLI DPI versus TOBI nebulised] Quality of life: change in CFQ-R eating Scale from: 0 to 100. Follow-up: 24 weeks	The mean change in quality of life: CFQ-R eating in the tobramycin groups was 0.66	The mean change in quality of life: CFQ-R eating in the colistin groups was 0.19 lower	P=0.925	372 (COLO/DPI/02/06)	⊕⊕⊕⊖ moderate [3,7]	
[COLI DPI versus TOBI nebulised] Quality of life: change in CFQ-R treatment burden Scale from: 0 to 100. Follow-up: 24 weeks	The mean change in quality of life: CFQ-R treatment burden in the control tobramycin was 2.75	The mean change in quality of life: CFQ-R treatment burden in the colistin groups was 2.87 higher	P=0.091	374 (COLO/DPI/02/06)	⊕⊕⊕⊖ moderate [3,7]	
[COLI DPI versus TOBI nebulised] Quality of life: change in CFQ-R health perception Scale from: 0 to 100. Follow-up: 24 weeks	The mean change in quality of life: CFQ-R health perception in the tobramycin groups was -2.71	The mean change in quality of life: CFQ-R health perception in the intervention groups was 2.96 higher	P=0.159	374 (COLO/DPI/02/06)	⊕⊕⊕⊖ moderate [3,7]	

Comparison 3.3. Colistin versus Tobramycin						
[COLI DPI versus TOBI nebulised] Quality of life: change in CFQ-R social Scale from: 0 to 100. Follow-up: 24 weeks	The mean change in quality of life: CFQ-R social in the tobramycin groups was 2.18	The mean change in quality of life: CFQ-R social in the colistin groups was 0.92 higher	P=0.153	374 (COLO/DPI/02/06)	⊕⊕⊕⊖ moderate [3,7]	
[COLI DPI versus TOBI nebulised] Quality of life: change in CFQ-R body image Scale from: 0 to 100. Follow-up: 24 weeks	The mean change in change in quality of life: CFQ-R body image in the tobramycin groups was 5.98	The mean change in quality of life: CFQ-R body image in the colistin groups was 1.85 higher	P=0.385	374 (COLO/DPI/02/06)	⊕⊕⊕⊖ moderate [3,7]	
[COLI DPI versus TOBI nebulised] Quality of life: change in CFQ-R role Scale from: 0 to 100. Follow-up: 24 weeks	The mean change in quality of life: CFQ-R role in the tobramycin groups was 1.87	The mean change in quality of life: CFQ-R role in the colistin groups was 1.22 lower	P=0.607	374 (COLO/DPI/02/06)	⊕⊕⊕⊖ moderate [3,7]	
[COLI DPI versus TOBI nebulised] Quality of life: change in CFQ-R weight Scale from: 0 to 100. Follow-up: 24 weeks	The mean change in quality of life: CFQ-R weight in the tobramycin groups was -1.93	The mean change in quality of life: CFQ-R weight in the colistin groups was 2.81 higher	P=0.461	374 (COLO/DPI/02/06)	⊕⊕⊕⊖ moderate [3,7]	
[COLI DPI versus TOBI nebulised] Quality of life: change in CFQ-R respiratory Scale from: 0 to 100. Follow-up: 24 weeks	The mean change in quality of life: CFQ-R respiratory in the tobramycin groups was 3.51	The mean change in quality of life: CFQ-R respiratory in the colistin groups was 0.53 lower	P=0.756	374 (COLO/DPI/02/06)	⊕⊕⊕⊖ moderate [3,7]	
[COLI DPI versus TOBI nebulised] Quality of life: change in	The mean change in quality of life: CFQ-R digestion in	The mean change in quality of life: CFQ-R digestion in the colistin groups	P=0.077	374 (COLO/DPI/02/06)	⊕⊕⊕⊖ moderate [3,7]	

Comparison 3.3. Colistin versus Tobramycin						
CFQ-R digestion Scale from: 0 to 100. Follow-up: 24 weeks	the tobramycin groups was 2.89	was 3.22 higher				
[COLI nebulised versus TOBI nebulised] Minor adverse events: sputum Follow-up: 4 weeks	113 per 1000	129 per 1000 (48 to 349)	RR 1.14 (0.42 to 3.08)	115 (Hodson 2002)	⊕⊖⊖⊖ very low[1,8]	
[COLI nebulised versus TOBI nebulised] Minor adverse events: pharyngitis Follow-up: 4 weeks	132 per 1000	49 per 1000 (13 to 178)	RR 0.37 (0.1 to 1.35)	115 (Hodson 2002)	⊕⊖⊖⊖ very low[1,8]	
[COLI nebulised versus TOBI nebulised] Minor adverse events: cough Follow-up: 4 weeks	94 per 1000	177 per 1000 (66 to 478)	RR 1.88 (0.7 to 5.07)	115 (Hodson 2002)	⊕⊖⊖⊖ very low[1,8]	
[COLI DPI versus TOBI nebulised] Minor adverse events: productive cough Follow-up: 24 weeks	228 per 1000	203 per 1000 (139 to 299)	RR 0.89 (0.61 to 1.31)	380 (COLO/DPI/02/06)	⊕⊖⊖⊖ very low[3,8]	
[COLI DPI versus TOBI nebulised] Minor adverse events: chest discomfort Follow-up: 24 weeks	176 per 1000	139 per 1000 (86 to 222)	RR 0.79 (0.49 to 1.26)	380 (COLO/DPI/02/06)	⊕⊖⊖⊖ very low[3,8]	
[COLI DPI versus TOBI nebulised] Minor adverse events: vomiting Follow-up: 24 weeks	41 per 1000	32 per 1000 (11 to 91)	RR 0.77 (0.27 to 2.19)	380 (COLO/DPI/02/06)	⊕⊖⊖⊖ very low[3,8]	

Comparison 3.3. Colistin versus Tobramycin						
[COLI nebulised versus TOBI nebulised] Serious adverse events: patients with >1 serious AE Follow-up: 4 weeks	151 per 1000	113 per 1000 (44 to 291)	RR 0.75 (0.29 to 1.93)	115 (Hodson 2002)	⊕⊖⊖⊖ very low[1,8]	
[COLI DPI versus TOBI nebulised] Serious adverse events: patients withdrawn Follow-up: 24 weeks	26 per 1000	118 per 1000 (46 to 304)	RR 4.54 (1.76 to 11.74)	380 (COLO/DPI/02/06)	⊕⊕⊕⊖ moderate[3]	
[COLI DPI versus TOBI nebulised] Serious adverse events: haemoptysis Follow-up: 24 weeks	67 per 1000	107 per 1000 (55 to 209)	RR 1.59 (0.81 to 3.1)	380 (COLO/DPI/02/06)	⊕⊖⊖⊖ very low[1,6]	
[COLI nebulised versus TOBI nebulised] Serious adverse events: dyspnoea - Follow-up: 4 weeks	94 per 1000	113 per 1000 (38 to 335)	RR 1.2 (0.4 to 3.55)	115 (Hodson 2002)	⊕⊖⊖⊖ very low[1,8]	
Serious adverse events: dyspnoea Follow-up: 24 weeks	269 per 1000	261 per 1000 (189 to 366)	RR 0.97 (0.7 to 1.36)	380 (COLO/DPI/02/06)	⊕⊖⊖⊖ very low[3,8]	
[COLI nebulised versus TOBI nebulised] Emergence of resistant organisms: emergence of highly tobramycin-resistant *P aeruginosa*	0 events	0 events	-	115 (Hodson 2002)	⊕⊕⊖⊖ low[1]	

Comparison 3.3. Colistin versus Tobramycin						
Follow-up: 24 weeks						
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Abbreviations: CFQ-R: cystic fibrosis questionnaire revised; CI: confidence interval; COLI: colistin; DPI: dry powder for inhalation; FEV_1: forced expiratory volume in 1 second; MD: mean difference; RR: risk ratio; TOBI: tobramycin						

1 The quality of the evidence was downgraded by 2 because this is an open trial, and risk of bias for randomisation and allocation concealment was unclear
2 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 clinical MID
3 The quality of the evidence was downgraded by 1 because this is an open trial, and risk of bias for randomisation was unclear
4 The quality of the evidence was downgraded by 2 because both studies were open trials, and risk of bias for randomisation and allocation concealment was unclear
5 The quality of the evidence was downgraded by 2, as the 95% CI is very large and crosses the line of no effect
6 The quality of the evidence was downgraded by 1 as the 95%CI crossed 1 default MID
7 Not calculable, p-value > 0.05
8 The quality of the evidence was downgraded by 2 as the 95%CI crossed 2 default MIDs

Table 119: Summary clinical evidence profile: Comparison 4.1. Tobramycin versus placebo

Comparison 4.1. Tobramycin versus placebo						
Outcomes	Illustrative comparative risks* (95% CI)		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Placebo	**Tobramycin**				
Lung function: mean % change in FEV_1 % predicted Scale from: 0 to 100 Follow-up: 1 to 3 months	Not reported	The mean lung function: mean % change in FEV_1 % predicted in the tobramycin groups was 9.36 higher (5.01 to 13.7 higher)		516 (Galeva 2013, Konstan 2011/ EVOLVE trial, Lenoir 2007, Ramsey 1993)	⊕⊕⊖⊖ low[1,2]	
Number of patients with 1 or more exacerbations	NMA outcome					
Suppression of the organism: eradication of the organism (negative culture) Follow-up: 4 weeks	Study population		RR 2.46 (1.20 to 5.04)	357 (Chuchalin 2007, Galeva 2013, Lenoir 2007)	⊕⊕⊕⊕ high	
	121 per 1000	299 per 1000 (146 to 612)				
	Moderate					
	143 per 1000	352 per 1000 (172 to 721)				
Suppression of the organism: eradication of the organism (negative culture)	100 per 1000	103 per 1000 (23 to 471)	RR 1.03 (0.23 to 4.71)	59 (Lenoir 2007)	⊕⊕⊕⊖ moderate [3]	

Comparison 4.1. Tobramycin versus placebo						
Follow-up: 6 weeks						
Suppression of the organism: eradication of the organism (negative culture) Follow-up: 8 weeks	120 per 1000	145 per 1000 (72 to 289)	RR 1.2 (0.6 to 2.4)	242 (Chuchalin 2007)	⊕⊕⊕⊖ moderate [3]	
Suppression of the organism: eradication of the organism (negative culture) Follow-up: 20 weeks	165 per 1000	334 per 1000 (194 to 574)	RR 2.03 (1.18 to 3.49)	235 (Chuchalin 2007)	⊕⊕⊕⊕ high	
Suppression of the organism: eradication of the organism (negative culture) Follow-up: 24 weeks	202 per 1000	239 per 1000 (144 to 397)	RR 1.18 (0.71 to 1.96)	243 (Chuchalin 2007)	⊕⊕⊕⊖ moderate [3]	
Suppression of the organism: change in *P aeruginosa* sputum density log10 CFU/g Follow-up: 4 weeks	The mean change in *P aeruginosa* sputum density log10 CFU/g in the placebo groups was 0	The mean change in *P aeruginosa* sputum density log10 CFU/g in the tobramycin groups was 1.2 lower (2.03 to 0.37 lower)		55 (Galeva 2013)	⊕⊕⊕⊖ moderate [4]	
Suppression of the organism: change in non-mucoid *P aeruginosa* sputum density log10 CFU/g Follow-up: 4 weeks	The mean change in non-mucoid *P aeruginosa* sputum density log10 CFU/g in the placebo groups was -0.15	The mean change in non-mucoid *P aeruginosa* sputum density log10 CFU/g in the tobramycin groups was 1.76 lower (2.52 to 1 lower)		95 (Konstan 2011/ EVOLVE trial)	⊕⊕⊖⊖ low[5]	
Suppression of the organism: change in mucoid *P aeruginosa* sputum density log10 CFU/g Follow-up: 4 weeks	The mean suppression of the organism: change in mucoid *P aeruginosa* sputum density log10 CFU/g in the	The mean suppression of the organism: change in mucoid *P aeruginosa* sputum density log10 CFU/g in the tobramycin groups was 2.18 lower		95 (Konstan 2011/ EVOLVE trial)	⊕⊕⊖⊖ low[5]	

Comparison 4.1. Tobramycin versus placebo						
	placebo groups was -0.43	(2.97 to 1.39 lower)				
Nutritional status: body weight change kg Follow-up: 12 weeks	The mean nutritional status: body weight change in the control groups was 0.16	The mean body weight change in the tobramycin groups was 0.23 higher (0.23 lower to 0.69 higher)		59 (Lenoir 2007)	⊕⊕⊕⊕ high	
Nutritional status: body weight change kg Follow-up: 24 weeks	The mean body weight change in the tobramycin groups was 1.05	The mean body weight change in the tobramycin groups was 0.75 higher (0.22 to 1.28 higher)		245 (Chuchalin 2007)	⊕⊕⊕⊖ moderate [4]	
Minor adverse events: minor adverse (any) Follow-up: 4 weeks	Study population		RR 0.66 (0.49 to 0.89)	150 (Galeva 2013, Konstan 2011/ EVOLVE trial)	⊕⊖⊖⊖ very low[4,6]	
	640 per 1000	422 per 1000 (314 to 570)				
	Moderate					
	423 per 1000	279 per 1000 (207 to 376)				
Minor adverse events: minor adverse events (any) Follow-up: 24 weeks	153 per 1000	156 per 1000 (84 to 288)	RR 1.02 (0.55 to 1.88)	246 (Chuchalin 2007)	⊕⊕⊖⊖ low[7]	
Minor adverse events: auditory impairment Follow-up: 4 weeks	77 per 1000	103 per 1000 (18 to 572)	RR 1.34 (0.24 to 7.43)	55 (Galeva 2013)	⊕⊕⊖⊖ low[7]	
Minor adverse events: auditory impairment Follow-up: 24 weeks	0 events	0 events	-	300 (Ramsey 1999)	⊕⊕⊕⊕ high	
Minor adverse events: auditory impairment Follow-up: 42 weeks	0 events	0 events	-	71 (Ramsey 1993)	⊕⊕⊕⊕ high	
Minor adverse events: cough Follow-up: 4 weeks	173 per 1000	289 per 1000 (14 to 1000)	RR 1.67 (0.08 to 36.11)	150 (Galeva 2013, Konstan 2011/ EVOLVE trial)	⊕⊖⊖⊖ very low[6,7,8]	
Minor adverse events: tinnitus	0 events	-	RR 17.26	520 (Ramsey 1999)	⊕⊕⊕⊖ moderate [4]	

Comparison 4.1. Tobramycin versus placebo						
Follow-up: 24 weeks			(1 to 297.54)			
Headaches Follow-up: 4 weeks	20 per 1000	7 per 1000 (1 to 67)	RR 0.36 (0.04 to 3.29)	95 (Konstan 2011/ EVOLVE trial)	⊕⊖⊖⊖ very low[5,7]	
Major adverse events: any Follow-up: 4 weeks	Study population		RR 0.52 (0.16 to 1.64)	150 (Galeva 2013, Konstan 2011/ EVOLVE trial)	⊕⊖⊖⊖ very low[6,7]	
	107 per 1000	55 per 1000 (17 to 175)				
	Moderate					
	39 per 1000	20 per 1000 (6 to 64)				
Major adverse events: any Follow-up: 24 weeks	259 per 1000	106 per 1000 (60 to 189)	RR 0.41 (0.23 to 0.73)	246 (Chuchalin 2007)	⊕⊕⊕⊕ high	
Major adverse events: haemoptysis Follow-up: 4 weeks	20 per 1000	22 per 1000 (1 to 338)	RR 1.07 (0.07 to 16.54)	95 (Konstan 2011/ EVOLVE trial)	⊕⊖⊖⊖ very low[5,7]	
Major adverse events: haemoptysis Follow-up: 24 weeks	309 per 1000	269 per 1000 (204 to 349)	RR 0.87 (0.66 to 1.13)	520 (Ramsey 1999)	⊕⊕⊕⊖ moderate [4]	
Major adverse events: pneumothorax Follow-up: 24 weeks	15 per 1000	4 per 1000 (0 to 35)	RR 0.25 (0.03 to 2.26)	520 (Ramsey 1999)	⊕⊕⊖⊖ low[7]	
Mortality Follow-up: 4 weeks	20 per 1000	7 per 1000 (0 to 173)	RR 0.35 (0.01 to 8.49)	95 (1 study)	⊕⊕⊖⊖ low[9]	
Mortality Follow-up: 3 to 12 months	17 per 1000	3 per 1000 (1 to 19)	RR 0.17 (0.03 to 1.09)	767 (Chuchalin 2007, Ramsey 1999)	⊕⊕⊕⊖ moderate [3]	
Emergence of resistant organisms: frequency of Tobramycin-resistant *P aeruginosa* Follow-up: 24 weeks	105 per 1000	204 per 1000 (90 to 463)	RR 1.95 (0.86 to 4.42)	672 (Chuchalin 2007, Ramsey 1999)	⊕⊖⊖⊖ very low[4,10]	
Emergence of resistant organisms: frequency of new isolates of drug resistant *B cepacia*	0 events	0 events	-	258 (Ramsey 1999)	⊕⊕⊕⊕ high	

Comparison 4.1. Tobramycin versus placebo						
Follow-up: 24 weeks						
Emergence of resistant organisms: frequency of new isolates of drug resistant *S maltophilia* Follow-up: 24 weeks	4 per 1000	12 per 1000 (1 to 111)	RR 3.05 (0.32 to 29.1)	520 (Ramsey 1999)	⊕⊕⊖⊖ low[7]	
Emergence of resistant organisms: frequency of new isolates of drug resistant A. xylosidans Follow-up: 24 weeks	4 per 1000	4 per 1000 (0 to 62)	RR 1.02 (0.06 to 16.15)	520 (Ramsey 1999)	⊕⊕⊖⊖ low[7]	
Emergence of resistant organisms: frequency of new isolates of drug resistant aspergillus Follow-up: 24 weeks	104 per 1000	21 per 1000 (7 to 59)	RR 0.2 (0.07 to 0.57)	389 (Ramsey 1999)	⊕⊕⊕⊕ high	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Abbreviations: CFU/G: colony forming units per gram; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; kg: kilogrammes; MD: mean difference; RR: risk ratio						

1 The quality of the evidence was downgraded by 1, as 1 of the trials had unclear risk of bias for the domains randomisation, allocation concealment, and blinding and another trial had unclear risk of bias for the domains randomisation, allocation concealment and high risk of bias for blinding
2 The quality of the evidence was downgraded by 1 due to moderate inconsistency (I2=51%). Sub-group analysis was not conducted, as all of the trials showed a beneficial effect of tobramycin
3 The quality of the evidence was downgraded by 1 as the 95% CI crossed the null effect
4 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 default MID
5 The quality of the evidence was downgraded by 2 due to unclear risk of bias for the domains randomisation, allocation concealment and high risk of bias for blinding
6 The quality of the evidence was downgraded by 2, as the largest trial had unclear risk of bias for the domains randomisation, allocation concealment and high risk of bias for blinding
7 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 default MIDs
8 The quality of the evidence was downgraded by 2 due to very serious inconsistency (I2=77%).
9 The quality of the evidence was downgraded by 2 as the 95% CI is very wide and it crossed the null effect. The study is underpowered to detect differences
10 The quality of the evidence was downgraded by 2 due to very serious inconsistency (I2=79%)

Table 120: Summary clinical evidence profile: Comparison 4.2. Tobramycin inhalation powder versus tobramycin inhalation solution

Comparison 4.2. Tobramycin inhalation powder versus tobramycin inhalation solution						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				

Comparison 4.2. Tobramycin inhalation powder versus tobramycin inhalation solution						
	Tobramycin inhalation solution (TOBI neb)	Tobramycin inhalation powder (TOBI DPI)				
Lung function: % mean change in FEV_1 % predicted Scale from: 0 to 100 Follow-up: 4 weeks	Not reported	The mean % mean change in FEV_1 % predicted in the TOBI DPI groups was 0.8 lower (3.9 lower to 2.3 higher)		517 (Konstan 2011a/EAGER trial)	⊕⊕⊖⊖ low[1,2]	
Lung function: % mean change in FEV_1 % predicted Scale from: 0 to 100 Follow-up: 20 weeks	Not reported	The mean % mean change in FEV_1 % predicted in the TOBI DPI groups was 1.10 higher (2.33 lower to 4.53 higher)		517 (Konstan 2011a/EAGER trial)	⊕⊕⊖⊖ low[1,2]	
Lung function: % mean change in FEV_1 % predicted Scale from: 0 to 100 Follow-up: 24 weeks	Not reported	The mean % mean change in FEV_1 % predicted in the TOBI DPI groups was 2.20 higher (1.11 lower to 5.51 higher)		517 (Konstan 2011a/EAGER trial)	⊕⊕⊖⊖ low[1,2]	
Number of patients with 1 or more exacerbations	NMA outcome					
Suppression of the organism: mean change in *P aeruginosa* sputum density log10 CFU Follow-up: 4 weeks	The mean change in *P aeruginosa* sputum density log10 CFU in the TOBI neb groups was -1.32	The mean change in *P aeruginosa* sputum density log10 CFU in the TOBI DPI groups was 0.44 lower (0.79 to 0.09 lower)		517 (Konstan 2011a/EAGER trial)	⊕⊕⊕⊖ moderate [1]	
Suppression of the organism: mean change in *P aeruginosa* sputum density log10 CFU Follow-up: 20 weeks	The mean change in *P aeruginosa* sputum density log10 CFU in the TOBI neb groups was -0.77	The mean change in *P aeruginosa* sputum density log10 CFU in the TOBI DPI groups was 0.84 lower (1.17 to 0.51 lower)		517 (Konstan 2011a/EAGER trial)	⊕⊕⊖⊖ low[1,3]	
Adverse events - any mild or moderate AE	684 per 1000	732 per 1000 (657 to 821)	RR 1.07 (0.96 to 1.2)	517 (Konstan	⊕⊕⊕⊖ moderate [1]	

Comparison 4.2. Tobramycin inhalation powder versus tobramycin inhalation solution						
Follow-up: 24 weeks				2011a/EAGER trial)		
Adverse events - any serious AE Follow-up: 24 weeks	292 per 1000	271 per 1000 (207 to 362)	RR 0.93 (0.71 to 1.24)	517 (Konstan 2011a/EAGER trial)	⊕⊕⊖⊖ low[1,3]	
mild AE: productive cough Follow-up: 24 weeks	196 per 1000	182 per 1000 (126 to 261)	RR 0.93 (0.64 to 1.33)	517 (Konstan 2011a/EAGER trial)	⊕⊖⊖⊖ very low[1,4]	
mild AE: headache	120 per 1000	114 per 1000 (71 to 184)	RR 0.95 (0.59 to 1.54)	517 (Konstan 2011a/EAGER trial)	⊕⊖⊖⊖ very low[1,4]	
mild AE: vomiting Follow-up: 24 weeks	57 per 1000	61 per 1000 (30 to 125)	RR 1.07 (0.53 to 2.17)	517 (Konstan 2011a/EAGER trial)	⊕⊖⊖⊖ very low[1,4]	
serious AE: dyspnoea Follow-up: 24 weeks	124 per 1000	156 per 1000 (100 to 243)	RR 1.25 (0.8 to 1.95)	517 (Konstan 2011a/EAGER trial)	⊕⊖⊖⊖ very low[1,4]	
serious AE: haemoptysis Follow-up: 24 weeks	124 per 1000	129 per 1000 (82 to 207)	RR 1.04 (0.66 to 1.66)	517 (Konstan 2011a/EAGER trial)	⊕⊖⊖⊖ very low[1,4]	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Abbreviations: CFU: colony forming units; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; MD: mean difference; RR: risk ratio						

1 The quality of the evidence was downgraded by 1 as this is an open trial, and randomisation is unclear
2 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 clinical MID
3 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 default MID
4 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 default MID

Table 121: Summary clinical evidence profile: Comparison 4.3. Tobramycin versus Aztreonam lysine

Comparison 4.3.Tobramycin versus Aztreonam						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Aztreonam lysine	Tobramycin				
[TOBI nebulised versus AZLI inhaled] Lung function: % change in FEV_1 % predicted Scale from: 0 to 100	The mean % change in FEV_1 % predicted in the aztreonam lysine groups was 2.05	The mean % change in FEV_1 % predicted in the tobramycin groups was 2.71 lower (2.88 to 2.54 lower)		268 (Assael 2013)	⊕⊕⊕⊖ moderate [1]	

Comparison 4.3.Tobramycin versus Aztreonam						
Follow-up: 3 months						
Number of patients with 1 or more exacerbations	NMA outcome					
[TOBI nebulised versus AZLI inhaled] Suppression of the organism: adj mean change sputum density log^{10} PA CFU/g- Follow-up: 20 weeks	The adjusted mean change sputum density log^{10} pa CFU/g in the aztreonam lysine groups was -0.55	The adjusted mean change sputum density log^{10} pa CFU/g in the tobramycin groups was 0.23 higher (0.3 lower to 0.76 higher)		194 (Assael 2013)	⊕⊕⊖⊖ low[1,2]	
[TOBI nebulised versus AZLI inhaled] Nutritional status: % adj mean weight change – Follow-up: 20 weeks	The adjusted mean weight change in the aztreonam lysine groups was 0.58	The adjusted mean weight change in the tobramycin groups was 0.52 lower (1.68 lower to 0.64 higher)		268 (Assael 2013)	⊕⊕⊖⊖ low[1,2]	
[TOBI nebulised versus AZLI inhaled] Quality of life: CFQR respiratory, adj mean change – Follow-up: 20 weeks	The adjusted mean change in CFQ-R respiratory in the aztreonam lysine groups was 6.3	The adjusted mean change in CFQ-R respiratory in the tobramycin groups was 4.1 lower (8.59 lower to 0.39 higher)		268 (Assael 2013)	⊕⊕⊖⊖ low[1,3]	
[TOBI nebulised versus AZLI inhaled] Minor adverse events: chest discomfort – Follow-up: 3 months	103 per 1000	99 per 1000 (48 to 202)	RR 0.96 (0.47 to 1.96)	268 (Assael 2013)	⊕⊖⊖⊖ very low[1,4]	
[TOBI nebulised versus AZLI inhaled] Minor adverse events: cough – Follow-up: 3 months	706 per 1000	791 per 1000 (685 to 904)	RR 1.12 (0.97 to 1.28)	268 (Assael 2013)	⊕⊕⊖⊖ low[1,2]	

Comparison 4.3.Tobramycin versus Aztreonam						
[TOBI nebulised versus AZLI inhaled] Minor adverse events: headache - Follow-up: 3 months	213 per 1000	205 per 1000 (128 to 326)	RR 0.96 (0.6 to 1.53)	268 (Assael 2013)	⊕⊖⊖⊖ very low[1,4]	
[TOBI nebulised versus AZLI inhaled] Minor adverse events: vomiting - Follow-up: 3 months	103 per 1000	106 per 1000 (53 to 214)	RR 1.03 (0.51 to 2.08)	268 (Assael 2013)	⊕⊖⊖⊖ very low[1,4]	
[TOBI nebulised versus AZLI inhaled] Major adverse events: dyspnoea - Follow-up: 3 months	228 per 1000	160 per 1000 (96 to 262)	RR 0.7 (0.42 to 1.15)	268 (Assael 2013)	⊕⊕⊖⊖ low[1,2]	
[TOBI nebulised versus AZLI inhaled] Major adverse events: haemoptysis Follow-up: 3 months	228 per 1000	160 per 1000 (96 to 262)	RR 0.7 (0.42 to 1.15)	268 (Assael 2013)	⊕⊕⊖⊖ low[1,2]	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Abbreviations: AZLI: aztreonam lysine; CFQ-R: cystic fibrosis questionnaire revised; CFU/g: colony forming units per gram; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; MD: mean difference; RR: risk ratio; TOBI: tobramycin						

1 The quality of the evidence was downgraded by 1 because this is an open trial
2 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 default MID
3 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 clinical MID
4 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 default MIDs

Table 122: Summary clinical evidence profile: Comparison 5. Combination of fosfomycin + tobramycin versus placebo

Comparison 5. Combination of fosfomycin + tobramycin versus placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Combination of fosfomycin + tobramycin (FTI)				

Comparison 5. Combination of fosfomycin + tobramycin versus placebo						
Lung function: relative change in FEV_1% predicted Scale from: 0 to 100 Follow-up: 4 weeks [FTI 80/20 mg]	Not reported	The relative change in FEV_1% predicted in the fosfomycin + tobramycin groups was 7.5 higher (3.6 to 11.4 higher)		70 (Trapnell 2012)	⊕⊕⊕⊖ moderate[1]	
Lung function: relative change in FEV_1% predicted Scale from: 0 to 100 Follow-up: 4 weeks [FTI160/40 mg]	Not reported	The mean relative change in FEV_1% predicted in the fosfomycin + tobramycin groups was 6.2 higher (2.42 to 9.98 higher)		73 (Trapnell 2012)	⊕⊕⊖⊖ low[1,2]	
Suppression of the organism: change in sputum *P aeruginosa* density, log10 CFU/g Follow-up: 4 weeks [FTI 80/20 mg]	Not reported	The mean change in sputum *P aeruginosa* density, log10 CFU/g in the fosfomycin + tobramycin groups was 1.04 lower (1.82 to 0.26 lower)		70 (Trapnell 2012)	⊕⊕⊖⊖ low[1,3]	
Suppression of the organism: change in sputum *P aeruginosa* density, log10 CFU/g mg Follow-up: 4 weeks [FTI160/40 mg]	Not reported	The mean change in sputum *P aeruginosa* density, log10 CFU/g in the fosfomycin + tobramycin groups was 0.28 lower (1.06 lower to 0.5 higher)		73 (Trapnell 2012)	⊕⊕⊖⊖ low[1,3]	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Abbreviations: CFU: colony forming units; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; FTI: Fosfomycin/ tobramycin inhaled; MD: mean difference; mg: milligrams; RR: risk ratio						

1 The quality of the evidence was downgraded by 1 due to unclear risk of bias for allocation concealment and data reporting
2 The quality of the evidence was downgraded by as the 95 % CI crossed 1 clinical MID
3 The quality of the evidence was downgraded by as the 95% CI crossed 1 default MID

Table 123: Summary clinical evidence profile: Comparison 6. Continuous alternating therapy versus intermittent treatment: aztreonam lysine + tobramycin or placebo + tobramycin

Comparison 6. Continuous alternating therapy versus intermittent treatment: aztreonam + tobramycin or placebo + tobramycin					
Outcomes	Illustrative comparative risks* (95% CI)	Relative	No of Participant	Quality of the	Comments

Comparison 6. Continuous alternating therapy versus intermittent treatment: aztreonam + tobramycin or placebo + tobramycin						
	Assumed risk	Corresponding risk	effect (95% CI)	s (studies)	evidence (GRADE)	
	Intermittent treatment: aztreonam lysine + tobramycin or placebo + tobramycin	Continuous alternating therapy				
Lung function: % change in FE1% predicted Scale from: 0 to 100 Follow-up: 20 weeks[1]	The mean % change in FEV_1% predicted in the intermittent treatment groups was 0.04	The mean % change in FEV_1% predicted in the continuous alternating therapy groups was 1.33 higher (1.05 to 1.61 higher)		88 (Flume 2016)	⊕⊕⊕⊖ moderate[2]	
Time to next pulmonary exacerbation	-	-	HR 0.89 (0.49 to 1.6)	88 (Flume 2016)	⊕⊕⊖⊖ low[2,3]	
Quality of life: change in CFQ-R Scale from: 0 to 100 Follow-up: 20 weeks[1]	The mean change in CFQ-R in the intermittent treatment groups was -2.06	The mean change in CFQ-R in the continuous alternating therapy groups was 3.06 higher (2.35 to 3.77 higher)		88 (Flume 2016)	⊕⊕⊖⊖ low[2,4]	
Minor adverse events: cough Follow-up: 3 months	435 per 1000	761 per 1000 (526 to 1000)	RR 1.75 (1.21 to 2.54)	88 (Flume 2016)	⊕⊕⊖⊖ low[2,5]	
Serious adverse events: dyspnoea Follow-up: 3 months	522 per 1000	308 per 1000 (183 to 527)	RR 0.59 (0.35 to 1.01)	88 (Flume 2016)	⊕⊕⊖⊖ low[2,5]	
Serious adverse events (not treatment related) Follow-up: 3 months	522 per 1000	501 per 1000 (334 to 751)	RR 0.96 (0.64 to 1.44)	88 (Flume 2016)	⊕⊖⊖⊖ very low[2,6]	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).						

Comparison 6. Continuous alternating therapy versus intermittent treatment: aztreonam + tobramycin or placebo + tobramycin
Abbreviations: CFQ-R: cystic fibrosis questionnaire reviewed; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; MD: mean difference; mg: milligrams; RR: risk ratio

1 Values at 4, 12 and 20 weeks were averaged
2 The quality of the evidence was downgraded by 1 due to unclear allocation concealment, blinding, and data collection/ reporting
3 The quality of the evidence was downgraded by 1 as the 95% CI crossed the null effect line
4 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 clinical MID
5 The quality of the evidence was downgraded by 1 as the 95%CI crossed 1 default MID
6 The quality of the evidence was downgraded by 2 as the 95%CI crossed 2 default MIDs

9.4.3.4.1 S Aureus

No relevant studies were identified.

9.4.3.4.2 B cepacia complex

No relevant studies were identified.

9.4.3.4.3 A fumigatus

The clinical evidence profile for the antimicrobial treatment of chronic infection with *A fumigatus* is presented in Table 65.

Table 124: Summary clinical evidence profile: Comparison 7. Itraconazole versus placebo

Comparison 7. Itraconazole versus placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Placebo	**Itraconazole**				
Lung function: percentage change in FEV_1 predicted from baseline Scale from: 0 to 100 Follow-up: mean 24 weeks	The mean lung function in the placebo group was: 0.32	The mean lung function change in the itraconazole group was 4.94 lower (15.33 lower to 5.45 higher)	-	35 (Aaron 2012)	⊕⊖⊖⊖ very low[1,2,3]	
Lung function: percentage change in FEV_1 predicted from baseline Scale from: 0 to 100 Follow-up: mean 48 weeks	Not reported	The mean lung function change in the itraconazole group was 3.71 lower (-13.26 lower to 20.68 higher)	Not estimable	35 (Aaron 2012)	⊕⊖⊖⊖ very low[1,2,3]	
Time to next pulmonary exacerbation Follow-up: mean 24 weeks	The median time to next exacerbation in the	The median time to next exacerbation in the itraconazole group was: 77 days	adjHR 1.34 (0.57 to 3.14)	35 (Aaron 2012)	⊕⊖⊖⊖ very low[1,2,4]	

Comparison 7. Itraconazole versus placebo						
	placebo group was: 134 days					
proxy: number of patients with an exacerbation requiring AB Follow-up: mean 24 weeks	389 per 1000	665 per 1000 (342 to 1000)	RR 1.71 (0.88 to 3.33)	36 (Aaron 2012)	⊕⊖⊖⊖ very low[1,2,5]	
proxy: number of patients with an exacerbation requiring AB Follow-up: mean 48 weeks	611 per 1000	831 per 1000 (544 to 1000)	RR 1.36 (0.89 to 2.08)	36 (Aaron 2012)	⊕⊖⊖⊖ very low[1,2,6]	
proxy: number of patients with an exacerbation admitted to hospital Follow-up: mean 24 weeks	176 per 1000	166 per 1000 (39 to 715)	RR 0.94 (0.22 to 4.05)	35 (Aaron 2012)	⊕⊖⊖⊖ very low[1,2,6]	
proxy: number of patients with an exacerbation admitted to hospital Follow-up: mean 48 weeks	176 per 1000	222 per 1000 (58 to 851)	RR 1.26 (0.33 to 4.82)	35 (Aaron 2012)	⊕⊖⊖⊖ very low[1,2,4]	
Quality of life - all domains CFQ-R Scale from: 0 to 100 Follow-up: mean 24 weeks	Not reported	Not reported	Not estimable, but no significant differences found	35 (Aaron 2012)	⊕⊖⊖⊖ very low[1,2,7]	
Quality of life – change in respiratory domain CFQ-R Scale from: 0 to 100 Follow-up: mean 24 weeks	The mean change in CFQ-R score for the respiratory domain in the placebo group was: 4.77	The mean change in CFQ-R score for the respiratory domain in the itraconazole group was: 3.76	Not estimable, but no significant differences (p=0.87)	35 (Aaron 2012)	⊕⊖⊖⊖ very low[1,2,7]	
Minor adverse events - increased dyspnoea Follow-up: mean 24 weeks	125 per 1000	111 per 1000 (18 to 700)	RR 0.89 (0.14 to 5.6)	34 (Aaron 2012)	⊕⊖⊖⊖ very low[1,2,6]	
Minor adverse events - rash Follow-up: mean 24 weeks	62 per 1000	111 per 1000 (11 to 1000)	RR 1.78 (0.18 to 17.8)	34 (Aaron 2012)	⊕⊖⊖⊖ very low[1,2,6]	

Comparison 7. Itraconazole versus placebo						
Minor adverse events - hyperglycaemia Follow-up: mean 24 weeks	0 per 1000	0 per 1000 (0 to 0)	RR 2.68 (0.12 to 61.58)	34 (Aaron 2012)	⊕⊖⊖⊖ very low[1,2,6]	
Minor adverse events - flu-like illness Follow-up: mean 24 weeks	0 per 1000	0 per 1000 (0 to 0)	RR 6.26 (0.35 to 112.7)	34 (Aaron 2012)	⊕⊖⊖⊖ very low[1,2,6]	
Minor adverse events - diarrhoea Follow-up: mean 24 weeks	62 per 1000	19 per 1000 (1 to 428)	RR 0.3 (0.01 to 6.84)	34 (Aaron 2012)	⊕⊖⊖⊖ very low[1,2,6]	
Minor adverse events (lower scores are better) - conjunctivitis Follow-up: mean 24 weeks	62 per 1000	19 per 1000 (1 to 428)	RR 0.3 (0.01 to 6.84)	34 (Aaron 2012)	⊕⊖⊖⊖ very low[1,2,6]	
Major adverse events - haemoptysis Follow-up: mean 24 weeks	62 per 1000	111 per 1000 (11 to 1000)	RR 1.78 (0.18 to 17.8)	34 (Aaron 2012)	⊕⊖⊖⊖ very low[1,2,6]	
Major adverse events - spontaneous pneumothorax Follow-up: mean 24 weeks	0 per 1000	0 per 1000 (0 to 0)	RR 2.84 (0.12 to 65.34)	35 (Aaron 2012)	⊕⊖⊖⊖ very low[1,2,6]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: CFQ-R: cystic fibrosis questionnaire reviewed; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; MD: mean difference; RR: risk ratio

1 The quality of the evidence was downgraded by 1 due to unclear allocation, data reporting and sample size
2 The quality of the evidence was downgraded by 1 due to indirectness, as the therapeutic dosages were not achieved in 2/3 of the participants
3 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 clinical MIDs.
4 The quality of the evidence was downgraded by 2 as the 95% CI crossed the null effect and it is very wide. The study in underpowered to detect differences between groups.
5 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 default MID.
6 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 default MIDs
7 Not calculable, as no data was provided in the study.

9.4.3.5 Economic evidence

Four economic evaluations of antimicrobial agents to suppress chronic infection with *P aeruginosa* were identified in the literature search conducted for this guideline. The methods and results of those studies are described in Appendix K. Full details of the search and economic article selection flow chart can be found in Appendix E and F, respectively. Data extraction tables and quality assessments of included studies can be found in Appendix L and M, respectively.

This area was prioritised for de novo economic modelling; consequently, a cost-utility model was developed. Due to study heterogeneity, it was considered inappropriate to undertake one reliable, fully incremental analysis; hence, 4 comparisons within the model were

developed. The model uses a lifetime horizon based on the assumption that antimicrobials to supress *P aeruginosa* are given on a long-term basis.

The model takes the form of a state transition model to estimate transitions between 3 lung function (FEV_1% predicted) strata. Transition probabilities between the 3 FEV_1% strata and the probability of experiencing an exacerbation each cycle were taken from the clinical evidence review. A post lung transplant health state was also included in the model to reflect the clinical pathway.

A series of scenario analyses were undertaken in order to test how sensitive the results were to uncertainty in individual parameters. The methods used to construct the model and the results of all analyses are reported in Appendix K.

Manufacturers of antimicrobials included in the model have agreed Patient Access Schemes (PAS) with the Department of Health to reduce the cost of their drug, to subsequently increase cost-effectiveness. To account for these discounts on the drug acquisition cost, there is an option in the model to apply them. For completeness, the committee applied those discounts in the model, to reassess their cost-effectiveness. Table 125 below provides the base case result using list prices and PAS prices over a lifetime horizon.

Table 125: Results from the economic model

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Comparison 1					
List price					
Placebo	£92,040	11.25	-	-	-
Nebulised colistimethate sodium	£105,872	11.52	£13,833	0.33	£52,168
Nebulised tobramycin	£244,919	11.57	£139,047	0.05	£2,824,240
Tobramycin dry powder	£274,658	11.43	£29,739	-0.14	Dominated
PAS price					
Placebo	No change	No change	-	-	-
Nebulised colistimethate sodium	No change	No change	No change	No change	No change
Nebulised tobramycin	Reduced	No change	Reduced	No change	Reduced (>£30,000)
Tobramycin dry powder	Reduced	No change	Reduced	No change	No change
Comparison 2					
List price					
Nebulised colistimethate sodium	£107,149	11.35	-	-	-
Nebulised tobramycin	£244,890	11.58	£137,741	0.23	£602,472
PAS price					
Nebulised colistimethate sodium	No change	No change	-	-	-
Nebulised tobramycin	Reduced	No change	Reduced	No change	Reduced (>£30,000)
Comparison 3					
List price					
Colistimethate sodium dry powder	£276,593	11.37	-	-	-
Nebulised tobramycin	£245,561	11.41	-£31,032	0.04	Dominant

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER
PAS price					
Colistimethate sodium dry powder	Reduced	No change	-	-	-
Nebulised tobramycin	Reduced	No change	Increased	No change	Increased (>£20,000)
Comparison 4					
List price					
Nebulised tobramycin	£245,830	11.35	-	-	-
Nebulised aztreonam lysine	£265,151	11.91	£19,321	0.56	£34,348
Combination [a]	£340,265	11.53	£75,114	-0.38	Dominated
PAS price					
Nebulised tobramycin	Reduced	No change	-	-	-
Nebulised aztreonam lysine	Reduced	No change	Reduced	No change	Reduced (<£30,000)
Combination [a]	Reduced	No change	Reduced	No change	No change

(a) 28 days aztreonam lysine (nebulised) alternating with 28 days tobramycin (nebulised)

9.4.3.6 Evidence statements

9.4.3.6.1 Antimicrobial regimens for the treatment of chronic P Aeruginosa

Aztreonam lysine

Comparison 1: Aztreonam lysine versus placebo

Lung function: FEV_1

Moderate quality evidence from 1 RCT with 157 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed a clinically significant improvement in lung function (measured as relative change in FEV_1% predicted) in the group of participants receiving Aztreonam lysine (75 mg/ day) compared to those in the placebo group at 28 days follow-up.

Number of people with exacerbations

NMA outcome

Time to next exacerbation

No evidence was found for this critical outcome.

Suppression of the organism

High quality evidence from two RCTs with 321 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in the suppression of *P aeruginosa* (measured as change in sputum density log 10 CFU/G) between the participants who were receiving Aztreonam lysine (75 mg/day) and those who were receiving placebo at 4 week follow-up.

Nutritional status: weight

High quality evidence from one RCT with 164 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed difference clinically significant improvement in the nutritional status (measured as % weight change in kg) between the participants who were receiving Aztreonam lysine (75 mg/day) compared to those who were receiving placebo at 4 week follow-up.

Quality of life

Very low to high quality evidence from two RCTs with 321 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed a clinically significant beneficial effect of Aztreonam lysine (75 mg/day) in the following domains of quality of life: eating and vitality (measured with the CFQ-R questionnaire) compared to placebo, at 4 week follow-up. However, very low to moderate quality evidence from the same trials showed no clinically difference in the following domains of quality of life: body image, digestion, eating, emotional functioning, physical functioning, respiratory symptoms, role/ school, social functioning, treatment burden and weight ((measured with the CFQ-R questionnaire) between both groups.

Moderate to high unexplained heterogeneity was found for the following domains: eating, emotional functioning, health perceptions, physical functioning, respiratory symptoms, role or school, treatment burden and vitality.

Mild adverse events

Low quality evidence from 1 RCT with 164 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in the occurrence of chest discomfort between the participants who were receiving Aztreonam lysine (75 mg/day) and those who were receiving placebo at 4 week follow-up.

Low quality evidence from 3 RCTs with 532 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in the occurrence of cough between the participants who were receiving Aztreonam lysine (75 mg/day) and those who were receiving placebo at 4 week follow-up.

Very low quality evidence from 2 RCTs with 321 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in the occurrence of headache between the participants who were receiving Aztreonam lysine (75 mg/day) and those who were receiving placebo at 4 week follow-up. Significant unexplained heterogeneity was found between both trials, although both showed no clinically significant differences between both treatment groups.

Serious adverse events

Low quality evidence from 1 RCT with 164 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in the occurrence of dyspnoea between the participants who were receiving Aztreonam lysine (75 mg/day) and those who were receiving placebo at 4 week follow-up.

Low quality evidence from 2 RCTs with 375 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in the occurrence of haemoptysis between the participants who were receiving Aztreonam lysine (75 mg/day) and those who were receiving placebo at 4 week follow-up.

Mortality

High quality evidence from 1 RCT with 211 people with cystic fibrosis and chronic *P aeruginosa* infection > 7 years showed that there were no deaths in either group (Aztreonam lysine 75 mg/day or placebo) at 4 week follow-up.

Emergence of resistant organisms

Low to moderate quality evidence from 1 RCT with 155 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in the number of people in whom *S aureus, S maltophilia* or *A xylosoxidans* was persistently isolated between the participants who were receiving Aztreonam lysine (75 mg/day) and those who were receiving placebo at 42 day follow-up.

High quality evidence from 1 RCT with 155 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed that *B Cepacia* was not isolated in the participants of either group (Aztreonam lysine 75 mg/day or placebo) at 42 days follow-up.

9.4.3.6.2 Azithromycin (high-dose only)

No evidence was found for this treatment.

9.4.3.6.3 Ciprofloxacin (oral)

Comparison 2: Ciprofloxacin versus placebo

Lung function

No evidence was found for this critical outcome.

Number of people with exacerbations

NMA outcome.

Time to next exacerbation

No evidence was found for this critical outcome.

Suppression of the organism

No evidence was found for this important outcome.

Nutritional status: weight

Very low quality evidence from 1 RCT with 40 adults with cystic fibrosis and chronic *P aeruginosa* infection showed no clinically significant difference in weight (kg) between the participants who were receiving Ciprofloxacin (500 mg. for 10 days/ every 3 months) and those who were receiving placebo at 12 months follow-up.

Quality of life

No evidence was found for this important outcome.

Mild adverse events

Very low quality evidence from 1 RCT with 40 adults with cystic fibrosis and chronic *P aeruginosa* infection showed no clinically significant difference in the occurrence of gastrointestinal adverse events between the participants who were receiving Ciprofloxacin

(500 mg. for 10 days/ every 3 months) and those who were receiving placebo at 12 months follow-up.

Serious adverse events

No evidence was found for this important outcome.

Mortality

Low quality evidence from 1 RCT with 40 adults with cystic fibrosis and chronic *P aeruginosa* infection showed no clinically significant difference in the mortality rate between the participants who were receiving Ciprofloxacin (500 mg. for 10 days/ every 3 months) and those who were receiving placebo at 12 months follow-up.

Emergence of resistant organisms

Very low quality evidence from 1 RCT with 40 adults with cystic fibrosis and chronic *P aeruginosa* infection showed no clinically significant difference in the number of people in whom resistant strains of *P aeruginosa* were isolated between the participants who were receiving Ciprofloxacin (500 mg. for 10 days/ every 3 months) and those who were receiving placebo at 12 months follow-up.

Very low quality evidence from 1 RCT with 40 adults with cystic fibrosis and chronic *P aeruginosa* infection showed no clinically significant difference in the number of people in whom resistant strains of *S aureus* were isolated between the participants who were receiving Ciprofloxacin (500 mg. for 10 days/ every 3 months) and those who were receiving placebo at 12 months follow-up.

9.4.3.6.4 Colistimethate sodium (dry powder, inhaled)

Comparison 3.1: Colistin versus placebo

Lung function: FEV_1

Low quality evidence from 1 RTC with 29 people with cystic fibrosis and chronic *P aeruginosa* infection >7 years showed no clinically significant difference in lung function (measure as change in FEV_1 % predicted) between the participants receiving colistin (1 million units, twice daily for 3 months) and those receiving placebo at 3 months follow-up.

Number of people with exacerbations

NMA outcome

Time to next exacerbation

No evidence was found for this critical outcome.

Suppression of the organism

Moderate quality evidence from 1 RCT with 40 people with cystic fibrosis and chronic *P aeruginosa* infection >7 years showed that *P aeruginosa* was not eradicated of the sputum of any patient (Colistin solution 1 million units, twice daily for 3 months or placebo) during the 3 month trial.

Nutritional status

No evidence was found for this important outcome.

Quality of life

No evidence was found for this important outcome.

Mild adverse events

No evidence was found for this important outcome.

Serious adverse events

No evidence was found for this important outcome.

Mortality

No evidence was found for this important outcome.

Emergence of resistant organisms

Moderate quality evidence from 1 RCT with 40 people with cystic fibrosis and chronic *P aeruginosa* infection >7 years reported that none of the patients in either group (Colistin solution 1 million units, twice daily for 3 months or placebo) were infected with other colistin-resistant microorganisms (*Ps. Cepacia, Serratia marcesens, Preteus mirabilis, Gram-positive organisms* or *fungi*) during the 3 month trial.

Moderate quality evidence from 1 RCT with 40 people with cystic fibrosis and chronic *P aeruginosa* infection >7 years reported that resistance to colistin was not developed in any patient (Colistin solution 1 million units, twice daily for 3 months or placebo) during the 3 month trial.

Moderate quality evidence from 1 RCT with 40 people with cystic fibrosis and chronic *P aeruginosa* infection >7 years reported no change in resistant pattern to other commonly used anti-pseudomonas treatments in any patient (Colistin solution 1 million units, twice daily for 3 months or placebo)during the 3 month trial.

Comparison 3.2: Colistin DPI versus colistin nebulised

Lung function: FEV_1

Very low quality evidence from 1 RCT with 31 people with cystic fibrosis and chronic *P aeruginosa* infection ≥8 years showed no clinically significant difference in lung function (measured as % mean change in FEV_1 % predicted) between the participants who were receiving Colistin DPI (125 mg/ twice daily) and those receiving Colistin inhalation solution (2 MU/ twice daily) at 4 week follow-up.

Number of people with exacerbations

NMA outcome

Time to next exacerbation

No evidence was found for this critical outcome.

Suppression of the organism

No evidence was found for this important outcome.

Nutritional status

No evidence was found for this important outcome.

Quality of life

No evidence was found for this important outcome.

Mild adverse events

Very low quality evidence from 1 RCT with 31 people with cystic fibrosis and chronic *P aeruginosa* infection ≥8 years showed no clinically significant difference in the occurrence of chest discomfort, cough and vomiting between the participants who were receiving Colistin DPI (125 mg/ twice daily) and those receiving Colistin inhalation solution (2 MU/ twice daily) at 8 week follow-up.

Serious adverse events

Very low quality evidence from 1 RCT with 31 people with cystic fibrosis and chronic *P aeruginosa* infection ≥8 years showed no clinically significant difference in the occurrence of dyspnoea between the participants who were receiving Colistin DPI (125 mg/ twice daily) and those receiving Colistin inhalation solution (2 MU/ twice daily) at 8 week follow-up.

Mortality

No evidence was found for this important outcome.

Emergence of resistant organisms

No evidence was found for this important outcome.

Comparison 3.3: Colistin versus Tobramycin

Lung function: FEV_1

Very low quality evidence from 1 RCT with 109 people with cystic fibrosis and chronic *P aeruginosa* infection > 7 years showed no clinically significant difference in lung function (measured as mean % change in FEV_1 % predicted) between the participants receiving Colistin (COLI neb 1MU/3 ml. twice daily) and those who were receiving Tobramycin (TOBI neb 300 mg/5ml twice daily) at 1 to 3 months follow-up.

Low quality evidence from 1 RCT with 374 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in lung function (measured as mean % change in FEV_1 % predicted) between the participants receiving Colistin (COLI DPI 120 mg. twice daily) and those who were receiving Tobramycin (TOBI neb 300 mg/5ml twice daily) at 4 and 12 week follow-up.

Low quality evidence from 2 RCTs with 658 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in lung function (measured as mean % change in FEV_1 % predicted) between the participants receiving Colistin and those who were receiving Tobramycin (COLI neb 1MU/3 ml. twice daily versus TOBI neb 300 mg/5ml twice daily and COLI DPI 120 mg. twice daily versus TOBI neb 300 mg/5ml twice daily) at 24 week follow-up.

Number of people with exacerbations

NMA outcome

Time to next exacerbation

Very low quality evidence from 1 RCT with 374 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in the time to next pulmonary exacerbation (measured as mean time to first additional anti-pseudomonal treatment) between the participants receiving Colistin (COLI DPI 120 mg. twice daily) and those who were receiving Tobramycin (TOBI neb 300 mg/5ml twice daily) during the 24 weeks duration of the trial.

Suppression of the organism

Low quality evidence from 1 RCT with 79 people with cystic fibrosis and chronic *P aeruginosa* infection > 7 years showed no clinically significant difference in the suppression of *P aeruginosa* (measured as change in sputum PA density log10 CFU/ml) between the participants receiving Colistin (COLI neb 1MU/3 ml. twice daily) and those who were receiving Tobramycin (TOBI neb 300 mg/5ml twice daily) at 4 week follow-up.

Nutritional status

Low quality evidence from 1 RCT with 374 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in the BMI change between the participants receiving Colistin (COLI DPI 120 mg. twice daily) and those who were receiving Tobramycin (TOBI neb 300 mg/5ml twice daily) at 24 week follow-up.

Quality of life

Moderate quality evidence from 1 RCT with 374 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no difference in change in quality of life (measured with the individual domains of the CFQ-R questionnaire) between the participants receiving Colistin (COLI DPI 120 mg. twice daily) and those who were receiving Tobramycin (TOBI neb 300 mg/5ml twice daily) at 24 week follow-up. The uncertainty for this outcome could not be calculated.

Mild adverse events

Very low quality evidence from 1 RCT with 115 people with cystic fibrosis and chronic *P aeruginosa* infection >7 years showed no clinically significant difference in the occurrence of sputum changes, pharyngitis or cough between the participants receiving Colistin (COLI neb 1MU/3 ml. twice daily) and those who were receiving Tobramycin (TOBI neb 300 mg/5ml twice daily) at 4 week follow-up.

Very low quality evidence from 1 RCT with 374 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in the occurrence of productive cough, chest discomfort or vomiting between the participants receiving Colistin (COLI DPI 120 mg. twice daily) and those who were receiving Tobramycin (TOBI neb 300 mg/5ml twice daily) at 24 week follow-up.

Serious adverse events

Very low quality evidence from 1 RCT with 115 people with cystic fibrosis and chronic *P aeruginosa* infection >7 years showed no clinically significant difference in the number of participants who experienced more than 1 serious adverse event between the participants receiving Colistin (COLI neb 1MU/3 ml. twice daily) and those who were receiving Tobramycin (TOBI neb 300 mg/5ml twice daily) at 4 week follow-up.

Very low quality evidence from 1 RCT with 115 people with cystic fibrosis and chronic *P aeruginosa* infection >7 years showed no clinically significant difference in the occurrence of

dyspnoea between the participants receiving Colistin (COLI neb 1MU/3 ml. twice daily) and those who were receiving Tobramycin (TOBI neb 300 mg/5ml twice daily) at 4 week follow-up.

Moderate evidence from 1 RCT with 374 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed a clinically significant higher number of people withdrawn from the study due to a serious adverse effect in the group of participants receiving Colistin (COLI DPI 120 mg. twice daily) compared to those who were receiving Tobramycin (TOBI neb 300 mg/5ml twice daily) at 24 week follow-up.

Very quality evidence from 1 RCT with 374 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in the occurrence of dyspnoea or haemoptysis between the participants receiving Colistin (COLI DPI 120 mg. twice daily) and those who were receiving Tobramycin (TOBI neb 300 mg/5ml twice daily) at 24 week follow-up.

Mortality

No evidence was found for this outcome.

Emergence of resistant organisms

Low quality evidence from 1 RCT with 115 people with cystic fibrosis and chronic *P aeruginosa* infection >7 years reported that none of the patients in either treatment group (COLI neb 1MU/3 ml. twice daily and TOBI neb 300 mg/5ml twice daily) developed highly tobramycin-resistant *P aeruginosa* at 24 week follow-up.

9.4.3.7 Fosfomycin (inhaled)

No evidence was found for this treatment.

9.4.3.8 Tobramycin (dry powder, inhaled)

Comparison 4.1: Tobramycin versus placebo

Lung function: FEV_1

Low quality evidence from 4 RCTs with 516 children, young people and adults with cystic fibrosis and chronic *P aeruginosa* infection showed a clinically significant improvement in lung function (measured as mean % change in FEV_1 % predicted) in the group of participants who were receiving tobramycin (TOBI DPI 112 mg daily, TOBI nebulised 300 mg or 600 mg daily) compared to those who were receiving placebo at 1 to 3 months follow-up. Moderate heterogeneity was found between the trials. Three trials showed a clinically significant improvement in the tobramycin group, whereas 1 trial showed no differences.

Number of people with exacerbations

NMA outcome

Time to next exacerbation

No evidence was found for this outcome.

Suppression of the organism

High quality evidence from 3 RCTs with 357 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed a clinically significant higher number of people in

whom *P aeruginosa* was eradicated (measured as negative culture) in the group of participants receiving Tobramycin (TOBI neb 300 mg or TOBI DPI 112 mg daily) compared to those who were receiving placebo at 4 week follow-up. Low heterogeneity was observed between the 3 trials, but all of them were consistent in showing a beneficial effect of tobramycin compared to placebo.

High quality evidence from 1 RCT with 242 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed a clinically significant higher number of people in whom *P aeruginosa* was eradicated (measured as negative culture) in the group of participants receiving Tobramycin (TOBI neb 300 mg daily) compared to those who were receiving placebo at 20 week follow-up. However, moderate quality evidence from the same trial showed no clinically significant difference in the eradication of *P aeruginosa* 8, and 24 week follow-ups.

Moderate quality evidence from 1 RCT with 59 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in the eradication of *P aeruginosa* (measured as negative culture) between the participants receiving Tobramycin (TOBI neb 300 mg daily) and those who were receiving placebo at 6 week follow-up.

Moderate quality evidence from 1 RCT with 55 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed a clinically significant decrease in *P aeruginosa* sputum density (log10 CFU/ml) in the group of participants receiving Tobramycin (TOBI DPI 112 mg daily) compared to those who were receiving placebo at 4 week follow-up.

Likewise, low quality evidence from another RCT with 95 people with cystic fibrosis and chronic *P aeruginosa* infection > 6 years showed a clinically significant decrease in *P aeruginosa* mucoid and non-mucoid sputum density (log10 CFU/ml) in the group of participants receiving tobramycin (TOBI DPI 112 mg) compared to those who were receiving placebo at 4 week follow-up.

Nutritional status: weight

High quality evidence from 1 RCT with 59 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in weight (kg) between the participants receiving Tobramycin (TOBI neb 300 mg daily) and those who were receiving placebo at 12 week follow-up.

Likewise, moderate quality evidence from another RCT with 245 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in weight (kg) between the participants receiving Tobramycin (TOBI neb 300 mg daily) and those who were receiving placebo at 24 week follow-up.

Quality of life

No evidence was found for this outcome.

Mild adverse events

Very low quality evidence from 2 RCTs with 150 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed a clinically significant lower occurrence of mild adverse events in the group of participants receiving Tobramycin (TOBI DPI 112 mg daily) compared to those who were receiving placebo at 4 week follow-up.

However, low quality evidence from 1 RCT with 245 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in the occurrence of minor adverse events between the participants receiving Tobramycin (TOBI neb 300 mg daily) and those who were receiving placebo at 24 week follow-up.

Low quality evidence from 1 RCT with 55 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in the occurrence of auditory impairment between the participants receiving tobramycin (TOBI DPI 112 mg) and those who were receiving placebo at 4 week follow-up. In addition,

Moreover, high quality evidence from 1 RCT with 300 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no cases of auditory impairment in either group (TOBI neb 300 mg daily or placebo) at 24 week follow-up. No cases were identified either at 42 week follow-up (n=71).

Moderate quality evidence from 1 RCT with 520 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed a clinically significant higher occurrence of tinnitus in the group of participants receiving Tobramycin (TOBI neb 300 mg daily) compared to those who were receiving placebo at 24 week follow-up.

Very low quality evidence from 2 RCTs with 150 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in the occurrence of cough between the participants receiving tobramycin (TOBI DPI 112 mg) and those who were receiving placebo at 4 week follow-up. High unexplained heterogeneity was found between both trials, although both of them showed no clinically significant differences between both groups.

Moderate quality evidence from 1 RCT with 300 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years no clinically significant difference in the occurrence of tinnitus between the participants receiving tobramycin (TOBI neb 300 mg daily) and those who were receiving placebo 24 week follow-up.

Very low quality evidence from 1 RCT with 95 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in the occurrence of headaches between the participants receiving tobramycin (TOBI DPI 112 mg) and those who were receiving placebo 4 week follow-up.

Very low quality evidence from 2 RCTs with 150 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in the occurrence of serious adverse events between the participants receiving tobramycin (TOBI DPI 112 mg) and those who were receiving placebo at 4 week follow-up.

However, high quality evidence from 1 RCT with 246 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed a clinically significant lower occurrence of serious adverse events in the group of participants receiving Tobramycin (TOBI neb 300 mg daily) compared to those who were receiving placebo at 24 week follow-up.

Very low quality evidence from 1 RCT with 95 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in the occurrence of haemoptysis between the participants receiving tobramycin (TOBI DPI 112 mg) and those who were receiving placebo 4 week follow-up.

Likewise, moderate quality evidence from one RCT with 520 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in the occurrence haemoptysis between the participants receiving Tobramycin (TOBI neb 300 mg daily) and those who were receiving placebo at 24 week follow-up.

Low quality evidence from 1 RCT with 520 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in the occurrence pneumothorax between the participants receiving Tobramycin (TOBI neb 300 mg daily) and those who were receiving placebo at 24 week follow-up.

Mortality

Low quality evidence from 1 RCT with 95 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in mortality between the participants receiving tobramycin (TOBI DPI 112 mg) and those who were receiving placebo 4 week follow-up.

Likewise, moderate quality evidence from two RTCs with 839 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in the mortality rate between the participants receiving Tobramycin (TOBI neb 300 mg daily) and those who were receiving placebo at 24 week follow-up.

Emergence of resistant organisms

Very low quality evidence from 2 RCTs with 672 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in the number of participants in whom tobramycin–resistant *P aeruginosa* was isolated between the group of participants receiving Tobramycin (TOBI neb 300 mg daily) and those who were receiving placebo at 24 week follow-up. Significant unexplained heterogeneity was found between both trials, with 1 of them showing a clinically significant harmful effect of tobramycin, and the other trial showing no differences between both groups.

High quality evidence from 1 RCT with 520 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed that drug-resistant *B Cepacia* was not isolated in the participants of either group (TOBI neb 300 mg daily or placebo) at 24 week follow-up

Low quality evidence from 1 RCT with 520 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed that drug-resistant *B Cepacia* was not isolated in the participants of either group (TOBI neb 300 mg daily or placebo) at 24 week follow-up

Low quality evidence from 1 RCT with 520 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in the frequency of new isolates of drug-resistant *A xylosoxidans* between the participants who were receiving Tobramycin (TOBI neb 300 mg daily) and those who were receiving placebo at 24 week follow-up.

High quality evidence from 1 RCT with 389 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed a clinically significant lower number of patients in whom new isolates of drug–resistant *Aspergillus* was isolated in the group of participants receiving Tobramycin (TOBI neb 300 mg daily) compared to those who were receiving placebo at 24 week follow-up.

Comparison 4.2: Tobramycin DPI versus tobramycin nebulised

Lung function: FEV_1

Low quality evidence from 1 RCT with 517 people with cystic fibrosis and chronic *P aeruginosa* infection ≥6 years showed no clinically significant difference in lung function (measured as % mean change in FEV_1% predicted) between the participants receiving tobramycin DPI (112 mg/ twice daily) and those receiving tobramycin inhalation solution (300 mg/ 5ml twice daily) at 4, 20 and 24 week follow-up.

Number of people with exacerbations

NMA outcome

Time to next exacerbation

No evidence was found for this critical outcome.

Suppression of the organism

Low to moderate quality evidence from 1 RCT with 517 people with cystic fibrosis and chronic *P aeruginosa* infection ≥6 years showed no clinically significant difference in change in sputum density (measured as log10 CFU) in the group of participants receiving tobramycin DPI (112 mg/ twice daily) compared with those receiving tobramycin inhalation solution (300 mg/ 5ml twice daily) at 4 and at 20 week follow-up.

Nutritional status

No evidence was found for this important outcome.

Quality of life

No evidence was found for this important outcome.

Mild adverse events

Moderate quality evidence from 1 RCT with 517 people with cystic fibrosis and chronic *P aeruginosa* infection ≥6 years showed no clinically significant difference in the occurrence of mild adverse events (any) between the participants receiving tobramycin DPI (112 mg/ twice daily) and those receiving tobramycin inhalation solution (300 mg/ 5ml twice daily) at 24 week follow-up.

Very low quality evidence from 1 RCT with 517 people with cystic fibrosis and chronic *P aeruginosa* infection ≥6 years showed no clinically significant difference in the occurrence of productive cough, headache or vomiting between the participants receiving tobramycin DPI (112 mg/ twice daily) and those receiving tobramycin inhalation solution (300 mg/ 5ml twice daily) at 24 week follow-up.

Serious adverse events

Low quality evidence from 1 RCT with 517 people with cystic fibrosis and chronic *P aeruginosa* infection ≥6 years no clinically significant difference in the occurrence of serious adverse events (any) in the group of participants receiving tobramycin DPI (112 mg/ twice daily) compared with those receiving tobramycin inhalation solution (300 mg/ 5ml twice daily) at 24 week follow-up.

Very low quality evidence from 1 RCT with 517 people with cystic fibrosis and chronic *P aeruginosa* infection ≥6 years showed no clinically significant difference in the occurrence of dyspnoea and haemoptysis between the participants receiving tobramycin DPI (112 mg/ twice daily) and those receiving tobramycin inhalation solution (300 mg/ 5ml twice daily) at 24 week follow-up.

Mortality

No evidence was found for this important outcome.

Emergence of resistant organisms

No evidence was found for this important outcome.

Comparison 4.3: Tobramycin versus Aztreonam lysine

Lung function: FEV_1

Moderate quality evidence from 1 RCT with 268 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in lung function (measured as % change in FEV_1 % predicted) between the group of patients receiving tobramycin inhalation solution (300 mg/ twice daily) and the patients receiving aztreonam lysine (75g/ 3-times daily) at 3 months follow-up.

Number of people with exacerbations

NMA outcome

Time to next exacerbation

No evidence was found for this critical outcome.

Suppression of the organism

Low quality evidence from 1 RCT with 194 people with cystic fibrosis and chronic *P aeruginosa* infection ≥6 years showed no clinically significant difference in the change of sputum density (measured as log10 CFU) between the group of patients receiving Tobramycin inhalation solution (300 mg/ twice daily) and the patients receiving Aztreonam lysine (75g/ 3-times daily) at 20 week follow-up.

Nutritional status: weight

Low quality evidence from 1 RCT with 268 people with cystic fibrosis and chronic *P aeruginosa* infection ≥6 years showed no clinically significant difference in the percentage of weight change (kg) between the group of patients receiving Tobramycin inhalation solution (300 mg/ twice daily) and the patients receiving Aztreonam lysine (75g/ 3-times daily) at 24 week follow-up.

Quality of life

Low quality evidence from 1 RCT with 261 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed a clinically significant decrease in quality of life (measured as change from baseline in the CFQ-R questionnaire respiratory domain) in the group of participants receiving tobramycin inhalation solution (300 mg/ twice daily) compared to those receiving Aztreonam lysine (75g/ 3-times daily) at 20 week follow-up.

Mild adverse events

Very low to low quality evidence with 268 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in the occurrence of chest discomfort, cough, headache and vomiting between the group of patients receiving Tobramycin inhalation solution (300 mg/ twice daily) and the patients receiving Aztreonam lysine (75g/ 3-times daily) at 3 months follow-up.

Serious adverse events

Low quality evidence with 268 people with cystic fibrosis and chronic *P aeruginosa* infection ≥6 years showed no clinically significant difference in the occurrence of dyspnoea and haemoptysis between the group of patients receiving Tobramycin inhalation solution (300 mg/ twice daily) and the patients receiving Aztreonam lysine (75g/ 3-times daily) at 3 months follow-up.

Mortality

No evidence was found for this outcome.

Emergence of resistant organisms

No evidence was found for this outcome.

Comparison 5. Combination of fosfomycin + tobramycin versus placebo

Lung function: FEV_1

Moderate quality evidence from 1 RCT with 70 adults with cystic fibrosis and chronic *P aeruginosa* infection showed a clinically significant improvement in lung function (measured as relative change in FEV_1 % predicted) in the group of participants receiving combination of fosfomycin and tobramycin (80/ 20 mg) compared to those receiving placebo at 4 week follow-up.

Likewise, low quality evidence from the same trial (N=73) showed a clinically significant improvement in lung function (measured as relative change in FEV_1 % predicted) in the group of participants receiving combination of fosfomycin and tobramycin (160/ 40 mg) compared to those receiving placebo at 4 week follow-up.

Number of people with exacerbations

NMA outcome

Time to next exacerbation

No evidence was found for this critical outcome.

Suppression of the organism

Low quality evidence from 1 RCT with 70 adults with cystic fibrosis and chronic *P aeruginosa* infection showed a clinically significant decrease in sputum *P aeruginosa* density (log10 CFU/g) in the group of participants receiving combination of fosfomycin and tobramycin (80/ 20 mg) compared to those receiving placebo at 4 week follow-up.

However, low quality evidence from the same trial (N=73) showed no clinically significant difference between a combination of fosfomycin and tobramycin (160/ 40 mg) and placebo at 4 week follow-up.

Nutritional status

No evidence was found for this important outcome.

Quality of life

No evidence was found for this important outcome.

Mild adverse events

No evidence was found for this important outcome.

Serious adverse events

No evidence was found for this important outcome.

Mortality

No evidence was found for this important outcome.

Emergence of resistant organisms

No evidence was found for this important outcome.

Comparison 6. Continuous alternating therapy versus intermittent treatment: aztreonam lysine + tobramycin or placebo + tobramycin

Lung function: FEV_1

Moderate quality evidence from 1 RCT with 88 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in lung function (measure as % change in FEV_1 % predicted) between the participants receiving continuous alternating therapy (tobramycin inhalation solution 300 mg daily for 28 days, followed by aztreonam lysine) and those on an intermittent regimen (tobramycin inhalation solution 300 mg daily for 28 days, followed by placebo) at 20 week follow-up. Values at 4, 12 and 20 weeks were averaged.

Number of people with exacerbations

NMA outcome

Time to next exacerbation

Low quality evidence from 1 RCT with 88 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in time to next exacerbation between the participants receiving continuous alternating therapy (tobramycin inhalation solution 300 mg daily for 28 days, followed by aztreonam lysine) and those on an intermittent regimen (tobramycin inhalation solution 300 mg daily for 28 days, followed by placebo).

Suppression of the organism

No evidence was found for this important outcome.

Nutritional status

No evidence was found for this important outcome.

Quality of life

Low quality evidence from 1 RCT with 88 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in quality of life (measured with the CFQ-R questionnaire) between the participants receiving continuous alternating therapy (tobramycin inhalation solution 300 mg daily for 28 days, followed by aztreonam lysine) and those on an intermittent regimen (tobramycin inhalation solution 300 mg daily for 28 days, followed by placebo) at 20 week follow-up. Values at 4, 12 and 20 weeks were averaged.

Mild adverse events

Low quality evidence from 1 RCT with 88 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed a clinically significant increase in the occurrence of cough in the group of participants receiving continuous alternating therapy (tobramycin

inhalation solution 300 mg daily for 28 days, followed by aztreonam lysine) compared to those on an intermittent regimen (tobramycin inhalation solution 300 mg daily for 28 days, followed by placebo) at 3 months follow-up.

Serious adverse events

Low quality evidence from 1 RCT with 88 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed no clinically significant difference in the occurrence of dyspnoea between the participants receiving continuous alternating therapy (tobramycin inhalation solution 300 mg daily for 28 days, followed by aztreonam) and those on an intermittent regimen (tobramycin inhalation solution 300 mg daily for 28 days, followed by placebo) at 3 months follow-up.

Very low quality evidence from 1 RCT with 88 people with cystic fibrosis and chronic *P aeruginosa* infection ≥ 6 years showed a clinically significant increase in the occurrence of serious adverse events (no treatment related) in the group of participants receiving continuous alternating therapy (tobramycin inhalation solution 300 mg daily for 28 days, followed by aztreonam lysine) compared to those on an intermittent regimen (tobramycin inhalation solution 300 mg daily for 28 days, followed by placebo) at 3 months follow-up.

Mortality

No evidence was found for this important outcome.

Emergence of resistant organisms

No evidence was found for this important outcome.

9.4.3.8.1 Antimicrobial regimens for the treatment of chronic S aureus

Cefradine (oral)

No evidence was found for this treatment.

Cotrimoxazole (oral)

No evidence was found for this treatment.

Doxycycline (oral)

No evidence was found for this treatment.

Flucloxacillin (oral)

No evidence was found for this treatment.

9.4.3.8.2 Antimicrobial regimens for the treatment of chronic B cepacia complex

Ceftazidime (inhaled)

No evidence was found for this treatment.

Cotrimoxazole (oral)

No evidence was found for this treatment.

Imipenem (oral)

No evidence was found for this treatment.

Meropenem (inhaled)

No evidence was found for this treatment.

Trimethoprim (oral)

No evidence was found for this treatment.

9.4.3.8.3 Antimicrobial regimens for the treatment of chronic A fumigatus

Amphotericin (inhaled)

No evidence was found for this treatment.

Itraconazole (oral)

Comparison 7: Itraconazole versus placebo

Lung function: FEV_1

Very low quality evidence from 1 RCT with 35 people with cystic fibrosis and chronically colonised with *A fumigatus* ≥ 6 years showed no clinically significant difference in lung function (measured as percentage change in FEV_1 predicted from baseline) between the participants who were receiving oral Itraconazole (5mg/kg once or twice daily) and those who were receiving placebo after 24 or 48 week follow-up.

Exacerbations

Very low quality evidence from 1 RCT with 35 people with cystic fibrosis and chronically colonised with *A fumigatus* ≥ 6 years showed no clinically significant difference in the time to next exacerbation between the participants who were receiving oral Itraconazole (5mg/kg once or twice daily) and those who were receiving placebo.

Very low quality evidence from 1 RCT with 35 people with cystic fibrosis and chronically colonised with *A fumigatus* ≥ 6 years showed no clinically significant difference in the number of patients requiring oral or IV antibiotics due to a pulmonary exacerbation between the participants who were receiving oral Itraconazole (5mg/kg once or twice daily) and those who were receiving placebo after 24 or 48 week follow-up.

Very low quality evidence from 1 RCT with 35 people with cystic fibrosis and chronically colonised with *A fumigatus* ≥ 6 years showed no clinically significant difference in the number of patients admitted to hospital due to a pulmonary exacerbation between the participants who were receiving oral Itraconazole (5mg/kg once or twice daily) and those who were receiving placebo after 24 or 48 week follow-ups.

Suppression of the organism

No evidence was found for this important outcome.

Nutritional status

No evidence was found for this important outcome.

Quality of life

Very low quality evidence from 1 RCT with 35 people with cystic fibrosis and chronically colonised with *A fumigatus* ≥ 6 years showed no differences in quality of life (measured as change in CFQ-R total score and respiratory domain) between the participants who were receiving oral Itraconazole (5mg/kg once or twice daily) and those who were receiving placebo after the 24-week treatment duration. The uncertainty around this outcome could not be calculated.

Mild adverse events

Very low evidence from one RCT with 35 people with cystic fibrosis and chronically colonised with *A fumigatus* ≥ 6 years showed no clinically significant difference in the occurrence of minor adverse events (including: increased dyspnoea, rash, hyperglycaemia, flu-like illness, diarrhoea and conjunctivitis) between the participants who were receiving oral Itraconazole (5mg/kg once or twice daily) and those who were receiving placebo during the 24-week treatment duration.

Serious adverse events

Very low quality evidence from one RCT with 35 people with cystic fibrosis and chronically colonised with *A fumigatus* ≥ 6 years showed no clinically significant difference in the occurrence of major adverse events (including: haemoptysis and spontaneous pneumothorax) between the participants who were receiving oral Itraconazole (5mg/kg once or twice daily) and those who were receiving placebo during the 24-week treatment duration.

Mortality

No evidence was found for this important outcome.

Emergence of resistant organisms

No evidence was found for this important outcome.

Posaconazole (oral)

No evidence was found for this treatment.

Voriconazole (oral)

No evidence was found for this treatment.

9.4.3.8.4 Economic evidence statements

One cost-benefit analysis (Iles 2003) on people with cystic fibrosis in the UK, compared 12 months before nebulised tobramycin use with 12 months during nebulised tobramycin use. They found that the introduction of nebulised tobramycin reduced the cost of hospital attendances and parenteral antibiotics, but did not offset the cost of nebulised tobramycin. This analysis is directly applicable given that the type of economic evaluation is unlikely to change the conclusions about cost-effectiveness and all other applicability criteria are met. The evidence is associated with serious limitations from the before and after type study used to inform the analysis.

One cost-utility analysis (Tappenden 2013) on people with cystic fibrosis in the UK, found that if colistimethate sodium dry powder is priced lower than that of nebulised tobramycin the ICER lies in the south-west quadrant of the cost-effectiveness plane reflecting a QALY loss and cost savings for colistimethate sodium dry powder compared with nebulised tobramycin. However, if colistimethate sodium dry powder is priced higher than that of nebulised

tobramycin the incremental cost is positive, and colistimethate sodium dry powder is dominated by nebulised tobramycin. The lifetime horizon and 'within-trial' analysis resulted in smaller incremental differences in both costs and QALYs, but led to the same conclusions. This analysis is directly applicable with minor limitations.

One cost-utility analysis (Tappenden 2014) on people with cystic fibrosis in the UK, over a lifetime horizon, found that using list prices, nebulised tobramycin dominated colistimethate sound dry powder and tobramycin dry powder has an ICER of £123,563 compared to nebulised tobramycin. When the revised patient access scheme discount was applied to colistimethate sodium dry powder, nebulised tobramycin was more expensive and less effective with an ICER of £288,563. When the revised patient access scheme discount was applied to tobramycin dry powder, it dominated nebulised tobramycin. This analysis is directly applicable with minor limitations.

One cost-utility analysis (Schecter 2015) on people with cystic fibrosis in the US, found that aztreonam dominated nebulised tobramycin over a 3 year time horizon. This analysis is partially applicable, due to the US third party payer perspective taken. The evidence is associated with serious limitations, including the potential conflict of interest and lack of detail in their methods.

The economic model developed for this review, found that nebulised colistimethate sodium, nebulised tobramycin and tobramycin dry powder were not cost-effective compared to placebo in the base case (list prices). Tobramycin dry powder was also dominated (more expensive and less effective) by the treatments in this comparison.

The economic model developed for this review, found that nebulised tobramycin is not cost-effective compared to nebulised colistimethate sodium, in the base case (list prices), with an ICER of £602,472.

The economic model developed for this review, found that nebulised tobramycin dominated (more effective and less expensive) colistimethate sodium dry powder, in the base case (list prices).

The economic model developed for this review, found that nebulised aztreonam is not cost-effective compared to nebulised tobramycin, in the base case (list prices), with an ICER of £34,348. The combination treatment (28 days aztreonam lysine alternating with 28 days nebulised tobramycin) was also dominated (more expensive and less effective) by aztreonam lysine in this comparison.

9.4.3.9 Evidence to recommendations

9.4.3.9.1 Relative value placed on the outcomes considered

The aim of this review was to determine the clinical and cost-effectiveness of different antimicrobial treatment regimens to suppress chronic pulmonary infection in people with cystic fibrosis.

The committee identified lung function and time to next pulmonary exacerbation as critical outcomes for this evidence review. Where no evidence was found for time to next pulmonary exacerbation, number of people experiencing a pulmonary exacerbation and number of hospital admissions due to a pulmonary exacerbation were taken as proxy outcomes. Suppression of the organism, nutritional status, quality of life, adverse events and emergence of resistant organisms were rated as important outcomes.

9.4.3.9.2 Consideration of clinical benefits and harms

The committee discussed the recommendations for each pathogen separately.

Chronic *P Aeruginosa*

The committee discussed the results from the network meta-analysis. They noted that it was not possible to conduct network meta-analysis for the critical outcome FEV_1 due to high unexplained heterogeneity.

The results from the NMA suggested that Aztreonam lysine was more effective than placebo or tobramycin at reducing the odds of experiencing a pulmonary exacerbation. This result has to be treated with caution as there was considerable uncertainty in the network.

The committee also discussed the results from the review, conventional pair-wise meta-analysis. They first reviewed the evidence comparing treatments against placebo.

With regards to colistin, the evidence showed that inhaled colistin was no better than placebo with regards to lung function. The committee noted this evidence was of low quality and came from a small single trial. Moderate quality evidence showed that inhaled colistin was not associated with the emergence of resistant organisms when compared to placebo. They looked at the evidence comparing different routes of administration. Very low quality evidence from one trial showed no differences between colistin DPI and inhaled colistin in lung function and in the occurrence of adverse events.

The committee discussed the evidence comparing tobramycin and placebo. They noted tobramycin was associated with a clinically significant improvement in lung function at 1 to 3 months. However, moderate heterogeneity was found between trials therefore, they agreed this result should be interpreted with caution. With regards to suppressing the organisms, the evidence showed contradicting results. High quality evidence showed that tobramycin was better than placebo at suppressing the organism (measured as having a negative culture) at 4 and 20 week follow-ups. In addition, low to moderate quality evidence showed a clinically significant reduction in sputum density at 4 week follow-ups. However, moderate quality evidence showed no clinically significant difference in the eradication of *P aeruginosa* 6, 8, and 24 week follow-ups. The evidence regarding side effects was not conclusive either, but tobramycin was associated with an increased risk in the occurrence of mild adverse events including tinnitus. They looked at the evidence comparing different routes of administration. They noted there were no clinically significant differences between tobramycin DPI and inhaled tobramycin in lung function, change in sputum density or adverse events. The quality of the evidence range from very low to moderate.

With regards to ciprofloxacin, the committee noted there was no evidence for the critical outcome lung function. No differences were found in weight.

They noted there was moderate quality evidence showing that aztreonam lysine was better than placebo for lung function, weight and quality of life. In addition, no clinically significant differences were found in the occurrence of adverse events or in the emergence of resistant organisms.

The committee also reviewed the evidence comparing colistin and tobramycin. Very low to low quality evidence showed no clinically significant differences in lung function at 4, 12 and 24 weeks. Likewise, very low quality evidence showed no differences in time to next additional anti-pseudomonal treatment. With regards to the important outcomes, no clinically significant differences were found for suppression of the organism (measured as change in sputum density), weight, quality of life, adverse events and emergence of resistant organisms. The quality of the evidence ranged from very low to moderate.

The committee reviewed the evidence comparing tobramycin and aztreonam. Moderate quality evidence showed no clinically significant differences in lung function at 3 month follow-up. Low quality evidence showed no differences in change in sputum density or quality of life at 20 week follow-ups, and in weight at 24 weeks. Finally, no differences were found in the occurrence of adverse events at 3 months.

The committee noted the combination of fosfomycin and high low-dose tobramycin was found to be significantly better than placebo in lung function at 4 week follow-up. This evidence came from a single trial and was rated as of low to moderate quality. Low quality evidence from the same trial showed a clinically significant decrease in sputum density in the group receiving low-dose tobramycin, but this different was not clinically significant in the high-dose group.

Finally the committee discussed the compassion between continuous alternating therapy with tobramycin followed by aztreonam and intermittent treatment with tobramycin followed by placebo. The evidence showed no differences between both treatment regimens in lung function (moderate quality), time to next exacerbation (low quality) and quality of life (low quality) at 20 weeks. However, they noted the risk of adverse events was higher in the participants in the continuous alternating therapy group.

The committee noted no evidence was found for high-dose azithromycin and fosfomycin.

The findings of the clinical evidence were discussed in the light of the economic evidence. In addition, the committee discussed the current recommendations from the NICE TA report 276 (Tappenden 2013) that looked at colistin and tobramycin for the treatment of chronic *P aeruginosa* in people with cystic fibrosis over the age of 6 years.

As recommended in the NICE TA report 276 the committee agreed that colistin should be used as first-line treatment and can be given as dry powder for inhalation to those people who cannot tolerate it in its nebulised form. This recommendation is consistent with clinical practice and the CF Trust consensus recommendations.

The committee discussed whether aztreonam lysine or tobramycin should be given as second line treatment in case clinical deterioration occurs despite regular colistin. Clinical deterioration was considered to be an increase in the number of exacerbations or a decline in pulmonary function (determined by spirometry). In line with NICE TA report 276, the committee agreed to recommend either aztreonam lysine, nebulised tobramycin or tobramycin dry powder (see the section on economic benefits and harms). This is because although they noted the NMA suggested aztreonam was better than placebo or tobramycin, there was lots of uncertainty regarding the results. In addition, the available direct evidence comparing aztreonam lysine and tobramycin did not favour either treatment.

The committee discussed their understanding that the effect of an antimicrobial may diminish over time with repeated exposure. This may account for improvements seen in clinical trials with new agents in treatment-naïve populations. Therefore, it would be appropriate to change between agents in line with an individual's response.

The committee noted that adherence to treatment can be a relevant issue and should be considered when prescribing treatment.

The committee noted that in practice, combinations of inhaled antimicrobials may be prescribed on alternate cycles, for example, colistin alternating with tobramycin or aztreonam lysine or tobramycin alternating with aztreonam lysine. However, in the absence of evidence, they did not write a recommendation.

The committee noted that other inhaled antimicrobials were in development but did not form part of this review as the data was not available when the review was undertaken (for example, levofloxacin inhalation solution). The omission of levofloxacin from the recommendations does not reflect a decision not to recommend it but rather the fact that it was not included in this review.

Chronic *S aureus*

No evidence was found for the treatment of chronic *S aureus*, therefore, recommendations were based on committee's clinical expertise. They noted the Cochrane review is empty.

The committee made separate recommendations for MSSA and MRSA. This is because MRSA treatment is more complex than MSSA treatment.

The committee's consensus was that long term oral antibiotic treatment to suppress MSSA could be justified whether the person is unwell or not, because this is a recognised and important pulmonary pathogen in children and adults. Supressing it might be expected to reduce the risk of progressive lung disease and of acute exacerbations caused by this infection. The choice of treatment would depend on disease severity.

With regards to MRSA, the committee agreed that there is no need to routinely give antibiotic treatment to suppress infection in people with chronic MRSA who are stable. They noted it is important to explain the risks and benefits of treatment to the person with cystic fibrosis and their families. However, they agreed that if *S aureus* is repeatedly isolated from a patient's respiratory samples and the lung function is deteriorating a course of antibiotics could be considered. This is because MRSA can be fatal in people who are unwell.

The committee acknowledged the infection control guideline (CG 139) and agreed that many of the principles are also applicable to people with cystic fibrosis.

Chronic *B cepacia* complex

No evidence was found for the treatment of *B cepacia* complex, therefore, recommendations were based on committee's clinical expertise. The committee noted that only a small number of people are infected with *B cepacia* complex, and most published studies are anecdotal reports.

The committee agreed that there is a strong emphasis in cross-infection prevention to avoid the spread of *B cepacia* complex between people with cystic fibrosis. However, they noted there is variability in the way people are treated.

Given that there is no evidence to support giving antibiotics to people with chronic *B cepacia* complex who are stable, the committee noted that it is important to discuss the possible risks of treating the infection, such as drug toxicity, with the person with cystic fibrosis and their family members or carers.

The committee agreed treatment could be considered for people with chronic *B cepacia* complex who are experiencing an exacerbation or whose lung function is deteriorating.

The committee noted the used of inhaled antibiotics can be considered. However, they agreed it is important to seek specialist microbiological advice on which antibiotic to use as healthcare professionals may have limited experience dealing with *B cepacia* complex.

Finally, the committee agreed treatment should be stopped if no benefit is observed.

Chronic *A fumigatus*

The committee acknowledged the evidence was scarce and of poor quality. They noted therapeutic azole levels were not achieved in many participants. Therefore, recommendations were mainly based on the committee's clinical knowledge and experience.

The committee agreed that, in people who are stable, there is no need to treat with antifungal agents to suppress infection. This is because it is known that chronic aspergillus colonisation can exist without associated deterioration in lung function. Treatment of this organism can be difficult and is associated with adverse events.

The committee discussed that, in people who are chronically infected with *A fumigatus* and deteriorating without an obvious explanation, a trial with an antifungal agent can be considered. They agreed to recommend a trial with an antifungal agent because this pathogen could be the cause of the deterioration in the lung function. They noted that their

first-line choice was itraconazole but that therapeutic levels of this agent are particularly difficult to achieve and it may be necessary to change to another antifungal such as voriconazole or posaconazole. Regardless, the choice of the antifungal agent should take *in vitro* sensitivities into account to ensure the optimal drug is used. They acknowledged that advice may be sought from a specialist microbiologist to inform choice. Finally, they highlighted that clinical response should be appropriately assessed and that treatment could be stopped or modified if no benefit was observed.

The committee acknowledge that it was important to distinguish between those who have respiratory symptoms due to infection with aspergillus and those who have clinical manifestations due to allergic sensitisation to aspergillus. For people with cystic fibrosis who have elevated aspergillus serology (aspergillus-specific IgG and/or IgE), declining pulmonary function and whose pulmonary treatment is optimised, the committee agreed that clinicians should think about treating allergic bronchopulmonary aspergillosis (ABPA) or other aspergillus airway disease, especially if a chest x-ray or CT scan shows consistent changes.

9.4.3.9.3 Consideration of economic benefits and harms

Antimicrobial regimens for the treatment of chronic *P aeruginosa*

The committee agreed that the use of a lifetime horizon in the economic model was appropriate. However, they acknowledged the limitation of extrapolating short-term trial results over a lifetime horizon. The committee noted that the model did not reflect the current treatment pathway where some people switch their treatment or receive a combination of treatments. However, the committee agreed that there was no clinical effectiveness data available on treatment switching or combinations to inform the model beyond the trial by Flume 2016. As a result, the committee considered the “with-in” trial analysis that did not extrapolate data to a lifetime horizon to address those limitations. The committee noted that trial participants were not treatment naïve which may underestimate the benefits and cost-effectiveness of those treatments in a naïve population.

The committee considered the impact of treatment adherence on cost-effectiveness, as cost-effectiveness may be overestimated beyond a trial setting, if the same benefits are not achieved. The committee advised that colistimethate sodium has a lower adherence than tobramycin because it requires more time and effort to administer. On the other hand, the committee also believed colistimethate tasted better than tobramycin which may increase adherence to colistimethate compared to tobramycin, especially in children. As a result, there are issues in both directions that could cancel out with little influence on the model. The committee added that people with cystic fibrosis may be more likely to adhere to a dry powder inhalation treatment than a nebulised treatment in view of the speed and convenience of drug delivery. However, newer nebulisers with quicker delivery time, such as the PARI eFlow jet nebuliser and I-neb, are increasing in use. For these reasons, it remains unclear whether dry powder inhalers would reduce treatment burden compared to newer quicker nebulisers.

It is current practice to offer people infected with chronic *P aeruginosa* antimicrobial treatment to prevent deterioration in their lung function. Despite this, the committee discussed how the benefits of antimicrobial treatment may not outweigh their costs. As a result, the committee questioned if current practice should be changed based on the economic model that found a small decrease in effectiveness for a large cost saving. Following this, the committee acknowledged that current NICE HTA recommendations state nebulised colistimethate sodium should be offered as a first-line option. However, the sources of evidence considered in NICE TA276 did not compare nebulised colistimethate sodium to “no treatment” which, again, questions if nebulised colistimethate sodium should be recommended.

If “no treatment” cannot be accepted as an option, the committee agreed that nebulised colistimethate sodium would be the most cost-effective antimicrobial and tobramycin dry powder would be the least as it was dominated (less effective and more expensive) by the other options in the economic model.

The committee agreed that it was reasonable to assume the exacerbation rate for nebulised colistimethate sodium was equal to nebulised tobramycin in the absence of data. The committee also agreed that given the current clinical pathway, they would have liked to have seen effectiveness evidence comparing nebulised colistimethate sodium, colistimethate dry powder and “no treatment”, especially as this evidence was not available during the submission of evidence in NICE TA276. To reduce this uncertainty, the committee considered a research recommendation to assess the clinical and cost-effectiveness of those options. However, the committee acknowledged a trial with a placebo arm would be unlikely to be approved.

The committee highlighted that current practice for inhaled therapies in cystic fibrosis follows the Clinical Commissioning Policy by NHS England who propose aztreonam lysine as a third line treatment following tobramycin. However, this recommendation is based primarily on cost and not cost-effectiveness that assesses if the additional benefit from aztreonam lysine outweigh its additional cost. Moreover, the cost-effectiveness of aztreonam lysine compared to nebulised tobramycin was published during the development of this guideline by Schechter 2015. Consequently, the comparison between nebulised tobramycin and aztreonam lysine was of greatest interest to the committee.

They agreed that the analysis by Schechter 2015 was favoured towards aztreonam lysine for several reasons. For example, the analysis included a much higher cost to manage an exacerbation (potentially as the analysis took a US third party perspective) and used a high drug acquisition cost for nebulised tobramycin than aztreonam lysine, influencing aztreonam lysine’s “dominant” result. Furthermore, participants included in the trial by Assael 2013 were not naïve to tobramycin, potentially with less to scope to benefit from tobramycin compared to aztreonam lysine.

However, the clinical evidence review also favoured aztreonam lysine over the other treatments under consideration. Based on the results from the economic model that was developed to reflect UK clinical practice, the committee agreed that aztreonam lysine could displace nebulised tobramycin as many of the analyses explored provided an ICER below NICE’s upper threshold for cost-effectiveness. However, given current NICE HTA recommendations, the committee agreed they could not recommend aztreonam lysine as the sole second-line option following colistimethate sodium. As a result, the committee prioritised a recommendation to consider aztreonam lysine or tobramycin when the person with a chronic infection is clinically deteriorating, despite regular inhaled colistimethate sodium.

The committee continued to discuss the combination treatment (28 days aztreonam lysine alternating with 28 days nebulised tobramycin) that was dominated by aztreonam lysine in the model. Given that a combination treatment incurs a continuous drug cost and demonstrated clinical effectiveness above nebulised tobramycin and below aztreonam lysine, the result was considered to accurately represent the available evidence. However, the committee vocalised their concerns that the RCTs identified in the clinical evidence review were flawed as they were often underpowered and included participants who were not treatment naive. The committee agreed a research recommendation was needed to demonstrate the clinical and cost effectiveness of combination treatments, but acknowledged that such a study would be impossible to conduct as the number of eligible participants would lead to another underpowered study. Overall, the committee acknowledged the limitations of the available evidence and agreed not to make a recommendation regarding combination treatments, as they believed clinical practice was clinically effective and cost-effective.

Antimicrobial regimens for the treatment of *A fumigatus*, *S aureus* and *B cepacia* complex

The committee advised that people with cystic fibrosis who have a stable chronic infection with *A fumigatus*, *S aureus* or *B cepacia* complex, and leave hospital untreated, feel anxious. To reduce their anxiety, the committee agreed that clinicians should inform their patients that there is no evidence on the effectiveness of suppressive antimicrobial treatment with the aim to reduce the number of people who insist on receiving treatment that is potentially cost-ineffective.

The committee advised that people who are chronically infected with S *aureus* are given flucloxacillin in UK clinical practice. They noted there is some variation when the treatment is initiated and stopped with regards to the severity of their symptoms. The committee acknowledged the higher price of oral solutions compared to capsules (NHS Electronic Drug Tariff September 2016: flucloxacillin 500mg capsules; £2.22/28 capsules, £0.08/500mg vs. flucloxacillin 250mg/5ml oral solution sugar free; £27.24/100ml, £2.72/500mg/10ml) and agreed that people who are chronically infected would be given the cheaper capsule preparation as they are unlikely to have swallowing difficulties at the age of chronic infection. Based on a dose of 4g/day, the cost of flucloxacillin in capsule form would be less than £1/day. Despite such low acquisition costs, the committee agreed that they should not be prescribed if they do not benefit the person with the chronic infection, especially as cystic fibrosis is a multi-system disorder associated with complex daily regimens. As a result, the committee concluded that antibiotics to suppress chronic MRSA should only be considered in people who are deteriorating, but not in people who have a stable chronic infection, as the cost and burden of treatment is likely to outweigh the benefits of treatment. Conversely, treatment should be considered to suppress chronic MSSA in people with stable pulmonary status given that the expected downstream costs associated with an unmanaged infection would outweigh the cost and burden of suppressive therapy.

The committee advised that the long-term use of drugs used to suppress *B cepacia* complex can have adverse effects associated with additional treatment costs and quality of life decrements. Consequently, the committee did not want to recommend the use of those drugs in people who are chronically infected and stable, adding that reducing their treatment burden may subsequently promote adherence to their existing regimens and outweigh the benefits of suppressive treatment. However, the committee agreed that people who are deteriorating should consider a trial of chronic suppressive treatment with an inhaled antibiotic. The committee also stated that clinicians should observe someone's response to treatment to ensure the cost of treatment is justified by suppression of the infection and to discontinue their treatment when they suspect the expected cost to exceed the expected benefit.

The committee advised that the first-line treatment for people who are chronically infected with *A fumigatus* is itraconazole. The committee discussed the clinical evidence that found no significant difference between itraconazole and usual care and concluded that the study was low quality with an undefined population. The committee also noted that the antimicrobials used to supress *A fumigatus* are relatively expensive compared to those used to suppress *B cepacia* complex and *S aureus*. As a result, the committee concluded that treatment in people who are deteriorating should take a stepwise approach, starting with the cheapest treatment (NHS Electronic Drug Tariff September 2016: itraconazole 100mg capsules; £3.42/15 capsules, £0.23/100mg). Based on a dose of 200mg twice daily, the cost of itraconazole in capsule from would be less than £1/day. Similarly to a stable chronic infection with *B cepacia* complex or *S aureus*, the committee agreed that people who have a stable chronic infection with *A fumigatus* should not be given routine antimicrobials treatment in an to attempt to suppress the chronic infection.

Overall, cost data has little use without associated benefits. Therefore, while the cost of long-term suppressive antimicrobial treatment could be significant, without knowing the benefits of

treatment we cannot know if they will be cost-effective. Therefore a research recommendation to assess the clinical effectiveness of suppressive antimicrobial treatment in people chronically infected with *S aureus*, *B cepacia* complex or *A fumigatus* will assess if the benefits can justify the costs in order to reduce current uncertainty in this area.

9.4.3.9.4 Quality of evidence

P aeruginosa

The quality of the evidence ranged from very low to high as assessed by GRADE. For the domain risk of bias, the studies were assigned the same risk of bias as in the Cochrane reviews and were not individually reviewed.

The main reasons that lead to downgrading the quality of the evidence was the risk of bias, many of the studies were open trials and there were issues in relation to data reporting, randomisation and allocation concealment.

Another reason that lead to downgrading the quality of the evidence was imprecision, as confidence intervals crossed 1 or 2 clinical or default MIDs.

No issues where identified in relation to the directness of the population.

S aureus

Not applicable, as no evidence was found for this pathogen.

***B Cepacia* Complex**

Not applicable, as no evidence was found for this pathogen.

A fumigatus

One study was found for the treatment of chronic *A fumigatus*. The evidence was considered low to very low quality as assessed by GRADE. The main reasons that lead to downgrading the quality of the evidence were the moderate risk of bias found in the study and the levels of imprecision. The evidence was downgraded further because the committee noted therapeutic dosages were not achieved in 2 out of 3 of the participants.

9.4.3.9.5 Other considerations

No equality issues were identified by the committee for this review question.

The committee agreed a research recommendation should not be prioritised for this topic. There is sufficient evidence to inform the management of chronic *P aeruginosa*. Studies on the management of *S aureus, B cepacia* complex, and *A fumigatus* are difficult to conduct.

In certain circumstances medicines are prescribed outside their licensed indications (off-label use) to children and young people because the clinical need cannot be met by licensed medicines; for example, for an indication not specified in the marketing authorisation, or administration of a different dose. At the time of publication (October 2017), colistimethate sodium DPI, nebulised tobramycin, tobramycin DPI and nebulised aztreonam did not have a UK marketing authorisation for use in children with cystic fibrosis for this indication. However, the Standing Committee on Medicines has issued a policy statement on the use of unlicensed medicines and the use of licensed medicines for unlicensed indications in children and young people. This states clearly that such use is necessary in paediatric practice and that doctors are legally allowed to prescribe medicines outside their licensed indications where there are no suitable alternatives and where use is justified by a responsible body of professional opinion.

It was noted that in the management of chronic infections a smaller pack size of drug may be available to assess the initial effects of the treatment (test dose), so as to minimise the potential for waste. Where a test pack is not available, the manufacturer may be able to offer alternative solutions to prevent waste in the event of a failed test dose. Without this test pack healthcare professionals may need to open a month's treatment to assess the effects and tolerance in each patient. However, the aim to reduce pharmacy waste is not exclusive to cystic fibrosis and should be considered as good practice in all disease areas.

9.4.3.9.6 Key conclusions

The guideline committee concluded that the recommendations from the NICE TA report 276 (Tappenden 2013) are current. They agreed colistin should be the first-line treatment for the management of chronic *P aeruginosa*. Aztreonam lysine or tobramycin can be given if the person continues to deteriorate. Although they noted aztreonam lysine has shown to be more cost-effective. The committee agreed there is no need to routinely give treatment to people who are chronically infected with *S aureus* or *A fumigatus*. Treatment should be considered if clinical deterioration is observed and the response to treatment should be assessed. Moreover, they noted that there is no evidence to support using antibiotics to suppress chronic *B cepacia* complex infection in people who have stable pulmonary status. The committee also agreed it is important discuss with the person with cystic fibrosis and the families about the benefits and harms of giving treatment.

9.4.4 Recommendations

S aureus

63. Offer flucloxacillin[4] as antibiotic prophylaxis against respiratory *Staphylococcus aureus* infection for children with cystic fibrosis from the point of diagnosis up to age 3, and consider continuing up to 6 years of age. Before starting flucloxacillin, discuss the uncertainties and possible adverse effects with their parents or carers (as appropriate). For children who are allergic to penicillins, consider an alternative oral anti-*Staphylococcus aureus* agent.

64. For children who are taking antibiotic prophylaxis and have a respiratory sample culture that is positive for *Staphylococcus aureus*:

- review prophylaxis adherence and help the child's parents or carers (as appropriate) with any difficulties they are having
- start treatment-dose anti-*Staphylococcus aureus* antibiotics
- restart prophylaxis after treatment, even if treatment has not been successful.

65. For people who are not taking prophylaxis and have a new *Staphylococcus aureus* infection (that is, previous respiratory sample cultures did not show *Staphylococcus aureus* infection):

- if they are clinically well, consider an oral anti-*Staphylococcus aureus* agent
- if they are clinically unwell and have pulmonary disease, consider oral or intravenous (depending on infection severity) broad-spectrum antibiotics that include an anti-*Staphylococcus aureus* agent.

[4] At the time of publication (October 2017), flucloxacillin did not have a UK marketing authorisation for use in people with cystic fibrosis for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

66. **Consider a long-term antibiotic to suppress chronic methicillin-sensitive *Staphylococcus aureus* (MSSA) respiratory infection in people whose pulmonary disease is stable.**

67. **For people with chronic MSSA respiratory infection who become clinically unwell with pulmonary disease, consider oral or intravenous broad-spectrum antibiotics (depending on infection severity) that include an anti-*Staphylococcus aureus* agent.**

68. **For people with new evidence of methicillin-resistant *Staphylococcus aureus* (MRSA) respiratory infection (with or without pulmonary exacerbation), seek specialist microbiological advice on treatment.**

69. **Do not routinely use antibiotics to suppress chronic MRSA in people with stable pulmonary disease.**

70. **If a person with cystic fibrosis and chronic MRSA respiratory infection becomes unwell with a pulmonary exacerbation or shows a decline in pulmonary function, seek specialist microbiological advice.**

71. **For guidance on preventing the spread of infection, refer to the NICE guideline on healthcare-associated infections.**

P aeruginosa

72. **If a person with cystic fibrosis develops a new *Pseudomonas aeruginosa* infection (that is, recent respiratory secretion sample cultures showed no infection):**
    - if they are clinically well:
        - commence eradication therapy with a course of oral or intravenous antibiotics, together with an inhaled antibiotic
        - follow this with an extended course of oral and inhaled antibiotics
    - if they are clinically unwell:
        - commence eradication therapy with a course of intravenous antibiotics together with an inhaled antibiotic
        - follow this with an extended course of oral and inhaled antibiotics.

73. **If eradication treatment is not successful despite treatment as recommended in 2, offer sustained treatment with an inhaled antibiotic. Consider nebulised colistimethate sodium as first-line treatment. (See recommendation 6 on using colistimethate dry powder for inhalation).**

74. **Depending on infection severity, use either an oral antibiotic or a combination of 2 intravenous antibiotics of different classes for people:**
    - who have chronic *Pseudomonas aeruginosa* infection (when treatment has not eradicated the infection) **and**
    - who become clinically unwell with a pulmonary disease exacerbation.

75. **If a person with chronic *Pseudomonas aeruginosa* infection repeatedly becomes clinically unwell with pulmonary disease exacerbations, consider changing the antibiotic regimens used to treat exacerbations.**

76. **Colistimethate sodium dry powder for inhalation (DPI) is recommended as an option for treating chronic pulmonary infection caused by *Pseudomonas aeruginosa* in people with cystic fibrosis only if:**
    - they would clinically benefit from continued colistimethate sodium but do not tolerate it in its nebulised form and thus tobramycin therapy would otherwise be considered **and**
    - the manufacturer provides colistimethate sodium DPI with the discount agreed as part of the patient access scheme to primary, secondary and tertiary care in the NHS.

[This recommendation is from Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis (NICE technology appraisal 276)]

77. **For people with chronic *Pseudomonas aeruginosa* infection who are clinically deteriorating despite regular inhaled colistimethate sodium, consider nebulised aztreonam, nebulised tobramycin, or tobramycin DPI (see recommendation 78 on using tobramycin DPI)[5].**

78. **Tobramycin DPI is recommended as an option for treating chronic pulmonary infection caused by *Pseudomonas aeruginosa* in people with cystic fibrosis only if:**
    - nebulised tobramycin is considered an appropriate treatment, that is, when colistimethate sodium is contraindicated, is not tolerated or has not produced an adequate clinical response **and**
    - the manufacturer provides tobramycin DPI with the discount agreed as part of the patient access scheme to primary, secondary and tertiary care in the NHS.

[This recommendation is from Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis (NICE technology appraisal 276)]

79. **People currently using tobramycin DPI or colistimethate sodium DPI that is not recommended according to recommendations 76 or 78 should be able to continue treatment until they and their clinician consider it appropriate to stop. For children and young people this decision should be made jointly by the clinician, the child or young person and their parents or carers.**

[This recommendation is from Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis (NICE technology appraisal 276)]

***Burkholderia cepacia* complex**

80. **For people with cystic fibrosis who develop a new *Burkholderia cepacia* complex infection (that is, recent respiratory sample cultures showed no *Burkholderia cepacia* infection):**

[5] At the time of publication (October 2017), Colistimethate sodium DPI, nebulised tobramycin, tobramycin DPI and nebulised aztreonam nebulised aztreonam and nebulised tobramycin did not have a UK marketing authorisation for use in children under 6 did with cystic fibrosis for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

- whether they are clinically well or not, give antibiotic eradication therapy using a combination of intravenous antibiotics
- seek specialist microbiological advice on the choice of antibiotics to use.

81. Be aware that there is no evidence to support using antibiotics to suppress chronic *Burkholderia cepacia* complex infection in people with cystic fibrosis who have stable pulmonary status. Discuss the possible risks (for example drug toxicity) of treating the infection with the person and their family members or carers (as appropriate).

82. For people with cystic fibrosis who have chronic *Burkholderia cepacia* complex infection (when treatment has not eradicated the infection) and who become clinically unwell with a pulmonary disease exacerbation:

- give a combination of oral or intravenous antibiotics
- seek specialist microbiological advice on which antibiotics to use.

83. For people with cystic fibrosis who have chronic *Burkholderia cepacia* complex infection and declining pulmonary status:

- consider sustained treatment with an inhaled antibiotic to suppress the infection
- seek specialist microbiological advice on which antibiotic to use
- stop this treatment if there is no observed benefit.

H influenzae

84. For people with cystic fibrosis who develop a Haemophilus influenzae infection (diagnosed by a positive respiratory sample culture) but do not have clinical evidence of pulmonary infection, treat with an appropriate oral antibiotic.

85. For people with cystic fibrosis who develop a Haemophilus influenzae infection (diagnosed by a positive respiratory sample culture) and are unwell with clinical evidence of pulmonary infection, treat with an appropriate antibiotic, given orally or intravenously depending on the severity of the illness.

Non tuberculous *mycobacteria*

86. For people with cystic fibrosis who are clinically well but whose airway secretions are persistently positive for non-tuberculous mycobacteria, discuss with them and their family members or carers (as appropriate):

- the clinical uncertainties about non-tuberculous mycobacterial infection **and**
- the possible benefits and risks (for example, drug toxicity) of treating it.

87. If a person with cystic fibrosis has a respiratory sample test positive for new non-tuberculous mycobacteria infection, repeat the test for confirmation.

88. If repeat testing confirms persistent non-tuberculous mycobacteria, do a chest CT scan to look for changes consistent with non-tuberculous mycobacteria disease.

89. Consider non-tuberculous mycobacterial therapy aimed at eradication for people with cystic fibrosis:

- whose airway secretions persistently test positive for non-tuberculous mycobacteria **and**
- who are clinically unwell with pulmonary disease, or who have a chest CT scan showing changes consistent with non-tuberculous mycobacteria disease **and**
- whose pulmonary disease has not responded to other recommended treatments.

Seek specialist microbiological advice on which antibiotics to use and on the duration of treatment.

***A fumigatus* complex**

90. Do not routinely use antifungal agents to suppress chronic *Aspergillus fumigatus* complex respiratory infection (diagnosed by persistently positive respiratory secretion sample cultures) in people with cystic fibrosis and stable pulmonary status.

91. For people with cystic fibrosis with chronic *Aspergillus fumigatus* complex respiratory infection and declining pulmonary status:

- consider sustained treatment with an antifungal agent to suppress the infection
- seek specialist microbiological advice on which antifungal agent to use
- stop treatment or change to a different agent if there is no benefit.

92. For people with cystic fibrosis with elevated aspergillus serology (aspergillus-specific IgG and/or IgE) and declining pulmonary function despite optimised pulmonary treatment, think about treating for allergic bronchopulmonary aspergillosis or other aspergillus airway disease, especially if there are consistent chest X-ray or CT scan changes.

Unidentified Infections

93. For people with cystic fibrosis who have a pulmonary disease exacerbation and no clear cause (based on recent respiratory secretion sample cultures) :

- use an oral or intravenous (depending on the exacerbation severity) broad-spectrum antibiotic
- continue collecting respiratory secretion samples, and change treatments if a pathogen is identified and a more appropriate treatment is available.

9.5 Immunomodulatory agents

Review question: What is the effectiveness of immunomodulatory agents in the management of lung disease?

9.5.1 Introduction

Progressive pulmonary disease is the primary cause of morbidity and mortality in adults with cystic fibrosis (CF). The decrease in lung function associated with chronic infection by a variety of organisms has been related to the severity of pulmonary inflammation.

In cystic fibrosis the cystic fibrosis transmembrane conductance regulator (CFTR) is defective. This results in alterations in the way airway epithelial cells direct the inflammatory response in the airways. Defects in CFTR are associated with increased production of pro-inflammatory mediators, including IL-8, which is a potent neutrophil attractor. As a result a large number of these inflammation-causing cells are directed to the airways causing high levels of inflammation and damage. These neutrophils are the primary effector cells responsible for the pathological manifestations of cystic fibrosis lung disease. Additionally, deficiencies in molecules regulating the immune response, such as IL-10, likely contribute to the generation of the excessive and persistent inflammatory response.

Therapies which reduce pulmonary inflammation may prove to be clinically efficacious and so reduce the damage caused by persistent infection and improve patient outcomes.

9.5.2 Description of clinical evidence

The aim of this review was to determine the clinical and cost effectiveness of immunomodulatory agents in children and young people and adults with cystic fibrosis.

We aimed to look at different immunomodulatory treatments, including inhaled corticosteroids, oral and IV corticosteroids, macrolide antibiotics, NSAIDs and monoclonal antibodies, compared to placebo or other immunomodulatory treatment.

Use of Azithromycin in an antimicrobial dose (greater than 250 mg 3 times a week or 500 mg 3 times a week for body weight over 40kg) was excluded from this evidence review and considered in the evidence review on antimicrobials for acute pulmonary infections.

We searched for systematic reviews of RCTs and RCTs assessing the effectiveness of immunomodulatory agents in people with cystic fibrosis.

For full details see review protocol in Appendix D.

Five Cochrane systematic reviews were identified in the search (Balfour-Lynn 2016, Cheng 2015, Jat 2013, Lands 2016, Southern 2012).

Four reviews were included in this evidence review. Where possible, data and risk of bias assessment was extracted directly from the Cochrane systematic reviews. Individual studies were retrieved for completeness and accuracy, and were also checked for additional outcomes of interest.

- Balfour-Lynn 2016 evaluated the effectiveness of inhaled corticosteroids compared to placebo or standard treatment. 3 RCTs on Fluticasone use were included from this review (Balfour-Lynn 1997, Balfour-Lynn 2006, De Boeck 2007).
- Cheng 2015 evaluated the effectiveness of oral corticosteroids compared to placebo or existing conventional therapy. 3 RCTs were included from this review: 2 trials examined use of Prednisone (Eigen 1995 and Auerbach 1985) and 1 trial examined use of Prednisolone (Greally 1994).
- Lands 2016 evaluated the effectiveness of oral NSAIDs compared to placebo or existing therapy. 3 RCTs were included from this review: 2 trials on use of ibuprofen (Konstan 1995 and Lands 2007) and 1 trial on piroxicam (Sordelli 1994).
- Southern 2012 evaluated the effectiveness of macrolide antibiotics compared to placebo, other antibiotic class, or other macrolide. 5 RCTs on Azithromycin were included from this review (Clement 2006, Equi 2002, Saiman 2003, Saiman 2010, Wolter 2002).

An additional Cochrane review (Jat 2015) evaluated the effectiveness of anti-IgE therapy for allergic bronchopulmonary aspergillosis in people with cystic fibrosis. The review reported on 1 clinical trial (Novartis 2008) of Omalizumab which terminated early. This clinical trial (Novartis 2008) was not included as the adverse events reported were not listed in the review protocol.

In addition, 1 observational study (Lai 2000) on the use of Prednisone and 1 RCT on the use of clarithromycin (Robinson 2012) were identified for inclusion in this evidence review.

No evidence was identified which reported on IV methylprednisolone use.

The presentation of evidence synthesis was divided in two parts based on the type of analysis which was used to produce these syntheses:

Two outcomes, the forced expiratory volume in 1 second (FEV_1) % predicted and the rate of pulmonary exacerbations, were considered for network meta-analysis (NMA). These were each split into short (1-10 months) and long-term (>10 months) treatment. Ten studies were included in the NMAs for FEV_1 % predicted and eight studies were included in the NMAs for rate of pulmonary exacerbations (see Section 1.1.2.1) Pairwise comparisons were performed for the rest of the outcomes included in the review protocol. Ten RCTs were included from the Cochrane systematic reviews for the outcomes of nutritional status, time to next pulmonary exacerbation, adverse effects and quality of life.

- If a study did not report standardised height or weight scores (such as BMI, z scores or standard deviation scores), the absolute value (in centimetres or kilograms) was included. Standard deviation scores reported were compared to a population of children without cystic fibrosis.
- The size of the studies ranged between 23 and 285 people with cystic fibrosis. Two studies included children (Auerbach 1985, De Boeck 2007), 8 studies included children and young people (Balfour-Lynn 1997, Clement 2006, Eigen 1995, Equi 2002, Greally 1994, Lai 2000, Lands 2007, Saiman 2010), 1 study included young people and adults (Wolter 2002), 5 studies included children, young people and adults (Balfour-Lynn 2006, Konstan 1995, Robinson 2012, Saiman 2003, Sordelli 1994).
- Three studies were conducted in the UK (Balfour-Lynn 1997, Balfour-Lynn 2006, Equi 2002), 6 in the USA (Auerbach 1985, Eigen 1995, Konstan 1995, Lai 2000, Saiman 2003, Saiman 2010), 1 in Belgium (De Boeck 2007), 1 in France (Clement 2006),1 in Ireland (Greally 1994), 1 in Canada (Lands 2007), 1 in Argentina (Sordelli 1994), 1 in Australia (Wolter 2002), 1 in the USA and Australia (Robinson 2012).

A summary of the studies included in this review is presented in Table 159. See study selection flow chart in Appendix F, study evidence tables in Appendix G, list of excluded studies in Appendix H, forest plots in Appendix I, and full GRADE profiles in Appendix J.

9.5.3 Summary of included studies

A summary of the included studies is presented in Table 126.

Table 126: Summary of included studies (NMA and non-NMA outcomes)

Study	Intervention/ Comparison	Population	Outcomes	Comments
Cochrane systematic reviews				
Balfour-Lynn 2016 Cochrane SR	Intervention: Any inhaled corticosteroid, using any inhalation device, for a period of ≥2 weeks Comparison: Placebo or standard treatment	People of any age, with confirmed diagnosis of cystic fibrosis, regardless of clinical severity.	• FEV_1 % predicted • time to next exacerbation • change in height (cm) • Change in height	AMSTAR score: 11/11 • Studies included from this review: Balfour-Lynn 1997, Balfour-Lynn 2006, De Boeck 2007

Cheng 2015 Cochrane SR	Intervention: Oral corticosteroids Comparison: Placebo or existing conventional therapy	People with defined cystic fibrosis, of any age, at all stages of lung disease.	• Mortality, at 6 months • Adverse effects, • Absolute change in weight (kg)	AMSTAR score: 10/11 Studies included from this review: Auerbach 1985, Eigen 1995, Greally 1994.
Lands 2016 Cochrane SR	Intervention: Oral NSAIDS for a minimum period of 2 months Comparison: Placebo or existing therapy	People with defined cystic fibrosis, of any age, and any stage of lung disease.	• Adverse effects • Annual rate of change in % ideal body weight overall and by age	AMSTAR score: 10/11 Studies included from this review: Konstan 1995, Lands 2007, Sordelli 1994.
Southern 2012 Cochrane SR	Intervention: Short or long term use of a macrolide antibiotic Comparison: Placebo, other antibiotic class, other macrolide	People with confirmed diagnosis of cystic fibrosis	• Time to next exacerbation • Change in weight • Exacerbation* • Adverse effects • Quality of life using CFQ-R	AMSTAR score: 11/11 Studies included from this review: Clement 2006, Equi 2002, Saiman 2003, Saiman 2010, Wolter 2002.
Primary studies included in the Cochrane SR				
Auerbach 1985 (USA) RCT	Intervention: Prednisone 2 mg/kg to a maximum of 60 mg Comparison: Placebo	N=45 children with cystic fibrosis Age range: 1 to 12 years Participants with mild to moderate pulmonary disease	• Mortality, at 6 months	Included in Cochrane SR Cheng 201 Included in pairwise comparisons only.
Balfour-Lynn 1997 (UK) Cross-over RCT	Intervention: Fluticasone (dry powder) 200 micrograms twice per day Comparison: Placebo	N=23 Mean age 10.3 years (range 7 to 17 years)	• Short-term FEV_1 % predicted (6 weeks)	Included in Cochrane SR Balfour-Lynn 2016 • Included in NMA only
Balfour-Lynn 2006 (UK) Cross-over RCT	Intervention: Fluticasone propionate via volumatic spacer given at equivalent dose taken (55% had 400 g/d fluticasone and 45% took lower dose); before trial entry	N=171 people with cystic fibrosis Age (mean, range): 14 (6 to 53) years in fluticasone group; 15.8 years in placebo	• Time to next exacerbation • Change in height (cm)	Included in Cochrane SR Balfour-Lynn 2016 Included in pairwise comparisons only.

	Comparison: Placebo via volumatic spacer. If previously given budesonide beclometasone, switched to fluticasone to 2:1 ratio.			
De Boeck 2007 (Belgium) RCT	Intervention: Fluticasone 500 mcg dry powder inhaler twice daily Comparison: Lactose placebo dispensed in identical canister	N=29 children with cystic fibrosis Mean age (SD): 8.2 (0.6) years intervention group; 9.0 (0.5) in the control group	• Change in height	Included in Cochrane SR Balfour-Lynn 2016 Included in NMA and pairwise comparisons.
Clement 2006 (France) RCT	Intervention: Azithromycin 250 mg tablets 3 times a week (>40 kg, 500 mg) Comparison: Placebo	N=82 children and young people with cystic fibrosis Age (mean, SD): 11 (3.3) years	• Time to next exacerbation • Change in BMI, z score at 12 months follow-up	Included in Cochrane SR Southern 2012 Included in NMA and pairwise comparisons.
Eigen 1995 (USA) RCT	Intervention: Prednisone 2 mg/kg or 1 mg/kg on alternate days to a maximum of 60 mg. Comparison: Placebo	N=285 children and young people with cystic fibrosis Age range: 6 to 14 years	• Adverse effects, up to 3 and 4 years follow-up	Included in Cochrane SR Cheng 2015 Included in NMA and pairwise comparisons.
Equi 2002 (UK) RCT	Intervention: Azithromycin 250 mg tablets (>40 kg, 500 mg) per day Comparison: Placebo	N=41 Aged:8 to 18 years	• Short-term FEV_1 % predicted (26 weeks) • Short-term exacerbations per patient (26 weeks)	Included in Cochrane SR Southern 2012 • Included in NMA only
Greally 1994 (Ireland) RCT	Intervention: Soluble prednisolone 2 mg/kg daily for 14 days then 1 mg/kg/day on alternate days for 10 weeks (maximum dose 40 mg) Comparison: Placebo	N=24 children and young people with cystic fibrosis Age range: 5.5 to 19.5 years	• Absolute change in weight (kg)	Included in Cochrane SR Cheng 2015 Included in pairwise comparisons only.
Konstan 1995 (USA) RCT	Intervention: Ibuprofen 20 – 30 mg/kg to a maximum	N=85 people with cystic fibrosis	• Adverse effects up to 4 years follow-up	Included in Cochrane SR Lands 2016

	of 1600 mg, determined by pharmacokinetic study Comparison: Placebo	Age range: 5 to 39	• Annual rate of change in % ideal body weight overall and by age	Included in NMA and pairwise comparisons.
Lands 2007 (Canada) RCT	After pharmacokinetic study: Intervention: Ibuprofen 200 mg tablets at a dose of 20 to 30 mg/kg to a maximum of 1600 mg Comparison: Placebo	N=142 children and young people with cystic fibrosis Age: 6 to 18 years	• Adverse effects, up to 2 years follow-up	Included in Cochrane SR Lands 2016 Included in NMA and pairwise comparisons.
Saiman 2003 (USA) RCT	Intervention: Azithromycin 250 mg tablets 3 days a week (>40 kg, 500 mg) Comparison: Placebo	N=185 people with cystic fibrosis Age: > 6 years	• Time to next exacerbation • Adverse effects at 6 months follow-up • Change in weight at 6 months follow-up, and quality of life using CFQ-R	Included in Cochrane SR Southern 2012 Included in NMA and pairwise comparisons.
Saiman 2010 (USA) RCT	Intervention: Azithromycin 250 mg tablets 3 times a week (>36 kg, 500 mg) Comparison: Placebo	N=263 children and young people with cystic fibrosis Age range: 6 to 18 years	• Time to next exacerbation* • Change in weight at 6 months follow-up	Included in Cochrane SR Southern 2012 Included in NMA and pairwise comparisons.
Sordelli 1994 (Argentina) RCT	Intervention: Piroxicam (16-25kg: 10mg/d; 26-45kg: 15mg/d; >46kg: 20mg/d) Comparison: Placebo	N = 41 children, young people and adults with cystic fibrosis Age range: 5 to 37 years	Long-term exacerbations per patient (12-19 months)	Included in Cochrane SR Lands 2016 Included in NMA only
Wolter 2002 (Australia) RCT	Intervention: Azithromycin 250mg daily Comparison: Placebo	N = 60 young people and adults with cystic fibrosis Mean age (SD): 27.9 (6.5) years	Short-term FEV_1 % predicted (12 weeks) Short-term exacerbations per patient (12 weeks)	Included in Cochrane SR Southern 2012 Included in NMA only
Additional primary studies				
Lai 2000 Retrospective cohort study (10 years follow up of a	Group 1: placebo Group 2: 1 mg Prednisone/kg	N = 224 Age range: 6 to 14 years	• Height and weight at 18 years of age	Included in pairwise comparisons only.

Double-blind multicentre RCT - Eigen 1995)	Group 3: 2 mg Prednisone/kg			
Robinson 2012 (USA and Australia) Cross-over RCT	Clarithromycin 500mg per day or placebo	N=63 children, young people and adults with cystic fibrosis Mean age (SD): 16 (10.5) years	• Short-term FEV_1 % predicted (22 weeks) • Short-term exacerbations per patient (22 weeks)	• Included in NMA only

CFQ-R: cystic fibrosis respiratory questionnaire; NSAIDS: non-steroidal anti-inflammatory drugs

9.5.4 Clinical evidence profile

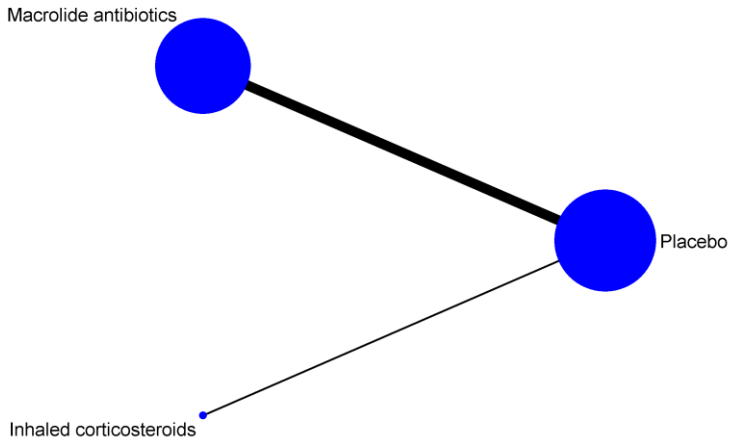
9.5.4.1 Clinical evidence profile for NMA outcomes (FEV_1 % predicted and rate of pulmonary exacerbations)

As treatment effects were found to vary over time, NMAs were conducted separately for short (1-10 months) and long (>10 months) of treatment.

9.5.4.1.1 FEV_1 % Predicted – Short-term (1-10 month) treatment

Six studies of 735 participants were included in the network of three classes of interventions – placebo, macrolide antibiotics (azithromycin, clarithromycin), inhaled corticosteroids (fluticasone) (Figure 8). The evidence was of moderate quality. Four studies were at low risk of bias and for the 2 other studies the risk of bias was unclear.

Figure 8: Network for FEV_1 % predicted short-term treatment



Note: Size of nodes are proportional to the number of patients in the network treated with a particular intervention. Thickness of connecting lines are proportional to the number of studies comparing two interventions.

Table 127 presents the results of the conventional pair-wise meta-analyses (head to head comparisons) (upper-right section of table), together with the results computed by the NMA for every possible treatment comparison (lower-left section of table). Both results are

presented as mean differences (95% CrI). These results were derived from a fixed effects mode l(Appendix N).

Macrolide antibiotics were found to have a clinically significant improvement versus placebo for limiting the decline in FEV_1 % predicted for people with cystic fibrosis treated for 1-10 months (Figure 9). Inhaled corticosteroids were not found to have a clinically significant effect on FEV_1 % predicted compared with placebo. Macrolide antibiotics were also not found to have a clinically significant effect over inhaled corticosteroids for short-term treatment. Incoherence could not be assessed as there were no closed loops of treatments.

In this analysis, macrolide antibiotics were found to have the highest probability (91.21%) of being the best treatment to improve/limit the decline in FEV_1 % predicted among interventions with a duration of 1-10 months (Table 128).

Table 127: Mean differences (95% CrI) from conventional (white area) and network meta-analysis (grey area) for FEV_1 % predicted with short-term treatment

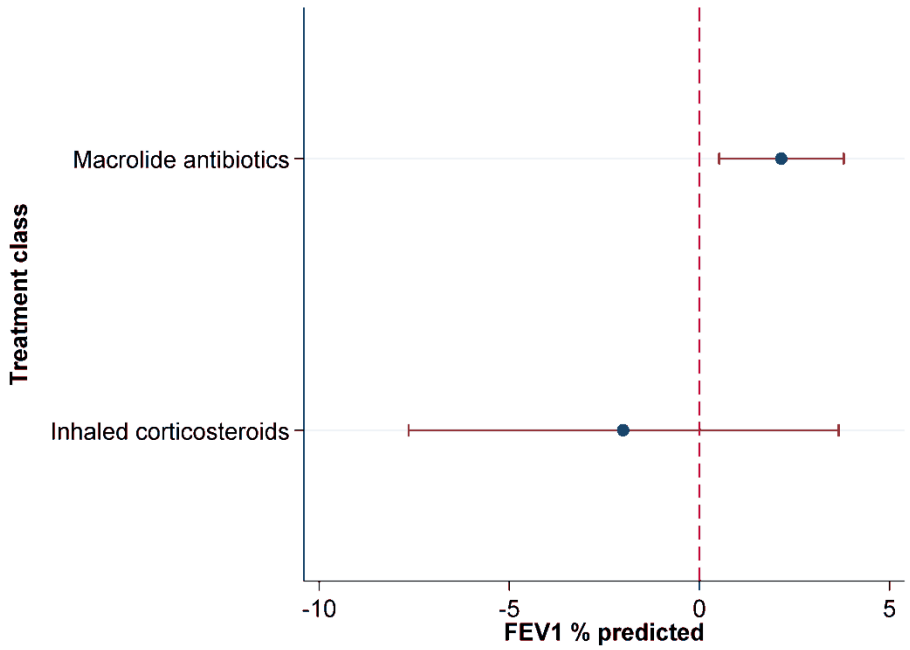
	Placebo	Macrolide antibiotics	Inhaled corticosteroids
Placebo		**2.16 (0.52, 3.79)**	-2.00 (-7.65, 3.67)
Macrolide antibiotics	2.16 (0.52, 3.79)		
Inhaled corticosteroids	-2.00 (-7.65, 3.67)	-4.16 (-10.04, 1.75)	

Results in the top right diagonal of the table are the mean differences and 95% CrI from the conventional meta-analyses of direct evidence between the column-defined treatments compared to the row-defined treatment. Mean differences greater than 0 favour the column-defined treatment.

Results in the bottom left are the mean differences and 95% CrI from the NMA model of direct and indirect evidence between the row-defined treatments compared to the column-defined treatments. Mean differences greater than 0 favour the row-defined treatment.

Numbers in bold denote results for which the 95% CrI does not include the null effect of 0

Figure 9: Forest plot showing mean differences (with their 95% CrI) of NMA estimates for each intervention versus placebo for FEV_1 % predicted with short-term treatment.



Note: Vertical dashed line shows the line of no effect

Table 128: Median treatment ranking (with their 95% CrI) of all interventions in the network and the probability of being the best treatment for improving/limiting the decline of FEV_1 % predicted in the short-term

	Median (95% CrI) treatment rank	Probability of being the best treatment (%)
Placebo	2 (2-3)	0.37%
Macrolide antibiotics	1 (1-2)	91.21%
Inhaled corticosteroid	3 (1-3)	8.41%

Table 129: Quality assessment of the evidence for the NMA for FEV_1 % predicted in the short-term

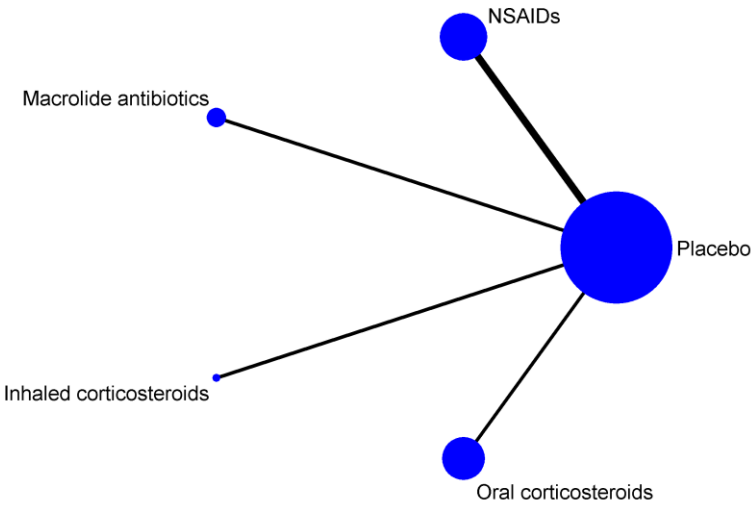
NMA	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Short term (1-10 months) FEV % predicted (6 studies)	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	Moderate

1 – No intervention has rank credible intervals ≤33% of total distribution of comparators

9.5.4.1.2 FEV_1 % Predicted - Long-term (>10 month) treatment

Five studies of 511 participants were included in the network of four classes of interventions – placebo, NSAIDs (ibuprofen), macrolide antibiotics (azithromycin), inhaled corticosteroids (fluticasone), and oral corticosteroids (prednisolone) (Figure 10). The evidence was of low quality. Two studies were at low risk of bias and for the other three studies the risk of bias was unclear.

Figure 10: Network for FEV_1 % predicted long-term treatment



Note: Size of nodes are proportional to the number of patients in the network treated with a particular intervention. Thickness of connecting lines are proportional to the number of studies comparing two interventions.

Table 130 presents the results of the conventional pair-wise meta-analyses (head to head comparisons) (upper-right section of table), together with the results computed by the NMA for every possible treatment comparison (lower-left section of table). Both results are presented as mean differences (95% CrI). These results were derived from a fixed effects model (Appendix N).

NSAIDs and oral corticosteroids were found to have a clinically significant improvement versus placebo for limiting the decline in FEV_1 % predicted for people with cystic fibrosis for >10 months of treatment (Figure 11). Long-term macrolide antibiotic treatment was not found to have a clinically significant effect on FEV_1 % predicted compared with placebo. There may be a clinically significant improvement of long-term oral corticosteroid treatment versus long-term macrolide antibiotic treatment, though there was insufficient evidence to confirm this. Incoherence could not be assessed as there were no closed loops of treatments.

In this analysis, long-term NSAID treatment was found to have the highest probability (65.2%) of being the best treatment to improve/limit the decline in FEV_1 %, followed by long-term oral corticosteroid treatment (12.9%) (Table 131).

Table 130: Mean differences (95% CrI) from conventional (white area) and network meta-analysis (grey area) for FEV_1 % predicted with long-term treatment

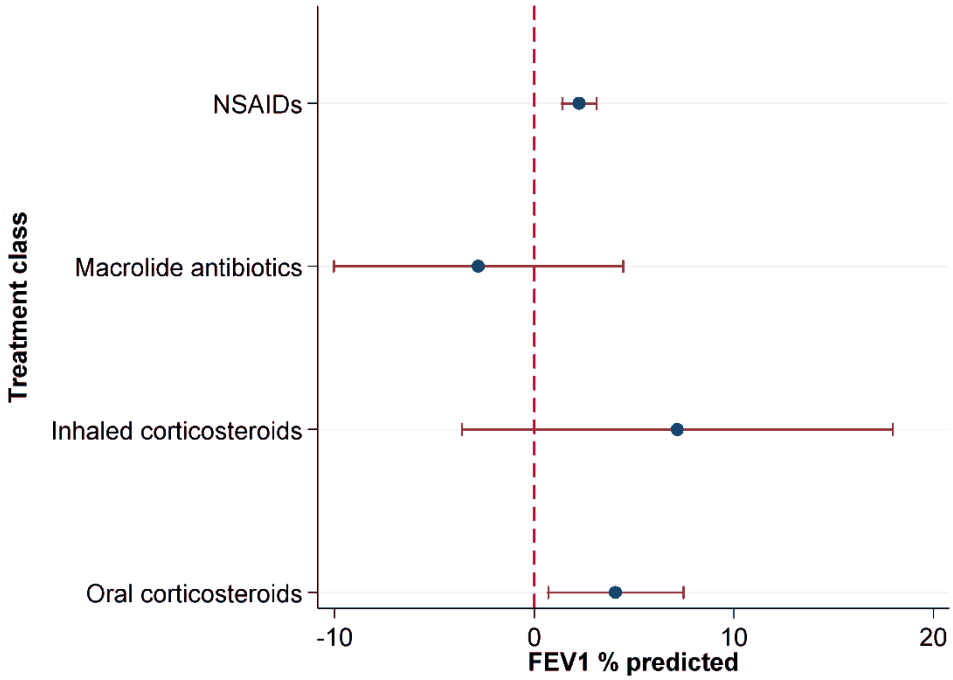
	Placebo	NSAIDs	Macrolide antibiotics	Inhaled corticosteroids	Oral corticosteroids
Placebo		**2.26** (1.40, 3.11)	-2.8 (-10.02, 4.44)	7.17 (-3.64, 17.95)	4.07 **(0.7, 7.49)**
NSAIDs	**2.26 (1.41, 3.11)**				
Macrolide antibiotics	-2.81 (-10.05, 4.45)	-5.07 (-12.34, 2.24)			
Inhaled corticosteroids	7.17 (-3.64, 17.95)	4.9 (-5.94, 15.73)	9.96 (-2.98, 22.95)		
Oral corticosteroids	**4.07 (0.7, 7.49)**	1.81 (-1.67, 5.33)	6.88 (-1.11, 14.92)	-3.09 (-14.39, 8.24)	

Results in the top right diagonal of the table are the mean differences and 95% CrI from the conventional meta-analyses of direct evidence between the column-defined treatments compared to the row-defined treatment. Mean differences greater than 0 favour the column-defined treatment.

Results in the bottom left are the mean differences and 95% CrI from the NMA model of direct and indirect evidence between the row-defined treatments compared to the column-defined treatments. Mean differences greater than 0 favour the row-defined treatment.

Numbers in bold denote results for which the 95% CrI does not include the null effect of 0

Figure 11:Forest plot showing mean differences (with their 95% CrI) of NMA estimates for each intervention versus placebo for FEV_1 % predicted with long-term treatment.



Note: Vertical dashed line shows the line of no effect

Table 131: Median treatment ranking (with their 95% CrI) of all interventions in the network and the probability of being the best treatment for improving/limiting the decline of FEV_1 % predicted in the long-term

	Median (95% CrI) treatment rank	Probability of being the best treatment (%)
Placebo	4 (3-5)	8.12%
NSAIDs	3 (1-4)	65.20%
Macrolide antibiotics	5 (2-5)	5.99%
Inhaled corticosteroids	1 (1-5)	7.82%
Oral corticosteroids	2 (1-3)	12.88%

Table 132: Quality assessment of the evidence for the NMA for FEV_1 % predicted in the long-term

NMA	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Long term (>10 months) FEV % predicted (3 studies)	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	Low

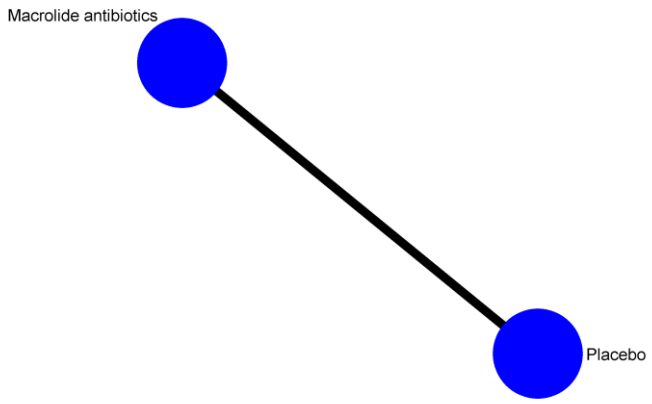
1 – Two included studies were at low risk of bias and for the other three studies the risk of bias was unclear.
2 – No intervention has rank credible intervals ≤33% of total distribution of comparators

9.5.4.1.3 Rate of pulmonary exacerbations - Short-term (1-10 month) treatment

Three studies of 226 participants were included in the network of 2 classes of interventions – placebo and macrolide antibiotics (azithromycin, clarithromycin) (Figure 12). The evidence

for this analysis was of moderate quality. One study was at low risk of bias and for the other 2 studies the risk of bias was unclear.

Figure 12: Network for rate of pulmonary exacerbations short-term treatment



Note: Size of nodes are proportional to the number of patients in the network treated with a particular intervention. Thickness of connecting lines are proportional to the number of studies comparing two interventions.

As there was only evidence on 2 classes of short-term treatments to reduce the rate of pulmonary exacerbations no NMA was performed for this outcome.

Very low quality evidence showed no clinically significant difference in the rate of exacerbations after short-term treatment between macrolide antibiotics and placebo (see Appendix N). This result was derived from a random effects pairwise analysis.

Table 133: Quality assessment of the evidence for the NMA for rate of exacerbations in the short-term

Fluticasone compared to placebo for cystic fibrosis						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed rate	**Corresponding rate**				
	Placebo	**Macrolide antibiotics**				
Rate of exacerbations after short-term (10 month) treatment	The mean rate of exacerbations per patient in the control groups was 0.56	The mean rate of exacerbations in the intervention groups was 0.42 (0.21 to 0.85)	Rate ratio 0.75 (0.37 to 1.51)	226 (Equi 2002, Robnson 2012, Wolter 2002)	⊕⊖⊕⊖ very low[1,2]	

**The basis for the assumed rate (e.g. the median control group rate across studies) is provided in footnotes. The corresponding rate (and its 95% confidence interval) is based on the assumed rate in the comparison group and the relative effect of the intervention (and its 95% CI).*

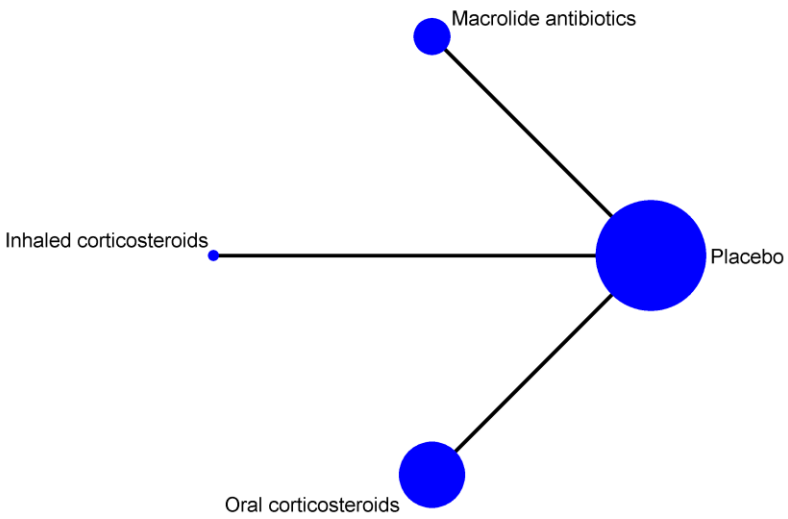
CI: Confidence interval;

1 Evidence was downgraded by 2 due to very serious inconsistency between studies
2 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs

9.5.4.1.4 Rate of pulmonary exacerbations - Long-term (>10 month) treatment

Three studies of 321 participants were included in the network of four classes of interventions – placebo, macrolide antibiotics (azithromycin), inhaled corticosteroids (fluticasone), and oral corticosteroids (prednisolone) (Figure 13). The evidence was of low quality. One study was at low risk of bias and for the other 2 the risk of bias was unclear.

Figure 13: Network for rate of pulmonary exacerbations long-term treatment



Note: Size of nodes are proportional to the number of patients in the network treated with a particular intervention. Thickness of connecting lines are proportional to the number of studies comparing two interventions.

Table 134 presents the results of the conventional pair-wise meta-analyses (head to head comparisons) (upper-right section of table), together with the results computed by the NMA for every possible treatment comparison (lower-left section of table). Both results are presented as mean differences (95% CrI). These results were derived from a fixed effects model (Appendix N).

There was considerable uncertainty throughout the network. No clinically significant differences were found between any of the treatments in the network. Incoherence could not be assessed as there were no closed loops of treatments.

In this analysis, long-term macrolide antibiotic treatment was found to have the highest probability (56.8%) of being the best treatment to reduce the rate of exacerbations, followed by long-term oral corticosteroid treatment (25.5%) (Table 135).

One study (Sordelli 1994) that provided information on NSAID efficacy was a candidate for inclusion into the network. However, as the NSAID used in the study (piroxicam) was considered to have potentially severe side effects and as the study was at high risk of bias (trial was unblinded and neither randomisation nor allocation methods were sufficiently described) it was not included in the final network.

As this was the only study providing information on NSAIDs, the results of the network were highly sensitive to it. Inclusion of this study did not affect estimates for other classes in the network, but provided an estimate for NSAID efficacy. This quality of evidence for this new network worsened from low to very low quality, with NSAIDs having the highest probability

(61.2%) of being the best treatment, followed by macrolide antibiotics (24.7%). Further results of this sensitivity analysis are reported in Appendix N.

Table 134: Rate ratios (95% CrI) from conventional (white area) and network meta-analysis (grey area) for the rate of exacerbations with long-term treatment

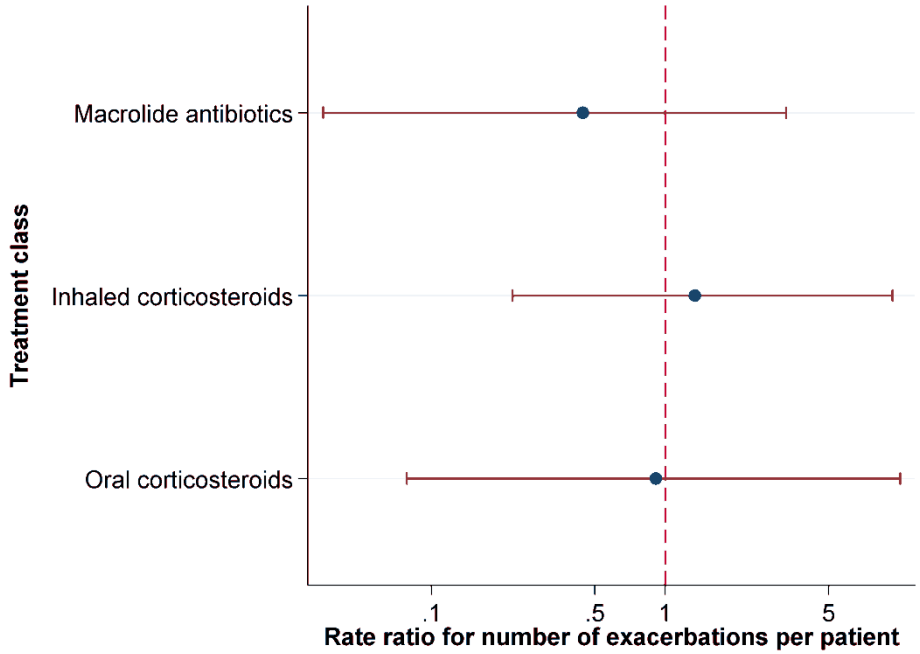
	Placebo	Macrolide antibiotics	Inhaled corticosteroids	Oral corticosteroids
Placebo		0.44 (0.03, 3.29)	1.34 (0.22, 9.37)	0.91 (0.08, 10.1)
Macrolide antibiotics	0.44 (0.03, 3.29)			
Inhaled corticosteroids	1.34 (0.22, 9.37)	3.14 (0.2, 72.84)		
Oral corticosteroids	0.91 (0.08, 10.1)	2.13 (0.09, 66.33)	0.67 (0.03, 13.54)	

Results in the top right diagonal of the table are the rate ratios and 95% CrI from the conventional meta-analyses of direct evidence between the column-defined treatments compared to the row-defined treatment. Rate ratios greater than 1 favour the column-defined treatment.

Results in the bottom left are the rate ratios and 95% CrI from the NMA model of direct and indirect evidence between the row-defined treatments compared to the column-defined treatments. Rate ratios greater than 1 favour the row-defined treatment.

Numbers in bold denote results for which the 95% CrI does not include the null effect of 1

Figure 14: Forest plot showing rate ratio (with their 95% CrI) of NMA estimates for each intervention versus placebo for the rate of exacerbations with long-term treatment.



Note: Vertical dashed line shows the line of no effect

Table 135: Median treatment ranking (with their 95% CrI) of all interventions in the network and the probability of being the best treatment for reducing the rate of exacerbations in the long-term

	Median (95% CrI) treatment rank	Probability of being the best treatment (%)
Placebo	3 (1-4)	6.37%
Macrolide antibiotics	1 (1-4)	56.82%

	Median (95% CrI) treatment rank	Probability of being the best treatment (%)
Inhaled corticosteroids	3 (1-4)	11.30%
Oral corticosteroids	2 (1-4)	25.51%

Table 136: Quality assessment of the evidence for the NMA for rate of exacerbations in the long-term

NMA	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Long term (>10 months) rate of exacerbations (4 studies)	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	Low

(x) 1 – One included study was at low risk of bias, one study was at high risk of bias, and for the other two the risk of bias was unclear

(y) 2 – No intervention has rank credible intervals ≤33% of total distribution of comparators

9.5.4.2 Clinical evidence profile for non-NMA outcomes (nutritional status, time to next pulmonary exacerbation, adverse events and quality of life)

The summary clinical evidence profile tables are presented in Table 137 - Table 140.

Table 137: Summary clinical evidence profile: Comparison 1. Fluticasone versus placebo

Comparison 1. Fluticasone versus placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Fluticasone				
Time to first exacerbation Follow-up: 6 months	460 per 10001	483 per 1000 (342 to 645)1	HR 1.07 (0.68 to 1.6838)[2]	171 (Balfour-Lynn 2006)	⊕⊕⊖⊖ low[1]	
Growth (change in height) SDS (standard deviation) score Follow-up: 12 months	The mean growth (change in height) in the placebo groups was -0.01 SDS	The mean growth (change in height) in the fluticasone groups was 0.37 SDS lower (0.77 lower to 0.03 higher)		30 (De Boeck 2007)	⊕⊕⊕⊖ moderate [3]	
Growth (change in height) in paediatric participants cm Follow-up: 8 months	The mean growth (change in height) in paediatric participants in the placebo	The mean growth (change in height) in paediatric participants in the fluticasone groups was 0.6 cm higher		80 (Balfour-Lynn 2006)	⊕⊕⊕⊖ moderate [3]	

Comparison 1. Fluticasone versus placebo						
	groups was 3.5 cm	(0.46 lower to 1.66 higher)				

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: CI: confidence interval; HR: hazard ratio; MD: mean difference; SDS: standard deviation score

1 The quality of the evidence was downgraded by 2 as 95%CI crossed the null effect line, and it is very wide.
2 Calculated by the NGA technical team from percentage of participants in group with at least 1 exacerbation.
3 The quality of the evidence was downgraded by 1 because 95%CI crossed 1 default MID.

Table 138: Summary clinical evidence profile: Comparison 2. Prednisone/ Prednisolone versus placebo

Comparison 2. Prednisone/ Prednisolone versus placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Placebo	**Prednisone/ Prednisolone**				
[2 mg prednisone] Absolute change in weight (kg) Follow-up: 12 weeks	The mean absolute change in weight in the placebo groups was 0.01 kg	The mean absolute change in weight in the prednisone groups was 0.34 kg higher (2.32 lower to 3 higher)		25 (Greally 1994)	⊕⊖⊖⊖ very low[1,2]	
[1 mg prednisone] Weight (Kg) Boys at 18 Years of Age	The mean absolute weight in the placebo groups was 63.7 kg	The mean weight in the prednisone groups was 4.6 kg lower (9.69 lower to 0.49 higher)		55 (Lai 2000)	⊕⊕⊖⊖ low[3]	
[2 mg prednisone] Weight (Kg) Boys at 18 Years of Age	The mean absolute weight in the placebo groups was 63.7 kg	The mean weight in the prednisone groups was 6.7 kg lower (11.59 to 1.81 lower)		52 (Lai 2000)	⊕⊕⊕⊖ moderate[4]	
[1 mg prednisone] Weight (Kg) Girls at 18 Years of Age	The mean absolute weight in the placebo groups was 51.9 kg	The mean weight in the prednisone groups was 0 kg higher (7.62 lower to 3.02 higher)		43 (Lai 2000)	⊕⊖⊖⊖ very low[2]	
[2 mg prednisone] Weight (Kg) Girls at 18 Years of Age	The mean absolute weight in the placebo groups was 51.9 kg	The mean weight in the prednisone groups was 1.7 kg higher		46 (Lai 2000)	⊕⊖⊖⊖ very low[2]	

		(3.37 lower to 6.77 higher)				
[1 mg prednisone] Height (cm) Boys at 18 Years of Age -	The mean absolute height in the placebo groups was 174.6 cm	The mean height in the prednisone groups was 3.9 cm lower (7.77 to 0.03 lower)		55 (Lai 2000)	⊕⊖⊖⊖ very low[3]	
[2 mg prednisone] Height (cm) Boys at 18 Years of Age	The mean absolute height in the placebo groups was 174.6 cm	The mean height in the prednisone groups was 4.1 cm lower (7.82 to 0.38 lower)		52 (Lai 2000)	⊕⊖⊖⊖ very low[3]	
[1 mg prednisone] Height at 18 Years of Age - Girls cm	The mean absolute height in the placebo groups was 160.3 cm	The mean height in the prednisone groups was 1 cm lower (4.54 lower to 2.54 higher)		43 (Lai 2000)	⊕⊖⊖⊖ very low[2]	
[2 mg prednisone] Height (cm) Girls at 18 Years of Age	The mean absolute height in the placebo groups was 160.3 cm	The mean height in the prednisone groups was 0.5 cm lower (4.43 lower to 3.43 higher)		46 (Lai 2000)	⊕⊖⊖⊖ very low[2]	
[1 mg prednisone] Adverse effects - Cataracts Follow-up: 4 years	74 per 1000	32 per 1000 (8 to 119)	RR 0.43 (0.11 to 1.61)	190 (Eigen 1995)	⊕⊖⊖⊖ very low[1,2]	
[2mg prednisone] Adverse effects - Cataracts Follow-up: 3 years	74 per 1000	116 per 1000 (47 to 286)	RR 1.57 (0.64 to 3.88)	190 (Eigen 1995)	⊕⊖⊖⊖ very low[1,2]	
[1 mg prednisone] Adverse effects - Diabetes mellitus Follow-up: 4 years	11 per 1000	32 per 1000 (3 to 298)	RR 3 (0.32 to 28.33)	190 (Eigen 1995)	⊕⊖⊖⊖ very low[1,2]	
[2 mg prednisone] Adverse effects -	11 per 1000	63 per 1000 (8 to 515)	RR 6.00 (0.74	190 (Eigen 1995)	⊕⊖⊖⊖ very low[1,2]	

Diabetes mellitus Follow-up: 3 years			to 48.89)			
[1 mg prednisone] Adverse effects – Glycosuria Follow-up: 4 years	42 per 1000	63 per 1000 (19 to 217)	RR 1.5 (0.44 to 5.15)	190 (Eigen 1995)	⊕⊖⊖⊖ very low[1,2]	
[2 mg prednisone] Adverse events – Glycosuria Follow-up: 3 years	42 per 1000	105 per 1000 (34 to 324)	RR 2.5 (0.81 to 7.69)	190 (Eigen 1995)	⊕⊕⊖⊖ low[1,3]	
[1 mg prednisone] Adverse effects - Hyperglycaemia Follow-up: 4 years	21 per 1000	32 per 1000 (5 to 185)	RR 1.5 (0.26 to 8.78)	190 (Eigen 1995)	⊕⊖⊖⊖ very low[1,2]	
[2 mg prednisone] Adverse effects - Hyperglycaemia Follow-up: 3 years	21 per 1000	105 per 1000 (24 to 468)	RR 5 (1.13 to 22.21)	190 (Eigen 1995)	⊕⊕⊖⊖ low[1,3]	
Mortality Follow-up: 4 years	42 per 1000	16 per 1000 (1 to 368)	RR 0.38 (0.02 to 8.83)	45 (Auberch 1985)	⊕⊕⊕⊖ low[5,6]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: CI: confidence interval; kg: kilogrammes; MD: mean difference; mg: milligrams; RR: risk ratio

1 The quality of the evidence was downgraded by 1, as allocation concealment and blinding were unclear.
2 The quality of the evidence Evidence downgraded by 2 due to serious imprecision as 95% CI crossed 2 default MIDs.
3 The quality of the evidence Evidence downgraded by 1 due to serious imprecision as 95% CI crossed 1 default MID.
4 The quality of the evidence was upgraded by 1 as there is evidence of dose-response within study
5 Allocation concealment and blinding were unclear, but the quality of the evidence was not downgraded for this outcome
6 The quality of the evidence was downgraded by 2 as 95%CI crossed the null effect line, and it is very wide.

Table 139: Summary clinical evidence profile: Comparison 3. Azithromycin versus placebo

Comparison 3. Azithromycin versus placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Azithromycin				
Time to next exacerbation: time free of exacerbation Follow-up: mean 6 months	Study population		HR 0.59 (0.44 to 0.79)	445 (Saiman 2003, Saiman 2010)	⊕⊕⊕⊕ high	
	348 per 1000	223 per 1000 (172 to 287)[1]				
	Moderate					
	348 per 1000	223 per 1000 (172 to 287)[1]				
Time to next exacerbation Follow-up: 12 months	Study population		HR 0.37 (0.217 to 0.6299)	82 (Clement 2006)	⊕⊕⊕⊕ high	
	48 per 1000[1]	18 per 1000 (11 to 30)[1]				
	Moderate					
	36 per 1000[1]	13 per 1000 (8 to 23)[1]				
Mild adverse effects of antibiotic treatment - Hearing impairment Follow-up: 6 months	10 per 1000	12 per 1000 (1 to 181)	RR 1.13 (0.07 to 17.74)	185 (Saiman 2003)	⊕⊕⊖⊖ low[2]	
Mild adverse effects of antibiotic treatment – Tinnitus Follow-up: 6 months	10 per 1000	12 per 1000 (1 to 181)	RR 1.13 (0.07 to 17.74)	185 (Saiman 2003)	⊕⊕⊖⊖ low[2]	
Change in BMI z score Follow-up: 12 months	The mean change in BMI z score in the placebo groups was -0.12	The mean change in BMI z score in the azithromycin groups was 0.15 higher (0.03 lower to 0.33 higher)		82 (Clement 2006)	⊕⊕⊕⊖ moderate[3]	
Change in weight (kg) Follow-up: 6 months	Not reported	The mean change in weight in the azithromycin groups was 0.62 higher (0.26 to 0.98 higher)		440 (Saiman 2003, Saiman 2010)	⊕⊕⊕⊖ moderate[3]	
Quality of life: change in CFQ-R total score	The mean change in total quality of life score (CFQ-R)	The mean change in total quality of life score (CFQ-R) in		177 (Saiman 2003)	⊕⊕⊕⊕ high	

Comparison 3. Azithromycin versus placebo						
Scale from: 0 to 100 Follow-up: 6 months	in the placebo groups was 0.1	the azithromycin groups was 1.6 higher (0.61 lower to 3.81 higher)				
Quality of life: change in CFQ-R physical domain Scale from: 0 to 100 Follow-up: 6 months	The mean change in physical domain of CFQ-R score in the placebo groups was -1.9	The mean change in physical domain of CFQ-R score in the azithromycin groups was 2.7 higher (0.09 to 5.31 higher)		177 (Saiman 2003)	⊕⊕⊕⊕ high	
Quality of life: change in CFQ-R psychosocial domain Scale from: 0 to 100 Follow-up: 6 months	The mean change in psychosocial domain of CFQ-R score in the placebo groups was 1.2	The mean change in psychosocial domain of CFQ-R score in the azithromycin groups was 0.4 higher (3 lower to 3.8 higher)		177 (Saiman 2003)	⊕⊕⊕⊕ high	
Quality of life: Change in CFQ-R body image domain Scale from: 0 to 100 Follow-up: 6 months	The mean change in body image domain of CFQ-R score in the placebo groups was -0.1	The mean change in body image domain of CFQ-R score in the azithromycin groups was 3.2 higher (0.24 lower to 6.64 higher)		177 (Saiman 2003)	⊕⊕⊕⊕ high	
**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).* *Abbreviations: BMI: body mass index; CFQ-R: cystic fibrosis questionnaire revised; CI: confidence interval; MD: mean difference; RR: risk ratio*						

1 Calculated by the NGA technical team from probability of remaining free from exacerbation.
2 The quality of the evidence Evidence downgraded by 2 due to serious imprecision as 95% CI crossed two2 default MIDs.
3 The quality of the evidence Evidence downgraded by 1 due to serious imprecision as 95% CI crossed one1 default MID.

Table 140: Summary clinical evidence profile: Comparison 4. Ibuprofen versus placebo

Comparison 4. Ibuprofen versus placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Ibuprofen				

Comparison 4. Ibuprofen versus placebo						
Adverse effects: increase in abdominal pain Follow-up: 2 years	56 per 1000	14 per 1000 (2 to 124)	RR 0.26 (0.03 to 2.24)	142 (Lands 2007)	⊕⊕⊖⊖ low[1]	
Adverse effects: Increase in abdominal pain Follow-up: 4 years	163 per 1000	122 per 1000 (42 to 353)	RR 0.75 (0.26 to 2.17)	84 (Konstan 1995)	⊕⊖⊖⊖ very low[1,2]	
Adverse effects: Gastrointestinal bleeding Follow-up: 2 years	0 per 1000	0 per 1000 (0 to 0)2	RR 3.08 (0.13 to 74.46)	142 (Lands 2007)	⊕⊕⊖⊖ low[1]	
Annual rate of change in % ideal body weight Follow-up: 4 years	The mean annual rate of change in % ideal body weight in the placebo groups was -0.94	The mean annual rate of change in % ideal body weight in the ibuprofen groups was 0.99 higher (0.17 to 1.81 higher)		84 (Konstan 1995)	⊕⊕⊖⊖ low[3,4]	
[Under 13 years at randomisation] Annual rate of change in % ideal body weight (by age) – Follow-up: 4 years	The mean annual rate of change in % ideal body weight (by age) - under 13 years at randomisation in the placebo groups was -1.5	The mean annual rate of change in % ideal body weight (by age) in the ibuprofen groups was 1.45 higher (0.33 to 2.57 higher)		49 (Konstan 1995)	⊕⊕⊖⊖ low[3,4]	
[13 years or older at randomisation] Annual rate of change in % ideal body weight (by age) Follow-up: 4 years	The mean annual rate of change in % ideal body weight (by age) - 13 years or older at randomisation in the placebo groups was -0.15	The mean annual rate of change in % ideal body weight (by age) in the ibuprofen groups was 0.34 higher (0.61 lower to 1.29 higher)		35 (Konstan 1995)	⊕⊖⊖⊖ very low[1,3]	
**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Abbreviations: CI: confidence interval; MD: mean difference; RR: risk ratio*						

1 The quality of the evidence downgraded by 2 due to serious imprecision as 95% CI crossed 2 default MIDs.
2 Absolute effect not calculable as there are 0 events in control (placebo) arm.
3 The quality of the evidence was downgraded by 1 due to reporting bias.
4 The quality of the evidence downgraded by 1 due to serious imprecision as 95% CI crossed 1 default MID.

9.5.5 Economic evidence

No economic evaluations of immunomodulatory agents were identified in the literature search conducted for this guideline. Full details of the search and economic article selection flow chart can be found in Appendix E and F, respectively.

This area was prioritised for de novo economic modelling; consequently, a cost-utility model was developed. The model uses a lifetime horizon based on the assumption that immunomodulatory agents are given on a long-term basis.

The model takes the form of a state transition model to estimate transitions between 3 lung function (FEV_1% predicted) strata. Transition probabilities between the three FEV_1% strata and the number of exacerbations experienced each cycle were taken from the NMA.

Treatment related adverse effects and post lung transplant health states were also included in the model to reflect the clinical pathway.

A series of deterministic sensitivity analyses were undertaken in order to test how sensitive the results were to uncertainty in individual parameters. Probabilistic sensitivity analysis was also conducted in the model to take account of the simultaneous effect of uncertainty relating to model parameter values. The methods used to construct the model and the results of all analyses are reported in Appendix K. Table 141 below presents the results from the base-case, where it is clear azithromycin dominates the alternatives as it is most the effective and least expensive option.

Table 141: Base case results from the economic model

Treatment	Total costs	Total QALYs	ICER
Macrolide (azithromycin)	£158,404	14.2	-
Oral corticosteroid (prednisolone)	£289,619	12.5	Dominated
NSAID (ibuprofen)	£291,035	12.3	Dominated
No treatment	£302,045	12.4	Dominated
Inhaled corticosteroid (fluticasone)	£411,046	11.1	Dominated

9.5.6 Evidence statements

9.5.6.1 Evidence statements for NMA outcomes (FEV_1 % predicted and rate of pulmonary exacerbations)

See section 9.5.4.1.

9.5.6.2 Evidence statements for non-NMA outcomes (nutritional status, time to next pulmonary exacerbation, adverse events and quality of life)

9.5.6.2.1 Corticosteroids

Inhaled Beclometasone

No evidence was found for this treatment.

Inhaled Budesonide

No evidence was found for this treatment.

Inhaled Fluticasone

Comparison 1. Fluticasone versus placebo

Time to next exacerbation

Low quality evidence from 1 RCT with 171 children, young people and adults with cystic fibrosis showed no clinically significant difference in the time to next exacerbation between fluticasone and placebo at 6 months follow-up.

Nutritional status

No evidence was found for this important outcome.

Quality of life

No evidence was found for this important outcome.

Adverse effects

Moderate quality evidence from 1 RCT with 30 children with cystic fibrosis showed no clinically significant difference in growth measured by change in height standard deviation score between fluticasone and placebo over 12 months follow-up.

Moderate quality evidence from 1 RCT with 80 people with cystic fibrosis showed no clinically significant difference in growth measured by change in height measured by centimetres between fluticasone and placebo over 8 months follow-up.

Mortality

No evidence was found for this important outcome.

9.5.6.2.2 Corticosteroids

IV Methylprednisolone

No evidence was found for this treatment.

Oral Prednisone/ Prednisolone

Comparison 2. Prednisone/ prednisolone versus placebo

Time to next exacerbation

No evidence was found for this critical outcome.

Nutritional status: weight and height

Very low quality evidence from 1 RCT with 25 children and young people with cystic fibrosis showed no clinically significant difference in weight measured in kilograms between 2 mg/kg prednisolone and placebo at 12 week follow-ups.

Low quality evidence from 1 observational study with 55 young people (males) with cystic fibrosis showed no clinically significant difference in weight measured in kilograms between 1 mg/kg prednisolone and placebo at the age of 18.

Moderate quality evidence from 1 observational study with 52 young people (males) with cystic fibrosis showed a clinically significant harmful effect of 2 mg/kg prednisolone in weight measured in kilograms compared to placebo at the age of 18.

Very low quality evidence from 1 observational study with 43 young people (females) with cystic fibrosis showed no clinically significant difference in weight measured in kilograms between 1 mg/kg prednisolone and placebo at the age of 18.

Very low quality evidence from 1 observational study with 46 young people (females) with cystic fibrosis showed no clinically significant difference in weight measured in kilograms between 2 mg/kg prednisolone and placebo at the age of 18.

Very low quality evidence from 1 observational study with 52 young people (males) with cystic fibrosis showed a clinically significant harmful effect of 1 mg/kg prednisolone in height measured in centimetres compared to placebo at the age of 18.

Very low quality evidence from 1 observational study with 52 young people (males) with cystic fibrosis showed a clinically significant harmful effect of 2 mg/kg prednisolone in height measured in centimetres compared to placebo at the age of 18.

Very low quality evidence from 1 observational study with 43 young people (females) with cystic fibrosis showed no clinically significant difference in height measured in centimetres between 1 mg/kg prednisolone and placebo at the age of 18.

Very low quality evidence from 1 observational study with 46 young people (females) with cystic fibrosis showed no clinically significant difference in height measured in centimetres between 2 mg/kg prednisolone and placebo at the age of 18.

Quality of life

No evidence was found for this important outcome.

Adverse effects

Very low quality evidence from 1 RCT with 190 children with cystic fibrosis showed no clinically significant difference in cataracts, diabetes mellitus, glycosuria and hyperglycaemia between 1 mg/kg prednisone and placebo at 4 years follow-up.

Very low quality evidence from 1 RCT with 190 children with cystic fibrosis showed no clinically significant difference in cataracts and diabetes mellitus between 2 mg/kg prednisone and placebo at 3 years follow-up.

Low quality evidence from 1 RCT with 190 children with cystic fibrosis showed no clinically significant difference in glycosuria between 2 mg/kg prednisone and placebo at 3 years follow-up.

Low quality evidence from 1 RCT with 190 children with cystic fibrosis showed a clinically significant harmful effect of 2 mg/kg prednisone compared with placebo for hyperglycaemia at 3 years follow-up.

Mortality

Low quality evidence with 45 children with cystic fibrosis showed no clinically significant difference in mortality between 2mg/kg prednisone and placebo at 4 years follow-up.

9.5.6.2.3 Macrolide antibiotics

Azithromycin

Comparison 3. Azithromycin versus placebo

Time to next exacerbation

High quality evidence from 2 RCT with 445 children and young people with cystic fibrosis showed a clinically significant beneficial effect of azithromycin in the time to next exacerbation compared to placebo at 6 months follow-up.

High quality evidence from 1 RCT with 82 children and young people with cystic fibrosis showed a clinically significant beneficial effect of azithromycin in the time to next exacerbation compared to placebo at 12 months follow-up.

Nutritional status: BMI and weight

Moderate quality evidence from 1 RCT with 82 children and young people with cystic fibrosis showed no clinically significant difference in change in BMI z score from baseline between azithromycin and placebo at 12 months follow-up.

Moderate quality evidence from 2 RCTs with 440 people with cystic fibrosis > 6 years showed a clinically significant beneficial effect of azithromycin in weight change measured in kilograms compared to placebo at 24 week follow-up.

Quality of life

High quality evidence from 1 RCT with 177 people with cystic fibrosis > 6 years showed no clinically significant difference in change in quality of life (measure with CFQ-R total score, and CFQ-R physical, psychosocial and body image domains) between azithromycin and placebo at 6 months follow-up.

Adverse effects

Low quality evidence from 1 RCT with 185 people with cystic fibrosis > 6 years showed no clinically significant difference in hearing impairment and tinnitus between azithromycin and placebo at 6 months follow-up.

Mortality

No evidence was found for this important outcome.

9.5.6.2.4 NSAIDs

Ibuprofen

Comparison 4. Ibuprofen versus placebo

Time to next exacerbation

No evidence was found for this critical outcome.

Nutritional status: weight

Low quality evidence from 1 RCT with 84 people with cystic fibrosis aged 5 to 39 years showed a clinically significant beneficial effect of ibuprofen in annual rate of change in percent ideal body weight compared to placebo at 4 years follow-up. However, this clinically beneficial significant effect was seen in children under 13 years only (n=49). Very low quality evidence from this study showed no clinically significant difference in change in percent ideal body weight in people with cystic fibrosis over 13 years (n=35) at 4 years follow-up.

Quality of life

No evidence was found for this important outcome.

Adverse effects

Low quality evidence from 1 RCT with 142 children with cystic fibrosis showed no clinically significant difference in increase of abdominal pain between ibuprofen and placebo at 2 years follow-up.

Very low quality evidence from 1 RCT with 84 children, young people and adults with cystic fibrosis showed no clinically significant difference in increase of abdominal pain between ibuprofen and placebo at 4 years follow-up.

Low quality evidence from 1 RCT with 142 children with cystic fibrosis showed no clinically significant difference in abdominal bleeding between ibuprofen and placebo at 2 years follow-up.

Mortality

No evidence was found for this important outcome.

9.5.6.3 Monoclonal antibody

Omalizumab

No evidence was found for this treatment.

9.5.6.4 Economic evidence statements

No evidence on cost-effectiveness in people with cystic fibrosis was available for this review.

The economic model found that azithromycin dominated (more effective and less expensive) the remaining treatments in the model (NSAIDs, oral corticosteroids, inhaled corticosteroids and “no treatment”). This result was also found in the extensive deterministic and probabilistic sensitivity analysis that were undertaken.

9.5.7 Evidence to recommendations

9.5.7.1 Relative value placed on the outcomes considered

The aim of this review was to determine the clinical and cost effectiveness of immunomodulatory agents in reducing pulmonary inflammation in children, young people and adults with cystic fibrosis.

The guideline committee identified FEV_1% predicted, time to next exacerbation and adverse events (particularly growth retardation in children) as critical outcomes for decision making. Quality of life, nutritional status and mortality were rated as important outcomes.

9.5.7.2 Consideration of clinical benefits and harms

The committee discussed the results of the evidence and their experience in clinical practice.

The committee discussed the NMA results that found azithromycin had the best probability of reducing exacerbations and one of the worst for improving lung function. Based on their clinical experience, the committee agreed azithromycin can reduce exacerbations, but may not necessarily improve lung function. They highlighted, however, that there is no evidence that supports a direct link between lung function and clinical exacerbations and the critical outcome is to reduce the number of pulmonary exacerbations. They noted azithromycin does not have such a problematic interaction profile compared to other alternative immunomodulatory agents. They also noted azithromycin is usually offered as first-line in current practice and they agreed to recommend it to people who are suffering a clinical deterioration (as assessed by lung function) and to those who present recurrent pulmonary exacerbations. They suggested that due to its pharmacokinetic profile, it can be administered

3 times per week, rather than daily. The committee discussed the duration of treatment as, in practice, it tends to be used for longer than the duration in studies. It was agreed that treatment should be reviewed periodically to assess response.

The committee agreed that oral corticosteroids can be considered if clinical deterioration continues despite treatment with azithromycin, where all other treatments have been maximised.

The committee noted there was less evidence on fluticasone than the other treatments in the NMA. It was tested in only 12 patients suggesting that more research on fluticasone is needed to increase the confidence in the results. They noted that in practice, fluticasone does not improve lung function to the extent the NMA inferred. In the absence of evidence-base and empirical evidence to support its use, they agreed to not recommend the use of inhaled corticosteroids.

The committee also noted the lack of evidence for omalizumab and that this is limited to case reports.

The committee acknowledged ibuprofen showed a beneficial effect in terms of lung function and nutritional status. However, they were reluctant to recommend it widely due to the high dose and therapeutic drug monitoring required (which is not universally available), its adverse effects profile and potential interaction with other drugs. Although the studies did not show significant adverse events for ibuprofen, they emphasised longer follow-up trials are needed to assess this. Moreover, none of the studies reported on renal function, which is known to be negatively affected by long-term ibuprofen use. The committee noted ibuprofen is not currently routinely used in clinical practice for the management of cystic fibrosis in the UK. Nevertheless, they agreed not to write a “do not do” recommendation, as they acknowledged ibuprofen may be suitable for some people (for example when azithromycin is not deemed appropriate).

The committee agreed it is important to assess tolerability and adverse effects in addition to efficacy when making decisions about treatment.

9.5.7.3 Consideration of economic benefits and harms

The committee stated that it was crucial the adverse effects of treatment were taken into consideration when making their recommendations as they may outweigh the benefits related to lung function and exacerbations the agents can provide. As a result, the economic modelling was used by the committee as one of many ways to assess those trade-offs.

NMAs were undertaken for this review question. This allowed the treatments identified in the review to be compared to a single comparator and enable the economic model to perform a fully incremental analysis that compares all treatments simultaneously in order to identify the most cost-effective treatment. However, in the network, there were a lot of indirect comparisons coming from a small number of head-to-head trials and, for most comparisons where direct evidence was available, it came from a single trial. Consequently, the NMAs were not over-interpreted by the committee when making their recommendations.

From their clinical experience, azithromycin can reduce exacerbations, but not necessarily improve lung function. Based on this, the committee accepted the results from the NMA that found azithromycin to have the best probability of reducing exacerbations and one of the worst for improving lung function.

On the other hand, the committee did not agree fluticasone improves lung function to the extent the NMA inferred. Following this, the committee noted that there was less evidence on fluticasone than the other treatments in the NMA, suggesting that more evidence on fluticasone was needed to increase their confidence in the results. The committee also questioned the inclusion of fluticasone in the economic model as it was no longer used as an

immunomodulatory agent in clinical practice. Subsequently, the committee recognised that the model provided sufficient evidence not to recommend fluticasone as an immunomodulatory agent, as it was dominated (more expensive and less effective) by its comparators in all analyses explored.

Conversely, the committee agreed that azithromycin should be offered as the first-line treatment given that it dominated (less expensive and more effective) all alternatives in the model and had the highest probability of being the most cost-effective agent in probabilistic analysis. The committee also noted that azithromycin is the first-line treatment in current clinical practice, particularly as it has a relatively small interactions profile.

The committee advised that ibuprofen and oral corticosteroids were associated with more serious treatment-related adverse effects in clinical practice than azithromycin. For this reason, the committee agreed that those agents would not be considered cost-effective compared to azithromycin as they would be dominated (more expensive and less effective). However, the committee agreed they could not recommend against those agents if azithromycin was no longer effective or contraindicated, given that clinical uncertainty was not completely removed by the economic model. One reason for this was the absence of exacerbation data for ibuprofen and the resulting ICER in the south-west quadrant (less expensive and less effective) for ibuprofen compared to “no treatment” when the exacerbation rates were equivalent. Given that there was evidence from the review that ibuprofen improved lung function, and clinical experience from the committee that immunomodulatory benefits were demonstrated by ibuprofen, the committee concluded they could not recommend against the use of ibuprofen.

Following this, the committee noted that mucolytic use would be optimised if azithromycin was no longer effective before a second line immunodulatory agent is considered. The committee added that NSAIDs are rarely used as immunomodulatory agents in clinical practice and concluded that a recommendation in favour of oral prednisolone would be appropriate following no beneficial effect from azithromycin and mucolytics. This was supported by the economic model that found oral prednisolone to dominate NSAIDs and “no treatment”, or, in other words, that oral prednisolone provides greater benefits at a lower cost. A recommendation was considered by the committee to regularly review the effectiveness, tolerability and side effects of immunomodulatory agents in order to lead to more timely identification to reduce the downstream costs to manage those events. However, the recommendation was subsequently removed as the committee agreed that treatment-related adverse effects should be monitored as part of good practice.

Overall, the results from the NMAs and subsequently, the model, were generally considered to be in line with UK practice, which is why the committee’s recommendations broadly follow those results. Committee consensus and current UK practice played a large part in informing their strong recommendations where the evidence was weaker.

9.5.7.4 Quality of evidence

The quality of the evidence presented in this report ranged from very low to high as assessed by GRADE. The main reasons that led to downgrading the quality of the evidence were:

- For the domain risk of bias, the studies were assigned the same risk of bias as in the Cochrane reviews and were not individually reviewed. The main biases that led to downgrading the quality of the evidence were selection process, lack of blinding, inadequate concealment, attrition and reporting bias.
- Another reason that led to downgrading the quality of the evidence was the imprecision, as confidence intervals crossed 1 or 2 MIDs. The committee noted that some trials were underpowered to detect a clinically important difference.

For the rate of exacerbations after short-term treatment inconsistency (heterogeneity) was found to be very serious and is likely to be due to substantial clinical heterogeneity in the

clinical history of patients that cannot be captured from the study reports. For other outcomes no serious inconsistency was found as most outcomes were reported by single studies, though clinical heterogeneity may still have been an issue. This can lead to issues when comparing treatments across different trials.

No issues were identified regarding the directness of the population (generalisability of the results).

9.5.7.5 Other considerations

No equality issues were identified by the committee for this review question.

The committee agreed a research recommendation was not needed as research is unlikely to change clinical practice. In addition, the committee were aware that there are large ongoing trials in this area.

9.5.7.6 Key conclusions

The committee concluded that azithromycin should be offered as long term treatment to people with cystic fibrosis who are deteriorating or having pulmonary exacerbations. The response to treatment should be assessed periodically and treatment may be stopped if there is no evidence of clinical benefit. Oral corticosteroids or NSIADs may be a suitable alternative, but it is important to assess tolerability and side effects regularly. The use of inhaled corticosteroids should not be considered as immunomodulatory treatment.

9.5.8 Recommendations

94. For people with cystic fibrosis and deteriorating lung function or repeated pulmonary exacerbations, offer long-term treatment with azithromycin at an immunomodulatory dose[6].

95. For people who have continued deterioration in lung function, or continuing pulmonary exacerbations while receiving long-term treatment with azithromycin, stop azithromycin and consider oral corticosteroids.

96. Do not offer inhaled corticosteroids as an immunomodulatory treatment for cystic fibrosis.

6 At the time of publication (October 2017), azithromycin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

10 Other monitoring, assessment and management

10.1 Nutritional Interventions

Review question: What is the clinical and cost effectiveness of nutritional interventions in people with cystic fibrosis?

10.1.1 Introduction

People with cystic fibrosis are at risk of poor nutritional status which is a strong predictor of morbidity and mortality. Nutritional deficiency and malnutrition in people with cystic fibrosis is affected by both pancreatic and clinical status. Pancreatic insufficiency results in nutrient and fat soluble vitamin malabsorption, added to by the increased energy and nutrient requirement associated with chronic lung infections. Additionally, growth spurts in childhood (particularly in the first year and at adolescence) increase nutritional requirements where there is an additional risk in cystic fibrosis. Optimising nutritional status is, therefore, an important part of routine care for all people with cystic fibrosis. Early detection and monitoring of nutritional decline is necessary to empower potentially beneficial treatments and interventions. The strategies commonly used include dietary advice, oral supplements, enteral tube feeding, the use of appetite stimulants and behavioural interventions.

10.1.2 Description of clinical evidence

The aim of this review was to determine the clinical and cost-effectiveness of nutritional interventions for people with cystic fibrosis.

The interventions reviewed were:

- oral supplementary prescribed feeds
- enteral tube feeding
- appetite stimulants (cyproheptadine, megace)
- dietary advice, or educational interventions
- psychological and behavioural interventions

Interventions were considered “behavioural” rather than educational if they were facilitated by psychologists, psychotherapists, or psychological therapists in training.

Systematic reviews of RCTs and RCTs were prioritised. Systematic reviews were assessed for inclusion against the protocol, and if relevant, their quality was assessed using AMSTAR. High-quality systematic reviews were included in our review, and where possible, data and quality assessment was taken directly from the review. Individual studies were also retrieved for completeness and accuracy, and were checked for additional outcomes of interest. Low-quality systematic reviews were excluded from the review, but the list of included studies was checked to identify relevant trials.

Cross-over RCTs, RCTs with less than 10 participants, quasi-randomised trials or studies published before or during 1997 were excluded unless these studies were included in 1 of the 4 Cochrane systematic reviews that were included in this review.

Given that no evidence was found for enteral tube feeding or quality of life (a critical outcome) in the RCTs, cohort studies were assessed for inclusion and data were reported from these studies only in relation to this intervention or this critical outcome not covered by the RCTs.

For full details see review protocol in Appendix D.

Five Cochrane reviews were included in the review:

- Chinuck (2014) evaluated the effectiveness of appetite stimulants compared to placebo; 3 RCTs were included in this review (Eubanks 2002, Homnick 2004, Marchand 2000)
- Goldbeck (2014) evaluated the effectiveness of behavioural interventions, assessing 2 comparisons: behavioural intervention versus wait list control; and behavioural management training plus nutritional intervention versus nutritional intervention alone; 4 RCTs were included in this review (Stark 1996, Stark 2009, Powers 2003)
- Morton (2015) evaluated the effectiveness of supplemental enteral tube feeding for 1 month or longer compared to no specific intervention; no studies were eligible for inclusion in the review
- Savage (2014) evaluated the effectiveness of nutrition education compared to standard treatment; 1 RCT was included in this review (Watson 2008)
- Smyth (2014) evaluated the effectiveness of oral calorie supplementation compared to additional nutritional advice or no intervention; 2 RCTs (Hanning 1993, Poustie 2006) and 1 quasi-randomised trial (Kalnins 2005) were included in this review.

In addition, 1 RCT (Powers 2015) was included. It evaluated a behavioural intervention compared to an educational intervention. Finally, 2 cohort studies (Bradley 2012, White 2013) were included. These studies evaluated the effectiveness of enteral tube feeding.

The size of the RCTs or cohort studies ranged from 9 to 102 participants. One study included infants and children (Powers 2003), 3 studies included children (Marchand 2000, Stark 1996, Powers 2015), 3 studies included children and young people (Hanning 1993, Poustie 2016, Stark 2009), 4 studies included children, young people and adults (Bradley 2012, Eubanks 2002, Homnick 2004, Kalnins 2005), 1 study included people older than 16 (Watson 2008) and 1 study included adults (White 2013).

Four studies (Hanning 1993, Homnick 2004, Stark 1996, Watson 2008) were considered indirect in terms of the population because no inclusion criteria related to underweight were specified, therefore the study population was unlikely to be representative of those who would receive the interventions in clinical practice.

Nine studies (Bradley 2012, Eubanks 2002, Kalnins 2005, Marchand 2000, Poustie 2006, Powers 2003, Stark 2009, Powers 2015, White 2013) were considered direct in terms of the population because the authors specified some inclusion criteria which related to either underweight, or reduced weight gain or body mass index (BMI), or pancreatic insufficiency, or need for nutritional supplementation.

Three studies were conducted in the UK (Poustie 2016, Watson 2008, White 2013), 8 in the USA (Bradley 2012, Eubanks 2002, Homnick 2004, Marchand 2000, Powers 2003, Powers 2015, Stark 1996, Stark 2009) and 2 in Canada (Hanning 1993, Kalnins 2005).

A summary of the studies included in this review is presented in Table 142. See study selection flow chart in Appendix F, study evidence tables in Appendix G, list of excluded studies in Appendix H, forest plots in Appendix I, and full GRADE profiles in Appendix J.

10.1.3 Summary of included studies

A summary of the studies that were included in this review are presented in Table 142.

Table 142: Summary of included studies

Study	Intervention/Comparison	Population	Outcomes	Comments
Cochrane systematic reviews				

Study	Intervention/Comparison	Population	Outcomes	Comments
Chinuck 2014 Cochrane SR	Appetite stimulants versus placebo (Eubanks 2002, Homnick 2004, Marchand 2000)	Adults and children with CF	• Change in weight (kg) • Change in weight z score • Change in FEV_1 (% predicted) • Number of pulmonary exacerbations • Number of adverse effects	
Goldbeck 2014 Cochrane SR	Comparison 1. Behavioural intervention versus usual care (Stark 1996) Comparison 2. Behavioural management training plus educational intervention versus educational intervention alone (Powers 2003, Stark 2009)	Children or adults with CF	• Change in weight (kg) • Change in weight z score • Change in BMI z score • Change in % ideal body weight • Change in weight % for age • Change in height (cm) • Change in height z score • Change in FEV_1 % predicted	
Morton 2015 Cochrane SR	Supplemental enteral tube feeding for 1 month or longer versus no specific intervention (No studies were included)	People with CF of any age	No studies were identified for inclusion in this review	
Savage 2014 Cochrane SR	Nutrition education versus usual care (Watson 2008)	Individuals of all ages with CF or family members or both	• Change in weight • Change in FEV_1 % predicted	
Smyth 2014 Cochrane SR	Comparison 1. Oral calorie supplementation versus usual care (Hanning 1993, Poustie 2006) Comparison 2. Oral calorie supplementation versus additional	People with CF	• Change in weight (kg) • Change in weight centile (percentile points) • Change in weight z score • Change in BMI (kg/m2)	

Study	Intervention/Comparison	Population	Outcomes	Comments
	nutritional advice (Kalnins 2005)		• Change in BMI centile (percentile points) • Change in weight for height (percentage) • Change in height (cm) • Change in height centile (percentile points) • Change in height z score • Change in FEV_1 (% predicted)	
Primary studies included in SRs				
Eubanks 2002 USA RCT	Intervention: Appetite stimulant • Megestrol acetate 10 mg/kg/day (adjusted at subsequent visits) Control: Placebo	N=17 participants (intervention: n=10; placebo: n=7) • Age: > 6 years • Inclusion criteria: pancreatic insufficiency, FEV_1>40% growth failure defined as no weight gain in the preceding 6 months	• Change in weight (kg) • Change in weight z score • Change in FEV_1% • Number of pulmonary exacerbations • Number of adverse events: ○ Constipation ○ Decreased morning cortisol levels	Included in Chinuck 2014 SR Duration: 6 months. After completion of the 6-month trial, the placebo group was offered MA for a further 6 months. Population was considered as direct.
Hanning 1993 Canada RCT	Intervention: oral calorie supplements Dietary supplements, drink powders, milk shakes, tinned puddings to achieve 25% of normal energy recommendations in addition to normal diet for 6 months Control: usual care	N=20 children and young people with CF (20 randomised, 16 studied) • Age: 7 to 15 years • Inclusion criteria: not reported	• Change in weight (kg) • Change in weight a s% expected for age and height • Change in height as % of expected for age • Change in FEV_1 % predicted	Included in Smyth 2014 SR Follow-up: 6 months Population was considered as indirect.
Homnick 2004 USA	Intervention: Appetite stimulant	N=18 people with CF enrolled, 16 completed study	• Change in weight z score	Included in Chinuck 2014 SR

Study	Intervention/Comparison	Population	Outcomes	Comments
RCT	Cyproheptadine hydrochloride 4mg 4 x daily Control: Placebo	(intervention: n=8; placebo: n=8) • Age: ≥5 years • Inclusion criteria: Ideal body weight for height <100%	• Change in height (cm) • Change in BMI (kg/m^2) • Change in BMI percentile • Change in % ideal body weight	Follow-up: 3 months Population was considered as indirect.
Kalnins 2005 Canada Quasi-randomised controlled trial	Intervention: Oral calorie supplementation • High calorie drink to increase energy intake by 20% of predicted energy needs Control: Nutritional counselling • Nutritional counselling to increase energy intake by 20% of predicted energy needs by eating high calorie foods.	• N=15 participants with CF were enrolled but 2 dropped out • Participants were aged >10 years. • Mean (SD) age on entry to trial: advice group:16.4 years(6.7); supplement group: 19.5 years (11.3). • < 90% ideal WFH or 5% reduction in ideal WFH over 3 months	• Change in weight (kg) • Change in weight z score • Change in weight for height (%) • Change in % ideal body weight • Change in height (cm) • Change in height z score • Change in FEV_1 (% predicted)	Included in Smyth 2014 SR Interventions implemented for 3 months, follow-up: 3 and 6 months Population was considered as direct.
Marchand 2000 USA RCT	Intervention: Appetite stimulant • Megasterol acetate 10 mg/kg/day for 12 weeks Control: Placebo	N=12 children with CF • Age: mean age 7.4 years. Range: 21 months to 10.4 years • Inclusion criteria were loss of weight or plateau in weight gain for more than 3 months, weight-for-height less than 85%, and a negative change in weight z score	• Change in weight z score • Number of pulmonary exacerbations • Fasting blood glucose levels • Decreased morning cortisol levels	Included in Chinuck 2014 SR Clinical assessment at week 0,6,12,24 and 36 Population was considered as direct.
Poustie 2006 UK RCT	Intervention 1: Oral calorie supplements Intervention 2: Routine dietary	N=102 children and young people aged 2 - 15 years with CF • Children with at least 1 of following	• Change in weight (kg) • Change in weight centile (percentile points)	Included in Smyth 2014 SR Interventions implemented for 12 months. Outcomes at 3, 6 and 12 months

Study	Intervention/Comparison	Population	Outcomes	Comments
	advice (usual care)	criteria: BMI <25th centile but > 0.4th centile; or no increase in weight over the previous 3 months; or 5% decrease in weight from baseline over a period of < 6 months	• Change in BMI (kg/m2) • Change in BMI centile (percentile points) • Change in height (cm) • Change in height centile (percentile points) • Change in FEV_1 % predicted	Population was considered as direct.
Powers 2003 USA RCT	Intervention 1: Behavioural management training plus educational intervention • Nutrition intervention with strategies for enhancing calorie intake • Behavioural management training for parents designed to encourage children to eat food consistent with CF dietary recommendations. Intervention 2: Educational intervention only	N=12 infants and children with CF • (intervention 1: n=7, intervention 2: n=5). • Age: Less than 3 years old. • Pancreatic insufficiency.	• Change in weight (kg) • Change in % ideal body weight • Change in weight % for age • Change in height (cm)	Included in Goldbeck 2014 SR Both groups received 8 sessions (45 to 60 minutes) over 1 year: Sessions 1 to 4 (3 months) intensive education Follow-up: 1 years Population was considered as direct.
Stark 1996 USA RCT	Intervention: Group behavioural intervention. • 7 weekly sessions - baseline assessment plus snack, breakfast, relaxation skills training, lunch, dinner and maintenance strategies	N=10 children with CF. • 1 withdrew from control group after randomisation. • Total sample n = 9 (intervention group: n=5, control group: n=4). • Age range: 5.3 years to 10.1 years; mean	• Change in weight (kg) • Change in weight (z score) • Change in height (cm) • Change in FEV_1 % predicted	Included in Goldbeck 2014 SR Duration of interventions: 6 weeks Population was considered as indirect.

Study	Intervention/Comparison	Population	Outcomes	Comments
	targeted over following 7 sessions. Control: Usual care (Wait list control) • Parent meeting and 7-day food diaries at times corresponding to baseline and last week of intervention	(SD) age: 7.3 years (1.7).		
Stark 2009 USA RCT	Intervention 1: Behavioural intervention • Behavioural intervention in group setting for change around nutrition an energy (Be-In-CHARGE!; n = 33) (available online at www.oup.com/us/pediatricpsych). Intervention 2: Nutrition education • Nutrition education in group setting	N=79 children and young people with CF • Number randomised, n = 79 • Received the intervention, n=67 (behavioural intervention plus nutrition education: n = 33, nutrition education: n = 34) • Age: 4 to 12 years • With pancreatic insufficiency; and weight for age and height ≤ 40th percentile.	• Change in weight (kg) • Change in BMI z score change • Change in height (cm) • Change in height z score • FEV_1 change • Parent satisfaction (reported narratively)	Included in Goldbeck 2014 SR Duration of interventions: 9 weeks. Timing of sessions: 7 sessions (each 90 minutes): pre-treatment (session 1), 2 weeks later 5 weekly groups sessions (sessions 2 to 6), 2 weeks later post-treatment (session 7; follow up) Follow-up: up to 2 years Population was considered as direct.
Watson 2008 UK RCT	Intervention: Nutrition education • General and disease-specific nutrition education ('Eat Well with CF') • Content: knowledge on general and disease-specific nutrition topics; self-management skills on goal setting in small incremental steps to	N=74 people with CF older than 16 years of age • participants were enrolled and stratified by disease severity into low or high risk disease. • Participants were randomly allocated into intervention (n = 37) and control (n = 37) group	• Change in FEV_1 (% predicted) • Change in weight • Quality of life (narrative reporting and p values only)	Included in Savage 2014 SR Duration of the intervention: 10 weeks. Outcomes measured at 6 and 12 months Population was considered as indirect.

Study	Intervention/Comparison	Population	Outcomes	Comments
	establish new behaviours • Mode of delivery: written material; supplementary workshops (introductory, weeks 5 and 10) and weekly telephone calls delivered by a dietitian Control: Usual care	• 48 participants completed the study through to 12-month follow-up assessment (23 in intervention group, 25 in control group) • Age: intervention group 26.4 (17.2 - 43.2) years; control group 24.2 (16.9 - 38.1) years		
Additional primary studies				
Bradley 2012 United States Cohort study	Intervention: Gastrostomy Control: No gastrostomy (usual care)	N=40 people with CF (20 in the intervention group, 20 in the control group) • Age range: 2 to 20 years • Each child in the intervention group was pair-matched on age, sex, pancreatic status, BMI and lung function with a children from the control group • Children who had a gastrostomy for reasons other than nutritional supplementation were excluded	• Change in weight z-score • Change in BMI z-score • Change in height z-score • Change in FEV_1 % predicted	Outcomes measured at 6 and 12 months Population was considered as direct.
Powers 2015 USA RCT	Behavioural intervention • Individualized nutritional counselling targeting increased energy intake and behavioural child management skills	N=78 children with CF and pancreatic insufficiency (intervention: n=36, control: n=42) • Age: 2 to 6 years • Confirmed pancreatic insufficiency; no restrictions in	• Change in weight z score • Change in height z score • Number of adverse events (digestive system)	Both treatments were delivered in person or telehealth (via telephone) Sessions occurred weekly for 8 weeks then monthly for 4 months (6 months). The control arm served as a

Study	Intervention/Comparison	Population	Outcomes	Comments
	Control: education and attention control treatment • Education on general nutrition information and other topics (e.g. infection control and bicycle safety)	consuming a high-fat diet.		behavioural placebo controlling for attention and contact frequency. Participants then returned to standard care for 1 year. Follow-up: 18 months Population was considered as direct.
White 2013 UK Cohort study	Intervention: Enteral tube feeding • Supplemental enteral tube feeding administered over 3 years • Overnight enteral tube feed Control: Usual care	• N=21 adults with CF (intervention: n=15, control: n=6) • Mean (SD) age: intervention: 21.8 (3.6); control: 23.0 (5.7) • All study participants fulfilled the criteria for commencement of enteral tube feeding (CF Trust, 2002): BMI<19 kg/m2 and/or 5% acute weight loss over a 2 month period with a failure or oral nutritional supplements to adequately improve nutritional status.	• Change in weight (kg) • Change in BMI (kg/m2) • Change in FEV_1 (%) • Change in IV treatment days	Initially n=17 accepted enteral tube feeding. However 2 people died during the baseline year and subsequent analyses were conducted on the surviving participants. Control group: people who declined enteral tube feeding Follow-up: 1 year Population was considered as direct.

BMI: body mass index; CF: cystic fibrosis; FEV 1: forced expiratory volume in 1 second; RCT: randomised controlled trial; SR: systematic review; WFH: weight for height

10.1.4 Clinical evidence profile

The summary clinical evidence profiles for this review question (nutrition interventions in people with CF) are presented in Table 143 to Table 150.

Table 143: Summary clinical evidence profile: Comparison 1.1 Oral calorie supplementation versus usual care

Comparison 1.1 Oral calorie supplementation versus usual care						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Usual care	Oral calorie supplementation				
Change in weight (kg) Follow-up: 3 months	The mean change in weight (kg) in the control group was 0.77	The mean change in weight (kg) oral calorie supplementation groups was 0.34 higher (0.07 lower to 0.75 higher)		99 (Poustie 2006)	⊕⊕⊕⊖ moderate[1]	
Change in weight (kg) Follow-up: 6 months	The mean change in weight (kg) in the usual care group was 1.33 in 1 study and 1.72 in the other study	The mean change in weight (kg) in the oral calorie supplementation groups was 0.47 higher (0.07 lower to 1.02 higher)		117 (Hanning 1993, Poustie 2006)	⊕⊕⊖⊖ low[1,2,3]	
Change in weight (kg) Follow-up: 1 year	The mean change in weight (kg) in the usual care group was 2.97	The mean change in weight (kg) in the oral calorie supplementation groups was 0.16 higher (0.68 lower to 1 higher)		102 (Poustie 2006)	⊕⊕⊕⊖ moderate[1]	
Change in height (cm) Follow-up: 3 months	The mean change in height (cm) in the usual care group was 1.68	The mean change in height (cm) in the oral calorie supplementation groups was 0.03 lower (0.36 lower to 0.3 higher)		99 (Poustie 2006)	⊕⊕⊕⊕ high	
Change in height (cm) Follow-up: 6 months	The mean change in height (cm) in the usual care group was 3.56	The mean change in height (cm) in the oral calorie supplementation groups was 0.47 lower (1.32 lower to 0.38 higher)		101 (Poustie 2006)	⊕⊕⊕⊕ high	
Change in height (cm) Follow-up: 1 year	The mean change in height (cm) in the usual care group was 5.85	The mean change in height (cm) in the oral calorie supplementation groups was 0.06 higher (0.5 lower to 0.62 higher)		102 (Poustie 2006)	⊕⊕⊕⊕ high	

Comparison 1.1 Oral calorie supplementation versus usual care						
Change in weight as % expected for age and height Follow-up: 6 months	The mean change in weight as % expected for age and height in the usual care group was -2.7	The mean change in weight as % expected for age and height in the oral calorie supplementation groups was 3.3 higher (6.27 lower to 12.87 higher)		16 (Hanning 1993)	⊕⊖⊖⊖ very low[2,4,5]	
Change in BMI (kg/m2) Follow-up: 3 months	The mean change in BMI (kg/m2) in the usual care group was 0.05	The mean change in BMI (kg/m2) in the oral calorie supplementation groups was 0.14 higher (0.08 lower to 0.36 higher)		99 (Poustie 2006)	⊕⊕⊕⊖ moderate[1]	
Change in BMI (kg/m2) Follow-up: 6 months	The mean change in BMI (kg/m2) in the usual care group was 0.15	The mean change in BMI (kg/m2) in the oral calorie supplementation groups was 0.24 higher (0.06 lower to 0.54 higher)		101 (Poustie 2006)	⊕⊕⊕⊖ moderate[1]	
Change in BMI (kg/m2) Follow-up: 1 year	The mean change in BMI (kg/m2) in the usual care group was 0.24	The mean change in BMI (kg/m2) in the oral calorie supplementation groups was 0.08 higher (0.28 lower to 0.44 higher)		102 (Poustie 2006)	⊕⊕⊕⊖ moderate[1]	
Change in BMI (centile) Follow-up: 3 months	The mean change in BMI (centile) in the usual care group was -0.56	The mean change in BMI (centile) in the oral calorie supplementation groups was 3.28 higher (0.7 lower to 7.26 higher)		99 (Poustie 2006)	⊕⊕⊕⊖ moderate[1]	
Change in BMI (centile) Follow-up: 6 months	The mean change in BMI (centile) in the usual care group was -1.29	The mean change in BMI (centile) in the oral calorie supplementation groups was 5.75 higher (0.22 to 11.28 higher)		101 (Poustie 2006)	⊕⊕⊕⊖ moderate[1]	
Change in BMI (centile) Follow-up: 1 year	The mean change in BMI (centile) the usual care group was -2.32	The mean change in BMI (centile) in the oral calorie supplementation groups was 2.99 higher (2.69 lower to 8.67 higher)		102 (Poustie 2006)	⊕⊕⊕⊖ moderate[1]	

Comparison 1.1 Oral calorie supplementation versus usual care						
Change in weight (centile) Follow-up: 3 months	The mean change in weight (centile) - in the usual care group was 0.4	The mean change in weight (centile) in the oral calorie supplementation groups was 1.72 higher (0.59 lower to 4.03 higher)		99 (Poustie 2006)	⊕⊕⊕⊖ moderate[1]	
Change in weight (centile) Follow-up: 6 months	The mean change in weight (centile in the usual care group was 0.63	The mean change in weight (centile) in the oral calorie supplementation groups was 2.12 higher (0.94 lower to 5.18 higher)		101 (Poustie 2006)	⊕⊕⊕⊖ moderate[1]	
Change in weight (centile) Follow-up: 1 year	The mean change in weight (centile) in the usual care group was -1	The mean change in weight (centile) in the oral calorie supplementation groups was 1.83 higher (1.77 lower to 5.43 higher)		102 (Poustie 2006)	⊕⊕⊕⊖ moderate[1]	
Change in height (centile) Follow-up: 3 months	The mean change in height (centile) - in the usual care group was 1.13	The mean change in height (centile) in the oral calorie supplementation groups was 0.56 lower (2.04 lower to 0.92 higher)		99 (Poustie 2006)	⊕⊕⊕⊖ moderate[1]	
Change in height (centile) Follow-up: 6 months	The mean change in height (centile) - in the usual care group was 1.98	The mean change in height (centile) in the oral calorie supplementation groups was 1.74 lower (4.4 lower to 0.92 higher)		101 (Poustie 2006)	⊕⊕⊕⊕ high	
Change in height (centile) Follow-up: 1 year	The mean change in height (centile) in the usual care group was 1.18	The mean change in height (centile) in the oral calorie supplementation groups was 0.65 lower (3.11 lower to 1.81 higher)		102 (Poustie 2006)	⊕⊕⊕⊖ moderate[1]	
Change in height as % of expected for age Follow-up: 6 months	The mean change in height as % of expected for age in the usual care group was 1.7	The mean change in height as % of expected for age in the oral calorie supplementation groups was 1.6 lower (21.54 lower to 18.34 higher)		16 (Hanning 1993)	⊕⊖⊖⊖ very low[2,4,5]	

Comparison 1.1 Oral calorie supplementation versus usual care						
Adverse effects	No evidence was found					
Change in FEV_1 % predicted Follow-up: 3 months	The mean change in FEV_1 % predicted in the usual care group was 5.37	The mean change in FEV_1 % predicted in the oral calorie supplementation groups was 7.92 lower (13.89 to 1.95 lower)		69 (Poustie 2006)	⊕⊕⊕⊖ moderate[6]	
Change in FEV_1 % predicted Scale from: 0 to 100Follow-up: 6 months	The mean change in FEV_1 % predicted in the usual care group was -4.3 in 1 study and 1.61 in the other study	The mean change in FEV_1 % predicted in the oral calorie supplementation groups was 3.84 lower (9.63 lower to 1.94 higher)		86 (Hanning 1993, Poustie 2006)	⊕⊕⊖⊖ low[2,3,6]	
Change in FEV_1 % predicted Follow-up: 1 year	The mean change in FEV_1 % predicted in the usual care group was -1.5	The mean change in FEV_1 % predicted in the oral calorie supplementation groups was 1.91 lower (8.57 lower to 4.75 higher)		70 (Poustie 2006)	⊕⊕⊕⊖ moderate[6]	
Quality of life	No evidence was found					
Pulmonary exacerbations	No evidence was found					
Patient or carer satisfaction	No evidence was found					

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*
Abbreviations: BMI: body mass index; CI: confidence interval; CF: cystic fibrosis; cm: centimetres; FEV_1: forced expiratory volume in 1 second; kg: kilogrammes; kg/m2: kilogrammes per metre square; MD: mean difference

1 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID
2 The quality of the evidence was downgraded by 1 because of high risk of bias in relation to the randomisation (the treated group appeared to be in better clinical condition at baseline in 1 study).
3 The inclusion criteria in the paper by Hanning et al. did not mention underweight therefore the population in the study is unlikely to be representative of people who would receive oral supplements in clinical practice; however the quality of the evidence was not downgraded because the inclusion criteria in the paper by Poustie et al. are likely to be representative of people who receive oral supplements in clinical practice
4 The quality of the evidence was downgraded by 1 because the inclusion criteria did not mention underweight therefore the population in the study is unlikely to be representative of people who would usually receive oral supplements
5 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 defaults MIDs
6 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 clinical MID

Table 144: Summary clinical evidence profile: Comparison 1.2 Oral calorie supplementation versus nutrition advice

Comparison 1.2 Oral calorie supplementation versus nutrition advice						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Nutrition advice	Oral calorie supplementation				
Change in weight (kg) Follow-up: 3 months	The mean change in weight (kg) in the nutrition advice group was 2.15	The mean change in weight (kg) in the oral calorie supplementation groups was 0.69 lower (3.3 lower to 1.92 higher)		13 (1 Kalnins 2005)	⊕⊖⊖⊖ very low[1,2]	
Change in weight for height (%) Follow-up: 3 months	The mean change in weight for height (%)in the nutrition advice group was 1.67	The mean change in weight for height (%)in the oral calorie supplementation groups was 0.96 lower (5.23 lower to 3.31 higher)		19 (1 Kalnins 2005)	⊕⊖⊖⊖ very low[1,2]	
Change in weight z score Follow-up: 3 months	The mean change in weight z score in the nutrition advice group was 0.1	The mean change in weight z score in the oral calorie supplementation groups was 0 higher (0.59 lower to 0.59 higher)		13 (1 Kalnins 2005)	⊕⊖⊖⊖ very low[1,2]	
Change in weight z score Follow-up: 6 months	The mean change in weight z score in the nutrition advice group was 0.2	The mean change in weight z score in the oral calorie supplementation groups was 0.3 lower (0.98 lower to 0.38 higher)		13 (1 Kalnins 2005)	⊕⊖⊖⊖ very low[1,2]	
Change in % ideal body weight Follow-up: 3 months	The mean change in % ideal body weight in the nutrition advice group was 1	The mean change in % ideal body weight in the oral calorie supplementation groups was 2 lower (10.59 lower to 6.59 higher)		13 (1 Kalnins 2005)	⊕⊖⊖⊖ very low[1,2]	
Change in % ideal body weight	The mean change in % ideal body weight in the	The mean change in % ideal body weight in the oral calorie		13 (1 Kalnins 2005)	⊕⊖⊖⊖ very low[1,2]	

Comparison 1.2 Oral calorie supplementation versus nutrition advice						
Follow-up: 6 months	nutrition advice group was 0	supplementation groups was 3 lower (11.59 lower to 5.59 higher)				
Change in height (cm) Follow-up: 3 months	The mean change in height (cm) in the nutrition advice group was 2.55	The mean change in height (cm) in the oral calorie supplementation groups was 0.38 lower (3.05 lower to 2.29 higher)		13 (1 Kalnins 2005)	⨁⊖⊖⊖ very low[1,2]	
Change in height z score Follow-up: 3 months	The mean change in height z score - in the nutrition advice group was 0.1	The mean change in height z score in the oral calorie supplementation groups was 0 higher (0.96 lower to 0.96 higher)		13 (1 Kalnins 2005)	⨁⊖⊖⊖ very low[1,2]	
Change in height z score Follow-up: 6 months	The mean change in height z score - in the nutrition advice group was 0.2	The mean change in height z score in the oral calorie supplementation groups was 0.1 lower (1.07 lower to 0.87 higher)		13 (1 Kalnins 2005)	⨁⊖⊖⊖ very low[1,2]	
Change in FEV_1 % predicted Scale from: 0 to 100 Follow-up: 6 months	The mean change in FEV_1 % predicted in the nutrition advice group was 1.6	The mean change in FEV_1 % predicted in the oral calorie supplementation groups was 8.2 lower (23.37 lower to 6.97 higher)		13 (1 Kalnins 2005)	⨁⊖⊖⊖ very low[1,3]	
Change in FEV_1 % predicted Scale from: 0 to 100 Follow-up: 6 months	The mean change in FEV_1 % predicted in the nutrition advice group was 4	The mean change in FEV_1 % predicted in the oral calorie supplementation groups was 8 lower (26.96 lower to 10.96 higher)		13 (1 Kalnins 2005)	⨁⊖⊖⊖ very low[1,3]	
Quality of life	No evidence was found					
Pulmonary exacerbations	No evidence was found					
Adverse effects	No evidence was found					
Patient or carer satisfaction	No evidence was found					

Comparison 1.2 Oral calorie supplementation versus nutrition advice
**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).* *Abbreviations: confidence interval; CF: cystic fibrosis; cm: centimetres; FEV_1: forced expiratory volume in 1 second; kg: kilogrammes; MD: mean difference*

1 The quality of the evidence was downgraded by 2 because of unclear risk of bias in relation to randomisation, high risk of bias in relation to allocation concealment, and inability to make judgment in relation to other bias.
2 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs
3 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 clinical MIDs

Table 145: Summary clinical evidence profile: Comparison 2. Enteral tube feeding versus usual care

Comparison 2. Enteral tube feeding versus usual care						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Usual care	Enteral tube feeding				
Change in weight (kg) Follow-up: 1 year	The mean change in weight (kg) the usual care group was -0.3	The mean change in weight (kg) in the enteral tube feeding groups was 7.60 higher (4.74 to 10.46 higher)		21 (White 2013)	⊕⊖⊖⊖ very low[1]	
Change in weight (kg) Follow-up: 2 years	The mean change in weight (kg) the usual care group was -0.8	The mean change in weight (kg) in the enteral tube feeding groups was 9.10 higher (5.43 to 12.77 higher)		21 (White 2013)	⊕⊖⊖⊖ very low[1]	
Change in weight (kg) Follow-up: 3 years	The mean change in weight (kg) the usual care group -0.1	The mean change in weight (kg) in the enteral tube feeding groups was 9.00 higher (5.21 to 12.79 higher)		21 (White 2013)	⊕⊖⊖⊖ very low[1]	
Change in weight z score - Scale from: -4 to 4. Follow-up: 6 months	The mean change in weight z score in the usual care group was 0.05	The mean change in weight z score in the enteral tube feeding groups was 0.62 higher (0.27 to 0.97 higher)		40 (Bradley 2012)	⊕⊖⊖⊖ very low[2,3]	

Comparison 2. Enteral tube feeding versus usual care						
Change in weight z score - Scale from: -4 to 4. Follow-up: 1 years	The mean change in weight z score in the usual care group was 0.2	The mean change in weight z score in the enteral tube feeding groups was 0.44 higher (0.11 to 0.77 higher)		40 (Bradley 2012)	⊕⊖⊖⊖ very low[2,3]	
Change in height z-score Scale from: -4 to 4. Follow-up: 6 months	The mean change in height z-score in the usual care group was 0.3	The mean change in height z-score in the enteral tube feeding groups was 0.2 higher (0.19 lower to 0.59 higher)		40 (Bradley 2012)	⊕⊖⊖⊖ very low[2,3]	
Change in height z-score Scale from: -4 to 4. Follow-up: 1 years	The mean change in height z-score in the usual care group was 0	The mean change in height z-score in the enteral tube feeding groups was 0.1 higher (0.29 lower to 0.49 higher)		40 (Bradley 2012)	⊕⊖⊖⊖ very low[2,3]	
Change in BMI z score Scale from: -4 to 4. Follow-up: 6 months	The mean change in BMI z score in the usual care group was 0.08	The mean change in BMI z score in the enteral tube feeding groups was 0.82 higher (0.48 to 1.16 higher)		40 (Bradley 2012)	⊕⊖⊖⊖ very low[2]	
Change in BMI z score Scale from: -4 to 4. Follow-up: 1 years	The mean change in BMI z score in the usual care group was 0.39	The mean change in BMI z score in the enteral tube feeding groups was 0.39 higher (0.09 to 0.69 higher)		40 (Bradley 2012)	⊕⊖⊖⊖ very low[2,3]	
Change in BMI (kg/m2) Follow-up: 1 years	The mean change in BMI in the usual care group was -0.2	The mean change in BMI (kg/m2) in the enteral tube feeding groups was 2.90 higher (2.2 to 3.6 higher)		21 (White 2013)	⊕⊖⊖⊖ very low[1]	
Change in BMI (kg/m2) Follow-up: 2 years	The mean change in BMI in the	The mean change in BMI (kg/m2) in the enteral tube		21 (White 2013)	⊕⊖⊖⊖ very low[1]	

Comparison 2. Enteral tube feeding versus usual care						
	usual care group was -0.3	feeding groups was 3.20 higher (2.33 to 4.07 higher)				
Change in BMI (kg/m2) Follow-up: 3 years	The mean change in BMI in the usual care group was 0.8	The mean change in BMI (kg/m2) in the enteral tube feeding groups was 2.50 higher (1.55 to 3.45 higher)		21 (White 2013)	⊕⊖⊖⊖ very low[1]	
Change in FEV_1 %predicted Scale from: 0 to 100. Follow-up: 6 months	The mean change in FEV_1 %predicted in the usual care group was 3.2	The mean change in FEV_1 %predicted in the enteral tube feeding groups was 4.5 lower (16.18 lower to 7.18 higher)		27 (Bradley 2012)	⊕⊖⊖⊖ very low[2,4]	
Change in FEV_1 %predicted Scale from: 0 to 100. Follow-up: 1 years	The mean change in FEV_1 %predicted in the usual care group was 6.6	The mean change in FEV_1 %predicted in the enteral tube feeding groups was 8.2 lower (20.5 lower to 4.1 higher)		27 (Bradley 2012)	⊕⊖⊖⊖ very low[2,5]	
Change in FEV_1 % predicted Scale from: 0 to 100 Follow-up: 1 years	The mean change in FEV_1% predicted in the usual care group was -5.3	The mean change in FEV_1 % predicted in the enteral tube feeding groups was 10.60 higher (10.34 lower to 31.54 higher)		21 (White 2013)	⊕⊖⊖⊖ very low[1,4]	
Change in FEV_1 % predicted Scale from: 0 to 100 Follow-up: 2 years	The mean change in FEV_1% predicted in the usual care group was -8	The mean change in FEV_1 % predicted in the enteral tube feeding groups was 12.20 higher (2.57 lower to 26.97 higher)		21 (White 2013)	⊕⊖⊖⊖ very low[1,5]	
Change in FEV_1 % predicted Scale from: 0 to 100 Follow-up: 3 years	The mean change in FEV_1% predicted in the usual care group was -11	The mean change in FEV_1 % predicted in the enteral tube feeding groups was 12.20 higher		21 (White 2013)	⊕⊖⊖⊖ very low[1,5]	

Comparison 2. Enteral tube feeding versus usual care						
		(1.84 lower to 26.24 higher)				
Change in IV treatment days Follow-up: 1 years	The mean change in IV treatment days in the usual care group was 2.8	The mean change in IV treatment days in the enteral tube feeding groups was 17.90 higher (5.96 lower to 41.76 higher)		21 (White 2013)	⊕⊖⊖⊖ very low[1,3]	
Change in IV treatment days Follow-up: 2 years	The mean change in IV treatment days in the usual care group was -8	The mean change in IV treatment days in the enteral tube feeding groups was 36.00 higher (5.06 to 66.94 higher)		21 (White 2013)	⊕⊖⊖⊖ very low[1,3]	
Change in IV treatment days Follow-up: 3 years	The mean change in IV treatment days in the usual care group was 7	The mean change in IV treatment days in the enteral tube feeding groups was 36.20 higher (6.29 lower to 78.69 higher)		21 (White 2013)	⊕⊖⊖⊖ very low[1,3]	
Quality of life	No evidence available					
Patient or carer satisfaction	No evidence available					
Adverse events	No evidence available					

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: BMI: body mass index; confidence interval; CF: cystic fibrosis; FEV_1: forced expiratory volume in 1 second; IV: intravenous; k/m2g: kilogrammes per square metre; MD: mean difference

1 The quality of the evidence was downgraded by 2 due to high risk of bias in relation to selection of the study population and comparability of the 2 groups
2 The quality of the evidence was downgraded by 1 because of high risk of bias in relation to comparability
3 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID
4 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 clinical MIDs
5 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 clinical MID

Table 146: Summary clinical evidence profile: Comparison 3. Appetite stimulants versus placebo

Comparison 3. Appetite stimulants versus placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				

Comparison 3. Appetite stimulants versus placebo						
	Placebo	Appetite stimulants				
Change in weight in kg. Follow-up: 3 months	The mean change in weight in kg. in the placebo group was 1.3 in 1 study, 1.1 in the other study	The mean change in weight in kg. in the appetite stimulants (megestrol acetate or cyproheptadine hydrochloride) groups was 2.97 higher (0.94 to 4.99 higher)		33 (Eubanks 2002, Homnick 2004)	⊕⊕⊖⊖ low[1]	
Change in weight in kg. Follow-up: 6 months	The mean change in weight in kg. in the placebo group was 1.5	The mean change in weight in kg. in the appetite stimulant (megestrol acetate) group was 3.8 higher (1.27 to 6.33 higher)		17 (Eubanks 2002)	⊕⊕⊖⊖ low[2]	
Change in weight z score Scale from: -4 to 4. Follow-up: 3 months	The mean change in weight z score in the 3 placebo groups was: 0.07, 0.04, -0.05	The mean change in weight z score in the appetite stimulants (megestrol acetate or cyproheptadine hydrochloride) groups was 0.61 higher (0.29 to 0.93 higher)		40 (Eubanks 2002, Homnick 2004, Marchand 2000)	⊕⊕⊖⊖ low[3]	
Change in weight z score Scale from: -4 to 4. Follow-up: 6 months	The mean change in weight z score in the placebo group was 0.02	The mean change in weight z score in the appetite stimulant (megestrol acetate) group was 0.74 higher (0.26 to 1.22 higher)		17 (Eubanks 2002)	⊕⊕⊖⊖ low[2]	
Change in height (cm) Follow-up: 3 months	The mean change I height in the placebo group was 1	The mean change in height (cm) in the appetite stimulant (cyproheptadine hydrochloride) group was		16 (Homnick 2004)	⊕⊖⊖⊖ very low[4,5,6]	

Comparison 3. Appetite stimulants versus placebo						
		0.2 higher (11.88 lower to 12.28 higher)				
Change in BMI (kg/m2) Follow-up: 3 months	The mean change in BMI in the placebo group was 0.29	The mean change in BMI (kg/m2) n the appetite stimulant (cyproheptadine hydrochloride) group was 0.88 higher (0.76 lower to 2.52 higher)		16 (Homnick 2004)	⊕⊖⊖⊖ very low[4,5,7]	
Change in BMI percentile Follow-up: 3 months	The mean change in BMI percentile in the placebo group was 1.78	The mean change in BMI centile in the appetite stimulant (cyproheptadine hydrochloride) group was 11.1 higher (0.15 to 22.05 higher)		16 (Homnick 2004)	⊕⊖⊖⊖ very low[4,5,7]	
Change in % ideal body weight Follow-up: 3 months	The mean change in % ideal body weight in the placebo group was 1.15	The mean change in % ideal body weight in the appetite stimulant (cyproheptadine hydrochloride) group was 5.14 higher (0.2 to 10.08 higher)		16 (Homnick 2004)	⊕⊖⊖⊖ very low[4,5,7]	
Change in FEV_1 % predicted Scale from: 0 to 100. Follow-up: 3 months	The mean change in FEV_1 % predicted in the placebo group was -3.7	The mean change in FEV_1 % predicted in the appetite stimulant (megestrol acetate) group was 13.55 higher (1.88 lower to 28.98 higher)		17 (Eubaks 2002)	⊕⊖⊖⊖ very low[2,8]	
Change in FEV_1 % predicted Scale from: 0 to 100. Follow-up: 6 months	The mean change in FEV_1% predicted in the placebo group was 0.83	The mean change in FEV_1 % predicted - at 6 months in the appetite stimulant (megestrol acetate) group was 5.64 higher		17 (Eubaks 2002)	⊕⊖⊖⊖ very low[2,8]	

Comparison 3. Appetite stimulants versus placebo						
		(4.43 lower to 15.71 higher)				
Quality of life	No evidence was found					
Number of pulmonary exacerbations Follow-up: 3 months	Study population		RR 1.67 (0.69 to 4)	12 (Marchand 2000)	⊕⊖⊖⊖ very low[6,9]	
	500 per 1000 in placebo group	835 per 1000 (345 to 1000) in megestrol acetate group				
Adverse effects: constipation Follow-up: 6 months	- (placebo group)	- (megestrol acetate group)	RR 2.18 (0.1 to 46.92)	17 (Eubanks 2002)	⊕⊖⊖⊖ very low[2,6]	
Adverse effects: high blood glucose Follow-up: 3 months	Fasting blood glucose levels remained unchanged in both groups (megestrol acetate and placebo). Values not reported			12 (Marchand 2000)	⊕⊕⊖⊖ low[10]	
Adverse effects: decreased morning cortisol levels <0.6mcg/dl Follow-up: 3 months	- (placebo group)	All participants in the intervention group (megestrol acetate) had normal morning cortisol levels at baseline; at follow-up 4 out of the 6 participants in the intervention group had morning cortisol levels decreased to <0.6mcg/dl		12 (Marchand 2000)	⊕⊕⊖⊖ low[10]	
Adverse effects: decreased morning cortisol levels <30nmol/L Follow-up: 6 months	- (placebo group)	- (megestrol acetate group)	RR 10.91 (0.72 to 164.61)	17 (Eubanks 2002)	⊕⊖⊖⊖ very low[2,6]	
Patient or carer satisfaction	No evidence available					

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: BMI: body mass index; confidence interval; CF: cystic fibrosis; FEV_1: forced expiratory volume in 1 second; IV: intravenous; kg: kilogrammes; kg/m2g: kilogrammes per square metre; MD: mean difference; nmol/L: nanomoles per litre; RR: risk ratio

1 The quality of the evidence was downgraded by 2 due to very serious risk of bias in relation to the evidence from the Eubanks 2002 paper and serious risk of bias in relation to the evidence from the Homnick 2004 paper
2 The quality of the evidence was downgraded by 2 due to unclear risk of bias in relation to allocation concealment, and high risk of bias in relation to incomplete outcome data and selective reporting.

3 The quality of the evidence was downgraded by 2 due to very serious risk of bias in relation to the evidence from the Eubanks 2002 paper, serious risk of bias in relation to the evidence from the Homnick 2004 paper, and very serious risk of bias in relation to the evidence from the Marchand 2000 paper.
4 The quality of the evidence was downgraded by 1 due to unclear risk of bias in relation to allocation concealment and high risk of bias in relation to selective reporting.
5 The evidence was downgraded by 1 because ideal body weight for height <100% was an inclusion criteria. However in clinical practice some people with ideal body weight for height under this cut-off may be considered with normal weight and therefore would not be the target population of appetite stimulants.
6 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs
7 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID
8 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 clinical MID
9 The quality of the evidence was downgraded by 2 due to unclear risk of bias in relation to random sequence generation and allocation concealment, and high risk of bias in relation to incomplete outcome data and selective reporting
10 The quality of the evidence was downgraded by 2 due to unclear risk of bias in relation to random sequence generation and allocation concealment, and high risk of bias in relation to incomplete outcome data, selective reporting, and bad reporting (relevant values not provided)
a. Reversible decrease: 30+ days after treatment levels went back up to 270 +-6.9 nmol/L

Table 147: Summary clinical evidence profile: Comparison 4. Nutrition education versus usual care

Comparison 4. Nutrition education versus usual care						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Standard treatment	Nutrition education				
Change in weight (kg) Follow-up: 6 months	The mean change in weight (kg) - in the standard treatment group was 0.8	The mean change in weight (kg) in the nutrition education groups was 0.4 lower (4.85 lower to 4.05 higher)		48 (Watson 2008)	⊕⊖⊖⊖ very low[1,2,3]	
Change in weight (kg) Follow-up: 1 year	The mean change in weight (kg) in the standard treatment group was 1.2	The mean change in weight (kg) in the nutrition education groups was 0.4 lower (4.87 lower to 4.07 higher)		48 (Watson 2008)	⊕⊕⊖⊖ low[1,2,4]	
Change in FEV_1 % predicted Scale from: 0 to 100 Follow-up: 6 months	The mean change in FEV_1 % predicted in the standard treatment group was 0.81	The mean change in FEV_1 % predicted in the nutrition education groups was 1.49 higher (8.84 lower to 11.82 higher)		48 (Watson 2008)	⊕⊖⊖⊖ very low[1,2,3]	
Change in FEV_1 % predicted	The mean change in FEV_1 % predicted in	The mean change in FEV_1 % predicted in		48 (Watson 2008)	⊕⊖⊖⊖ very low[1,2,5]	

Comparison 4. Nutrition education versus usual care						
Scale from: 0 to 100 Follow-up: 1 year	the standard treatment group was -0.79	the nutrition education groups was 0.99 higher (9.29 lower to 11.27 higher)				
Quality of life: CF-QOL, physical functioning Scale from: 0 to 100 Follow-up: 6 months		p-value= 0.05		48 (Watson 2008)	⊕⊕⊖⊖ low[2,6]	
Quality of life: CF-QOL, physical functioning Scale from: 0 to 100 Follow-up: 12 months		p-value= 0.61		48 (Watson 2008)	⊕⊕⊖⊖ low[2,6]	
Quality of life: CF-QOL, social functioning Scale from: 0 to 100 Follow-up: 6 months		p-value= 0.85		48 (Watson 2008)	⊕⊕⊖⊖ low[2,6]	
Quality of life: CF-QOL, social functioning Scale from: 0 to 100 Follow-up: 12 months		p-value= 0.54		48 (Watson 2008)	⊕⊕⊖⊖ low[2,6]	
Quality of life: treatment issues CF-QOL, Follow-up: 6 months		p-value= 0.74		48 (Watson 2008)	⊕⊕⊖⊖ low[2,6]	
Quality of life: CF-QOL, treatment issues Scale from: 0 to 100 Follow-up: 12 months		p-value= 0.68		48 (Watson 2008)	⊕⊕⊖⊖ low[2,6]	
Quality of life: CF-QOL, chest symptoms		p-value= 0.59		48 (Watson 2008)	⊕⊕⊖⊖ low[2,6]	

Comparison 4. Nutrition education versus usual care						
Follow-up: 6 months						
Quality of life: CF-QOL, chest symptoms Scale from: 0 to 100 Follow-up: 12 months		p-value= 0.62		48 (Watson 2008)	⊕⊕⊖⊖ low[2,6]	
Quality of life: CF-QOL, emotional responses Scale from: 0 to 100 Follow-up: 6 months		p-value= 0.45		48 (Watson 2008)	⊕⊕⊖⊖ low[2,6]	
Quality of life: CF-QOL, emotional responses Scale from: 0 to 100 Follow-up: 12 months		p-value= 0.07		48 (Watson 2008)	⊕⊕⊖⊖ low[2,6]	
Quality of life: CF-QOL, concerns for the future Scale from: 0 to 100 Follow-up: 6 months		p-value= 0.46		48 (Watson 2008)	⊕⊕⊖⊖ low[2,6]	
Quality of life: CF-QOL, concerns for the future Scale from: 0 to 100 Follow-up: 12 months		p-value= 0.03		48 (Watson 2008)	⊕⊕⊖⊖ low[2,6]	
Quality of life: CF-QOL, interpersonal relationship Scale from: 0 to 100 Follow-up: 6 months		p-value= 0.75		48 (Watson 2008)	⊕⊕⊖⊖ low[2,6]	
Quality of life: CF-QOL, interpersonal relationship		p-value= 0.64		48 (Watson 2008)	⊕⊕⊖⊖ low[2,6]	

Comparison 4. Nutrition education versus usual care						
Scale from: 0 to 100 Follow-up: 12 months						
Quality of life: CF-QOL, body image Scale from: 0 to 100 Follow-up: 6 months		p-value=0.24		48 (Watson 2008)	⊕⊕⊖⊖ low[2,6]	
Quality of life: CF-QOL, body image Scale from: 0 to 100 Follow-up: 12 months		p-value=0.59		48 (Watson 2008)	⊕⊕⊖⊖ low[2,6]	
Quality of life: CF-QOL, career issues Scale from: 0 to 100 Follow-up: 6 months		p-value=0.15		48 (Watson 2008)	⊕⊕⊖⊖ low[2,6]	
Quality of life: CF-QOL, career issues Scale from: 0 to 100 Follow-up: 12 months		p-value=0.28		48 (Watson 2008)	⊕⊕⊖⊖ low[2,6]	
Pulmonary exacerbations	No evidence was found					
Adverse effects	No evidence was found					
Patient or carer satisfaction	No evidence was found					
**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).* *Abbreviations: CI: confidence interval; CF: cystic fibrosis; CFQOL: cystic fibrosis quality of life questionnaire; FEV1: forced expiratory volume in 1 second; kg: kilogrammes; MD: mean difference*						

1 The quality of the evidence was not downgraded despite unclear risk of bias in relation to blinding and selective reporting, because objective measures are unlikely to be influenced by the lack of blinding
2 The quality of the evidence was downgraded by 1 because there were no inclusion criteria related to underweight, therefore the study population is unlikely to be representative of people who would receive this intervention in clinical practice
3 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs
4 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID
5The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 clinical MIDs
6 The quality of the evidence was downgraded by 1 because of unclear risk of bias in relation to selective reporting and high risk of bias due to bad reporting (only p values and U test statistic provided)

Table 148: Summary clinical evidence profile: Comparison 5.1 Behavioural intervention versus usual care

Comparison 5.1 Behavioural intervention versus usual care						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Usual care	Behavioural intervention				
Change in weight (kg) Follow-up: 6 weeks	The mean change in weight (kg) in the usual care group was 0	The mean change in weight (kg) in the behavioural intervention groups was 1.7 higher (4.02 lower to 7.42 higher)		9 (Stark 1996)	⊕⊖⊖⊖ very low[1,2,3]	
Change in height (cm) Follow-up: 6 weeks	The mean change in height (cm) in the usual care group was 1.3	The mean change in height (cm) in the behavioural intervention groups was 0.1 lower (16.75 lower to 16.55 higher)		9 (Stark 1996)	⊕⊖⊖⊖ very low[1,2,3]	
Change in weight z score Follow-up: 6 weeks	The mean change in weight z score in the usual care group was -0.05	The mean change in weight z score in the behavioural intervention groups was 0.5 higher (0.19 lower to 1.19 higher)		9 (Stark 1996)	⊕⊕⊖⊖ very low[1,2,4]	
Change in FEV_1 % predicted Scale from: 0 to 100 Follow-up: 6 weeks	The mean change in FEV_1 % predicted in the usual care group was 0.5	The mean change in FEV_1 % predicted in the behavioural intervention groups was 6.5 lower (28.09 lower to 15.09 higher)		9 (Stark 1996)	⊕⊖⊖⊖ very low[1,2,5]	
Quality of life	No evidence was found					
Pulmonary exacerbations	No evidence was found					
Adverse effects	No evidence was found					
Patient or carer satisfaction	No evidence was found					

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: CI: confidence interval; CF: cystic fibrosis; cm: centimetres; FEV_1: forced expiratory volume in 1 second; MD: mean difference

1 The quality of the evidence was downgraded by 1 due to unclear risk of bias in relation to random sequence generation, allocation concealment and selective reporting. Cochrane rated the risk of bias for blinding as high however objective measures are unlikely to be influenced by the lack of blinding.
2. The quality of the evidence was downgraded by 1 because there were no inclusion criteria related to underweight or calorie intake therefore the study population is unlikely to be representative of people who would receive this intervention in clinical practice
3 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs
4 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID
5 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 clinical MIDs

Table 149: Summary clinical evidence profile: Comparison 5.2 Behavioural intervention versus education and attention control treatment

Comparison 5.2 Behavioural intervention versus education and attention control treatment						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Educational intervention	Behavioural intervention				
Change in weight z score Follow-up: 6 months	The mean change in weight z score in the educational intervention group was 0.06	The mean change in weight z score in the intervention groups was 0.06 higher (0.1 lower to 0.22 higher)		78 (Powers 2015)	⊕⊕⊕⊖ moderate[1,2]	
Change in weight z score Follow-up: 18 months	The mean change in weight z score in the educational intervention group was 0.11	The mean change in weight z score in the behavioural intervention groups was 0.04 higher (0.2 lower to 0.28 higher)		78 (Powers 2015)	⊕⊕⊕⊕ high[1]	
Change in height z score Follow-up: 18 months	The mean change in weight z score in the educational intervention group was -0.02	The mean change in height z score in the behavioural intervention groups was 0.11 higher (0.02 lower to 0.24 higher)		78 (Powers 2015)	⊕⊕⊕⊖ moderate[1,2]	
Change in FEV_1	No evidence was found					
Quality of life	No evidence was found					
Pulmonary exacerbations	No evidence was found					
Adverse effects (digestive system)	Study population		RR 1.61 (1.14 to 2.27)	78 (Powers 2015)	⊕⊕⊕⊖ moderate[1,2]	
	500 per 1000	805 per 1000 (570 to 1000)				
	Moderate					

Comparison 5.2 Behavioural intervention versus education and attention control treatment						
Follow-up: 6 months	500 per 1000	805 per 1000 (570 to 1000)				
Patient or carer satisfaction	No evidence was found					
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Abbreviations: CI: confidence interval; MD: mean difference						

1 The quality of the evidence was not downgraded although there was unclear risk of bias in relation to allocation concealment and blinding, because objective measures are unlikely to be influenced by the lack of blinding.
2 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID

Table 150: Summary clinical evidence profile: Comparison 5.3. Behavioural management training + educational intervention versus educational intervention alone

Comparison 5.3. Behavioural management training + educational intervention versus educational intervention alone						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Educational intervention alone	Behavioural management training + nutritional intervention				
Change in weight (kg) Follow-up: 2 months	The mean change in weight (kg) in the control group was 0.92	The mean change in weight (kg) in the behavioural management training + nutritional intervention groups was 0.55 higher (0 to 1.1 higher)		67 (Stark 2009)	⊕⊕⊕⊖ moderate[1]	
Change in weight (kg) Follow-up: 1 year	The mean change in weight (kg) in the educational intervention group was 1.75	The mean change in weight (kg) in the behavioural management training + nutritional intervention groups was 0.43 lower (1.27 lower to 0.41 higher)		8 (Powers 2003)	⊕⊖⊖⊖ very low[2,3]	
Change in weight (kg)	The mean change in weight (kg) in the	The mean change in weight (kg)		59 (Stark 2009)	⊕⊕⊕⊖ moderate[1]	

Comparison 5.3. Behavioural management training + educational intervention versus educational intervention alone						
Follow-up: 2 years	educational intervention group was 6.45	in the behavioural management training + nutritional intervention groups was 0.52 higher (1.34 lower to 2.38 higher)				
Change in BMI z score Follow-up: 2 months	The mean change in BMI z score in the educational intervention group was 0.18	The mean change in BMI z score in the behavioural management training + nutritional intervention groups was 0.2 higher (0.02 lower to 0.42 higher)		67 (Stark 2009)	⊕⊕⊕⊖ moderate[1]	
Change in BMI z score Follow-up: 2 years	The mean change in BMI z score in the educational intervention group was -0.22	The mean change in BMI z score in the behavioural management training + nutritional intervention groups was 0.35 higher (0 to 0.7 higher)		59 (Stark 2009)	⊕⊕⊕⊖ moderate[1]	
Change in % ideal body weight Follow-up: 1 year	The mean change in % ideal body weight in the educational intervention group was 9.4	The mean change in % ideal body weight in the behavioural management training + nutritional intervention groups was 0.91 lower (37.52 lower to 35.7 higher)		7 (Powers 2003)	⊕⊖⊖⊖ very low[2,3]	
Change in weight % for age Follow-up: 1 year	The mean change in weight % for age in the educational intervention group was 4.8	The mean change in weight % for age in the behavioural management training + nutritional intervention groups was		8 (Powers 2003)	⊕⊖⊖⊖ very low[2,3]	

Comparison 5.3. Behavioural management training + educational intervention versus educational intervention alone						
		0.6 lower (17.25 lower to 16.05 higher)				
Change in height (cm) Follow-up: 1 year	The mean change in height (cm) in the educational intervention group was 7.13	The mean change in height (cm) in the behavioural management training + nutritional intervention groups was 2.03 lower (4.87 lower to 0.81 higher)		(Powers 2003)	⊕⊖⊖⊖ very low[2,3]	
Change in height (cm) Follow-up: 2 years	The mean change in height (cm) in the educational intervention group was 13.54	The mean change in height (cm) in the behavioural management training + nutritional intervention groups was 0.2 lower (1.45 lower to 1.05 higher)		59 (Stark 2009)	⊕⊕⊕⊕ high	
Change in height z score Follow-up: 2 years	The mean change in height z score in the educational intervention group was 0.04	The mean change in height z score in the behavioural management training + nutritional intervention groups was 0.01 lower (0.17 lower to 0.15 higher)		59 (Stark 2009)	⊕⊕⊕⊖ moderate[1]	
Change in FEV_1 % predicted Scale from: 0 to 100 Follow-up: 2 years	The mean change in FEV_1 in the educational intervention group was -5	The mean change in FEV_1 in the behavioural management training + nutritional intervention groups was 5.16 higher (8.49 lower to 18.81 higher)		28 (Stark 2009)	⊕⊕⊖⊖ low[4]	
Quality of life	No evidence was found					
Adverse effects	No evidence was found					
Time to next exacerbation	No evidence was found					

Comparison 5.3. Behavioural management training + educational intervention versus educational intervention alone					
Patient or carer satisfaction	Parents in both groups reported high ratings of satisfaction with treatment (>6 in a 7 point scale)		67 (Stark 2009)	⊕⊕⊕⊖ moderate[5]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: BMI: body mass index; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; kg: kilogrammes; cm: centimetres; MD: mean difference

1 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID
2 The quality of the evidence was downgraded by 1 because of unclear risk of bias in relation to random sequence generation, allocation concealment and incomplete outcome data. Cochrane rated the risk of bias in relation to blinding as high risk however objective measures are unlikely to be influenced by a lack of blinding.
3 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs
4 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 clinical MIDs
5 The quality of the evidence was downgraded by 1 due to bad reporting (narrative reporting only)

10.1.5 Economic evidence

No economic evaluations of nutritional interventions were identified in the literature search conducted for this guideline. Full details of the search and economic article selection flow chart can be found in Appendix E and F, respectively.

This review question was not prioritised for de novo economic modelling. To aid consideration of cost-effectiveness relevant resource and cost use data are presented in Appendix K.

10.1.6 Evidence statements

10.1.6.1 Oral calorie supplementation

10.1.6.1.1 Comparison 1.1. Oral calorie supplementation versus usual care

Indices of nutrition and growth: weight

Moderate quality evidence from 1 RCT with 99 children and young people with cystic fibrosis 2 to 15 years old showed no clinically significant difference in weight (measured as change in kg and change in weight centile) in the group of participants receiving oral calorie supplementation compared to the participants in the control group receiving usual care at 3 months follow-up.

Similarly, low quality evidence from 2 RCTs with 117 children and young people with cystic fibrosis 2 to 15 years old showed no clinically significant difference in weight (measured as change in kg) in the group of participants receiving oral calorie supplementation compared to the participants in the control group receiving usual care at 6 months follow-up.

Similarly, moderate quality evidence from 1 RCT with 101 children and young people with cystic fibrosis 2 to 15 years old showed no clinically significant difference in weight (measured as change in weight centile) in the group of participants receiving oral calorie supplementation compared to the participants in the control group receiving usual care at 6 months follow-up.

Very low quality evidence from 1 RCT with 16 children and young people with cystic fibrosis 7 to 15 years old showed no clinically significant difference in weight (measured as change in percentage expected for age and height) in the group of participants receiving oral calorie supplementation compared to the participants in the control group receiving usual care at 6 months follow-up.

Likewise, moderate quality evidence from 1 RCT with 102 children and young people with cystic fibrosis 2 to 15 years old showed no clinically significant difference in weight (measured as change in kg and change in weight centile) in the group of participants receiving oral calorie supplementation compared to the participants in the control group receiving usual care at 1 year follow-up.

Indices of nutrition and growth: BMI

Moderate quality evidence from 1 RCT with 99 children and young people with cystic fibrosis 2 to 15 years old showed no clinically significant difference in BMI (measured as change in kg/m^2 and as change in BMI centile) in the group of participants receiving oral calorie supplementation compared to the participants in the control group receiving usual care at 3 months follow-up.

Similarly, moderate quality evidence from 1 RCT with 101 children and young people with cystic fibrosis 2 to 15 years old showed no clinically significant difference in BMI (measured as change in kg/m2 and as change in BMI centile) in the group of participants receiving oral calorie supplementation compared to the participants in the control group receiving usual care at 6 months follow-up.

Likewise, moderate quality evidence from 1 RCT with 102 children and young people with cystic fibrosis 2 to 15 years old showed no clinically significant difference in BMI (measured as change in kg/m2 and as change in BMI centile) in the group of participants receiving oral calorie supplementation compared to the participants in the control group receiving usual care at 1 year follow-up.

Indices of nutrition and growth: height

High to moderate quality evidence from 1 RCT with 99 children and young people with cystic fibrosis 2 to 15 years old showed no clinically significant difference in height (measured as change in cm and as change in height centile) in the group of participants receiving oral calorie supplementation compared to the participants in the control group receiving usual care at 3 months follow-up.

Likewise, high quality evidence from 1 RCT with 101 children and young people with cystic fibrosis 2 to 15 years old showed no clinically significant difference in height (measured as change in cm and change in height centile) in the group of participants receiving oral calorie supplementation compared to the participants in the control group receiving usual care at 6 months follow-up.

Very low quality evidence from 1 RCT with 16 children and young people with cystic fibrosis 7 to 15 years old showed no clinically significant difference in height (measured as change in percentage expected for age) in the group of participants receiving oral calorie supplementation compared to the participants in the control group receiving usual care at 6 months follow-up.

High to moderate quality evidence from 1 RCT with 102 children and young people with cystic fibrosis 2 to 15 years old showed no clinically significant difference in height (measured as change in cm and change in height centile) in the group of participants receiving oral calorie supplementation compared to the participants in the control group receiving usual care at 1 year follow-up.

Lung function: FEV_1

Moderate quality evidence from 1 RCT with 69 children and young people with cystic fibrosis 2 to 15 years old showed a clinically significant decrease in lung function (measured as change in FEV_1 % predicted) in the group of participants receiving oral calorie

supplementation compared to the participants in the control group receiving usual care at 3 months follow-up.

However, low quality evidence from 2 RCTs with 86 children and young people with cystic fibrosis 2 to 15 years old showed no clinically significant change in lung function (measured as change in FEV_1 % predicted) in the group of participants receiving oral calorie supplementation compared to the participants in the control group receiving usual care at 6 months follow-up.

Similarly, moderate quality evidence from 1 RCT with 70 children and young people with cystic fibrosis 2 to 15 years old showed no clinically significant change in lung function (measured as change in FEV_1 % predicted) in the group of participants receiving oral calorie supplementation compared to the participants in the control group receiving usual care at 1 year follow-up.

Quality of life

No evidence was found for this critical outcome.

Pulmonary exacerbations

No evidence was found for this important outcome.

Adverse effects

No evidence was found for this important outcome.

Patient or carer satisfaction

No evidence was found for this important outcome.

10.1.6.1.2 Comparison 1.2. Oral calorie supplementation versus nutritional advice

Indices of nutrition and growth: weight

Very low quality evidence from 1 quasi-RCT with 13 people with CF >10 years old showed no clinically significant difference in weight (measured as change in kg, change in Z-score, change in percentage weight for height, change in percentage of ideal body weight) between the group of participants receiving oral calorie supplementation for 3 months and the participants receiving nutritional advice at 3 months follow-up.

Very low quality evidence from 1 quasi-RCT with 13 people with CF >10 years old showed no clinically significant difference in weight (measured as change in z score and change in percentage of ideal body weight) between the group of participants receiving oral calorie supplementation for 3 months and the participants receiving nutritional advice at 6 months follow-up.

Indices of nutrition and growth: height

Very low quality evidence from 1 quasi-RCT with 13 people with cystic fibrosis >10 years old showed no clinically significant difference in height (measured as change in cm and change in Z-score) between the group of participants receiving oral calorie supplementation for 3 months and the participants receiving nutritional advice at 3 months follow-up.

Very low quality evidence from 1 quasi-RCT with 13 people with cystic fibrosis >10 years old showed no clinically significant difference in height (measured as change in Z-score) between the group of participants receiving oral calorie supplementation for 3 months and the participants receiving nutritional advice at 6 months follow-up.

Lung function: FEV_1

Very low quality evidence from 1 quasi-RCT with 13 people with cystic fibrosis >10 years old showed a clinically significant decrease in lung function (measured as change in FEV_1 % predicted) in the group of participants receiving oral calorie supplementation for 3 months compared to the participants receiving nutritional advice at 3 and at 6 months follow-up.

Quality of life

No evidence was found for this critical outcome.

Pulmonary exacerbations

No evidence was found for this important outcome.

Adverse effects

No evidence was found for this important outcome.

Patient or carer satisfaction

No evidence was found for this important outcome.

10.1.6.2 Enteral tube feeding

10.1.6.2.1 Comparison 2. Enteral tube feeding versus usual care

Indices of nutrition and growth: weight

Very low quality evidence from 1 cohort study with 21 adults with cystic fibrosis showed a clinically significant improvement in weight (measured as change in kg) in the group receiving enteral tube feeding compared to those who received usual care at 1,2 and 3 years follow-up.

Very low quality evidence from 1 cohort study with 40 people with cystic fibrosis aged 2 to 20 years showed a clinically significant improvement in weight (measured as change in z score) in the group receiving gastrostomy compared to those who received usual care at 6 months and 1 year follow-up.

Indices of nutrition and growth: height

Very low quality evidence from 1 cohort study with 40 people with cystic fibrosis aged 2 to 20 years showed no clinically significant increase in height (measured as change in z score) between the group receiving gastrostomy and those who received usual care at 6 months and 1 year follow-up.

Indices of nutrition and growth: BMI

Very low quality evidence from 1 cohort study with 21 adults with cystic fibrosis showed a clinically significant improvement in BMI (measured as change in kg/m2) in the group receiving enteral tube feeding compared to those who received usual care at 1,2 and 3 years follow-up.

Very low quality evidence from 1 cohort study with 40 people with cystic fibrosis aged 2 to 20 years showed a clinically significant improvement in BMI (measured as change in z score) in the group receiving gastrostomy compared to those who received usual care at 6 months and 1 year follow-up.

Lung function: FEV_1

Very low quality evidence from 1 cohort study with 21 adults with cystic fibrosis showed no clinically significant improvement in lung function (measured as change in FEV_1 % predicted) between the group receiving enteral tube feeding and those who received usual care at 1,2 and 3 years follow-up.

Very low quality evidence from 1 cohort study with 27 people with cystic fibrosis aged 2 to 20 years showed no clinically significant difference in lung function (measured as change in FEV_1 % predicted) between the group receiving gastrostomy and those who received usual care at 6 months and 1 year follow-up.

Quality of life

No evidence was found for this critical outcome.

Days on IV treatment (proxy outcome for pulmonary exacerbations)

Very low quality evidence from 1 cohort study with 21 adults with cystic fibrosis showed no clinically significant improvement in IV treatment (measured as change in number of days of treatment) between the group receiving enteral tube feeding and those who received usual care at 1 and 3 years follow-up. However, the same evidence found a clinically significant increase in IV treatment (measured as change in number of days of treatment) in the group receiving enteral tube feeding compared to those who received usual care at 2 years follow-up.

Adverse effects

No evidence was found for this important outcome.

Patient or carer satisfaction

No evidence was found for this important outcome.

10.1.6.3 Appetite stimulants

10.1.6.3.1 Comparison 3. Appetite stimulants versus placebo

Indices of nutrition and growth: weight

Low quality evidence from 2 RCTs with 33 people with cystic fibrosis aged ≥5 years showed a clinically significant difference in weight (measured as change in kg) between the group of participants receiving an appetite stimulant (megestrol acetate or cyproheptadine hydrochloride) and the group receiving placebo at 3 months follow-up.

Low quality evidence from 3 RCTs with 40 people with cystic fibrosis aged ≥21 months showed a clinically significant improvement in weight (measured as change in weight z score) in the group of participants receiving an appetite stimulant (megestrol acetate or cyproheptadine hydrochloride) as opposed to the group receiving placebo at 3 months follow-up.

Very low quality evidence from 1 RCT with 16 people with cystic fibrosis aged ≥5 years showed a clinically significant improvement in weight (measured as change in % ideal body weight) in the group of participants receiving an appetite stimulant (cyproheptadine hydrochloride) compared to the group receiving placebo at 3 months follow-up.

Low quality evidence from 1 RCT with 17 people with cystic fibrosis older than 6 years showed a clinically significant improvement in weight (measured as change in kg and as change in weight z score) in the group of participants receiving an appetite stimulant (megestrol acetate) as opposed to the group receiving placebo at 6 months follow-up.

Indices of nutrition and growth: height

Very low quality evidence from 1 RCT with 16 people with cystic fibrosis aged ≥5 years showed no clinically significant difference in height (measured as change in cm) between the group of participants receiving an appetite stimulant (cyproheptadine hydrochloride)and the group receiving placebo at 3 months follow-up.

Indices of nutrition and growth: BMI

Very low quality evidence from 1 RCT with 16 people with cystic fibrosis aged ≥5 years showed no clinically significant difference in BMI (measured as change in kg/m2) between the group of participants receiving an appetite stimulant (cyproheptadine hydrochloride) and the group receiving placebo at 3 months follow-up.

However, very low quality evidence from 1 RCT with 16 people with cystic fibrosis aged ≥5 years showed a clinically significant improvement in BMI (measured as change in percentile) in the group of participants receiving an appetite stimulant (cyproheptadine hydrochloride) compared to the group receiving placebo at 3 months follow-up.

Lung function: FEV_1

Very low quality evidence from 1 RCT with 17 people with cystic fibrosis older than 6 years showed no clinically significant difference in lung function (measured as change in FEV_1 % predicted) between the group of participants receiving an appetite stimulant (megestrol acetate) and the group receiving placebo at 3 and 6 months follow-up.

Pulmonary exacerbations

Very low quality evidence from 1 RCT with 12 children with cystic fibrosis aged 21 months to 10.4 years showed no clinically significant difference in the number of pulmonary exacerbations between the group of participants receiving an appetite stimulant (megestrol acetate) and the group receiving placebo at 3 months follow-up.

Adverse effects

Very low quality evidence from 1 RCT with 17 people with cystic fibrosis older than 6 years showed no clinically significant difference in the number of constipation events between the group of participants receiving an appetite stimulant (megestrol acetate) and the group receiving placebo at 6 months follow-up.

Low quality evidence from 1 RCT with 12 children with cystic fibrosis aged 21 months to 10.4 years showed that fasting blood glucose levels remained unchanged in both the group of participants receiving an appetite stimulant (megestrol acetate) and the group receiving placebo at 3 months follow-up. Imprecision and clinical significance could not be calculated.

Low quality evidence from 1 RCT with 12 children aged 21 months to 10.4 years with cystic fibrosis showed that all participants in the group receiving an appetite stimulant (megestrol acetate) had normal cortisol levels at baseline; at 3 months follow-up 4 out of the 6 participants in this same group had morning cortisol levels decreased to <0.6 mcg/dl. The values for the control group were not reported. Imprecision and clinical significance could not be calculated.

Very low quality evidence from 1 RCT with 17 people with cystic fibrosis older than 6 years showed no clinically significant difference in the number of people with decreased morning cortisol levels <30nmol/L between the group of participants receiving an appetite stimulant (megestrol acetate) and the group receiving placebo at 6 months follow-up. The study described that 7 out of 10 people receiving an appetite stimulant had decreased morning cortisol levels <30nmol/L at 6 months follow-up, however after completing a 1-month-long wean from the appetite stimulant, levels increased to 270 +-6.9 nmol/L.

Quality of life

No evidence was found for this critical outcome.

Patient or carer satisfaction

No evidence was found for this important outcome.

10.1.6.4 Nutrition education/dietary advice

10.1.6.4.1 Comparison 4. Nutrition education versus standard treatment

Indices of nutrition and growth: weight

Low to very low quality evidence from 1 RCT with 48 people with cystic fibrosis older than 16 years showed no clinically significant different in weight (measured as change in kg) between the group of participants receiving a nutrition education intervention for 10 weeks and those who received usual care at 6 and 12 months follow-up.

Lung function: FEV_1

Very low quality evidence from 1 RCT with 48 people with cystic fibrosis older than 16 years showed no clinically significant difference in lung function (measured as change in FEV_1 % predicted) between the group of participants receiving a nutrition education intervention for 10 weeks and those who received usual care at 6 and 12 months follow-up.

Quality of life

Low quality evidence from 1 RCT with 48 people with cystic fibrosis older than 16 years showed the following differences in health-related quality of life measured with the CF-QOL questionnaire: the control group scored significantly higher in physical functioning than the intervention group at 6 months (p-value=0.05) and the control group scored significantly higher in concerns for the future (meaning it had less concerns) than the intervention group at 12 months follow-up. This outcome was reported narratively only and imprecision could not be calculated.

Time to next exacerbation

No evidence was found for this important outcome

Adverse effects

No evidence was found for this important outcome

Patient and carer satisfaction

No evidence was found for this important outcome

10.1.6.5 Psychological and behavioural interventions

10.1.6.5.1 Comparison 5.1 Behavioural intervention versus usual care

Indices of nutrition and growth: weight

Very low quality evidence from 1 RCT with 9 children with cystic fibrosis aged 5 to 10 years showed no clinically significant difference in weight (measured as change in kg and change in z score) between the group of participants receiving a group behavioural intervention and those who received usual care at 6 week follow-up.

Indices of nutrition and growth: height

Very low quality evidence from 1 RCT with 9 children with cystic fibrosis aged 5 to 10 years showed no clinically significant difference in height (measured as change in cm) between the

group of participants receiving a group behavioural intervention and those who received usual care at 6 week follow-up.

Lung function: FEV_1

Very low quality evidence from 1 RCT with 9 children with cystic fibrosis aged 5 to 10 years showed no clinically significant difference in lung function (measured as change in FEV_1 % predicted) between the group of participants receiving a group behavioural intervention and those who received usual care at 6 week follow-up.

Quality of life

No evidence was found for this critical outcome

Time to next exacerbation

No evidence was found for this important outcome

Adverse effects

No evidence was found for this important outcome

Patient and carer satisfaction

No evidence was found for this important outcome

10.1.6.5.2 Comparison 5.2. Behavioural intervention versus education and attention control treatment

Indices of nutrition and growth: weight

Moderate to high quality evidence from 1 RCT with 78 children with cystic fibrosis aged 2 to 6 years showed no clinically significant difference in weight (measured as change in z score) between the group of participants receiving a behavioural intervention and those who received an education and attention control treatment at 6 and 18 months follow-up.

Indices of nutrition and growth: height

Moderate quality evidence from 1 RCT with 78 children with cystic fibrosis aged 2 to 6 years showed no clinically significant difference in height (measured as change in z score) between the group of participants receiving a behavioural intervention and those who received an education and attention control treatment at 18 months follow-up.

Lung function: FEV_1

No evidence was found for this critical outcome

Quality of life

No evidence was found for this critical outcome

Time to next exacerbation

No evidence was found for this important outcome

Adverse effects

Moderate quality evidence from 1 RCT with 78 children with cystic fibrosis aged 2 to 6 years showed a clinically significant higher number of adverse effects to the digestive system in the group of participants receiving a behavioural intervention compared to those who received an education and attention control treatment at 6 months follow-up.

Patient and carer satisfaction

No evidence was found for this important outcome

10.1.6.5.3 Comparison 5.3. Behavioural management training + educational intervention versus educational intervention alone

Indices of nutrition and growth: weight

Moderate quality evidence from 1 RCT with 67 children and young people with cystic fibrosis aged 4 to 12 years showed no clinically significant difference in weight (measured as change in kg) between the group receiving a combination of a behavioural and educational intervention for 2 months and those who received the educational intervention alone for 2 months at 2 months follow-up.

Very low quality evidence from 1 RCT with 8 infants and children less than 3 years old with cystic fibrosis showed no clinically significant difference in weight (measured as change in kg, as change in % ideal body weight at as change in % weight for age) between the group receiving a combination of a behavioural and educational intervention for 1 year and those who received the educational intervention alone for 1 year at 1 year follow-up.

Moderate quality evidence from 1 RCT with 59 children and young people with cystic fibrosis aged 4 to 12 years showed no clinically significant difference in weight (measured as change in kg) between the group receiving a combination of a behavioural and educational intervention for 2 months and those who received the educational intervention alone for 2 months at 2 years follow-up.

Indices of nutrition and growth: BMI

Moderate quality evidence from 1 RCT with 67 children and young people with cystic fibrosis aged 4 to 12 years showed no clinically significant difference in BMI (measured as change in z score) between the group receiving a combination of a behavioural and educational intervention for 2 months and those who received the educational intervention alone for 2 months at 2 months follow-up.

Moderate quality evidence from 1 RCT with 59 children and young people with cystic fibrosis aged 4 to 12 years showed no clinically significant difference in BMI (measured as change in z score) between the group receiving a combination of a behavioural and educational intervention for 2 months and those who received the educational intervention alone for 2 months at 2 years follow-up.

Indices of nutrition and growth: height

Very low quality evidence from 1 RCT with 7 infants and children less than 3 years old with cystic fibrosis showed no clinically significant difference in height (measured as change in cm) between the group receiving a combination of a behavioural and educational intervention for 1 year and those who received the educational intervention alone for 1 year at 1 year follow-up.

High to moderate quality evidence from 1 RCT with 59 children and young people with cystic fibrosis aged 4 to 12 years showed no clinically significant difference in height (measured as change in cm and change in z score) between the group receiving a combination of a behavioural and educational intervention for 2 months and those who received the educational intervention alone for 2 months at 2 years follow-up.

Lung function: FEV_1

Low quality evidence from 1 RCT with 28 children and young people with cystic fibrosis aged 4 to 12 years showed no clinically significant difference in lung function (measured as change in FEV_1 % predicted) between the group of participants receiving a combination of a behavioural and educational intervention for 2 months and those who received the educational intervention alone for 2 months at 2 years follow-up.

Quality of life

No evidence was found for this critical outcome

Time to next exacerbation

No evidence was found for this important outcome

Adverse effects

No evidence was found for this important outcome

Patient and carer satisfaction

Moderate quality evidence from 1 RCT with 67 children and young people with cystic fibrosis aged 4 to 12 years showed that parents in both groups (the group receiving a combination of a behavioural and educational intervention for 2 months and the group receiving the educational intervention only for 2 months) reported high ratings of satisfaction with treatment (>6 in a 7 point scale) at 2 months follow-up. The outcome was reported narratively only and the imprecision could not be assessed.

10.1.6.6 Economic evidence statements

No evidence on cost-effectiveness in people with cystic fibrosis was available for this review.

10.1.7 Evidence to recommendations

10.1.7.1 Relative value placed on the outcomes considered

The aim of this review was to determine the clinical and cost effectiveness of nutritional interventions in improving health outcomes for people with cystic fibrosis.

The committee chose change in weight, height, body mass index (BMI), z score or other indices of nutrition or growth, lung function (FEV_1) and quality of life as critical outcomes for decision making. Changes to body composition detected by anthropometric measures, pulmonary exacerbations, patient and parent or carer satisfaction and adverse effects (including diarrhoea, reduced appetite, abdominal bloating and episodes of distal intestinal obstruction syndrome) were rated as important. For appetite stimulants, the following adverse effects were also rated as important outcomes high blood glucose and adrenal insufficiency.

10.1.7.2 Consideration of clinical benefits and harms

People with cystic fibrosis often suffer from undernutrition due to faecal fat loss, increased energy requirements caused by chronic infections and malabsorption due to pancreatic insufficiency. It is well established that nutrition is important for lung function and overall health, therefore, different nutritional interventions to improve the nutritional status and growth of people with cystic fibrosis should be considered. Because nutrition is such an important component of overall health and a considerable problem among people with cystic fibrosis, the committee agreed that dietitians should be an integral part of the multidisciplinary team caring for the person with cystic fibrosis and review the patient regularly. This should be from an individualised basis considering a myriad of factors, including current diet, salt and water intake, bowel habit in relation to pancreatic enzyme use as well as family circumstances and needs and capabilities before recommending any nutritional intervention.

If there are nutrition concerns, the committee recommended, based on their clinical experience and expertise, to encourage people to increase portion size and eat high-energy

foods in order to increase calorie intake and counterbalance increased energy requirements and malabsorption.

The committee noted that the available evidence showed that oral calorie supplements are not effective in improving nutrition or growth in people in cystic fibrosis. Therefore, the committee agreed not to recommend them as a routine intervention for the general population of people with cystic fibrosis. They discussed whether to recommend them if there are nutrition concerns. They noted that out of 3 studies on oral nutritional supplements, the population in 2 studies (Hanning 1993 and Kalnins 2005) was small (between 15 and 20 participants) and did not represent the population that dietitians would actually consider offering nutrition interventions to because inclusion criteria were either unclear (Hanning 1993) or used relatively high thresholds for weight (Kalnins 2005) to define the study populations. Only one study (Poustie 2006, 102 participants) showed no effectiveness of oral nutritional supplements in a population defined by inclusion criteria that were similar to the thresholds for additional nutritional support outlined in the CF Trust consensus document on nutritional management of cystic fibrosis. The committee agreed that supplements, if effective, would be preferable, from a patient's perspective, to enteral tube feeding, which is an invasive technique, or to appetite stimulant drugs which may be associated with adverse effects. Therefore, based on their clinical experience and expertise, they agreed that oral nutritional supplements should be considered on a trial basis for people requiring additional nutrition who had not responded to dietary advice before considering more invasive interventions.

The committee noted that the evidence showed enteral tube feeding to be effective in improving nutrition and growth in people with cystic fibrosis. The committee agreed that the capacity and the capabilities of the person and family should always be carefully considered before embarking on this.

The committee looked at appetite stimulants as an alternative to enteral tube feeding. The committee noted that evidence on megestrol acetate and cyproheptadine hydrochloride shows that they can improve nutritional status and growth. However, the committee noted that the evidence was based on studies with small sample size and discussed whether appetite stimulants can have adverse effects such as hyperglycaemia and adrenal insufficiency. There was no evidence available on adverse effects of cyproheptadine hydrochloride and limited evidence available on adverse effects of megestrol acetate, which was limited to either 3 or 6 months follow-up. This evidence showed no clinically significant difference in constipation at 6 months and no difference in fasting blood glucose levels at 3 months (clinical significance could not be calculated) between participants receiving megestrol acetate and those receiving placebo. According to the evidence, some participants had decreased morning cortisol levels after receiving megestrol acetate, however, in one study with 3 months follow-up values in the control group were not reported, while in the other study with 6 months follow-up there was no clinically significant difference with the control group, and values increased after the intervention group stopped receiving megestrol acetate. The committee discussed that although many people with cystic fibrosis considering appetite stimulants might already have diabetes, and in their clinical experience, adrenal insufficiency is not very often observed, they agreed to recommend them only in adults, short-term (for example up to 3 months) and after all other options had been fully explored. Moreover, possible adverse effects should be explained so that an informed decision can be made. The committee discussed whether the appetite stimulants for which the evidence was reviewed (megestrol acetate and cyproheptadine hydrochloride) should be named in the recommendations. However, they agreed not to endorse these specifically because of the limitations of the evidence. The decision about these treatments should be based on the whole clinical picture as well as the patient's preferences and capabilities.

The committee agreed that oral calorie supplements, enteral feeding and appetite stimulants should be closely monitored and discontinued if there are no positive outcomes.

10.1.7.3 Consideration of economic benefits and harms

The committee advised that oral supplements should not be routinely offered to all people with cystic fibrosis as dietary modifications are at least as effective and do not take away from NHS resources. Moreover, the cost of oral supplementation could be substantial over the longer term, especially if they are used to substitute rather than complement a healthy diet. A single measure could cost £2.45 (BNF August 2016, Scandishake® oral powder 85g sachet), but the specific supplement would depend on the person's deficiencies which could require a more expensive preparation.

However, the committee agreed that oral supplements should be used to complement a person's diet for acute use, during periods of ill health, such as an exacerbation, when they are nutritionally unwell and have the scope to benefit from oral supplementation when their normal diet is insufficient. Following this, the committee agreed that a research recommendation to assess the clinical and cost-effectiveness of oral supplementation in people with cystic fibrosis who are nutritionally unwell, would assess if the benefits from the acute use of oral supplementation can justify the costs to reduce current uncertainty in this area. However, a research recommendation was not prioritised, given that the findings would not contradict a recommendation to consider a trial of oral nutritional supplements if dietary modifications are not effective.

Conversely, in the longer term, the committee stated that optimal nutrition can prevent a decline in lung function. This iterates that the studies included in the clinical evidence review were too short to demonstrate the differences seen in clinical practice over several years. As a result, longer term studies would be needed to justify the additional cost of interventions compared to usual care when the aim is to maintain lung function.

The high upfront cost of tube feeding and the initial monitoring schedule was recognised by the committee. They acknowledged that tube feeding is associated with adverse effects (incurring a treatment cost and disutility) and can negatively impact social interactions during meal times. Despite this, the committee considered a role for tube feeding in the event of failure of efficacy or intolerance of alternative interventions where the benefits could outweigh the costs. The committee also added that the most appropriate type of tube feeding would be determined through a discussion with the dietitian, the person with cystic fibrosis and their family, to ensure their quality of life is maximised.

The committee advised that appetite stimulants are associated with severe side effects such as high blood glucose and adrenaline insufficiency. They should not be offered as a first-line option as the expected cost to manage those complications could outweigh the benefits from an increased appetite. Moreover, the cost of appetite stimulants could soon overtake the cost of tube feeding when they are prescribed on a long-term basis (BNF NHS Drug Tariff price, August 2016; cyproheptadine hydrochloride 4mg 4 times daily, £24.28/month; megace 480mg/day, £59.34/month).

Overall, the committee agreed that appropriate dietary modifications should be considered, before initiating oral supplements, tube feeding or appetite stimulants. Therefore, options associated with the least cost and resource use would be considered first. The committee were reluctant to specify the second-line intervention in their recommendations as this would depend on the capabilities and preferences of the person with cystic fibrosis and their family or carers. The committee added that there would need to be a decline in health, or faltering growth, before an intervention more costly and invasive than advice is considered.

10.1.7.4 Quality of evidence

The quality of the evidence presented in this review range from very low to high as assessed by GRADE.

For the domain risk of bias, the studies were assigned the same risk of bias as in the Cochrane reviews and were not individually reviewed. The main biases that lead to downgrading the quality of the evidence included randomisation, allocation concealment, and reporting bias.

Sample sizes of the studies are relatively small and statistical power might therefore be too low to show an effect. Another problem with the studies are that the intervention time and the follow-up time are not necessarily adequate to detect an effect in some outcomes (for example change in weight).

No serious issues were found regarding inconsistency (heterogeneity), as most comparisons included only one study.

Some issues regarding indirectness were also identified. The committee discussed that the participants in some of the studies on nutrition interventions among people with cystic fibrosis do not represent the population that dietitians would actually consider offering nutrition interventions to, instead the studies might include all people at a cystic fibrosis clinic, not just the ones with faltering growth or undernutrition.

10.1.7.5 Other considerations

The committee agreed that studies with longer follow-up are needed (over 18 months) as the aim of nutritional interventions is to prevent long term deterioration in lung function rather than improving it in the short term.

They also discussed that a possible explanation for interventions not proving to be effective is the lack of adherence.

At the time of publication (October 2017), there are no medicines available in the UK specifically licensed as appetite stimulants. However, there are clinical situations in which the off-label use of a medicine may be judged by the prescriber to be in the best clinical interests of the patient. As a result, the committee agreed they could recommend the off-label use of those medicines because the clinical need cannot be met by a licensed product and there is sufficient evidence and/or experience of using the medicines to demonstrate their safety and efficacy to support this.

No equality issues were identified by the committee for this review question.

The committee agreed that a research recommendation was not a priority in this area although it was noted that there was a lack of studies about nutritional interventions and children with faltering growth.

10.1.7.6 Key conclusions

The committee concluded that a dietitian should be an integral part of the multidisciplinary team caring for the person with cystic fibrosis. The evidence showed that enteral tube feeding and appetite stimulants are effective in improving nutritional status and growth in people with cystic fibrosis. However, because of the invasive nature of enteral tube feeding and the concern for potential adverse effects of appetite stimulants, dietary modifications through nutritional advice should always be considered as the first choice of treatment for a person with cystic fibrosis with undernutrition or faltering growth. The committee did not recommend routine use of oral calorie supplements for people with cystic fibrosis because no evidence was found to justify this. However, they did recommend that if there are signs that raise nutrition concerns, a trial of oral supplementation should be considered before proceeding to more invasive approaches.

10.1.8 Recommendations

97. The cystic fibrosis specialist dietitian should offer advice on the benefits of optimal nutrition, and at the annual assessment, review the person's:

- total nutritional intake, including energy intake (calories)
- estimated nutritional needs
- pancreatic enzyme replacement therapy, if appropriate.

98. Encourage people to increase calorie intake by increasing portion size and eating high-energy foods, if there is concern about their nutrition (including weight loss and inadequate weight gain).

99. If increased portion size and high-energy foods are not effective, consider a trial of oral nutritional supplements.

100. If attempts to increase calorie intake are not effective, consider:

- supplementation with enteral tube feeding, or
- for adults, a short-term trial of an appetite stimulant (for example up to 3 months)[7].

10.2 Exocrine pancreatic insufficiency

Review question: In people with cystic fibrosis, what is the most effective regimen of pancreatic enzyme replacement therapy (PERT) in the treatment of exocrine pancreatic insufficiency?

10.2.1 Introduction

Cystic Fibrosis causes a number of gastrointestinal complications. Exocrine pancreatic insufficiency (PI) is a common gastrointestinal complication which affects people with cystic fibrosis.

Pancreatic insufficiency is caused by a progressive fibrotic process that begins in-utero. Pancreatic cells are damaged by deposits of dehydrated pancreatic secretions and replaced with fibrous scar tissue. The pancreas no longer functions effectively and produces reducing amounts of enzymes essential for digestion. Pancreatic exocrine insufficiency is the major cause of maldigestion of dietary macronutrients including fat, protein and carbohydrate. Untreated it will result in sub-optimal nutritional status, impaired growth and development, deficiency of fat soluble vitamins and symptoms of malabsorption such as steatorrhoea.

Pancreatic exocrine insufficiency is treated by the administration of pancreatic enzyme replacement therapy (PERT) with all fat and protein containing meals, snacks and drinks. PERT preparations contain variable concentrations of lipase, protease and amylase. The preparation chosen is dependent on clinical and individual requirements. The aim of PERT is to ensure adequate digestion of all nutrients thereby controlling the symptoms of malabsorption and ensuring growth, development and the maintenance of normal nutritional and fat soluble vitamin status.

[7] At the time of publication (October 2017), appetite stimulants did not have a UK marketing authorisation for use in people with cystic fibrosis for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

An understanding of the signs and symptoms of pancreatic insufficiency are crucial to ensure its effective management with PERT. Pancreatic enzyme requirements vary at different times, influenced by respiratory health, changing nutritional requirements throughout childhood, and progressing pancreatic insufficiency. The purpose of this evidence review is to determine the optimal PERT regimen to manage pancreatic exocrine insufficiency in people with cystic fibrosis.

10.2.2 Description of clinical evidence

The objectives of this review were to evaluate the effectiveness of the following regimens in the treatment of exocrine pancreatic insufficiency:

- PERT given with an acid neutralising or suppressing agent in comparison with PERT alone.
- A high dose of PERT in comparison with a low dose of PERT.

We looked for systematic reviews of randomised controlled trial (RCTs) and RCTs (including cross-over trials).

For full details see review protocol in Appendix D.

One Cochrane Review was identified for this review question (Somaraju 2014) which evaluated the efficacy and safety of pancreatic enzyme replacement therapy in children and adults with cystic fibrosis. However, most comparisons of interest were different from those stated in our evidence review protocol as the Cochrane looked at enteric coated PERT compared to non-enteric coated PERT and enteric coated microspheres compared to tablets. The committee agreed that both non-enteric coated and tablets were not commonly used in clinical practice in the UK. It also did not included studies with less than 28 days follow-up. The individual relevant studies have been identified for potential inclusion in our review.

For comparison 1, the effectiveness and safety of adding an acid supressing agents (an H2 receptor antagonists or a protein pump inhibitor) to PERT therapy, 4 RCTs (Durie 1980, Heijerman 1991, Heijerman 1993 and Francisco 2002) were included.

For comparison 2, the effectiveness and safety of high dose versus low dose PERT, 4 RCTs (Heijerman 1991 – same as for comparison 1 -, Brady 1991, Mitchell 1982 and Beker 1994), were included.

3 studies were conducted in the USA (Brady 1991, Beker 1994, Francisco 2002), 2 in Holland (Heijerman 1991, Heijerman 1993), 1 in Canada (Durie 1990) and 1 in New Zealand (Mitchel 1982).

With regards to the population, 4 studies were done in a children's population (Beker 1994, Brady 1991, Durie 1980, Mitchell 1982) and 2 with adults (Heijerman 1991, Heijerman 1993). One study included both adults and children population (Francisco 2002).

All studies had cross-over design. In all of them the patients were allocated to at least 2 different interventions, with a variable follow-up (from 5 to 28 days). In all studies a stool collection was performed for the last 3 days of each treatment period and analysed for fat.

Of the outcomes listed in the protocol, all studies reported on the critical reduction of steatorrhoea and faecal fat. All seven studies measured faecal fat excretion (FFE), either as grams of fat per kg per 24 hours (Brady 1991), as grams of fat lost in the stool per 24 hours (Brady 1991, Beker 1994, Durie 1980) or as fat excreted as a percentage of dietary fat intake (Brady 1991, Durie 1980, Heijerman 1991, Heijerman 1993). Three studies measured fat absorption as a percentage of intake (Beker 1994, Francisco 2002, Mitchell 1982) (the coefficient of fat absorption, CFA). One study reported on resolution of symptoms of malabsorption (Mitchel 1982) and 1 study reported side effects of the treatment (Brady 1994).

No results were found for weight or BMI, health-related quality of life and patient satisfaction

A summary of the included studies is included in Table 151. See also study selection flow chart in Appendix F, study evidence tables in Appendix G, list of excluded studies in Appendix H, forest plots in Appendix I, and full GRADE profiles in Appendix J.

10.2.3 Summary of included studies

A summary of the studies that were included in this review are presented in Table 151.

Table 151: Summary of included studies

Study	Intervention/ comparison	Population	Outcomes	Comments
Beker 1994 (USA) Cross-over RCT	High-dose: 1500u lipase per kg/body for meals & 750u lipase per kg/body for snacks. Low-dose: 500u lipase per kg/body for meals & 250u lipase per kg/body for snacks. Additional information: • Daily fat intake (g): 100g in both groups.	N=21 children and young people with CF Age (SD, range): 11.5; 5 to 28 years	Reduction of steatorrhoea and faecal fat • Faecal fat excretion (FFE) (g/24 h) • Fat absorption (CFA) (% of intake) Adverse event • Constipation • Elevations in serum uric acid levels	
Brady 1991 (USA) Cross-over RCT	High-dose: median 12 (8 to 18) capsules per meal Low-dose: median 3 (2 to 5) capsules per meal. Additional information: Constituent enzymes per capsule: 7.020u of lipase. Daily fat intake (g) 94±6 in both groups.	N=9 children with CF Age (median, range): 9; 6 to 10 years	Reduction of steatorrhoea and faecal fat • Faecal fat excretion (FFE) (% of intake) • Faecal fat excretion (FFE) (g/kg/24h) • Faecal fat excretion (FFE) (g/24h)	
Durie 1980 (Canada) Cross-over RCT	Pancrelipase alone: 26 Pancrease capsules (Cotazym) per day , 6 per meal and 3 per snack Pancrelipase + Cimetidine (200 & 300 mg. tablets)	N=21 children and young people with CF Age: 10 to 17 years	Reduction of steatorrhoea and faecal fat • Faecal fat excretion (FFE) (g/24h) • Faecal fat excretion (FFE) (% of intake)	
Francisco 2002 (USA) Cross-over RCT	Pancrease (MT10 or MT16) + adjunct low-dose or high-dose Ranitidine. Children weighting ≤40 kg were given ranitidine 5 mg/kg or 10 mg/kg daily, divided into 2 equal doses 30 minutes before breakfast and dinner. Children weighting >40 kg and adults received 150 mg or 300 mg twice daily.	N=22 people with CF 12 children and young people, age: 6 to 17 years; 10 adults, age: 18 to 36 years	Reduction of steatorrhoea and faecal fat • Fat absorption (CFA) (%)	

Study	Intervention/ comparison	Population	Outcomes	Comments
	Pancrease (MT10 or MT16) + adjunct Omeprazole (adults only) 20 mg daily, 30 minutes before breakfast Pancrease (MT10 or MT16) + placebo Additional information: diet fat was kept constant			
Heijerman 1991 (Netherlands) Cross-over RCT	High-dose 4 capsules x 3 times per day Low-dose 2 capsules x 3 times per day. Additional information: Constituent enzymes per capsule 5000u lipase, 2900u lipase, 330u protease. Fat intake was not standardized	N=9 adults with CF Age (median, range): 29; 23 to 42 years	Resolution of symptoms of malabsorption • Faecal fat excretion (FFE) (% of intake)	Both high-dose and low-dose are low-dose and very low-dose in current practice: indirect evidence
Heijerman 1993 (Netherlands) Cross-over RCT	Pancrease 2 caps, 3 per day and Omeprazole placebo Pancrease 2 caps, 3 per day + Omeprazole 20 mg once in the morning Additional information: Constituent enzymes per capsule of Pancrease: 5000 units lipase, 2900 units amylase, 330 units protease per capsule	N=11 adults with cystic fibrosis Age: 20 to 42	Resolution of symptoms of malabsorption • Faecal fat excretion (FFE) (% of intake)	This dose is a very-low dose in current practice: indirect evidence
Mitchell 1982 (New Zealand) Cross-over RCT	High-dose 22 capsules/day Low-dose 11 capsules/ day Pancrease®. Additional information: Constituent enzymes per capsule 4,000 USNF lipase units; 25,000 USNF protease units; 20,000 amylase units. Fat intake was not standardized	N=12 children and young people with CF Age: (mean, SD): 9.6±2.1 years	Resolution of symptoms of malabsorption • Faecal fat excretion (FFE) (g/kg/day) • Faecal fat excretion (FFE) (g/day) • Fat absorption (CFA) (%) Resolution of symptoms of malabsorption • Stool frequency (bowel actions/ day) • Abdominal pain	

CF: cystic fibrosis; CFA: coefficient of fat absorption; FFE: faecal fat excretion; RCT: randomised controlled trial; SD: standard deviation

10.2.4 Clinical evidence profile

The clinical evidence profiles for this review question are presented in Table 152 to Table 157.

10.2.4.1 Acid suppressing agents as adjuvant therapy to PERT

Table 152: Summary clinical evidence profile: Comparison 1.1. PERT + cimetidine versus PERT alone in children

Comparison 1.1. PERT + cimetidine versus PERT alone in children						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	PERT alone	PERT + cimetidine				
Faecal fat excretion (FFE) Measured as % of intake (consumed that is excreted) Follow-up: 14 days	The mean faecal fat excretion (as % of intake) in the PERT alone group was 27.7	The men faecal fat excretion (as % if intake) in the PERT + cimetidine group was 17.8 (p<0.01)		21 (Durie 1980)[1, 2]	⊕⊕⊖⊖ low[3,4]	
Faecal fat excretion (FFE) Measured as g/24 hours Follow-up: 14 days	The mean faecal fat excretion (as g/24 h) in the control PERT alone was 31.3	The mean faecal fat excretion (as g/24 h) in the PERT cimetidine group was 11 lower (18.577 to 3.423 lower)		21 (Durie 1980)[1, 2]	⊕⊕⊖⊖ low[5,6,7]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: CI: confidence interval; FFE: faecal fat excretion; g: grams; MD: mean difference; PERT: pancreatic endocrine enzyme therapy

1 Cross-over trial
2 Treatment details: Cotazym 26 capsules/ day + Cimetadine 20 mg/kg/day or placebo
3 The quality of evidence was downgraded by 1 due to unclear randomisation, concealment and single-blinding. The quality of the evidence was further downgraded by 1 due to the quality of the statistical analysis. Means are provided instead of medians, although it is not normally distributed.
4 Imprecision was not assessed, as it was considered not appropriate. See footnote 3.
5 The quality of evidence was downgraded by 1 due to unclear randomisation, concealment and single-blinding.
6 The quality of the evidence was downgraded by 2 because method of measuring fat excreted is inaccurate, as it does not take into account fat intake.
7 The quality of the evidence was downgraded by 1 because the CI crossed 1 clinical MID

Table 153: Summary clinical evidence profile: Comparison 1.2. PERT + Ranitidine versus PERT alone in children

Comparison 1.2. PERT + Ranitidine versus PERT alone in children						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				

	PERT alone	PERT + ranitidine				
[PERT + low dose ranitidine] Fat absorption (CFA) Measured as % of intake (consumed fat that is absorbed) Follow-up: 12 days	The median fat absorption(as % of intake) in the PERT alone group was 80.37	The median fat absorption (as % of intake) in the PERT + low dose ranitidine group was 83.60 p=0.87*		12 (Francisco 2002) [1,2]	⊕⊕⊕⊕ high[3,4]	
[PERT + high dose ranitidine] Fat absorption (CFA) Measured as % of intake (consumed fat that is absorbed) Follow-up: 12 days	The median fat absorption (as % of intake) in the PERT alone group was 80.37	The median fat absorption (as % of intake) in the PERT + high dose ranitidine group was 80.91 p=1*		12 (Francisco 2002) [1,5]	⊕⊕⊕⊕ high[3,4]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: CFA: coefficient of fat absorption; CI: confidence interval; MD: mean difference; PERT: pancreatic endocrine enzyme therapy

** The paper provided raw data. Medians and p-values were calculated by the NGA technical team*
1 Cross-over trial
2 Treatment details: Pancrease M10 or M16 + ranitidine or placebo. Children weighting ≤40 kg were given 5 mg/kg. Children weighting >40 kg received 150 mg. twice daily.
3 Imprecision cannot be calculated from medians.
4 Reporting bias not detected, but drugs were provided by the Pharmaceutical industry
5 Treatment details: Pancrease M10 or M16 + ranitidine or placebo. Children weighting ≤40 kg were given 10 mg/kg. Children weighting >40 kg received 300 mg. twice daily.

Table 154: Summary clinical evidence profile: Comparison 1.3. PERT + Omeprazole versus PERT alone in adults

Comparison 1.3. PERT + Omeprazole versus PERT alone in adults						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	PERT alone	PERT + omeprazole				
Fat absorption (CFA) Measured as % of intake (consumed fat that is absorbed) Follow-up: 12 days	The median fat absorption (as % of intake) in the PERT alone group was 88.59	The median fat absorption (as % of intake) in the PERT + omeprazole groups was 87.40 p≤0.05*		9 (Francisco 2002)[1,2]	⊕⊕⊕⊖ moderate[3,4]	

[low-dose PERT + omeprazole or placebo] Faecal fat excretion (FFE) Measured as % of intake (consumed that is excreted) Follow)-up: 4 weeks	The median faecal fat excretion (as % of intake) in the PERT alone group was 20	The median faecal fat excretion (as % of intake) in the PERT + omeprazole group was 14 p>0.05		9 (Heijerman 1991)[1,5]	⊕⊖⊖⊖ very low[6,7,8,9]	
[high-dose PERT + omeprazole or placebo] Faecal fat excretion (FFE) Measured as % of intake (consumed that is excreted) Follow-up: 4 weeks	The median faecal fat excretion (as % of intake) in the PERT alone group was 18	The median faecal fat excretion (as % of intake) in the PERT + omeprazole group was 9 p<0.01		9 (Heijerman 1991)[1,10]	⊕⊖⊖⊖ very low[6,7,8,9]	
Faecal fat excretion (FFE) Measured as % of intake (consumed that is excreted) Follow-up: 4 weeks	The median fat excretion (as % of intake) in the PERT alone group was 20	The median faecal fat excretion (as % of intake) in the PERT + omeprazole group was 17 p>0.05		11 (Heijerman 1993)[1,11]	⊕⊕⊖⊖ low[12,13]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: CFA: coefficient of fat absorption; CI: confidence interval; FFE: faecal fat excretion; PERT: pancreatic endocrine enzyme therapy

** The paper provided raw data. Medians and p-values were calculated by the NGA technical team*
1 Cross-over trial
2 Treatment details: Pancrease M10 or M16 + omeprazole 20 mg/day or placebo
3 Imprecision cannot be calculated from medians
4 Reporting bias not detected, but drugs were provided by the Pharmaceutical industry. Quality of evidence was downgraded by 1 due to small population (n=9).
5 Treatment details: PERT 2 capsules x 3 times per day + Omeprazole 20mg/day or placebo. Constituent enzymes per capsule 5000u lipase, 2900u lipase, 330u protease. Fat intake was not standardized.
6 The quality of the evidence was downgraded by 1 due to unclear randomisation and concealment
7 The quality of the evidence was of evidence downgraded by 2 as this dosage is not used in current practice
8 Imprecision cannot be calculated from medians.
9 Reporting bias not detected. Evidence downgraded by 1 due to small sample size (n=9).
10 Treatment details: PERT 4 capsules x 3 times per day + Omeprazole 20mg/day or placebo. Constituent enzymes per capsule 5000u lipase, 2900u lipase, 330u protease. Fat intake was not standardized.
11 Treatment details: PERT 2 capsules x 3 times per day + Omeprazole 20mg/day or placebo. Constituent enzymes per capsule 5000u lipase, 2900u lipase, 330u protease. Fat intake was not standardized.
12 The quality of the evidence was of evidence downgraded by 2 as this dosage is not used in current practice
13 Imprecision cannot be calculated from medians

Table 155: Summary clinical evidence profile: Comparison 1.4. PERT + Ranitidine versus PERT alone in adults

Comparison 1.4. PERT + Ranitidine versus PERT alone in adults						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	PERT alone	PERT + ranitidine				
[PERT + low-dose ranitidine] Fat absorption (CFA) Measured as % of intake (consumed fat that is absorbed) Follow-up: 12 days	The median fat absorption (as % of intake) in the control group was 89.20	The median fat absorption (as % of intake) in the intervention group was 93.06 p=0.01*		10 (Francisco 2002)[1,2]	⊕⊕⊕⊕ high[3,4]	
[PERT + high-dose ranitidine] Fat absorption (CFA) Measured as % of intake (consumed fat that is absorbed)Follow-up: 12 days	The median fat absorption (as % of intake) in the control group was 88.59	The median fat absorption (as % of intake) in the intervention group was 88.92 p≤0.05*		9 (Francisco 2002)[1,5]	⊕⊕⊕⊖ moderate[3,4,6]	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Abbreviations: CFA: coefficient of fat absorption; CI: confidence interval; PERT: pancreatic endocrine enzyme therapy						

** The paper provided raw data. Medians and p-values were calculated by the NGA technical team*
1 Cross-over study
2 Treatment details: Pancrease M10 or M16 + ranitidine 150 mg. twice daily or placebo
3 Imprecision cannot be calculated from medians.
4 Reporting bias not detected, but drugs were provided by the Pharmaceutical industry
5 Treatment details: Pancrease M10 or M16 + ranitidine 300 mg. twice daily or placebo
6 Reporting bias not detected. Evidence downgraded by 1 due to small sample size (n=9).

10.2.4.2 High-dose PERT versus low-dose of PERT

Table 156: Summary clinical evidence profile: Comparison 2.1. High dose PERT versus low dose PERT in children

Comparison 2.1. High dose PERT versus low dose PERT in children						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control					

Faecal fat excretion (FFE) (g/kg/day) Follow-up: 14 days	The mean faecal fat excretion (g/kg/day) in the control group was 0.437	The mean faecal fat excretion (g/kg/day) in the intervention groups was 0.141 lower (0.253 to 0.029 lower)		9 (Brady 1991)[1,2]	⊕⊖⊖⊖ very low[3,4,5,6,a]	a. This method of measuring fat excreted is inaccurate, as it does not take into account fat intake.
Faecal fat excretion (FFE) Measured as % of intake (consumed that is excreted) Follow-up: 14 days	The mean faecal fat excretion (as % of intake) in the control group was 13	The mean faecal fat excretion (as % of intake) in the intervention groups was 0 higher (0 to 0 higher)		9 (Brady 1991)[1,2]	⊕⊖⊖⊖ very low[3,4,5,6]	
Faecal fat excretion (FFE) (g/day) Follow-up: 9 days	-	The mean faecal fat excretion (g/day) in the intervention groups was 5 lower (8.877 to 1.123 lower)		30 (Brady 1991, Beker 1994)[1,2,3]	⊕⊖⊖⊖ very low[4,5,7,a]	a. This method of measuring fat excreted is inaccurate, as it does not take into account fat intake.
Faecal fat excretion (FFE) (g/day) Follow-up: 4 weeks	The mean faecal fat excretion (g/day) in the control group was 11.5	The mean faecal fat excretion (g/day) in the intervention groups was 8.7		12 (Mitchell 1982)[2,8]	⊕⊖⊖⊖ very low[4,9,10,11,a]	The MD could not be calculated a. This method of measuring fat excreted is inaccurate, as it does not take into account fat intake.
Fat absorption (CFA) Measured as % of intake (consumed	The mean fat absorption (as % of intake) in	The mean fat absorption in the intervention (as % of intake)		12 (Mitchell 1982)[2,8]	⊕⊖⊖⊖ very low[4,9,11,12]	

fat that is absorbed) Follow-up: 4 weeks	the control group was 85.4	groups was 89.5				
Fat absorption (CFA) Measured as % of intake (consumed fat that is absorbed) Follow-up: 9 days	The mean fat absorption (as % of intake) in the control group was 86.2	The mean fat absorption (as % of intake) in the intervention groups was 91.2		21 (Beker 1994)[2,3]	⊕⊖⊖⊖ very low[4,12,13,14]	The MD could not be calculated
Stool frequency (bowel movements/ day, self-report) Follow-up: 4 weeks	The mean stool frequency in the intervention group was 1.8	The mean stool frequency in the intervention groups was 0.1 lower (0.189 lower to 0.011 higher)		12 (Mitchell 1982)[2,8]	⊕⊖⊖⊖ very low[4,9,11]	
Abdominal pain self-report Follow-up: 4 weeks	Not reported	No differences were found between both groups	Not estimable[14]	12 (Mitchell 1982)[2,8]	⊕⊖⊖⊖ very low[4,9,11,15]	
Adverse events (constipation, elevation in serum uric acid levels) self-report Follow-up: 9 days	None	None	Not estimable[14]	21 (Beker 1994)[2,3]	⊕⊖⊖⊖ very low[4,13,14,15]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: CFA: coefficient of fat absorption; CI: confidence interval; FFE: faecal fat excretion; g: grams; kg: kilogrammes; MD: mean difference; ns: not significant; PERT: pancreatic endocrine enzyme therapy; SEM: standard error of measurement

1 Cross-over trial
2 Treatment details: high-dose 12 (8 to 18) & low-dose 3 (2 to 5) capsules per meal. Constituent enzymes per capsule: 7.020u of lipase. Daily fat intake (g) 94±6 in both groups.
3 Treatment details: high-dose: 1500u lipase per kg/body for meals & 750u lipase per kg/body for snacks. Low-dose: 500u lipase per kg/body for meals & 250u lipase per kg/body for snacks. Daily fat intake (g): 100g in both groups.
4 The quality of the evidence was downgraded by 2 as these doses are not used in current practice. Low-dose is in fact very low dose, and high-dose is just low-dose
5 Imprecision could not be calculated, as SD was not available for the control group
6 Reporting bias not detected, although funding not reported. Evidence downgraded by 1 due to small sample (n=9)
7 The quality of the evidence was downgraded by 1 due to unclear randomisation and concealment in both studies.
8 Treatment details: high-dose 22 capsules/day & low-dose 11 capsules/ day Pancrease®. Constituent enzymes per capsule 4,000 USNF lipase units; 25,000 USNF protease units; 20,000 amylase units.
9 The quality of the evidence was downgraded by 1 due to unclear randomisation and concealment. It is unclear if blinding was done, but given the outcome this may not have an impact.

10 The quality of the evidence was downgraded by 1 as the results are poorly reported: authors do not report p-value and MD cannot be calculated
11 Reporting bias not detected, although Pancrelipase capsules were provided by Ethnor Pty Ltd.
12 The quality of the evidence was downgraded by 2 due to the quality of the statistical analysis. Means are provided instead of medians, although it is not normally distributed, therefore differences cannot be calculated as it is not appropriate.
13 The quality of the evidence was downgraded by 1 because it is an open-label study.
14 Reporting bias not detected, although the study is partly funded by a grant from Johnson Pharmaceutical.
15 Imprecision cannot be calculated.

Table 157: Summary clinical evidence profile: Comparison 2.2. High-dose PERT versus low-dose PERT in adults

Comparison 2.2. High-dose PERT versus low-dose PERT in adults						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control					
Faecal fat excretion (FFE) Measured as % of intake (consumed that is excreted) Follow-up: 14 days	The median faecal fat excretion (% of intake) in the control groups was 20 (12 to 44)	The median faecal fat excretion (% of intake) in the intervention groups was 18 (10 to 34); p>0.05		9 (Heijerman 1991)[1,2]	⊕⊖⊖⊖ very low[3,4,5,6]	
**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).* *Abbreviations: CI: confidence interval; FFE: faecal fat excretion; PERT: pancreatic endocrine enzyme therapy*						

1 Cross-over trial
2 High-dose 4 capsules x 3 times per day & low-dose 2 capsules x 3 times per day. Constituent enzymes per capsule 5000u lipase, 2900u lipase, 330u protease. Fat intake was not standardized.
3 Evidence downgraded by 1 due to unclear randomisation and concealment.
4 Evidence downgraded by 2 as these doses are not used in current practice. Low-dose is in fact very low dose, and high-dose is just low-dose
5 Imprecision cannot be calculated from medians
6 Reporting bias not detected. Evidence downgraded by 1 due to small sample size (n=9).

10.2.5 Economic evidence

No economic evaluations of interventions relevant to PERT were identified in the literature search conducted for this guideline. Full details of the search and economic article selection flow chart can be found in Appendix E and F, respectively.

This review question was not prioritised for de novo economic modelling. To aid consideration of cost-effectiveness, relevant resource and cost use data are presented in Appendix K.

10.2.6 Evidence statements

10.2.6.1 Comparison 1. Acid suppressing agents as adjuvant therapy to PERT

10.2.6.1.1 Evidence for children

Reduction of steatorrhea and faecal fat excretion

Low quality evidence from 1 cross-over trial with 21 children with cystic fibrosis showed that the mean faecal fat excretion (measured as percentage of consumed fat that is excreted) was lower when the children received Cimetidine (20 mg/kg/day) in addition to PERT treatment than when they received PERT and placebo at 2 week follow-up. However, the uncertainty around this could not be calculated.

Low quality evidence from 1 cross-over trial with 21 children with cystic fibrosis showed that there was a clinically significant difference in the reduction of faecal fat excretion (measured as g/ 24 hours) when the children received Cimetidine (20 mg/kg/day) in addition to PERT than when they received PERT and placebo at 2 week follow-up. This method of measuring fat excreted is inaccurate, as it does not take into account fat intake.

Fat absorption

High quality evidence from 1 cross-over trial with 12 children with cystic fibrosis showed no differences in the median of fat absorption (measured as % of consumed fat that is absorbed) between adding low-dose Ranitidine (5 mg/kg for children weighting under 40 kg or 150 mg twice daily for children weighting over 40kg) or placebo to PERT treatment at 12 days follow-up. However, the uncertainty around this could not be calculated.

High quality evidence from 1 cross-over trial with 12 children with cystic fibrosis showed no differences in the median of fat absorption (measured as % of consumed fat that is absorbed) between adding high-dose Ranitidine (10 mg/kg for children weighting under 40 kg or 300 mg twice daily for children weighting over 40kg) or placebo to PERT treatment at 12 days follow-up. However, the uncertainty around this could not be calculated.

Resolution of symptoms of malabsorption

No evidence was found for this critical outcome in children.

Weight

No evidence was found for this critical outcome in children.

Quality of life

No evidence was found for this important outcome in children.

Satisfaction

No evidence was found for this important outcome in children.

Adverse events

No evidence was found for this important outcome in children.

10.2.6.1.2 Evidence for adults

Reduction of steatorrhea and faecal fat excretion

Very low quality evidence from 1 cross-over trial with 9 adults with cystic fibrosis showed no difference in the median faecal fat excretion (measured as percentage of consumed fat that is excreted) between adding Omeprazole (20 mg/day) or placebo to low-dose PERT treatment at 4 week follow-up. However, the uncertainty around this could not be calculated.

Very low quality evidence from 1 cross-over trial with 9 adults with cystic fibrosis showed a decrease in the median faecal fat excretion (measured as percentage of consumed fat that is excreted) when the participants received Omeprazole (20 mg/day) in addition to high-dose PERT treatment than when they received PERT and placebo at 4 week follow-up. However, the uncertainty around this could not be calculated.

Low quality evidence from 1 cross-over trial with 11 adults with cystic fibrosis showed no difference in the median faecal fat excretion (measured as percentage of consumed fat that is excreted) between adding Omeprazole (20 mg/day) or placebo to PERT treatment at 4 week follow-up. However, the uncertainty around this could not be calculated.

Fat absorption

Moderate quality evidence from 1 cross-over trial with 9 adults with cystic fibrosis showed that the fat absorption (measured as % of consumed fat that is absorbed) was higher when the participants received omeprazole (20 mg/day) in addition to PERT treatment than when they received PERT and placebo at 12 days follow-up. However, the uncertainty around this could not be calculated.

High quality evidence from 1 cross-over trial with 10 adults with cystic fibrosis showed that the fat absorption (measured as % of consumed fat that is absorbed) was higher when the participants received low-dose Ranitidine (150 mg twice daily) in addition to PERT treatment than when they received PERT and placebo at 12 days follow-up. However, the uncertainty around this could not be calculated.

Moderate quality evidence from 1 cross-over trial with 10 adults with cystic fibrosis showed that the fat absorption (measured as % of consumed fat that is absorbed) was higher when the participants received high-dose Ranitidine (300 mg twice daily) in addition to PERT treatment than when they received PERT and placebo. However, the uncertainty around this could not be calculated.

Weight

No evidence was found for this critical outcome in adults.

Resolution of symptoms of malabsorption

No evidence was found for this critical outcome in adults.

Quality of life

No evidence was found for this important outcome in adults.

Satisfaction

No evidence was found for this important outcome in adults.

Adverse events

No evidence was found for this important outcome in adults.

10.2.6.2 Comparison 2. High versus low dose of PERT

10.2.6.2.1 Evidence for children

Reduction of steatorrhea and faecal fat excretion

Very low quality evidence from 1 cross-over trial with 9 children with cystic fibrosis showed that the mean faecal fat excretion (measured as g/kg/day) was lower when the children were allocated to the high-dose treatment arm at 2 week follow-up. However, the uncertainty around this could not be calculated. This method of measuring fat excreted is inaccurate, as it does not take into account fat intake.

Very low quality evidence from 1 cross-over trial with 9 children with cystic fibrosis showed that the mean faecal fat excretion (measured as percentage of consumed fat that is excreted) was lower when the children were allocated to the high-dose treatment arm at 2 week follow-up. However, the uncertainty around this outcome cannot be calculated.

Very low quality evidence from 2 cross-over trials with 30 children with cystic fibrosis showed that the mean faecal fat excretion (measured as g/day) was lower when the children were allocated to the high-dose treatment arm at 4 week follow-up at 4 week follow-up. However, the uncertainty around this could not be calculated. This method of measuring fat excreted is inaccurate, as it does not take into account fat intake.

Very low quality evidence from 1 cross-over trial with 12 children with cystic fibrosis showed no difference in the faecal fat excretion (measured as g/day) between the high-dose and the low-dose PERT treatment arms at 4 week follow-up. However, the uncertainty around this could not be calculated. This method of measuring fat excreted is inaccurate, as it does not take into account fat intake.

Fat absorption

Very low quality evidence from 2 cross-over trials with 33 children with cystic fibrosis showed that the fat absorption (measured as % of consumed fat that is absorbed) was higher when the children were allocated to the high-dose treatment arm at 9 days and at 4 week follow-up. However, the uncertainty around this could not be calculated.

Weight

No evidence was found for this critical outcome.

Resolution of symptoms of malabsorption

Very low quality evidence from 1 cross-over trial with 12 children with cystic fibrosis showed no clinically significant difference in stool frequency between the high and the low dose PERT treatment arms at 4 week follow-up.

Very low quality evidence from 1 cross-over trial with 12 children with cystic fibrosis showed no difference in the occurrence of abdominal pain between the high and the low dose PERT treatment arms at 4 week follow-up. However the uncertainty around this outcome could not be calculated.

Adverse Events

Very low quality evidence from 1 cross-over trial with 21 children with cystic fibrosis showed no episodes of constipation or elevation in serum acid levels in both high and low dose treatment arms at 9 days follow-up.

10.2.6.2.2 Evidence for adults

Reduction of steatorrhea and faecal fat excretion

Very low quality evidence from 1 cross-over trial with 9 adults with cystic fibrosis showed no clinically significant difference in the reduction of faecal fat excretion (measured as percentage of intake) between high dose and low dose PERT treatment arms at 2 week follow-up.

Fat absorption

No evidence was found for this important outcome.

Weight

No evidence was found for this critical outcome.

Resolution of symptoms of malabsorption

No evidence was found for this critical outcome.

Adverse events

No evidence was found for this important outcome.

10.2.6.3 Economic evidence statements

No evidence on cost-effectiveness in people with cystic fibrosis was available for this review.

10.2.7 Evidence to recommendations

10.2.7.1 Relative value placed on the outcomes considered

The aim of this review was to evaluate the effectiveness of PERT given with an acid neutralising or suppressing agent in comparison with PERT alone and to evaluate the effectiveness of a high dose of PERT in comparison with a low dose of PERT in the treatment of exocrine pancreatic insufficiency.

The critical outcomes specified by the committee were reduction of steatorrhoea using measures such as faecal fat excretion (total or as a percentage of fat consumption) and the coefficient of fat absorption (the percentage of consumed fat absorbed, based on the difference between fat consumed and fat excreted in the stool),weight, BMI (also % weight for height if available) and resolution of symptoms of malabsorption. Quality of life, satisfaction and drug related side effects were rated as important outcomes.

10.2.7.2 Consideration of clinical benefits and harms

The committee noted that pancreatic enzyme insufficiency is a common disorder among people with cystic fibrosis that prevents digestion and absorption of nutrients. This results in nutrient malabsorption and other symptoms such as diarrhoea. These, in turn, can affect quality of life and, eventually, result in malnutrition. Based on this, the committee agreed that all people with cystic fibrosis should be offered a test if there are signs or symptoms

suggestive of malabsorption. This recommendation was based on their clinical knowledge and experience.

The committee discussed the technique that should be used to assess exocrine pancreatic insufficiency. They agreed direct pancreatic stimulation tests (such as the direct pancreatic stimulation test) are invasive, uncomfortable for the person and costly. Instead, they recommended the use of non-invasive techniques, such as stool elastase estimation, as it is a non-invasive easy to perform alternative. They noted there are other alternatives, such as the analysis of the percentage of fat absorbed or excreted, but they agreed they are uncomfortable for the person, as a 72-hours stool collection is needed, and they rely on the person accurately recording food intake.

The committee agreed that the use of PERT is well-established in clinical practice as it is known that PERT treatment is useful in overcoming enzyme deficiency in people with cystic fibrosis. However, they noted there is uncertainty regarding the optimal doses of enzymes needed.

The committee acknowledged the evidence presented comparing different treatment dosages, but they agreed it was of limited use because it was rated as of very low quality.. They noted that although normalisation of fat absorption and thus prevention of steatorrhoea would ideally be achieved with PERT, demonstrating this was in practice difficult. The reasons for this, as indicated above, are the measurement of stool fat entails stool collection and measurement of dietary fat intake over a period of days in order to calculate the coefficient of fat absorption. This approach is rarely done other than in a research context, as it is considered troublesome and impractical.

The committee acknowledged that the evidence suggested improved fat absorption with higher doses of pancreatic enzyme replacement therapy. However, dosage was likely to vary on an individual basis since the severity of pancreatic insufficiency was not uniform in people with cystic fibrosis. Optimal dose might differ depending on body size and dietary composition and intake. Infants and young children have a higher intake of fat proportionately than older children, young people and adults.

Based on this, the committee agreed to recommend to offer PERT to people with cystic fibrosis with pancreatic insufficiency and that the dose should be adjusted for each person in order to minimise symptoms of malabsorption. This recommendation is consistent with clinical practice and aligned with the CF Trust Consensus recommendations (CF Trust, Nutritional Management of Cystic Fibrosis 2016).

The committee agreed that evidence regarding the effectiveness of PERT dose and acid suppression in relation to resolution of malabsorption symptoms, improvement in weight and improvement in patient satisfaction or health-related quality of life was very limited and of very low quality or completely lacking. They noted that the normal clinical approach to determining individual need was an empirical one, for instance titrating the PERT dose in terms of units of lipase against the amount of fat being ingested. A standard dose, related to age in children, was usually given and adjustment then made based on the clinical response in terms of trying to achieve a normal bowel habit and the resolution of any malabsorption symptoms. They recommended that, in people with confirmed pancreatic exocrine insufficiency, the dose was titrated against symptoms and regularly reviewed. High enzyme concentration products would aid treatment optimisation where there was a higher dose requirement.

The committee noted that trials were of short duration and therefore it was not possible to assess whether prescribing high dose PERT treatment or adding an antacid had an impact on weight. They also noted the dosages used are very low compared to those used in clinical practice. In addition, most trials included a very small sample size and were underpowered to detect differences between treatment arms.

10.2.7.3 Consideration of economic benefits and harms

Based on their clinical expertise, the committee agreed PERT should be tested when symptoms or signs suggesting malabsorption occur, as the results of the test in those individuals would be used to improve their management strategy. For this reason, the committee made a recommendation to reinforce best practice to test for PERT using a non-invasive technique. Following this, the committee discussed if the test should be repeated annually in children and young people. However, they agreed the test would not add any additional information to a clinical assessment if the person is asymptomatic. Therefore, to prevent a cost-ineffective use of resources, a frequency was not recommended. Instead, the test should be repeated if symptoms or signs suggesting malabsorption occur, at any age.

When the committee discussed the management of PERT, it was noted that the dose-response may justify the additional cost of high-concentration PERT over low-concentration PERT. With regards to acid suppression, the committee agreed the clinical evidence was too uncertain to justify the costs for intermittent malabsorption. However, in people with cystic fibrosis with persistent symptoms of malabsorption, the committee believed the benefits from acid suppression would justify the costs. Overall, the committee agreed clinical judgement is necessary to provide the most cost-effective treatment as the optimal dose and concentration of enzymes is individualised based on weight and drug adherence.

10.2.7.4 Quality of evidence

The quality of the evidence presented in this report ranged from very low to high as assessed by GRADE. The main reasons that lead to downgrading the quality of the evidence were the following.

For the domain risk of bias, the 6 trials included in the review were assessed as having unclear or high risk of bias regarding randomisation and concealment methods. All of the trials were of cross-over design, but given the nature of the intervention it is not expected that treatments have a carry-over effect.

The committee noted that there were issues regarding indirectness of the intervention as the dosage used in some of the studies was much lower than current practice. In addition, they noted that measuring fat excretion or fat absorption as grams per 24 hours is inaccurate as it does not take into account daily intake.

Most trials were underpowered to detect a difference between both treatment groups.

Finally, there were some concerns regarding the statistical analysis used and the type of data reported. Due to this limitation most of the results could not be meta-analysed.

Imprecision could not be assessed when results were provided in medians.

10.2.7.5 Other considerations

No equality issues were identified by the committee for this review question.

The committee agreed that a research recommendation was not prioritised for this topic because clinical practice is already established. Additionally, there are treatments which are known, based on clinical expertise, to be useful in the treatment of pancreatic exocrine insufficiency.

At the time of publication (October 2017), cimetidine is the only H2 receptor antagonist licensed for this indication. In addition, none of the proton pump inhibitors available in the UK are licensed for this indication. However, there are clinical situations in which the off-label use of a medicine may be judged by the prescriber to be in the best clinical interests of the patient. As a result, the committee agreed they could recommend the off-label use of acid suppression agents because the clinical need may not be met by a licensed product and

there is sufficient evidence and/or experience of using the medicines to demonstrate their safety and efficacy to support this.

10.2.7.6 Key conclusions

The committee concluded that people with cystic fibrosis with pancreatic insufficiency should be offered oral pancreatic enzyme replacement therapy. Although the evidence showed some indication that high-dose PERT treatment may have a beneficial impact in both faecal fat excretion and fat absorption when compared to standard or low-dose treatment, without an increase in side effects, the committee agreed that the dose should be adjusted to minimise symptoms of malabsorption.

In addition, the committee noted that there was some indication that addition of acid suppressants to PERT treatment may reduce faecal fat excretion and therefore the use of an acid suppressant agents can be considered in people with cystic fibrosis who have persistent symptoms of malabsorption despite optimal PERT therapy.

10.2.8 Recommendations

101. Test for exocrine pancreatic insufficiency in people with cystic fibrosis, using a non-invasive technique such as stool elastase estimation. If the test result is normal, repeat it if symptoms or signs suggesting malabsorption occur.

102. Offer oral pancreatic enzyme replacement therapy to people with exocrine pancreatic insufficiency. Adjust the dose as needed to minimise any symptoms or signs of malabsorption.

103. Consider an acid suppression agent (for example an H2 receptor antagonist or a proton pump inhibitor)[8] for people who have persistent symptoms or signs of malabsorption despite optimal pancreatic enzyme replacement therapy.

10.3 Distal intestinal obstruction syndrome

Review question: What are the effective strategies for treatment and secondary prevention of distal ileal obstruction syndrome?

10.3.1 Introduction

Cystic fibrosis can cause a number of gastro-intestinal problems. One gastro-intestinal problem characteristic of cystic fibrosis is a blockage in the bowel known as distal intestinal obstruction syndrome (DIOS), which is also known as distal ileal obstruction syndrome. DIOS is a specific cystic fibrosis-related clinical problem and, therefore, is best managed by clinical teams with experience of treating people with cystic fibrosis. Approximately 7-8% of people with cystic fibrosis will experience an episode of DIOS in their lifetime. Symptoms of DIOS are abdominal pain, abdominal distension, nausea and vomiting. Typical clinical examination findings include a distended abdomen, a palpable mass in the right iliac fossa and reduced or absent bowel sounds. Radiological imaging, usually involving an abdominal x-ray, ultrasound scan or CT-scan, helps to confirm the diagnosis. DIOS is much more common in those patients who have exocrine pancreatic insufficiency. The pathophysiology is not fully

[8] At the time of publication (October 2017), acid suppression agents did not have a UK marketing authorisation for use in people with cystic fibrosis for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

understood, but there are often multiple contributory factors including, dehydration, salt loss, rapid increase in pancreatic enzyme dosage or poor compliance with pancreatic enzyme therapy, altered gut motility and pH and dietary factors.

A number of patients suffer recurrent episodes in their lifetime. This review will look at the evidence for strategies both to prevent DIOS and for treating episodes of DIOS if they occur.

10.3.2 Description of clinical evidence

The aim of this review was to identify the effective strategies of primary treatment (acute treatment) in those with a diagnosis of cystic fibrosis and DIOS. Additionally, this review aimed to identify the effective strategies for the secondary prevention of DIOS.

Systematic reviews and RCTs that assessed the effectiveness of primary and secondary treatments for DIOS were eligible for inclusion in this review. However, no relevant systematic reviews or RCTs were identified. Hence, as per the protocol, conference abstracts of RCTs and non-randomised comparative studies were also considered although none was identified for inclusion and no evidence was available to inform the review.

For full details see review protocol in Appendix D.

See also study selection flow chart in Appendix F, and list of excluded studies in Appendix H.

10.3.3 Summary of included studies

Not applicable, as no studies were identified for inclusion in this review.

10.3.4 Clinical evidence profile

Not applicable, as no studies were identified for inclusion in this review.

10.3.5 Economic evidence

No economic evaluations of interventions relevant to DIOS were identified in the literature search conducted for this guideline. Full details of the search and economic article selection flow chart can be found in Appendix E and F, respectively.

This review question was not prioritised for de novo economic modelling. To aid consideration of cost-effectiveness, relevant resource and cost use data are presented in Appendix K.

10.3.6 Evidence statements

Not applicable, as no clinical or economic studies were identified for inclusion in this review.

10.3.7 Evidence to recommendations

10.3.7.1 Relative value placed on the outcomes considered

The aim of this review was to identify the most effective strategies for the primary treatment and secondary prevention of DIOS.

For the primary treatment, when a person presented with acute abdominal pain and other symptoms due to DIOS, the committee identified the following outcomes as critical reduction in clinical manifestations, adverse events from treatment and treatment failure. Patient satisfaction and duration of hospital stay were rated as important outcomes.

For the secondary prevention of DIOS, the committee identified the following outcomes as critical reduction in clinical manifestations, adverse events from treatment and recurrence of DIOS. Patient satisfaction was rated as an important outcome.

10.3.7.2 Consideration of clinical benefits and harms

The committee noted the absence of trials in the review. They agreed that there are difficulties in undertaking RCTs of treatments for those presenting with DIOS. In particular, the clinical presentation varies considerably. Some people have relatively minor symptoms (for example abdominal pain) while others might have symptoms of intestinal obstruction with vomiting. The approach to managing these patients would be tailored to their individual difficulties. Given the lack of evidence, the list of recommendations as part of this topic are derived from both current good practice and the committee expert opinion. In addition, the committee emphasised the variability in practice and the need to define a correct treatment.

Treatment of an acute episode of DIOS

Although the diagnosis of DIOS was not part of this review, the committee considered it was important to make recommendations on the recognition of DIOS in people with cystic fibrosis. Therefore, by consensus based on their clinical knowledge and experience, they agreed recommendations on this.

First, the committee highlighted the importance of making a differential diagnosis of acute abdominal pain in people with cystic fibrosis. Some causes of abdominal pain that may resemble DIOS include constipation, appendicitis, intussusception and cholecystitis. Their correct identification is important in order to decide the adequate treatment approach.

Although the symptoms of DIOS are variable, they agreed that DIOS should be suspected in people with cystic fibrosis who have an acute onset of peri-umbilical or right lower quadrant abdominal pain, and any of the following signs or symptoms are present; a palpable faecal mass in the right lower quadrant, faecal loading in the right lower quadrant on a plain abdominal radiograph, especially if associated with small intestine air-fluid levels and clinical features of partial or complete intestinal obstruction, such as vomiting (especially bilious) and abdominal distension. In the absence of clinical or radiological features of DIOS, additional imaging techniques, such as an abdominal ultrasound scan or an abdominal CT scan, can be considered.

They noted that people with cystic fibrosis presenting to non-cystic fibrosis clinical settings might be assumed to have appendicitis or other suspected causes for intestinal obstruction when DIOS was more likely. Therefore, they may be more likely to be subjected to unnecessary and potentially harmful surgical intervention.

Although it is common for a distinction to be made between complete versus impending DIOS the committee choose not to make this distinction. They agreed it was more accurate to view the syndrome as consisting of a continuum, some presenting with acute pain and evidence of stool retention in the distal ileum (either a palpable mass in the right iliac fossa or based on radiological imaging), while others might have overt clinical and radiological evidence of distal small intestinal obstruction. It was worth noting that some people with cystic fibrosis have evidence of a palpable mass in the right lower quadrant of the abdomen for years without developing the symptoms of DIOS.

As noted above, the committee recognised the lack of RCTs for the treatment of DIOS and the prevention of recurrent DIOS. However, they agreed there are certain basic principles which govern currently accepted management.

The committee discussed that an important contributor to the development of DIOS were dehydration of intestinal mucus due to the underlying defect in the cystic fibrosis conductance regulator. Other possible contributors were the increased viscosity of luminal

contents and alterations in intestinal motility (delayed small intestinal transit) in cystic fibrosis. Although DIOS can occur in people with cystic fibrosis who are pancreatic sufficient, there is speculation that fat malabsorption can increase the risk either by increasing luminal content viscosity or by delaying intestinal transit (the ileal brake mechanism). For these reasons, the committee agreed that adequate hydration and, if necessary rehydration, was advisable in those presenting with DIOS. Encouraging ample oral fluid intake was advisable in those who were experiencing recurrent episodes of DIOS. In the latter group it was also a rational approach to review and attempt to optimise oral pancreatic enzyme replacement therapy as a preventive measure.

The committee noted that there are 2 approaches to medical therapy for DIOS currently in common use. Diatrizoate meglumine and diatrizoate sodium solution (Gastrografin) could be given either orally or via an enteral tube. They considered that this was often the quickest and most effective way of dealing with a blockage and adverse effects, if any, were usually minor. In addition, this is usually patient preference due to its tolerability and ease to take. Based on this, the committee agreed that this medication treatment regimen could be considered as first-line treatment.

If this was unsuccessful, the committee recommended a trial of treatment with stool softeners such as osmotic laxatives containing polyethylene glycol (PEG) in an iso-osmotic electrolyte solution (Macrogols). This could be taken orally or administered through an enteral tube.

Occasionally, if these measures proved unsuccessful in relieving the DIOS symptoms, recourse to surgery to alleviate the obstruction could be considered. However, they emphasised surgery should only be considered as a last resource. The committee noted that consultation with a surgeon may identify colonoscopic washout as an option before surgery. However, the committee decided not to include this in the recommendations because colonoscopic washout was not included in the review protocol and, therefore, evidence on this was not reviewed.

Secondary prevention

In addition to the potential value of enhanced oral fluid intake and optimisation of pancreatic enzyme replacement, as discussed above, the committee recommended trying a stool softening agent such as osmotic laxatives containing polyethylene glycol (PEG) in an iso-osmotic electrolyte solution (Macrogols). There was no clinical trial evidence for the effectiveness of such agents in this setting. However, the committee considered that they made rational sense and were readily tolerated. If recurrent DIOS was a concern it was reasonable to give a trial of prophylaxis with them. Osmotic laxatives, as described above, are commonly used in the long-term management of chronic constipation and are free of serious adverse effects.

10.3.7.3 Consideration of economic benefits and harms

The committee considered imaging studies to reduce the number of false positives as some people with cystic fibrosis have potentially serious conditions such as appendicitis or intussusception that might mimic the symptoms of DIOS. For this reason, the committee agreed imaging studies would be a cost-effective use of NHS resources as they would minimise the foregone risks and additional treatment costs associated with unidentified cases.

The committee also added that DIOS can be a serious and costly condition that negatively impacts a person's health-related quality of life if incorrectly managed. Therefore, it would be necessary to manage suspected DIOS in a specialist cystic fibrosis centre, with supervision from specialists who have expertise in recognising and treating the condition and its complications, in order to minimise the number of incorrectly managed cases. As a result, a recommendation was prioritised to ensure resource allocations in this area are maintained.

According to the committee people with acute onset of DIOS symptoms can respond to an intravenous fluids to regain adequate hydration or osmotic laxative containing polyethylene glycol. These treatments are relatively inexpensive treatment at a cost of less than £10 per month. However, the committee noted that the more expensive treatment, diatrizoate, is often chosen as the first-line treatment in current clinical practice based on experience that it is the most effective first-line treatment with the potential for fewer side effects. Moreover, cheaper alternatives would overtake the cost of diatrizoate when they are required for longer durations to achieve the same effects.

Following this, the committee also agreed that the cost and distress incurred by a surgical procedure would be overtaken by pharmacological treatments that require ongoing costs and treatment burden. As a result, the committee made a recommendation to consider surgery if prolonged pharmacological treatment is not effective.

When making their recommendations, the committee referred to previous guidance (Colombo 2011) that recommends a stepwise approach to DIOS treatment. This involves using the least invasive options first and surgery only as a last resort. As a result, the committee believed guideline recommendations are not likely to represent a change in current practice and resource use.

10.3.7.4 Quality of evidence

Not applicable, as no studies were identified for inclusion in this review.

10.3.7.5 Other considerations

The guideline committee were not aware of any published trial and it was their clinical experience that the choice of a treatment over another was mainly empirically based. Current good practice guidance (Colombo 2011) was acknowledged by the Guideline committee, which they agreed was largely in line with their clinical experience.

The committee discussed potential equality issues. They noted adults may be more likely to go into a local hospital if the live far from the specialist centre. However, they agreed there was no need to draft additional recommendations as they had already recommended that suspected DIOS should be managed in a specialist cystic fibrosis centre, with supervision from specialists who have expertise in recognising and treating the condition and its complications. The committee noted that the expertise of these specialists should also cover the specialty areas of colonoscopy and gastroenterology.

The Guideline committee agreed that a research recommendation was not prioritised for this topic because clinical practice is already established and there are treatments which are known (based on clinical expertise) to be useful for people who are acutely ill and for secondary prevention.

At the time of publication (October 2017), diatrizoate meglumine, diatrizoate sodium solution and osmotic polyethylene glycol and electrolyte solution did not have a UK marketing authorisation for use in people with cystic fibrosis for this indication. However, there are clinical situations in which the off-label use of a medicine may be judged by the prescriber to be in the best clinical interests of the patient. As a result, the committee agreed they could recommend the off-label use of those medicines because the clinical need cannot be met by a licensed product and there is sufficient evidence and/or experience of using the medicines to demonstrate their safety and efficacy to support this.

10.3.7.6 Key conclusions

The Guideline committee concluded that in the absence of relevant published evidence, recommendations are based on their clinical experience, expert opinion and existing guidance. They agreed treatment of DIOS should be provided in a cystic fibrosis centre. The

less invasive treatments should be the first choice for treating DIOS as they are generally effective in almost all people with DIOS.

10.3.8 Recommendations

104. Be aware that a variety of conditions can cause acute abdominal pain and resemble distal intestinal obstruction syndrome in people with cystic fibrosis, for example:

- constipation
- appendicitis
- intussusception
- cholecystitis.

105. Suspect distal intestinal obstruction syndrome in people with cystic fibrosis who have an acute onset of peri-umbilical or right lower quadrant abdominal pain and any of the following:

- a palpable mass in the right lower quadrant
- faecal loading in the right lower quadrant on a plain abdominal X-ray, especially if associated with small intestine air-fluid levels
- clinical features of partial or complete intestinal obstruction, such as vomiting (especially bilious) and abdominal distension.

106. For people who have an acute onset of peri-umbilical abdominal pain but no other clinical or radiological features of distal intestinal obstruction syndrome, consider further imaging, for example with an:

- abdominal ultrasound scan, or
- abdominal CT scan.

107. Manage suspected distal intestinal obstruction syndrome in a specialist cystic fibrosis centre, with supervision from specialists who have expertise in recognising and treating the condition and its complications.

108. Offer oral or intravenous fluids to ensure adequate hydration (and rehydration if needed) for people with distal intestinal obstruction syndrome.

109. Consider diatrizoate meglumine and diatrizoate sodium solution (orally or via an enteral tube) as first-line treatment for distal intestinal obstruction syndrome.

110. If diatrizoate meglumine and diatrizoate sodium solution (Gastrografin) is not effective, consider using an iso-osmotic polyethylene glycol and electrolyte (PEG) solution (macrogols) (orally or via an enteral tube) as a second-line treatment.

111. Consider surgery as a last resort, if prolonged treatment with a PEG solution is not effective.

112. To reduce the risk of distal intestinal obstruction syndrome recurring:

- encourage people to drink plenty of fluids
- optimise pancreatic enzyme replacement therapy (see recommendations on Exocrine pancreatic insufficiency).

- consider advising regular treatment with a stool-softening agent such as lactulose or a PEG solution.

10.4 Monitoring for liver disease

Review question 1. What is the diagnostic accuracy of tests to detect / strategies to detect early and late cystic fibrosis liver disease?

Review question 2. What is the diagnostic and prognostic value of different strategies to detect cystic fibrosis liver disease and predict progression (including progression to cirrhosis and portal hypertension with (out) oesophageal varices)?

10.4.1 Introduction

The estimated prevalence of liver involvement in cystic fibrosis is reported to be between 26% and 45%. Clinical presentation with hepatomegaly and splenomegaly usually occurs within the first 10 years of age. There may be progression from focal hepatic biliary fibrosis to the development of cirrhosis and then portal hypertension with, or without, oesophageal varices complications (Debray 2011).

Diagnosis of cystic fibrosis-related liver disease is typically made by clinical examination (presence or absence of hepatosplenomegaly), biochemical tests, radiological methods (for example ultrasound scanning) and, where necessary, histological assessment (for example liver biopsy). Current UK practice uses clinical examination and biochemical liver testing to determine a baseline and to monitor progression of disease thereafter annually. Ultrasound is not usually offered on an annual basis to those without any signs of liver disease, but may be performed at intervals. Early detection of hepatic injury and fibrosis enables early treatment which may prevent further damage or even reverse very early damage.

There are currently no universally accepted definitions of liver disease (early, progressive, late) and these vary according to tests performed.

More recently, new definitions of liver disease have come into practice as a result of recommendations that are based on results from monitoring tests performed at clinical review. For example, clinical examination and routine liver function testing, with ultrasound imaging only being used if necessary. Broadly, cystic fibrosis-related liver disease is diagnosed if certain criteria are met. For example, some have suggested diagnosis based on 2 of the following conditions being met on at least 2 consecutive examinations spanning a set period (for example 3 months to 1 year):

- hepatomegaly confirmed by ultrasound,
- 2 abnormal (>upper limit of normal) serum liver enzyme levels (e.g. alanine aminotransferase, ALT; aspartate aminotransferase, AST; alkaline phosphatase, ALP, gamma-glutamyl transferase, GGT), or
- ultrasound abnormalities other than hepatomegaly (increased heterogeneous echogenicity, nodularity, irregular margins).

If liver disease has not developed by adulthood, it may be that the person will not develop it. Therefore, the committee queried the value of using ultrasound at annual review, in addition to clinical examination and biochemical liver function tests, when there was no indication of liver disease from either test.

10.4.2 Description of clinical evidence

The aim of this review was to assess the diagnostic accuracy of different diagnostic strategies to detect cystic fibrosis- related liver disease (including cirrhosis, portal

hypertension and oesophageal varices) defined by gold standard tests and to identify whether any tests are useful in predicting the progression of cystic fibrosis-related liver disease.

No “test and treat” RCTs, were available. Thus, for the diagnostic part of the review we looked for SRs of diagnostic studies, cross-sectional diagnostic studies, and case-control studies. For the prognostic question we searched for SRs of prognostic studies and cohort studies.

For full details see review protocol in Appendix D.

Eleven studies were included in this review (Fagundes 2004, Karlas 2012, Kitson 2013, Lewindon 2011, Lindblad 1999, Mueller-Abt 2008, Patriquin 1999, Rath 2012, Rath 2013, Sadler 2015, Witters 2009).

Studies were from Germany (Karlas 2012, Rath 2012, Rath 2013), Sweden (Lindblad 1999), Belgium (Witters 2009), Australia (Kitson 2013, Lewindon 2011, Mueller-Abt 2008), Canada (Patriquin 1999, Sadler 2015) and Brazil (Fagundes 2004).

With regards to study design, 7 were prospective cohorts (Fagundes 2004, Karlas 2012, Lewindon 2011, Patriquin 1999, Rath 2012, Rath 2013, Sadler 2015), 3 were retrospective cohorts (Lindblad 1999, Mueller-Abt 2008, Witters 2009) and 1 was a case control study (Kitson 2013) with population sizes ranging from 30 to 280 participants.

With regards to the population, 3 studies recruited children and young people (Lewindon 2011, Mueller-Abt 2008, Patriquin 1999), 3 studies only recruited adults (Karlas 2012, Kitson 2013, Sadler 2015) and 5 studies recruited both children and adults (Fagundes 2004, Lindblad 1999, Rath 2012, Rath 2013, Witters 2009), 1 of which reported children’s and adults’ results separately (Rath 2012).

Evidence was available for the following, used as reference standards to detect cystic fibrosis-related liver disease: clinical examination, biochemical testing, clinical examination and biochemical testing in combination, ultrasound, published cystic fibrosis-related liver disease definitions (incorporating clinical examination, biochemical testing and ultrasound), and biopsy. No evidence was available for MRI or CT scanning used as the reference standard.

Evidence was available for the following index tests: single biochemical tests (ALT, AST, GGT, and ALP), formulas using biochemical and other parameters (APRI and Forns score), ultrasound, transient elastography (FibroScan®) and clinical examination and ultrasound (in combination).

The definitions of cystic fibrosis-related liver disease varied according to the gold standard used and mostly incorporated more severe disease (cirrhosis). In a few studies, either separate data was available for or the reference standard was limited to definitions of cystic fibrosis-related liver disease (without cirrhosis), cirrhosis or portal hypertension (with or without oesophageal varices).

Diagnostic data (sensitivity, specificity, likelihood ratios) were available or calculated from information available in the full text of the report for all comparisons. Area under receiver operating characteristic curve (AUROC) data was less frequently presented in study reports.

Prognostic data for the development of cystic fibrosis-related liver disease and portal hypertension were available from 3 studies (Kitson 2013, Lewindon 2011, Woodruff 2016).

A summary of the included studies is presented in Table 158. See study selection flow chart in Appendix F, study evidence tables in Appendix G, list of excluded studies in Appendix H, forest plots in Appendix I, and full GRADE profiles in Appendix J.

10.4.3 Summary of included studies

A summary of the 11 studies included in this review is presented in Table 158

Table 158: Summary of studies

Study	Index test	Reference standard	Population	Target condition
Fagundes 2004 (Brazil) Prospective cohort study	• Williams ultrasound score: • normal ultrasound results (score = 3) • or abnormal (score > 3).	• Clinical and biochemical criteria. • Abnormal clinical examination: ○ the presence of a palpable spleen ○ and/or hepatomegaly (presence of a palpable liver more than 2.5 cm below the right costal margin of firm consistency). • Abnormal biochemistry: ○ a significant and persistent increase of at least 1.5 times the upper limit of the reference range, ○ of at least 2 of the enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP) or gamma-glutamyl transpeptidase (GGT), for a period of more than 6 months.	N=70 infants, children and young people with CF Mean age (SD): 10.9 (6.4) Participants were followed prospectively at a CF outpatient clinic at a Brazilian university and who underwent clinical, biochemical and ultrasound examinations.	• CFLD (includes cirrhosis)
Karlas 2012 (Germany) Case control study	• Transient elastography (TE): • AST/Platelets-Ratio-Index (APRI) • Forns score was calculated according to the formula: score=7.811-3.131 x platelet count (109 /l)+ 0.781 x ln GGT (UI/l) + 3.467 x ln age (years)-0.014xcholesterol (mg/dl)	• Cystic fibrosis-related liver disease: at least 2 of the following conditions present on at least 2 consecutive examinations spanning a 1-year period (Sokol 1999, Colombo 2002): ○ (1) Ultrasound confirmed hepatomegaly; ○ (2) elevated serum liver enzyme levels of ALT, AST, AP, or GGT; ○ (3) ultrasound abnormalities other than hepatomegaly (i.e., increased, heterogeneous echogenicity, nodularity, irregular	N=55 adults with CF, n=14 with CFLD • Mean age (SD): 31.9 (8.8) • Participants were prospectively investigated at presentation to the pulmonary outpatient clinic for clinical routine examinations. • Healthy probands and patients with alcoholic liver cirrhosis served as controls to	• CFLD (includes cirrhosis) • Liver cirrhosis

Study	Index test	Reference standard	Population	Target condition
		margins, splenomegaly). • Liver cirrhosis: distinct ultrasonographic signs (i.e. coarse nodularity, presence of portal hypertension and rarefication of peripheral portal veins) and clinical signs (e.g. oesophageal varices, splenomegaly)	establish test ranges	
Kitson 2013 Australia Case control study	• Transient elastography (TE): (FibroScan®) • AST/Platelets-Ratio-Index (APRI) performed at baseline	• CFLD: according to established criteria if least 2 of the following conditions on consecutive examinations spanning a one-year period were present: ○ (i) Hepatomegaly and/or splenomegaly confirmed by ultrasound, ○ (ii) abnormal serum liver enzyme levels, consisting of elevation above the upper limit of normal of 2 of the following: ALT, AST, GGT, ○ (iii) ultrasound abnormalities other than hepatomegaly (increased, heterogeneous echogenicity, nodularity, irregular margins; splenomegaly; presence of porto-systemic collateral veins; ascites).	N=50 adults with CF • 25 with CFLD, mean age (SD): 30.5 (9.3) • 25 without CFLD, mean age (SD): 34.1 (9.8) • Participants were prospectively studied at a large CF referral centre in Australia.	• CFLD (includes cirrhosis) • Portal Hypertension • Oesophageal varices
Lemaitre 2016 (France) Retrospective cohort study	• Transient Elastography: Results were expressed in kilopascal (kPa) using the Metavir scoring system • Index test: Biliary and Hepatic Magnetic Resonance Imaging	• Liver function test or ultrasound: Details not reported	N=25 adults with CF • Median age, years (range): 25 (18 to 43) • The sample included adult with CF, investigated by hepatobiliary MRI and by transient elastography for liver stiffness measurement	• CFLD

Study	Index test	Reference standard	Population	Target condition
			(LSM) between July 2009 and July 2010	
Lewindon 2011 (Australia) Prospective cohort study	• Clinical examinations: Hepatomegaly with or without splenomegaly • Serum ALT levels performed at enrolment • Ultrasound images were obtained after fasting. Briefly, liver images were recorded as nodular edge, nodular, heterogeneous, or normal echogenicity with or without splenomegaly. Normal US was defined as normal echogenicity with no splenomegaly. US evidence of PHT included a nodular liver with splenomegaly.	• Dual pass percutaneous liver biopsy with US guidance under general anaesthesia for fibrosis scoring, the Scheuer F0-F4 staging system was used (F0 =no fibrosis, F4 = cirrhosis). Only sections with at least five portal tracts were deemed adequate for assessment.	N=40 children and young people with CF • Age range: 2.38 to 18.73 years, median=10.64 years at enrolment) • Participants were attending a cystic fibrosis referral clinic with suspected cystic fibrosis liver disease defined as the following: • hepatomegaly (HM) with or without splenomegaly • a persistent (>6-month) elevation of serum alanine aminotransferase (ALT; level > 1.5 x upper limit of normal) • abnormal liver US findings (abnormal echogenicity or a nodular edge)	• F1-F4 fibrosis • F2-F4 significant fibrosis
Lindblad 1999 (Sweden) Prospective cohort study	• Ultrasonography characterized as normal or pathological (increased and/or irregular echogenicity) • Liver function test included serum activities of alanine transaminase (ALT), aspartate transaminase (AST), and g-glutamyltransferase (gGT) (with an upper reference level of ,0.8, ,0.8,	• Liver biopsy performed under general anaesthesia in patients younger than 16 years and under local anaesthesia in older patients. The biopsies were evaluated regarding fibrosis (normal; slight, enlarged portal zones; moderate, tendency towards septa formation; severe, bridging fibrosis; and cirrhosis, complete septa with regenerative noduli). Steatosis, bile duct proliferation, and inflammation were classified as absent,	N=41 children, young people and adults with CF • Median age: 19 years, range 5 to 43 years • Participants were cared for at the Stockholm CF centre and attended the centre 2 or more times between 1976 and 1993 and who received biopsy in 1989-1993.	• Moderate or severe fibrosis and cirrhosis and/or moderate to severe steatosis • Moderate or severe fibrosis and cirrhosis

Study	Index test	Reference standard	Population	Target condition
	and ,0.5 µkata/l, respectively). • Combined US and LFT	slight, moderate, or severe. A minimum of 4 portal zones were evaluated in each biopsy. • Definitions: Biochemical liver disease (BLD) was defined as elevation above the upper reference level of any serum liver enzyme included in the LFT for at least 2 consecutive years in patients 4 years of age or older. A patient was thereafter classified as BLD even if LFT results were later normalized. Clinical liver disease was defined as multilobular cirrhosis (MLC) and always included clinical (hepato) splenomegaly with oesophageal varices or signs of hypersplenism and biopsy-proven cirrhosis. All other patients were classified as having no liver disease (NLD).		
Mueller-Abt 2008 (Australia) Retrospective cohort study	• US scans obtained after a 4-hour fast in children under 2 years and a 6-hour fast in children over 2 years. There were 3 categories on the summary interpretation of findings: normal, indeterminate (suggestion of liver disease but no definite signs of cirrhosis) and cirrhosis. Increased hepatic echogenicity, heterogeneity and/or increased attenuation in the absence of nodularity of the liver surface	Percutaneous liver biopsy using ultrasound guidance. Two samples, to limit sampling error, were obtained from the right lobe, at least 6 portal tracts were available for analysis. Scheuer-Score of 0 was regarded as normal, a score of 1–2 as mild to moderate reversible periportal changes and 3–4 was assessed as definite fibrosis/cirrhosis.	N= 30 infants, children and young people with CF. • Age range 11 months to 17 years. • Participants were attending the CF clinic with evidence of 2 out of 3 of the following criteria: biochemical liver disease (persistent elevation of ALT above upper limit of normal over a period of at least 6 months), clinical hepatomegaly or hepatosplenomegaly or sonographic	• Liver disease (includes cirrhosis) (F1-F4 fibrosis score) • Cirrhosis (F3-F4 fibrosis score)

Study	Index test	Reference standard	Population	Target condition
	were classified as indeterminate. Splenomegaly as an isolated finding was also regarded as indeterminate. All patients with nodularity of the liver surface were classified as cirrhosis.		evidence of liver disease	
Patriquin 1999 (Canada) Prospective cohort study	• Liver function tests included aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyltransferase (GGT).	• US scans were obtained without sedation after a 4-hour fast in children aged 2–6 years and after an 8-hour fast in patients older than 6 years. US included a survey of the entire abdomen as well as a detailed examination of liver architecture. • US signs were interpreted as follows: hypoechogenicity with prominent portal tracks as enema, hyperechogenicity as steatosis, hyperechogenicity with increased attenuation and nodules within or at the edge of the liver as cirrhosis. Signs of portal hypertension also were sought and Doppler US used to assess presence and direction of blood flow and detection of oesophageal varices. US signs were compared with liver function	N=195 children, young people and adults with CF • Mean age: 8.5 years, range 1 to 23 years. • Participants were attending a CF clinic who underwent abdominal US and a standard set of liver function tests over 1 year.	• CFLD (includes cirrhosis)
Rath 2012 (Germany) Prospective cohort study	• Transient elastography (TE): Liver stiffness by TE was evaluated using the same FibroScan® device in all patients. Non-invasive measurements were on the right lobe of the liver	• Diagnosis of CFLD was established according to recent guidelines if least 2 of the following conditions on at least 2 consecutive examinations spanning a one-year period were present: ○ (i) Hepatomegaly (liver span >2 cm below the costal margin on the medioclavicular line)	N=70 adults with CF; • n=32 without CFLD, mean age (SD) 32.3 (9.3); • n=29 with CFLD, mean age (SD) 30.6 (8.6); • n=9 with LD and portal hypertension,	• CFLD (includes cirrhosis)

Study	Index test	Reference standard	Population	Target condition
	through the intercostal space at a depth of 25 and 65 mm from skin surface. In children below 15 kg of weight the FibroScan® S probe was used. For each patient, the stiffness value was calculated as the median of ten successful measurements. TE was considered valid if 10 successful measurements with a success rate ≥ 60% and an interquartile range ≤ 30% of the median were obtained. Results are expressed in kilopascal (kPa). Total examination time was approximately 5 minutes per patient.	confirmed by ultrasound, ○ (ii) 2 abnormal serum liver enzyme levels (ALT, AST, γGT > ULN), ○ (iii) ultrasound abnormalities other than hepatomegaly (increased, heterogeneous echogenicity, nodularity, irregular margins). • Diagnosis of PHT was based on clinical and lab data combined with sonographic or endoscopic signs of PHT.	mean age (SD) 21.4 (1.7).	
Rath 2013 (Germany) Prospective cohort study	• Alkaline phosphatase (ALP) • AST/Platelets-Ratio-Index (APRI) • Transient elastography (TE): Liver stiffness by TE was evaluated using the same FibroScan® (Echosens, Paris, France) device in all patients. Non-invasive measurements were performed on the right lobe of the liver through the intercostal space	• Diagnosis of CFLD was established according to recent guidelines if least 2 of the following conditions on at least 2 consecutive examinations spanning a 1-year period were present: ○ (i) Hepatomegaly (liver span >2 cm below the costal margin on the medioclavicular line) confirmed by ultrasound, ○ (ii) 2 abnormal serum liver enzyme levels (ALT, AST, γGT > ULN), ○ (iii) ultrasound abnormalities other than hepatomegaly (increased, heterogeneous	N=45 children, young people and adults with CF; • n=28 without CFLD; mean age (SD) 21.4 (11.8) (5 to 50 years) • and n=17 with CFLD; mean age (SD) 29 (10.8) (14 to 47) • Setting not confirmed.	• CFLD (includes cirrhosis)

Study	Index test	Reference standard	Population	Target condition
	at a depth of 25 and 65 mm from skin surface. In children below 15 kg of weight the FibroScan® S probe was used. For each patient, the stiffness value was calculated as the median of ten successful measurements. TE was considered valid if 10 successful measurements with a success rate ≥ 60% and an interquartile range ≤ 30% of the median were obtained. Results are expressed in kilopascal (kPa). Total examination time was approximately 5 minutes per patient.	echogenicity, nodularity, irregular margins).		
Sadler 2015 (Canada) Prospective cohort study	• Liver stiffness measurement by transient elastography (TE) using FibroScan® probe. • Aspartate aminotransferase to Platelets-Ratio-Index (APRI) was calculated as (AST/upper limit of normal for AST) x (100/platelets (x109/L)).	• Diagnosis of CFLD was established according to previously published criteria if least 2 of the following conditions were present: ○ (i) Hepatomegaly and/or splenomegaly confirmed by ultrasonography, ○ (ii) abnormal liver biochemistry consisting of elevated levels of any 2 of ALT, AST, or GGT, ○ (iii) ultrasound abnormalities other than hepatomegaly (increased, heterogeneous echogenicity, nodularity, irregular margins, splenomegaly presence).	N=127 adults with CF • Median age, years (interquartile range): 27 (22 to 37) • Participants were attending a CF clinic of Calgary and Southern Alberta.	• CFLD (includes cirrhosis)

Study	Index test	Reference standard	Population	Target condition
Witters 2009 (Belgium) Prospective cohort study	• Transient elastography (TE): (FibroScan®) – Liver disease was defined as a result above the age-related upper limit of normal liver stiffness • Ultrasound: Normal ultrasound results (Williams score = 3). Liver disease was defined as a Williams score of ≥ 4 (i.e. intermediate coarse to irregular liver parenchyma, liver edge nodularity and/or moderate to severe periportal fibrosis).	• The North-American cystic fibrosis foundation (CFF) consensus workgroup Definition of CFLD: the presence of either clinical or biochemical liver disease. • Clinical liver disease was defined as the presence of hepatomegaly or splenomegaly • Biochemical liver disease was defined as the elevation of 2 of these tests: Liver tests (AST, ALT, alkaline phosphatase, bilirubin and gamma-GT). All CF patients from January 1996 to July 2007 were studied and patients with persistently elevated liver tests were identified (3–6 months, 1.5 times age-dependent upper limit of normal).	N=66 children, young people and adults with CF • Mean age (SD): 13.6 (7.8) • Participants were followed up in CF clinic at a university hospital	• Clinical CFLD (includes cirrhosis) • Biochemical CFLD (includes cirrhosis) • CFF guideline defined (clinical or biochemical) CFLD (includes cirrhosis)
Woodruff 2016 (USA) Prospective cohort study	• Monitoring strategy based on the assessment of liver function tests. • Median follow-up: 7.23 years	• Not relevant (prognostic study)	N=298 children with CF identified • Mean age at diagnosis (SD): 3.8 weeks (2.4 to 5.7)	• CFLD

Abbreviations: ALT: alkaline phosphatase; AST: alanine aminotransferase; APRI: Aspartate aminotransferase to Platelets-Ratio-Index; CF: cystic fibrosis; CFF: cystic fibrosis consensus; CFLD: cystic fibrosis liver disease; cm: centimetres; GGT: gamma-glutamyl transpeptidase; LFT: liver function test; MRI: magnetic resonance; SD: standard deviation; TE: transient elastography; PHT: portal hypertension

10.4.4 Clinical evidence profile

Summary clinical evidence profile tables are not applicable to this review. Please see clinical evidence GRADE profiles in Appendix J.

10.4.5 Economic evidence

No economic evaluations of tests to detect related liver disease in people with cystic fibrosis were identified in the literature search conducted for this guideline. Full details of the search and economic article selection flow chart can be found in Appendix E and F, respectively. To aid consideration of cost-effectiveness relevant resource and cost use data are presented in Appendix K.

10.4.6 Evidence statements

10.4.6.1 Review question 1. What is the diagnostic accuracy of tests to detect/ strategies to detect early and late cystic fibrosis-related liver disease?

10.4.6.1.1 Target condition: cystic-fibrosis liver disease (includes cirrhosis)

Clinical examination (hepatomegaly, splenomegaly)

Test 1. Diagnostic accuracy of clinical liver examination (versus biopsy)

High quality evidence from 1 cohort study of 40 children with cystic fibrosis found that clinical liver examination was not useful for ruling in (no serious imprecision) or for ruling out (no serious imprecision) cystic fibrosis-related liver disease (F1-F4 fibrosis).

Sensitivity was 68 (95% CI: 61-77)* and specificity was 33 (95% CI: 10-65)*.

Liver function blood tests (AST, ALT, GGT, Alkaline phosphatase, bilirubin, albumin, platelets and clotting) and indices based on these tests (e.g. APRI, Forns score, INR ratio)

Test 2. Diagnostic accuracy of ALT, AST and GGT (versus ultrasound)

High quality evidence was available from 1 cohort study of 195 children, young people and adults with cystic fibrosis that examined the use of ALT, AST and GGT at unspecified thresholds for detecting cystic fibrosis-related liver disease found that:

- ALT was not useful for ruling in (no serious imprecision) or ruling out (no serious imprecision) cystic fibrosis-related liver disease
- AST was not useful for ruling in (serious imprecision) or ruling out (no serious imprecision) cystic fibrosis-related liver disease
- GGT was moderately useful for ruling in cystic fibrosis-related liver disease (serious imprecision), but was not useful for ruling out cystic fibrosis-related liver disease (no serious imprecision).

Sensitivities were 63.6 (95% CI: 34.4-86.0)*, 47.4 (95% CI: 33.4-60.6)* and 50.0 (95% CI: 22.0-75.1)* respectively and specificities were 79.0 (95% CI: 75.3-82.2)* and 87.9 (95% CI: 84.5-91.1)* and 90.4 (95% CI: 87.1-93.4)* respectively.

Note: Ultrasound signs were interpreted as follows: hypoechogenicity with prominent portal tracts as oedema, hyperechogenicity as steatosis, hyperechogenicity with increased attenuation and nodules within or at the edge of the liver as cirrhosis. Signs of portal hypertension also were sought and Doppler ultrasound used to assess presence and direction of blood flow and detection of oesophageal varices.

Test 3. Diagnostic accuracy of ALT, AST and GGT (versus biopsy)

Moderate quality evidence from 1 cohort study of 41 children, young people and adults with cystic fibrosis found that liver function testing (ALT, AST and GGT at thresholds of 0.8, 0.8 and 0.5 μkata respectively):

- was not useful for ruling in (no serious imprecision) or for ruling out (serious imprecision) moderate or severe fibrosis/cirrhosis with steatosis;
- was not useful for ruling in, but was very useful (no serious imprecision) for ruling out (serious imprecision) moderate or severe fibrosis/cirrhosis.

Sensitivities were 83 (95% CI: 68-94)* and 100 (95% CI: 78-100)* and specificities were 44 (95% CI: 26-58)* and 44 (95% CI: 33-44)* respectively.

Test 4. Diagnostic accuracy of ALT testing (versus biopsy)

Moderate quality evidence from 1 cohort study of 40 children and young people with cystic fibrosis found that ALT testing was not useful for ruling in (very serious imprecision) or for ruling out (no serious imprecision) cystic fibrosis-related liver disease (F1-F4 fibrosis).

Sensitivity was 30 (95% CI: 0-0.60)* and specificity was 98 (95% CI: 96-100)*.

Test 5. Diagnostic accuracy of alkaline phosphatase (ALP) (versus practice guideline cystic fibrosis-related liver disease definitions)

Moderate quality evidence from 1 cohort study of 45 children, young people and adults with cystic fibrosis found that use of ALP (age and gender specific cut-offs) was not useful for ruling in (serious imprecision) or for ruling out (serious imprecision) cystic fibrosis-related liver disease.

Sensitivity was 70.6 (95% CI: 49.5-85.5)* and specificity was 82.1 (95% CI: 69.3-91.2)*

Note: Practice guideline definitions included criteria for clinical, biochemical and ultrasound testing.

Test 6. Diagnostic accuracy of APRI (versus practice guideline cystic fibrosis-related liver disease definitions)

Low, moderate and high quality evidence from 3 cohort studies of children, young people and adults with cystic fibrosis (n=45, 55 and 122) examined the use of APRI at various thresholds to detect cystic fibrosis-related liver disease.

- APRI thresholds of 0.133 in children and adults and of 0.4 and 0.5 in adults were moderately useful for ruling in (very serious imprecision), but not useful for ruling out (no serious imprecision) cystic fibrosis-related liver disease
  - sensitivities were 47.1 (95% CI: 28.2-56.7)*, 50 (95% CI: 29-69)* and 50 (95% CI: 29-68)* and specificities were 93.1 (95% CI: 82.0-98.7)*, 92 (95% CI: 88-95)* and 94 (95% CI: 90-97)* respectively.
- An APRI threshold of 0.231 in adults was not useful for ruling in (no serious imprecision), but was moderately useful for ruling out (very serious imprecision) cystic fibrosis-related liver disease
  - sensitivity was 85.7 (95% CI: 60-97.4)* and specificity 70.7 (95% CI: 62.0-74.7)*.

Note: Practice guideline definitions included criteria for clinical, biochemical and ultrasound testing.

Test 7. Diagnostic accuracy of Forns score (versus practice guideline cystic fibrosis-related liver disease definitions)

Moderate quality evidence from 1 cohort study of 55 adults with cystic fibrosis found that use of Forns score at a threshold of 2.154 was not useful for ruling in (no serious imprecision) but was moderately useful for ruling out (very serious imprecision) cystic fibrosis-related liver disease.

Sensitivity was 92.9 (95% CI: 67.8-99.6)* and specificity was 61.0 (95% CI: 52.4-63.3)*.

Note: Practice guideline definitions included criteria for clinical, biochemical and ultrasound testing.

Imaging techniques

Test 8. Diagnostic accuracy of ultrasound (versus clinical cystic fibrosis-related liver disease definition)

Low quality evidence from 1 cohort study of 66 children, young people and adults with cystic fibrosis found that use of ultrasound at a threshold of Williams score ≥4 was not a useful test for ruling in (no serious imprecision) or for ruling out (no serious imprecision) cystic fibrosis-related liver disease.

Sensitivity was 66.7 (95% CI: 25.0-93.9)* and specificity was 66.7 (95% CI: 62.5-69.4)*.

Note: Diagnosis of cystic fibrosis-related liver disease according to the presence or absence of hepatomegaly or splenomegaly determined by clinical examination.

Test 9. Diagnostic accuracy of ultrasound (versus biochemical definition)

Low quality evidence from 1 cohort study of 66 children, young people and adults with cystic fibrosis found that use of ultrasound at a threshold of Williams score≥4 was not useful for ruling in (no serious imprecision) or ruling out (no serious imprecision) cystic fibrosis-related liver disease.

Sensitivity was 50.0 (95% CI: 14.3-85.6)* and specificity was 66.7 (95% CI: 63.1-70.2)*.

Note: Diagnosis of cystic fibrosis-related liver disease was defined as persistently elevated results (3–6 months, 1.5 times age-dependent upper limit of normal) for 2 of these liver tests: AST, ALT, alkaline phosphatase, bilirubin and gamma-GT.

Test 10. Diagnostic accuracy of ultrasound (versus clinical and or biochemical definition)

Moderate quality evidence from 1 cohort study of 70 infants, children, young people and adults with cystic fibrosis found that use that use of ultrasound at a threshold of Williams score ≥4 was moderately useful for ruling in (very serious imprecision), but not for ruling out (no serious imprecision) cystic fibrosis-related liver disease.

However moderate quality evidence from another cohort study of 66 children, young people and adults with cystic fibrosis found that use of ultrasound at a threshold of Williams score ≥4 was not useful for ruling in (no serious imprecision) and for ruling out (no serious imprecision) cystic fibrosis-related liver disease.

Sensitivities were 50.0 (95% CI: 22.0-75.1)* and 63.6 (95% CI: 33.6-87.0)* and specificities were 91.7 (95% CI: 87.0-95.8)* and 70.9 (95% CI: 64.9-75.6)* respectively.

Note: Diagnosis of cystic fibrosis-related liver disease was defined using clinical and biochemical criteria.

Test 11. Diagnostic accuracy of ultrasound (versus biopsy)

High, moderate and low quality evidence was available from 3 cohort studies of infants, children, young people and adults with cystic fibrosis (n=30, 40 and 41) that examined ultrasound imaging.

- Ultrasound imaging was not useful for ruling in (serious imprecision) or for ruling out (serious imprecision) F1-F4 fibrosis in children
  - sensitivities were 81 (95% CI: 73-89)* and 65 (95% CI: 55-74)* and specificities were 44 (95% CI: 17-73)* and 57 (95% CI: 22-87)* respectively (high quality evidence from 2 studies).

- Ultrasound imaging was not useful for ruling in (no serious imprecision) or ruling out (no serious imprecision) moderate or severe fibrosis/cirrhosis with steatosis
  - sensitivity was 70 (95% CI: 54-80)* and specificity was 78 (95% CI: 58-92)* (moderate quality evidence from 1 study).
- Ultrasound testing was not useful for ruling in (no serious imprecision), but moderately useful for ruling out (very serious imprecision) moderate or severe fibrosis/cirrhosis without steatosis
  - sensitivity was 86 (95% CI: 61-97)* and specificity was 70 (95% CI: 58-76)* (low quality evidence from 1 study).

Test 12. Diagnostic accuracy of MRI (versus liver function tests or abnormal ultrasound)

Moderate quality evidence from 1 cohort study of 23 adults with cystic fibrosis found that use of MRI to detect 1 abnormal sign was not useful to rule in (very serious imprecision) or to rule out (no serious imprecision) cystic fibrosis-related liver disease.

Sensitivity 36.4 (95% CI: 14.7-51.1) and specificity was 83.3 (95% CI: 63.5-96.8)*.

Note: details of the diagnosis of cystic fibrosis-related liver disease according to liver function tests or abnormal ultrasound were not reported in the study.

Liver stiffness measurement (transient elastography or FibroScan®)

Test 13. Diagnostic accuracy of transient elastography (versus clinical cystic fibrosis-related liver disease definition)

Low quality evidence from 1 cohort study of66 children, young people and adults with cystic fibrosis found that use of transient elastography at a threshold of 5.63kPa for <12 years and 6.50kPa for ≥12 years was moderately useful for ruling in (serious imprecision) and for ruling out (very serious imprecision) cystic fibrosis-related liver disease.

Sensitivity was 83.3 (95% CI: 38.7-99.1)* and specificity was 85.0 (95% CI: 80.5-86.6)*

Note: Diagnosis of cystic fibrosis-related liver disease according to the presence or absence of hepatomegaly or splenomegaly determined by clinical examination.

Test 14. Diagnostic accuracy of transient elastography (versus biochemical definition)

Low quality evidence from 1 cohort study of 66 children, young people and adults with cystic fibrosis found that use of transient elastography at a threshold of 5.63kPa for <12 years and 6.50kPa for ≥12 years was not a useful test for ruling in (serious imprecision) or ruling out (serious imprecision) cystic fibrosis-related liver disease.

Sensitivity was 50.0 (95% CI: 14.5-85.3)* and specificity was 83.3 (95% CI: 79.8-86.9).

Note: Diagnosis of cystic fibrosis-related liver disease was defined as persistently elevated results (3–6 months, 1.5 times age-dependent upper limit of normal) for 2 of these liver tests: AST, ALT, alkaline phosphatase, bilirubin and gamma-GT.

Test 15. Diagnostic accuracy of transient elastography (versus clinical and or biochemical definition)

Moderate quality evidence from 1 cohort study of 66 children, young people and adults with cystic fibrosis found that use of transient elastography at a threshold of 5.63kPa for <12 years and 6.50kPa for ≥12 years was moderately useful for ruling in (very serious imprecision) but not useful for ruling (serious imprecision).

Sensitivity was 63.6 (95% CI: 34.4-86.0)* and specificity was 87.3 (95% CI: 81.4-91.8)*.

Note: Diagnosis of cystic fibrosis-related liver disease was defined using clinical and biochemical criteria.

Test 16. Diagnostic accuracy of transient elastography (versus practice guideline cystic fibrosis-related liver disease definition)

High quality evidence from 1 cohort study (n=136; 75 children and 61 adults) found that use of transient elastography at a threshold of 5.5kPa was not a useful test for ruling in (serious imprecision) or ruling out (no serious imprecision) cystic fibrosis-related liver disease.

Sensitivities were 53.3 (95% CI 43.2 to 61.2) and 55.2 (95% CI 40.7 to 66.8), and specificities were 76.7 (95% CI 61.4 to 88.4) and 78.1 (95% CI 60.0 to 88.7) in children and adults respectively.

Note: Diagnosis of cystic fibrosis-related liver disease was established according to published guidelines (Debray 2011) if least 2 of the following conditions on at least 2 consecutive examinations spanning a 1-year period were present: (i) Hepatomegaly (liver span >2 cm below the costal margin on the medioclavicular line) confirmed by ultrasound, (ii) 2 abnormal serum liver enzyme levels (ALT, AST, γGT > ULN), (iii) ultrasound abnormalities other than hepatomegaly (increased, heterogeneous echogenicity, nodularity, irregular margins).

Test 17. Diagnostic accuracy of transient elastography (versus practice guideline cystic fibrosis-related liver disease definitions)

Low, moderate and high quality evidence from 3 cohort studies and 1 case control study of children, young people and adults with cystic fibrosis (n=45, 49, 127 and 50) was available that examined the use of transient elastography at various thresholds to detect cystic fibrosis-related liver disease as defined by practice guidelines.

- At a threshold of 3.7 transient elastography was not useful for ruling in (no serious imprecision) or for ruling out (very serious imprecision) cystic fibrosis-related liver disease in a population of adults
  - sensitivity was 89 (95% CI: 66-98)* and specificity was 37 (95% CI: 33-38)*.
- At a threshold of 5.3 kPa transient elastography was not useful for ruling in (serious imprecision) or for ruling out (serious imprecision) cystic fibrosis-related liver disease in a population of adults
  - sensitivity was 67 (95% CI: 43-85)* and specificity was 83 (95% CI: 79-86)*.
- At a threshold of 5.9kPa transient elastography was very useful (very serious imprecision) for ruling in but not useful for ruling out (no serious imprecision) cystic fibrosis-related liver disease in a population of adults
  - sensitivity was 42.9 (95% CI: 2s.6-49.6)* and specificity was 97.1 (95% CI: 89.0-99.8)*.
- At a threshold of 6.0 kPa, transient elastography was moderately useful (very serious imprecision) for ruling in but not useful for ruling out (no serious imprecision) cystic fibrosis-related liver disease in a population of adults
  - sensitivity was 56 (95% CI: 34-75)* and specificity was 91 (95% CI: 87-94)*.
- At a threshold of 6.3kPa, transient elastography was very useful for ruling in (very serious imprecision, but at least moderately useful) and moderately useful (serious imprecision) for ruling out cystic fibrosis-related liver disease in a population of children, young people and adults
  - sensitivity was 82.4 (95% CI: 64.2-85.3)* and specificity was 98.2 (95% CI: 87.4-100)*.

- At a threshold of 6.8kPa, transient elastography was moderately useful for ruling in (very serious imprecision) but not useful for ruling out (serious imprecision) cystic fibrosis-related liver disease in a population of adults
  - sensitivity was 76 (95% CI: 61.6-82.5)* and specificity was 92 (95% CI: 77.6-98.5)*.
- Note: Practice guideline definitions included criteria for clinical, biochemical and ultrasound testing.

Test 18. Diagnostic accuracy of transient elastography (versus liver function tests or abnormal ultrasound)

Very low quality evidence from 1 cohort study of 23 adults with cystic fibrosis found that use of transient elastography to detect F2-F4 fibrosis was not useful to rule in (serious imprecision) or to rule out (very serious imprecision) cystic fibrosis-related liver disease. Sensitivity was 75 (95% CI: 24.2-98.6)* and specificity was 84.2 (95% CI: 73.5-69.2)*.

Note: details of the diagnosis of cystic fibrosis-related liver disease according to liver function tests or abnormal ultrasound were not reported in the study.

Combination of tests

Test 19. Diagnostic accuracy of ALT, AST and GGT + ultrasound (versus biopsy)

Moderate and low quality evidence from 1 cohort study of 41 children, young people and adults with cystic fibrosis found that combined use of liver function testing (ALT, AST and GGT at thresholds of 0.8, 0.8 and 0.5 μkata/ respectively) and ultrasound imaging

- was not useful for ruling in (serious imprecision) or ruling out (no serious imprecision) moderate or severe fibrosis/cirrhosis with steatosis
  - sensitivity was 65 (95% CI: 50-76)* and specificity was 78 (95% CI: 58-92)*.
- was not useful for ruling in (serious imprecision) but were moderately useful (very serious imprecision) for ruling out in moderate or severe fibrosis/cirrhosis without steatosis
  - sensitivity was 86 (95% CI: 62-97)* and specificity was 74 (95% CI: 62-80)*.

Test 20. Diagnostic accuracy of clinical liver examination + ALT + ultrasound imaging (versus biopsy)

High and moderate quality evidence from 1 cohort study of 40 children with cystic fibrosis found that combined use of clinical liver examination, ALT testing and ultrasound imaging:

- was not useful for ruling in (serious imprecision) or for ruling out (very serious imprecision) cystic fibrosis-related liver disease (F1-F4 fibrosis)
  - sensitivity was 97 (95% CI: 85-100)* and specificity was 13 (95% CI: 4-15)*.
- was not useful for ruling in (serious imprecision) or for ruling out (very serious imprecision) cystic fibrosis-related liver disease (F2-F4 significant fibrosis)
  - sensitivity was 82 (95% CI: 62-95)* and specificity was 48 (95% CI: 33-57)*.

10.4.6.1.2 Target condition: cirrhosis only

Clinical examination (hepatomegaly, splenomegaly)

No evidence was found.

Liver function blood tests (AST, ALT, GGT, Alkaline phosphatase, bilirubin, albumin, platelets and clotting) and indices based on these tests (e.g. APRI, Forns score, INR ratio)

Test 1. Diagnostic accuracy of APRI (versus clinical examination + ultrasound)

Low quality evidence from 1 cohort study of 14 adults with cystic fibrosis and cystic fibrosis-related liver disease found that APRI at a threshold of 0.334 was moderately useful for ruling in (very serious imprecision) and moderately useful for ruling out (very serious imprecision) cirrhosis.

Sensitivity was 83.3.7 (95% CI: 45.0-98.5) and specificity was 87.5 (95% CI: 58.8-98.9).

Note: Diagnosis of cystic fibrosis-related liver disease (Sokol 1999, Colombo 2002) if at least 2 of the following conditions present on at least 2 consecutive examinations spanning a 1-year period: (1) Ultrasound confirmed hepatomegaly;(2) elevated serum liver enzyme levels of ALT, AST, AP, or GGT;(3) ultrasound abnormalities other than hepatomegaly (increased, heterogeneous echogenicity, nodularity, irregular margins, splenomegaly). Liver cirrhosis: distinct ultrasonographic signs (coarse nodularity, presence of portal hypertension and rarefication of peripheral portal veins) and clinical signs (for example oesophageal varices, splenomegaly).

Test 2. Diagnostic accuracy of Forns score (versus clinical examination + ultrasound)

Low quality evidence from 1 cohort study of 14 adults with cystic fibrosis and cystic fibrosis-related liver disease found that Forns score at a threshold of 4.059 was very useful for ruling in (very serious imprecision) and not useful for ruling out (no serious imprecision) cirrhosis.

Sensitivity was 66.7 (95% CI: 30.1-75.0) and specificity was 94.1 (95% CI: 68.3-100).

Note: Diagnosis of cystic fibrosis-related liver disease (Sokol 1999, Colombo 2002) if at least 2 of the following conditions present on at least 2 consecutive examinations spanning a 1-year period: (1) Ultrasound confirmed hepatomegaly;(2) elevated serum liver enzyme levels of ALT, AST, AP, or GGT;(3) ultrasound abnormalities other than hepatomegaly (increased, heterogeneous echogenicity, nodularity, irregular margins, splenomegaly). Liver cirrhosis: distinct ultrasonographic signs (coarse nodularity, presence of portal hypertension and rarefication of peripheral portal veins) and clinical signs (for example oesophageal varices, splenomegaly).

Imaging techniques

Test 3. Diagnostic accuracy of ultrasound (versus biopsy)

Moderate quality evidence from 1 cohort study of 30 infants, children and young people with cystic fibrosis found that ultrasound was a moderately useful test to rule in (very serious imprecision) but not useful to rule out (no serious imprecision) fibrosis.

Sensitivity was 0.57 (95% CI: 0.36-0.64)* and specificity was 0.94 (95% CI: 0.75-1.00)*.

Liver stiffness measurement (transient elastography or FibroScan®)

Test 4. Diagnostic accuracy of transient elastography (versus clinical examination + ultrasound)

Low quality evidence from 1 cohort study of 14 adults with cystic fibrosis and cystic fibrosis-related liver disease found that transient elastography at a threshold of 4.4kPa was not

useful to rule in (serious imprecision), but was very useful to rule out (very serious imprecision) cirrhosis.

Sensitivity was 92.3 (95% CI: 56.2-100)* and specificity was 75 (95% CI: 45.7-81.2)*.

Note: Diagnosis of cystic fibrosis-related liver disease (Sokol 1999, Colombo 2002) if at least 2 of the following conditions present on at least 2 consecutive examinations spanning a 1-year period: (1) Ultrasound confirmed hepatomegaly;(2) elevated serum liver enzyme levels of ALT, AST, AP, or GGT;(3) ultrasound abnormalities other than hepatomegaly (increased, heterogeneous echogenicity, nodularity, irregular margins, splenomegaly). Liver cirrhosis: distinct ultrasonographic signs (coarse nodularity, presence of portal hypertension and rarefication of peripheral portal veins) and clinical signs (for example oesophageal varices, splenomegaly).

Combination of tests

No evidence was found.

10.4.6.2 Target condition: portal hypertension

Clinical examination (hepatomegaly, splenomegaly)

No evidence was found.

Liver function blood tests (AST, ALT, GGT, Alkaline phosphatase, bilirubin, albumin, platelets and clotting) and indices based on these tests (e.g. APRI, Forns score, INR ratio)

Test 1. Diagnostic accuracy of APRI (versus clinical examination)

Low quality evidence was available from 1 case control study of 50 adults with cystic fibrosis (25 with cystic fibrosis-related liver disease and 25 without cystic fibrosis-related liver disease) found that APRI at a threshold of 0.49 was very useful for ruling in (very serious imprecision) and moderately useful for ruling out (very serious imprecision) portal hypertension in the whole adult population and in those with cystic fibrosis-related liver disease.

Sensitivities were 87.5 (95% CI: 52.0-99.3)* and 87.5 (95% CI: 54.8-98.9)* respectively and specificities were 92.9 (95% CI: 86.1-95.1)*and 94.1 (95% CI: 78.7-99.5)*respectively.

Note: Diagnosis of cystic fibrosis-related liver disease (Sokol 1999, Colombo 2002) if at least 2 of the following conditions present on at least 2 consecutive examinations spanning a 1-year period: (1) Ultrasound confirmed hepatomegaly;(2) elevated serum liver enzyme levels of ALT, AST, AP, or GGT;(3) ultrasound abnormalities other than hepatomegaly (increased, heterogeneous echogenicity, nodularity, irregular margins, splenomegaly). Liver cirrhosis: distinct ultrasonographic signs (coarse nodularity, presence of portal hypertension and rarefication of peripheral portal veins) and clinical signs (for example oesophageal varices, splenomegaly). Portal hypertension: platelet count <140x109/L, splenomegaly, presence of porto-systemic collateral veins, portal diameter >13mm, or ascites.

Test 2. Diagnostic accuracy of Forns score (versus clinical examination)

Low quality evidence was available from 1 case control study of 50 adults with cystic fibrosis (25 with cystic fibrosis-related liver disease and 25 without cystic fibrosis-related liver disease) found that Forns score at a threshold of 0.68 was moderately useful for ruling in (serious imprecision) and moderately useful for ruling out (very serious imprecision) portal

hypertension in the whole adult population and in those with cystic fibrosis-related liver disease.

Sensitivities were 87.5 (95% CI: 53.2-99.3)*and 87.5 (95% CI: 50.7-99.3)* respectively and specificities were 82.4 (95% CI: 66.2-87.9)*and 85.7 (95% CI: 78.7-88.0)* respectively.

Note: Diagnosis of cystic fibrosis-related liver disease (Sokol 1999, Colombo 2002) if at least 2 of the following conditions present on at least 2 consecutive examinations spanning a 1-year period: (1) Ultrasound confirmed hepatomegaly;(2) elevated serum liver enzyme levels of ALT, AST, AP, or GGT;(3) ultrasound abnormalities other than hepatomegaly (increased, heterogeneous echogenicity, nodularity, irregular margins, splenomegaly). Liver cirrhosis: distinct ultrasonographic signs (coarse nodularity, presence of portal hypertension and rarefication of peripheral portal veins) and clinical signs (for example oesophageal varices, splenomegaly). Portal hypertension: platelet count <140x109/L, splenomegaly, presence of porto-systemic collateral veins, portal diameter >13mm, or ascites.

Imaging techniques

No evidence was found.

Liver stiffness measurement (transient elastography or FibroScan®)

Test 3. Diagnostic accuracy of transient elastography (versus clinical examination)

Low quality evidence was available from 1 case control study of 50 adults with cystic fibrosis (25 with cystic fibrosis-related liver disease and 25 without cystic fibrosis-related liver disease) found that transient elastography at a threshold of 8.9kPa was moderately useful (very serious imprecision) for ruling in portal hypertension in the whole adult population but was not useful (serious imprecision) in those with cystic fibrosis-related liver disease. This threshold was moderately useful to rule out (very serious imprecision) portal hypertension in the whole adult population and in those with cystic fibrosis-related liver disease.

Sensitivities were 87.5 (95% CI: 51.4-99.3)*and 87.5 (95% CI: 52.9-99.3)* respectively and specificities were 90.5 (95% CI: 83.6-92.7)* and 76.5 (95% CI: 60.2-82.0)* respectively.

Note: Diagnosis of cystic fibrosis-related liver disease (Sokol 1999, Colombo 2002) if at least 2 of the following conditions present on at least 2 consecutive examinations spanning a 1-year period: (1) Ultrasound confirmed hepatomegaly;(2) elevated serum liver enzyme levels of ALT, AST, AP, or GGT;(3) ultrasound abnormalities other than hepatomegaly (increased, heterogeneous echogenicity, nodularity, irregular margins, splenomegaly). Liver cirrhosis: distinct ultrasonographic signs (coarse nodularity, presence of portal hypertension and rarefication of peripheral portal veins) and clinical signs (for example oesophageal varices, splenomegaly). Portal hypertension: platelet count <140x109/L, splenomegaly, presence of porto-systemic collateral veins, portal diameter >13mm, or ascites.

Test 4. Diagnostic accuracy of transient elastography (versus biochemical and imaging)

High quality evidence was available from 1 cohort study of 70 adults with cystic fibrosis found that transient elastography at a threshold of 11.5kPa was very useful for ruling in (serious imprecision, but at least moderately useful) but not for ruling out (no serious imprecision) portal hypertension.

Sensitivity was 66.7 (95% CI: 36.2-77.2)* and specificity was 98.4 (95% CI: 93.9-99.9)*.

Note: Diagnosis of cystic fibrosis-related liver disease was established according to published guidelines (Debray 2011) if least 2 of the following conditions on at least 2 consecutive examinations spanning a 1-year period were present: (i) Hepatomegaly (liver

span >2 cm below the costal margin on the medioclavicular line) confirmed by ultrasound, (ii) 2 abnormal serum liver enzyme levels (ALT, AST, γGT > ULN), (iii) ultrasound abnormalities other than hepatomegaly (increased, heterogeneous echogenicity, nodularity, irregular margins). Diagnosis of portal hypertension was based on clinical and lab data combined with sonographic or endoscopic signs of portal hypertension (defined splenomegaly, increased portal vein pressure in duplex Doppler sonography, platelet count 150,000/mm3, oesophageal varices or other signs of portal hypertension on oesophagogastroduodenoscopy.

Combination of tests

No evidence was found.

10.4.6.2.1 Target condition: oesophageal varices

Clinical examination (hepatomegaly, splenomegaly)

No evidence was found.

Liver function blood tests (AST, ALT, GGT, Alkaline phosphatase, bilirubin, albumin, platelets and clotting) and indices based on these tests (e.g. APRI, Forns score, INR ratio)

Test 1. Diagnostic accuracy of APRI (versus published definition)

Low quality evidence was available from 1 case control study of 23 adults with cystic fibrosis (13 with cystic fibrosis-related liver disease, and 10 without cystic fibrosis-related liver disease) found that APRI at a threshold of 0.49 was very useful for ruling in (very serious imprecision) and very useful for ruling out (very serious imprecision) oesophageal varices in the whole adult population and in those with cystic fibrosis-related liver disease.

Sensitivities were 100 (95% CI: 60.0-100)* and 100 (95% CI: 62.9-100)* respectively and specificities were 94.1(95% CI: 80.0-94.1)* and 93.3(95% CI: 63.7-93.3)* respectively.

Test 2. Diagnostic accuracy of Forns score (versus published definition)

Very low quality evidence was available from 1 case control study of 23 adults with cystic fibrosis (13 with cystic fibrosis-related liver disease, and 10 without cystic fibrosis-related liver disease) found that Forns score at a threshold of 0.68 was moderately useful for ruling in (serious imprecision) and very useful for ruling out (very serious imprecision) oesophageal varices in the whole adults population and in those with cystic fibrosis-related liver disease.

Sensitivities were 100 (95% CI: 62.9-100)* and 100 (95% CI: 58.9-100)* respectively and specificities were 85.7 (95% CI: 53.9-85.7)* and 88.2 (95% CI: 73.7-88.2)* respectively.

Imaging techniques

No evidence was found.

Liver stiffness measurement (transient elastography or FibroScan®)

Test 3. Diagnostic accuracy of transient elastography (versus published definition)

Very low quality evidence was available from 1 case control study of 23 adults with cystic fibrosis (13 with cystic fibrosis-related liver disease, and 10 without cystic fibrosis-related liver disease) found that transient elastography at a threshold of 8.9kPa was not useful to rule in

(no serious imprecision), but was very useful to rule out cirrhosis (very serious imprecision) oesophageal varices in adults.

Sensitivity was 100 (95% CI: 57.8-100)* and specificity was 76.5 (95% CI: 61.6-76.5)*.

Combination of tests

No evidence was found.

10.4.6.3 Review question 2. What is the diagnostic and prognostic value of different strategies to detect cystic fibrosis-related liver disease and predict progression (including progression to cirrhosis and portal hypertension without oesophageal varices)?

10.4.6.3.1 Strategy 1. Clinical examination (hepatomegaly, splenomegaly)

Prognosis of liver disease

No evidence was identified.

Prognosis of cirrhosis

No evidence was identified.

Prognosis of portal hypertension

No evidence was identified.

10.4.6.3.2 Strategy 2. Liver function blood tests (AST, ALT, GGT, Alkaline phosphatase, bilirubin, albumin, platelets and clotting) and indices based on these tests (e.g. APRI, Forns score, INR ratio)

Prognosis of liver disease

High quality evidence from 1 prospective cohort study of 298 children with cystic fibrosis described a significant association between:

- an elevated AST ≥ 1.5 ULN
- an elevated GGTP ≥ 1.5 ULN

and the risk of developing cystic fibrosis-related liver disease at a median of 7 years follow-up.

However, no significant association was described for the following:

- an elevated AST ≥ 2.0 ULN
- an elevated ALT ≥ 1.5 ULN
- an elevated ALT ≥ 2.0 ULN
- an elevated GGTP ≥ 2.0 ULN.

Prognosis of cirrhosis

No evidence was identified.

Prognosis of portal hypertension

No evidence was identified.

10.4.6.3.3 Strategy 3. Imaging techniques

Prognosis of liver disease

No evidence was identified.

Prognosis of cirrhosis

No evidence was identified.

Prognosis of portal hypertension

No evidence was identified.

10.4.6.3.4 Strategy 4. Liver stiffness measurement - transient elastography (FibroScan®)

Prognosis of liver disease

No evidence was identified.

Prognosis of cirrhosis

No evidence was identified.

Prognosis of portal hypertension

No evidence was identified.

10.4.6.3.5 Strategy 5. Combination of different strategies

Prognosis of liver disease

Combination of transient elastography and biopsy

Low quality evidence from 1 case control study of 50 adults with cystic fibrosis set in a cystic fibrosis referral centre described a significant association between increasing liver stiffness and increasing risk of developing cystic fibrosis-related liver disease (adjOR: 2.74 (95% CI 1.53-4.89, p=0.001).

Prognosis of cirrhosis

No evidence was identified

Prognosis of portal hypertension

Combination of transient elastography and biopsy

High quality evidence from 1 cohort study of 40 children and young people with cystic fibrosis set in a cystic fibrosis clinic in a city hospital described a significant association between increasing fibrosis stage on biopsy and increasing risk of developing portal hypertension in adults from birth (adjHR: 3.9 (p<0.001, no 95% CI given) and from the time of biopsy (adjHR: 3.4 (p<0.002, no 95% CI given).

10.4.6.4 Economic evidence statements

No evidence on cost-effectiveness in people with cystic fibrosis was available for this review.

10.4.7 Evidence to recommendations

10.4.7.1 Relative value placed on the outcomes considered

The aim of this review was to assess the accuracy of different diagnostic strategies to detect cystic fibrosis-related liver disease (including cirrhosis, portal hypertension and oesophageal varices) defined by gold standard tests. Additionally, the aim was to identify whether any tests are useful in predicting the progression of cystic fibrosis-related liver disease.

As sensitivity and specificity reflect patient outcomes these were considered critical outcomes for this review. Consequences for people with cystic fibrosis following diagnosis were considered by the committee. Likelihood ratios were considered to be critical diagnostic outcomes because they provide information about a test's usefulness in assisting the healthcare professional to make a diagnosis. AUROC diagnostic data, which inform the best thresholds for defining disease, were regarded as important but not critical to the review.

Sensitivity was used to evaluate imprecision for the detection of cystic fibrosis-related liver disease, including cirrhosis. Early accurate identification of disease might be important because there was a possibility that early use of ursodeoxycholic acid treatment might prevent liver disease progression. Specificity was used to evaluate imprecision for the detection of portal hypertension or oesophageal varices. This was because accurate identification of those without disease would avoid unnecessary referral to specialist hepatology centres and unnecessary investigation for this complication of advances cystic fibrosis-related liver disease.

Adjusted hazard ratios (adjHRs) and odds ratios (ORs) were regarded as critical prognostic outcomes for assessing the risk or probability of developing clinically significant liver disease (cirrhosis, portal hypertension, oesophageal varices) in the future based on current available information. Estimates that were not adjusted for confounders were excluded from the review.

10.4.7.2 Consideration of clinical benefits and harms

The committee agreed that their priority was early detection and treatment of liver disease in people with cystic fibrosis. Early detection may prevent further damage and, in some case, may be reversible. They agreed that irreversible liver disease would be under liver specialist management and was out with the scope of this guideline.

The committee discussed the importance of reducing the likelihood of a false negative diagnosis which could result in the withholding of potentially effective ursodeoxycholic acid treatment. The committee agreed that the impact of a false negative diagnosis would be mitigated by the slow progression of the disease and that the subsequent annual review would provide a further opportunity for identification. They noted that a false positive result might lead to unnecessary treatment and have a negative psychological impact.

It was noted that, while neonates with cystic fibrosis can demonstrate transient liver dysfunction (manifested by a temporary derangement of liver function tests), any perceived harm of starting unnecessary treatment is likely to be offset by the benefit of preventing irreversible liver damage.

The committee discussed the relative benefits and harms associated with the different diagnostic tests. Although the gold standard test for identification of liver pathology in cystic fibrosis is histological examination of biopsy samples, this is rarely performed in practice as it is invasive, may miss focal lesions and has associated risks for example with respect to general anaesthesia or infection. CT scanning and MRI scanning are also used as gold standards because of the high definition images that are obtained. But the evidence review found no evidence for CT or MRI scanning as the reference standard. The committee noted that although these investigations are not invasive, they are expensive and not routinely

performed. The committee noted that there would be exposure to radiation with CT scans, which the patient may receive for other systemic investigations. Overall, the committee did not find evidence to support the use of liver biopsy, MRI and CT scans for the detection of liver disease in people with cystic fibrosis and did not make recommendations regarding their use.

The committee considered that interpretation of ultrasound images could be subjective in some respects. However, transient elastography produces an objective score that might be more reliable in detecting liver disease. The committee noted that unlike transient elastography, which uses sound waves to estimate liver stiffness, images from ultrasound provide information of the staging of disease progression occurring in the liver including portal hypertension when Doppler is used. Instead of an image, FibroScan® produces sound waves that limit the results that can be interpreted. Overall, the committee agreed there was little evidence to support the use of FibroScan® for early stage detection of liver disease and agreed that, because treatment with ursodeoxycholic acid would have already been initiated, the value of adding this test to a diagnostic regimen was diminished.

The development of new liver disease after late adolescence is very unusual. Therefore, the committee agreed that routine repeat ultrasounds may not be necessary in adults with previous normal scans. The value of annual review in adults is more to monitor the progression of liver disease rather than detect new liver disease.

Children with persistently elevated liver function tests or significant abnormalities on the ultrasound of liver and spleen need to be referred to a specialist paediatric liver unit. In children with cystic fibrosis the objective of monitoring would be to detect early evidence of liver disease, to look for evidence of disease progression and progression to chronic liver disease and its complications including portal hypertension. Clinical examination is routinely performed when people with cystic fibrosis attend for clinic appointments. Clinical examination would be unlikely to detect early disease but progression might reveal important signs such as hepatosplenomegaly. The committee, therefore, recommended that a clinical assessment for evidence of liver disease should be conducted annually for people with cystic fibrosis. The committee noted that some centres include an ultrasound scan at this clinical assessment, However, the evidence did not support specific recommendations on routine ultrasound screening. The committee agreed that decisions on the tests to be included at clinical assessment should be made at individual centres using clinical judgement.

It is currently common practice to perform blood test investigations to look for evidence of liver disease. The committee recommended that blood liver function tests should be performed in people with cystic fibrosis every year.

The committee recognised that ultrasound can detect evidence of liver disease, for example changes in liver echogenicity as well as advanced changes suggestive of portal hypertension. It can also detect the presence of gallstones which sometimes occur in cystic fibrosis. Transient elastography does not reveal these specific changes although it can detect increased liver stiffness suggestive of liver fibrosis and progressive liver disease. Ultrasound scanning is commonly used to monitor cystic fibrosis-related liver disease. The committee agreed that this may not be necessary if there was no evidence of liver disease, but that a liver ultrasound scan should be performed if the blood liver function tests were abnormal.

FibroScan® gives measurement of liver stiffness. If liver stiffness is present, the person is usually referred to a specialist liver service. The lay members on the committee pointed out that from a patient perspective, FibroScan® is very quick and easy to do and may not require further referral or referral time wait. However, the committee felt the added value of FibroScan® was unclear and it was unclear what decisions should follow an abnormal FibroScan® result.

10.4.7.3 Consideration of economic benefits and harms

The economic harms associated with an incorrect diagnosis are much smaller for early stage than late stage liver disease. If the majority of people with cystic fibrosis are incorrectly diagnosed as not having liver disease (false negatives), they are likely to be picked up at their next annual review. The question arises as to whether additional monitoring between the annual reviews is cost-effective. On the other hand, the committee noted the cost of monitoring for liver disease would be relatively insignificant when compared with the downstream costs associated with liver cirrhosis and subsequent portal hypertension that could require management with a liver transplant. However, the committee agreed such cases would be rare and concluded that more frequent assessments would not be a cost-effective use of resources.

The committee noted that if abnormal liver function blood tests are the first indication of liver disease, there are potential cost savings to the NHS if those tests can replace ultrasound scans at the annual review. This saving is particularly the case in adults who are unlikely to develop liver disease without prior suspicion. Following this, the committee agreed that a recommendation in favour of liver function blood tests as the first assessment was warranted.

However, the committee agreed that the results from an ultrasound scan could lead to a change in the management strategy when, for example, cirrhosis and portal hypertension (with Doppler) are detected. Given that an ultrasound can add additional information to an abnormal liver function blood test, a recommendation in that subgroup was considered as a cost-effective use of ultrasound scans.

10.4.7.4 Quality of evidence

Most of the evidence was derived from cohort studies. Outcomes presented within these studies were often downgraded to moderate or low for serious or very serious imprecision of sensitivity or specificity estimates. Evidence for detection of portal hypertension was largely derived from a single included case control study and was low quality at best and downgraded to very low quality for imprecision of specificity for some outcomes. The settings in cystic fibrosis or liver clinics were similar in all the studies.

The committee were concerned that the included studies were heterogeneous in terms of their population and the reference standards used. The committee noted that a small body of evidence was included overall and that the studies provided no evidence regarding early cystic fibrosis-related liver disease as specified in the review question. The studies provided evidence for cystic fibrosis-related liver disease which included those with cirrhosis. Some studies included those with clinically significant liver disease states (portal hypertension with or without oesophageal varices), although this was not always specified clearly. There was also some evidence that related to cirrhosis alone and to portal hypertension with or without oesophageal varices. However no studies with participants with early disease were retrieved. Although the point estimates for likelihood ratios for several comparisons indicated that the index test would be moderately or very useful for ruling in or ruling out disease, the 95% CIs for these point estimates were mostly wide and there was uncertainty as to whether tests would be useful at all. Two exceptions were:

- High quality evidence from 1 cohort study of children and adults found that transient elastography at a threshold of 6.3kPa was at least moderately useful to rule in cystic fibrosis-related liver disease. The definition of cystic fibrosis-related liver disease was based on practice guidelines requiring biochemical and ultrasound testing.
- A second cohort study provided high quality evidence that transient elastography at a threshold of 11.5kPa was at least moderately useful to rule in portal hypertension.

There was no evidence that examined the use of MRI or CT scanning as reference tests or evidence that examined the use of ultrasound in addition to clinical and biochemical testing in adults with no history of cystic fibrosis-related liver disease.

There were very little data available regarding tests that were useful to predict the development of clinically significant liver disease. One study provided low quality evidence of an association between increasing liver stiffness detected by transient elastography and the probability of developing cystic fibrosis-related liver disease in adulthood. A second study provided high quality evidence of an association between increasing fibrosis detected by biopsy and the later development of portal hypertension. The paucity of prognostic outcome data did not permit determination of a “best” reference standard from the evidence review. As such, liver disease was defined in accordance with each reference standard.

10.4.7.5 Other considerations

No equality issues were identified by the committee for this review question.

The committee discussed the need for a research recommendation in this topic. They noted FibroScan® gives measurement of liver stiffness. This can be useful to select who should be referred for further specialist service. From the patient perspective, FibroScan® is very quick and easy to do and may not require further referral or referral time wait. Based on this, the committee agreed it would be important to assess the added value of performing FibroScan® in people with cystic fibrosis, as good quality evidence is lacking for this population. However, the committee agreed this area was not a priority overall for a research recommendation.

10.4.7.6 Key conclusions

The committee chose not to make a recommendation regarding performance of clinical examination at other appointments for monitoring leaving this to clinical judgement.

The committee agreed that generally it was good practice to repeat liver function tests that were abnormal to confirm their accuracy, although this would depend on the clinical context. Therefore, they did not make a recommendation about this as this is part of routine clinical practice and judgement.

The committee decided that if there is evidence of chronic progressive liver disease based on clinical assessment, liver function tests or the findings of an ultrasound scan the person should be referred to a liver specialist.

Alternatively, if investigations for liver disease (such as a clinical examination, liver function tests, ultrasound imaging or FibroScan®) are persistently normal, then the cessation of treatment with ursodeoxycholic acid should be considered. Monitoring for future liver damage should continue in line with the annual monitoring schedule.

10.4.8 Recommendations

113. Perform a clinical assessment and liver function blood tests at the annual review for people with cystic fibrosis.

114. Refer people with cystic fibrosis to a liver specialist if they have any of the following:

- chronic progressive liver disease, based on clinical assessment, liver function blood tests or the findings on a liver ultrasound scan
- liver failure, based on clinical assessment and liver function tests

- portal hypertension, haematemesis, splenomegaly or findings on a liver ultrasound scan.

10.5 Ursodeoxycholic acid

Review question: What is the effectiveness of ursodeoxycholic acid for preventing liver disease progression in people with cystic fibrosis?

10.5.1 Introduction

People with cystic fibrosis can develop cystic fibrosis related liver disease (CFRLD) as a complication of their disease. Monitoring for the early detection of CFRLD is therefore part of the overall routine care for all people with cystic fibrosis. CFRLD is a common complication in cystic fibrosis, with clinical presentation of hepatomegaly or splenomegaly usually around 10 years of age (see Complications review). The early detection and monitoring of CFRLD is therefore important in order to initiate and monitor potentially beneficial treatments.

Ursodeoxycholic acid (UDCA) is a commonly prescribed drug in people with cystic fibrosis. It is a bile acid analogue which may act to improve biliary flow in people with CFRLD. The current practice and indications for prescribing this drug varies widely. Although UDCA is an inexpensive and well tolerated drug, it represents an additional treatment burden for people with cystic fibrosis. It is within this context that this review of effectiveness has been conducted.

10.5.2 Description of clinical evidence

The objective of this review was to assess the clinical and cost effectiveness of UDCA for preventing liver disease progression in people with cystic fibrosis.

We looked for systematic reviews of RCTs including cross-over trials. Comparative cohort studies were not considered for inclusion, as enough evidence was retrieved from RCTs.

For full details see review protocol in Appendix D.

One Cochrane systematic review was identified for this review question (Cheng 2014) which included evidence from 3 RCTs (Colombo 1996, Merli 1994 and O'Brien 1992). Where possible, data and risk of bias assessment were extracted directly from the Cochrane systematic reviews. Individual studies were retrieved for completeness and accuracy, and were also checked for additional outcomes of interest.

All the RCTs included had either 6 or 12 months follow-up. No RCTs from the time of publication of the Cochrane systematic review and this review where found.

One RCT had cross-over study design (Merli 1994), and was conducted with 51 participants allocated to UDCA for 6 months, a wash out period of 1 month and then placebo for 6 months.

The trials were conducted in Italy and Ireland, and the population ranged from 12 to 55 participants. All the trials included children, young people and adults with cystic fibrosis. Two of the trials included people with liver disease (Colombo 1996, O'Brian 1992), and 1 included people with and without liver disease (Merli 1994).

Where change in hepatocellular enzyme or bilirubin was not reported in the RCT, the final value of the enzyme or bilirubin was reported.

A summary of the included studies is presented in Table 159. See also study selection flow chart in Appendix F, study evidence tables in Appendix G, list of excluded studies in Appendix H, forest plots in Appendix I, and full GRADE profiles in Appendix J.

10.5.3 Summary of included studies

A summary of the studies that were included in this review are presented in Table 159.

Table 159: Summary included studies

Study	Intervention/Comparison	Population	Outcomes	Comments
Cochrane systematic reviews				
Cheng 2014 Cochrane systematic review	Comparison: UDCA vs placebo (Colombo 1996, Merli 1994, O'Brien 1992)	People with CF diagnosed by sweat test and clinical symptoms.	• Lack of normalisation of liver enzymes (ALT, AST and GGT)	
Primary studies included in the SR				
Colombo 1996 (Italy) RCT	UDCA • 6 months • at a daily dose of 1 to 3 300 mg capsules Placebo	N=55 children, young people and adults with CF and chronic liver disease with persistent alterations of serum liver enzymes. Median age (range): 13.8 years (4 to 22 years)	• Percentage change in hepatocellular enzymes: ALT, AST and GGT. • Liver failure • Liver transplantation	
Merli 1994 (Italy) Cross-over trial	UDCA • dose of 12 mg/kg per day Placebo	N=51 children, young people and adults with CF. Median age (range): 14 years (8 to 32) Participants with CFRLD and no CFRLD included.	• Change in hepatocellular enzymes (AST, ALT, GGT) • No development of liver disease	
O'Brien 1992 (Ireland) RCT	UDCA • 20 mg/kg per day No treatment	N=12 children, young people and adults with CF and liver disease based on hepatomegaly and/ or splenomegaly. Median age (range): 17 (12 to 20) in the intervention group; 17.5 (14 to 25 in the control group)	• Change in hepatocellular enzymes (AST, ALT, GGT) • Final bilirubin value	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CF: cystic fibrosis; GGT, gammaglutamyl transferase; mg/ kg: milligrams per kilogram; OR: odds ratio; SR: systematic review; UDCA: ursodeoxycholic acid

10.5.4 Clinical evidence profile

The summary clinical evidence profiles for this review question (UDCA) are presented in, Table 160.

Table 160: Summary clinical evidence profile: Comparison 1. UDCA versus Placebo or control

Comparison 1. UDCA versus Placebo or control						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo/control	UDCA				
Lack of normalisation of AST Follow-up: 6 months	Study population		RR 1.51 (0.83 to 2.78)	14 (Merli 1994, O'Brien 1992)[1]	⊕⊕⊕⊖ moderate[2]	
	625 per 1000	944 per 1000 (519 to 1000)				
	Moderate					
	750 per 1000	1000 per 1000 (622 to 1000)				
Lack of normalisation of ALT Follow-up: 6 months	Study population		RR 0.69 (0.27 to 1.74)	12 (Merli 1994, O'Brien 1992)1	⊕⊕⊕⊖ moderate[2]	
	750 per 1000	518 per 1000 (203 to 1000)				
	Moderate					
	833 per 1000	575 per 1000 (225 to 1000)				
Lack of normalisation of GGT Follow-up: 6 months	Study population		RR 0.6 (0.16 to 2.29)	10 (Merli 1994, O'Brien 1992)1	⊕⊕⊖⊖ low[3]	
	500 per 1000	300 per 1000 (80 to 1000)				
	Moderate					
	333 per 1000	200 per 1000 (53 to 763)				
Final bilirubin value (umol/l) Follow-up: 6 months	The mean final bilirubin value in the control groups was 9.2	The mean final bilirubin value in the UDCA groups was 4 higher (3.72 lower to 11.72 higher)		12 (O'Brien 1992)	⊕⊕⊖⊖ low[3]	
Percentage change in AST Follow-up: 12 months	The mean percentage change in ALT in the control groups was -17 %	The mean percentage change in ALT in the UDCA groups was 13 lower (29.35 lower to 3.35 higher)		27 (Colombo 1996)	⊕⊕⊖⊖ low[2,7]	
Percentage change in ALT Follow-up: 12 months	The mean percentage change in ALT in the control groups was -17 %	The mean percentage change in ALT in the UDCA groups was 13 lower (29.35 lower to 3.35 higher)		27 (Colombo 1996)	⊕⊕⊖⊖ low[2,4]	

Comparison 1. UDCA versus Placebo or control						
Percentage change in GGT Follow-up: 12 months	The mean percentage change in GGT in the control groups was -15 %	The mean percentage change in GGT in the UDCA groups was 11 lower (36.74 lower to 14.74 higher)		27 (Colombo 1996)	⊕⊕⊖⊖ low[2,4]	
No development of liver disease Follow-up: 6 months	None of the participants developed liver disease.	None of the participants developed liver disease.	Not calculable5	11 (Merli 1994)1	⊕⊕⊕⊕ high	
Liver failure (jaundice) Follow-up: 12 months	1/15	0/13	Not calculable6	28 (Colombo 1996)	⊕⊕⊕⊖ moderate [4]	
Liver transplantation Follow-up: 12 months	-	1 person in the UDCA group was withdrawn to receive transplantation	Not applicable	28 (Colombo 1996)	⊕⊕⊕⊖ moderate [4]	Outcome reported narratively
**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).* *Abbreviations: CFLD: ALT: alanine aminotransferase; AST: aminotransferase; cystic fibrosis liver disease; CI: confidence interval; GGT: gamma glutamyltransferase; MD: mean difference; RR: risk ratio; UDCA: ursodeoxycholic acid*						

1 Merli (1994) used a cross-over study design
2 The quality of the evidence was downgraded by 1 because the 95% CI crosses 1 default MID.
3 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs.
4 The quality of the evidence was downgraded by 1 due to lack of allocation concealment reporting.
5 RR not calculable - no development of liver disease in 11/11 participants who did not have CF related liver disease at entry in this cross-over trial.
6 Not calculable - 0 events in placebo arm.

10.5.5 Economic evidence

No economic evaluations of interventions relevant to UDCA were identified in the literature search conducted for this guideline. Full details of the search and economic article selection flow chart can be found in Appendix E and F, respectively.

This review question was not prioritised for de novo economic modelling. To aid considerations of cost-effectiveness the cost of UDCA over the course of 1 week and a month of continued has been estimated for all preparations.

Drug acquisition costs are taken from the NHS Electronic Drug Tariff October 2015. For an indication of primary biliary cirrhosis the BNF recommends a dose of 12–16 mg/kg daily in 3 divided doses for 3 months, then 12–16 mg/kg once daily at bedtime. Conversely in the studies by Merli 1994 and O'Brien 1992, participants received 12mg/kg daily and 20mg/kg daily, respectively.

For illustrative purposes, the costs in Table 161 are based 600mg daily as this was considered to be representative of the typical person with cystic fibrosis in clinical practice.

Table 161: Acquisition cost of UDCA

UDCA preparation	Quantity	Basic price	Cost per unit	Cost per day	Cost per week	Cost per month
150mg tablets	60	£19.02	£0.32	£1.27	£8.88	£39.82
300mg tablets	60	£38.86	£0.65	£1.30	£9.07	£40.67
250mg capsules	60	£25.29	£0.51	£1.21	£8.50	£38.12
Oral suspension sugar free 250mg/5ml	250ml	£26.98	£0.45[a]	£1.08[b]	£7.55	£33.89

(a) unit equals 5ml
(b) 2.4x 5ml

10.5.6 Evidence statements

10.5.6.1 Comparison 1. UDCA versus placebo or control

Change of hepatocellular enzymes or bilirubin level

Moderate quality evidence from 2 RCTs with 14 children, young people and adults with cystic fibrosis showed no clinically significant difference in lack of normalisation of AST between the group of participants receiving UDCA (12 or 20 mg/kg/day or) and those in the control group at 6 months follow-up.

Moderate quality evidence from 2 RCTs with 12 children, young people and adults with cystic fibrosis showed no clinically significant difference in lack of normalisation of ALT between the group of participants receiving UDCA (12 or 20 mg/kg/day or) and those in the control group at 6 months follow-up.

Low quality evidence from 2 RCTs with 10 children, young people and adults with cystic fibrosis showed no clinically significant difference in lack of normalisation of GGT between the group of participants receiving UDCA (12 or 20 mg/kg/day or) and those in the control group at 6 months follow-up.

Low quality evidence from 1 RCT with 12 children, young people and adults with cystic fibrosis showed no clinically significant difference in final bilirubin values (umol/l.) between the group of participants receiving UDCA (20 mg/kg/day) and those in the control group at 6 months follow-up.

Low quality evidence from 1 RCT with 27 children, young people and adults with cystic fibrosis showed no clinically significant difference in percentage change in AST, ALT and GGT between the group of participants receiving UDCA (1 to 3 300 mg. capsules per day) and those in the control group at 12 months follow-up.

No development of liver disease

High quality evidence from 1 cross-over trial with 11 participants found that participants who did not have cystic fibrosis related liver disease who received both UDCA and placebo did not develop liver disease at 6 months follow up.

Liver failure

Moderate quality evidence from 1 RCT with 28 participants reported that 1 participant taking UDCA had liver failure due to jaundice and no liver failure was found in placebo arm during the follow-up period of 12 months. There was no difference between UDCA and placebo.

Liver transplantation

Moderate quality evidence from 1 RCT with 28 participants reported that 1 participant taking UDCA required liver transplantation which was performed successfully and no liver transplantation was required in the placebo arm during the follow-up period of 12 months. There was no difference between UDCA and placebo.

A Cochrane systematic review of RCTs reported that none of the participant in 2 of the trials (Merli 1994 and O'Brien 1992) required liver transplantation (with personal communication with authors).

Liver related mortality

No evidence was found for this important outcome. However, a Cochrane systematic review of RCTs reported there was no deaths in 2 of the trials (Merli 1994 and O'Brien 1992, with personal communication with authors).

Development of portal hypertension

No evidence was found for this critical outcome. However, a Cochrane SR of RCTs reported that no development of portal hypertension occurred amongst participants in 2 RCTs (Merli 1994 and O'Brien 1992, with personal communication with authors).

Quality of life

No evidence was found for this important outcome.

10.5.6.2 Economic evidence statements

No evidence on cost-effectiveness in people with cystic fibrosis was available for this review.

10.5.7 Evidence to recommendations

10.5.7.1 Relative value placed on the outcomes considered

The objective of this review was to assess the clinical and cost effectiveness of UDCA for preventing liver disease progression in people with cystic fibrosis.

The committee agreed change of hepatocellular enzyme levels, progression to liver failure and development of portal hypertension indicated by an enlarged spleen (increased by at least 15%) and development of varices or ultrasound evidence of portal hypertension were critical outcomes for consideration in decision making. Health related quality of life, liver transplantation, liver related mortality and no development of liver disease were rated as important outcomes.

10.5.7.2 Consideration of clinical benefits and harms

The committee discussed the use of UDCA for primary prevention and secondary prophylaxis.

With regards to the use of UDCA in people with cystic fibrosis without liver disease, the committee noted most of the participants in the trials had pre-existing evidence of liver disease. Therefore, there was a lack of evidence to support the use of UDCA as primary prophylaxis aimed at preventing the onset of liver disease.

The committee noted that infants with cystic fibrosis who have meconium ileus, about 10-15%, were at increased risk of developing liver disease. However, in the absence of evidence showing a benefit, they did not recommend the use of UDCA even in these infants.

The committee discussed when UDCA should be given to prevent progression of liver disease and the duration of administration. They noted the available trials were small and the duration of follow-up was no more than a year. Consequently, it was unsurprising that there was no evidence for clinical benefit with UDCA in terms of preventing development of portal hypertension, liver failure or mortality.

The evidence did not show differences in terms of normalisation of hepatobiliary enzymes (including AST, ALT and GGT), final bilirubin values at 6 months or in percentage change in hepatobiliary enzymes (including AST, ALT and GGT) at 12 months between UDCA and placebo. However, the committee noted that signs of advanced liver disease, including portal hypertension were present at baseline for most of the participants. The fact that the liver disease had already progressed to this degree before starting UDCA might have led to an underestimate the potential benefit effect of UDCA in preventing disease progression.

The committee therefore recommended that if the liver function tests were abnormal, treatment with UDCA could be considered. The optimal duration of treatment was unknown and so they recommended that clinicians should think about discontinuing it if the liver function tests returned to normal levels and there was no clinical or ultrasound scan evidence of liver disease. If, subsequently, monitoring showed a recurrence of liver function test abnormality then the clinician would again consider giving UDCA. The committee also agreed that if the abnormal liver function tests did not resolve with UDCA and remained persistently abnormal, the clinician should consider referring to a liver specialist.

The committee did not made specific recommendations on the degree of abnormality of the various liver function tests used that should be considered abnormal or on the advisability of repeating blood tests when considering UDCA. They recognised that this was a complex area that required clinical expertise and judgement. A minor elevation of AST for example might not be significant whereas elevation of the serum bilirubin would be a reason for concern.

The committee believed that UDCA was considered safe for use, although in higher dosages it might cause diarrhoea.

10.5.7.3 Consideration of economic benefits and harms

The preparations of UDCA are comparable and relatively inexpensive in the short-term at a cost of approximately £1.08 to £1.27 a day (600mg daily) for capsules and oral suspension, respectively. However, the costs of prolonged use could be significant. Without knowing the benefits of UDCA in people with cystic fibrosis without liver disease, we cannot know if UDCA is a cost-effective prophylactic. Consequently, the committee agreed not to recommend UDCA in people with cystic fibrosis without evidence of liver disease.

Following this, the committee added that portal hypertension and liver disease were reported at baseline for many participants in the studies included in the clinical evidence review. As a result, they stated that this could potentially underestimate the cost-effectiveness of UDCA to prevent the initiation of liver disease.

The committee agreed that, although UDCA is relatively inexpensive and it has a good safety profile, this does not justify the continued prescription of these drugs without evidence of effectiveness. As a result, the committee made a recommendation to reduce unnecessary treatment costs and treatment burden by stopping UDCA if the annual clinical assessments show no evidence of liver disease.

No evidence was reviewed for subsequent treatment, thus, the committee made recommendations to think about referrals to a specialist to reinforce best practice.

10.5.7.4 Quality of evidence

The quality of the evidence presented in this report ranged from low to high as assessed by GRADE.

The risk of bias was one of the reasons that lead to downgrading the quality of the evidence, in particular lack of allocation concealment.

Imprecision also lead to downgrading the quality of the evidence as the confidence interval crossed 1 or 2 clinical or default MIDs (minimal important difference).

Inconsistency was not an issue as most outcomes were reported by a single study.

The evidence was not downgraded for indirectness. However, the committee noted that some of the participants had signs of liver disease at enrolment and, therefore, evidence on preventing development of liver disease is lacking.

10.5.7.5 Other considerations

No equality issues were identified by the committee for this review question.

The committee agreed to draft a research recommendation for this topic. They noted liver disease is the third most common cause of mortality in people with cystic fibrosis. Around 10 to 30% of people with cystic fibrosis will develop CFRD (See complications review). Children with meconium ileus are at an increased risk of liver disease. Starting treatment with UDCA from diagnosis may reduce this risk. UDCA appears safe, and is well tolerated and cheap. Routine use could increase people's overall quality of life and reduce the need for subsequent treatment for liver disease, but more research is needed into the effectiveness and safety of this treatment.

The licensed indications of ursodeoxycholic acid vary depending on the preparation. In addition, the preparations that are licensed for this indication are not licensed for all ages. For this reason, the prescriber should check individual brands for licensing and follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. The General Medical Council's Prescribing guidance: prescribing unlicensed medicines, should be sought for further information.

10.5.7.6 Key conclusions

The Guideline committee concluded that in the absence of evidence, they would not recommend using UDCA as primary prophylaxis.

The committee agreed that the available evidence did not show that UDCA was beneficial in achieving normalisation of hepatobiliary enzymes in people with cystic fibrosis and pre-existing liver disease. They noted the limitations of the evidence as most of the participants in the studies had signs of advanced liver disease at baseline. Therefore, the fact that the liver disease had already progressed to this degree before starting UDCA might have led to an underestimate the potential benefit effect of UDCA in preventing disease progression. They agreed longer studies would be needed to assess whether UDCA is effective in terms of preventing development of portal hypertension, liver failure or mortality. Moreover, the committee noted liver disease is a serious complication of cystic fibrosis and so is very important to delay its progression. Based on all this, the committee agreed UDCA could be considered if liver function tests were abnormal. They agreed to monitor for response to treatment and refer to specialist advice if abnormal results are persistent.

10.5.8 Recommendations

115. If liver function blood tests are abnormal, perform a liver ultrasound scan and consider ursodeoxycholic acid treatment[9].

116. Think about stopping ursodeoxycholic acid if liver function blood tests return to normal and clinical assessment and liver ultrasound scan show no liver disease.

117. If ursodeoxycholic acid is stopped, monitor for re-emergence of liver disease using clinical assessment and liver function blood tests.

118. Think about referring people with cystic fibrosis to a liver specialist if the liver function blood test results are persistently abnormal despite treatment with ursodeoxycholic acid.

10.5.9 Research recommendations

4. Should all children with meconium ileus receive ursodeoxycholic acid from diagnosis?

Table 162: Research recommendation justification

Research question	Should all children with meconium ileus receive ursodeoxycholic acid from diagnosis?
Why this is needed	
Importance to 'patients' or the population	Liver disease is the third commonest cause of death in cystic fibrosis. Meconium ileus is a risk factor for the development of cystic fibrosis related liver disease. It is possible that ursodeoxycholic acid (UDCA) decreases the incidence or severity of cystic fibrosis related liver disease. UDCA is relatively inexpensive and well tolerated, and if it decreased the incidence or severity of cystic fibrosis related liver disease this could improve quality of life and decrease mortality.
Relevance to NICE guidance	If UDCA changed the incidence or severity of cystic fibrosis related liver disease, this would change the recommendations for monitoring and treatment. • High: the research is essential to inform future updates of key recommendations in the guideline.
Relevance to the NHS	Financial cost of regular therapy and treatment burden to the patient. Cost savings if decreased incidence and severity of liver disease
National priorities	No document identified.
Current evidence base	UDCA can improve deranged biochemical tests of liver function, but it is unclear whether if given to high risk groups it is able to alter the incidence or severity of disease.
Equality	This intervention is of particular relevance to infants born with meconium ileus who are at increased risk of cystic fibrosis related liver disease.
Feasibility	The proposed research can be carried out within a realistic timescale and at an acceptable cost. There are no ethical or technical issues.
Other comments	None

[9] At the time of publication (October 2017), ursodeoxycholic acid did not have a UK marketing authorisation for adults with cystic fibrosis for this indication. The prescriber should check individual brands for licensing in children and young people and follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

Table 163: Research recommendation statements

Criterion	Explanation
Population	Children with cystic fibrosis and meconium ileus
Intervention	• Ursodeoxycholic acid (UDCA)
Comparators	• Usual care • Placebo
Outcomes	• Health related quality of life (CF-QOL, CFQR) • Change of hepatocellular enzymes or bilirubin level • Liver failure • Liver transplantation • Liver related mortality • Development of cystic fibrosis related-disease (enlarged spleen, development of varices, ultrasound evidence of portal hypertension) • No development of cystic fibrosis liver disease • Resource use • Unit costs
Study design	Randomised control trial
Timeframe	Two years of randomisation and 5 year of follow up, providing recruitment numbers are sufficient to achieve population numbers of sufficient size to answer the research question.

10.6 Monitoring for cystic fibrosis related diabetes

10.6.1 Introduction

Diabetes mellitus is a common complication of cystic fibrosis. It differs from both type 1 and 2 diabetes mellitus encountered in people without cystic fibrosis and so is referred to as CF-related diabetes (CFRD). It is caused by a combination of slow progressive loss of the insulin-producing β-cells in the pancreas and the development of end-organ resistance to insulin. The prevalence of CFRD increases with age. Although symptoms of CFRD can include weight loss, thirst and increased urinary frequency, its onset can be insidious. Without treatment, uncontrolled CFRD can lead to a number of significant complications including more frequent respiratory exacerbations, an accelerated loss of lung function and a decline in nutritional status. People with cystic fibrosis are therefore regularly screened for CFRD, so treatment can be started early to prevent any complications. The clinical management of CFRD differs from other forms of diabetes mellitus in dietary advice and the use of agents to control blood sugar levels.

10.6.2 Description of clinical evidence

The aim of this review was to determine what criteria should be used to determine the need for insulin therapy to achieve optimal patient outcomes.

As the committee anticipated a lack of evidence to respond to this question, we also aimed to determine what thresholds of glucose dysregulation are associated with more rapid progression of lung disease (as a proxy measure to determine which criteria should be used to instigate treatment with insulin in people with cystic fibrosis).

We searched for systematic reviews, test-and-treat randomized controlled trials (RCTs) and prospective and retrospective comparative cohort studies. Conference abstracts were also considered in the absence of full published RCTs.

For full details see review protocol in Appendix D.

No studies were identified.

See study selection flow chart in Appendix F, and list of excluded studies in Appendix H.

10.6.3 Summary of included studies

Review question 1. What criteria should be used to determine the need for insulin therapy to achieve optimal patient outcomes?

No studies were identified for this question.

Review question 2. What thresholds of glucose dysregulation are associated with more rapid progression of lung disease?

No studies were identified for this question.

10.6.4 Clinical evidence profile

Not applicable, as no evidence was found for this review.

10.6.5 Economic evidence

No economic evaluations of strategies to monitor for the onset of CFRD were identified in the literature search conducted for this guideline. Full details of the search and economic article selection flow chart can be found in Appendix E and F, respectively.

This review question was not prioritised for de novo economic modelling. To aid consideration of cost-effectiveness relevant resource and cost use data on the OGTT and CGM are presented in Appendix K.

10.6.6 Evidence statements

Not applicable, as no clinical or economic evidence was found for this review.

10.6.7 Evidence to recommendations

10.6.7.1 Relative value placed on the outcomes considered

The aim of this review was to define what criteria should be used to determine the need for insulin therapy to achieve optimal patient outcomes.

The committee chose change in lung function (FEV_1), forced vital capacity (FVC), lung clearance index (LCI), pulmonary exacerbations and body mass index (BMI) (z-scores for children) as critical outcomes for decision making. Adverse events and patient acceptability or satisfaction were rated as important outcomes.

10.6.7.2 Consideration of clinical benefits and harms

The committee recognised that diabetes is a very common complication in people with cystic fibrosis and it is important to identify it without delay. They highlighted early treatment with insulin is very important as it may improve lung function and weight. However, they recognised the lack of evidence in relation to these matters and were aware of a lack of consensus in clinical practice.

The committee emphasised that glucose may fluctuate in people with cystic fibrosis. The tests used to diagnose diabetes in the general population may not be suitable for the detection of CFRD. For this reason, they agreed that single point tests, when used alone, are not useful for the identification of CFRD. This is supported by a previous Health Technology Assessment (HTA 2012) and the American Diabetes Association (ADA 2010).

The committee discussed the use of the oral glucose tolerance test (OGTT) at length. They noted this test is commonly used to monitor for CFRD in current practice and is the test of choice for many professionals. The use of this test is also recommended by the American Diabetes Association [consensus recommendation] (ADA 2010) and the European Cystic Fibrosis Foundation (Alan 2014). However, they also noted the OGTT may not be an ideal test given that, as mentioned above, glucose dysregulation in CFRD is a dynamic and variable process. Based on this, they agreed OGTT may not be completely reliable and, if used and found abnormal, it should be backed up with dynamic testing. This will ensure that glucose regulation is assessed over several days. The committee discussed the important fact that hyperglycaemia associated with glucose dysregulation in CFRD can have a negative effect on clinical outcomes even before the usual diagnostic criteria for diabetes are met.

The committee discussed the potential benefit of continuous glucose monitoring (CGM). CGM would detect glucose dysregulation more reliably as it monitors the blood sugar level continuously for several days rather than relying on a single or few glucose measurements. This test is increasingly used in clinical practice for the detection of the onset of diabetes in people with cystic fibrosis. However, they acknowledged there is currently no evidence to require the routine use of this test. In addition, some drawbacks were also noted. CGM is more difficult to perform and to interpret compared to the OGTT and it has to be administered by trained staff, making it difficult to generalise its use to all cystic fibrosis clinics.

The committee agreed monitoring for CFRD should be done annually and should start from the age of 10, as recommended by the American Diabetes Association (ADA 2010) and the US Cystic Fibrosis Foundation (Moran 2010). This recommendation is consistent with current practice. Apart from the process of annual monitoring, investigation should be undertaken in a number of specific contexts. If people with cystic fibrosis have symptoms or signs of diabetes such as polydipsia and polyuria they should be appropriately investigated as recommended in existing NICE diabetes guidelines for children, young people and adults. In addition, the committee recommended consideration be given to investigating those with cystic fibrosis who, despite optimising their pulmonary management, have unexplained weight loss or an unexplained deterioration in lung function as measured by pulmonary spirometry, increased frequency of pulmonary exacerbations or lethargy and malaise. They also recommended monitoring for people taking long-term systemic corticosteroids or enteral tube feeding, in whom glucose dysregulation may occur. Monitoring should be done using CGM or serial glucose monitoring.

With regards to monitoring diabetes during pregnancy, the committee referred to the current NICE guidelines on Diabetes in Pregnancy (NG3 2015). They do not specifically address monitoring of CFRD in pregnancy. The committee noted that insulin therapy is often needed in pregnant women with cystic fibrosis as the threshold for commencing insulin is lower than in those without cystic fibrosis. They recommended that either CGM or an OGTT should be performed at the end of the first and second trimesters of pregnancy. This timing is consistent with recommendations from the US Cystic Fibrosis Foundation (Moran 2010).

10.6.7.3 Consideration of economic benefits and harms

The committee stated that people with cystic fibrosis require their own clinic space when attending for an OGTT to reduce their risk of cross-infection. This incurs a larger cost (£50) than OGTTs undertaken in a shared clinic space (NICE NG3 2015, 2-sample OGTT: £22.06). The committee added that in cases with an abnormal OGTT result, further dynamic

tests such as serial blood sugar monitoring or CGM would be performed after a few days to obtain a complete picture of glucose levels.

Given that single-point tests can result in more false positives and negatives than two, or three point tests, the committee agreed that their recommendations should favour dynamic testing. This would reduce the number of people with cystic fibrosis that incur the downstream costs from an incorrect diagnosis. They ordered their recommendation on the type of test to that effect. However, when OGTT is performed, the committee agreed normal results have a higher specificity and sensitivity than abnormal results. Therefore, abnormal results should be followed by CGM or serial blood glucose monitoring to outweigh the potential costs of an incorrect diagnosis.

Unlike CGM in confirmed diabetes, the duration of CGM to monitor for its onset would be up to 5 to 7 days. For this reason, the committee stated that CGM systems would be shared across the clinic when used to monitor for the onset of CFRD. This would reduce the cost per person from approximately £3,500 per year (NICE NG17 2015) to £20 per year, including attendances and delays to receive and return the system. Following this, the committee questioned if CGM was the most expensive investigation. The cost of OGTT could overtake the cost of CGM if several visits were required, more so in children who require extra staff time to fit a cannula for their OGTT.

However, the committee noted that the majority of clinics do not have access to CGM systems or the expertise on how to use and interpret them appropriately in this population. The committee noted that each centre would require several CGM systems to ensure enough people were monitored by the centre each week. As a result, recommending CGM would lead a change in current practice and would incur upfront training costs and capital costs to implement.

Overall, the committee agreed they could not change current practice from the OGTT to CGM because there was not enough evidence to support the large injection of resources. As a result, the committee made a recommendation in favour of dynamic testing to allow centres to decide which strategy is cost-effective for them to provide. The committee also prioritised a research recommendation to identify the best strategy to diagnose CFRD in people with cystic fibrosis in order to mitigate current uncertainty in this area.

The committee outlined the populations at high risk of CFRD in their recommendations that may require more frequent monitoring. Those populations were prioritised as their condition could escalate much quicker between the annual reviews, leading to more intense and costly management.

10.6.7.4 Quality of evidence

Not applicable, as no evidence was found for this review.

10.6.7.5 Other considerations

The committee discussed potential equality issues. They noted cystic fibrosis related diabetes is common in females. However, they agreed care is the same for both genders so there was no need to draft additional recommendations.

Given the lack of evidence, and the uncertainty in relation to what is the best strategy to detect the onset of diabetes in people with cystic fibrosis, the committee agreed a research recommendation was useful. They highlighted it would be important to look at OGTT and CGM. Better testing would also provide guidance on when treatment with insulin should be initiated in people with cystic fibrosis.

10.6.7.6 Key conclusions

The guideline committee concluded that early detection of CFRD is very important. They noted OGTT is often used in clinical practice. However, they agreed it is an unreliable test and, if used, it should be backed up with dynamic testing over several days. They suggested CGM could be used instead as it monitors the blood sugar level continuously. Children should be monitored for the onset of CFRD from the age of 10 years. Monitoring should be done as part of the annual assessment and if there are symptoms suggestive of diabetes.

10.6.8 Recommendations

119. Diagnose cystic-fibrosis-related diabetes using one of the following:

- continuous glucose monitoring (CGM)
- serial glucose testing over several days
- oral glucose tolerance testing (OGTT) – if OGTT is abnormal perform CGM or serial glucose testing over several days to confirm the diagnosis.

120. Test for cystic-fibrosis-related diabetes (as detailed in recommendation on diagnosing cystic-fibrosis-related diabetes) in people with cystic fibrosis annually from 10 years of age.

121. Test for cystic-fibrosis-related diabetes at the end of the first and second trimesters of pregnancy, using CGM or OGTT.

122. Test for cystic-fibrosis-related diabetes in people with cystic fibrosis who are taking long-term systemic corticosteroids or receiving enteral tube feeding, using CGM or serial glucose monitoring.

123. Think about testing for cystic-fibrosis-related diabetes in people who still have any of the following despite optimised cystic fibrosis treatment:

- unexplained weight loss
- a deterioration in lung function as measured by spirometry
- increased frequency of pulmonary exacerbations
- excessive tiredness.

10.6.9 Research recommendations

5. What is the most effective strategy to detect diabetes in people with cystic fibrosis?

Table 164: Research recommendation justification

Research question	What is the most effective strategy to detect diabetes in people with cystic fibrosis?
Why this is needed	
Importance to 'patients' or the population	People with cystic fibrosis are at high risk of developing cystic fibrosis related diabetes (CFRD). The onset can be insidious but without institution of therapy is associated with accelerated progression of lung disease. A strategy for the early identification of CFRD will allow treatment to be commenced in a timely manner and help prevent the clinical decline associated with this condition.

Research question	What is the most effective strategy to detect diabetes in people with cystic fibrosis?
	Currently there are 10,800 people with cystic fibrosis, of whom 3,759 are age >10 years screened for CFRD in 2015. Further 1,192 were not screened, but could have been eligible.
Relevance to NICE guidance	High: the research is essential to inform future updates of key recommendations in the guideline. The guideline committee spent some time debating the optimal testingstrategy for CFRD. They agreed it was important for clinical care but there are differences in clinical practice between cystic fibrosis centres. They found no suitable evidence to guide their decision.
Relevance to the NHS	It may help prevent both the progression of lung disease and the development of long term complications of diabetes in this population, both of which incur increased utilisation of healthcare resources
National priorities	None
Current evidence base	A search was undertaken to find evidence to inform the development of this current guideline; no suitable evidence base was identified.
Equality	No equality issues
Feasibility	No equality issues
Other comments	None

Table 165: Research recommendation statements

Criterion	Explanation
Population	People with cystic fibrosis age >10 years
Intervention	Continuous Glucose Monitoring (CGM), followed up with insulin treatment (Possible sub-groups according to different levels of glucose dysregulation)
Comparators	Current method (OGTT), followed up with insulin treatment
Outcomes	• Change in lung function (measured with FEV_1, FVC, LCI) • Time to next pulmonary exacerbation • Change in weigh or BMI • Adverse events (for example hypoglycaemic episodes due to insulin therapy) • Patient acceptability/ satisfaction (with insulin therapy) • Resource use • Unit costs
Study design	Test-and-treat randomised controlled trial (RCT)
Timeframe	1 year

10.7 Monitoring for low bone mineral density

Review question: What is the most effective strategy to monitor for the identification of reduced bone mineral density in people with CF?

10.7.1 Introduction

Improved survival in people with cystic fibrosis has contributed to the development of co-morbidities. Low bone mineral density is a common co-morbidity affecting people with CF. It is, however, more frequently seen in adolescents and adults. Low bone mineral density can lead to the development of osteoporosis which results in the increased risk of fragility fractures.

The aetiology of low bone mineral density in people with cystic fibrosis is multifactorial. Contributory risk factors include poor nutritional status, delayed puberty, cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction, physical inactivity, deficiencies of calcium, vitamins D and K, recurrent respiratory exacerbations, corticosteroid treatment and hypogonadism. Medical and nutritional interventions should aim to optimise these multiple factors that affect bone health.

An important part of standard cystic fibrosis care is the prevention and recognition of low bone mineral density. Current bone health consensus committees recommend the monitoring of bone health using dual energy x-ray absorptiometry (DXA) scans. Although, the age to commence and frequency of scanning is variable and dependent on the presence of risk factors.

10.7.2 Description of clinical evidence

The objective of this review was to determine the most effective strategy to monitor for the identification of reduced mineral density in people with cystic fibrosis.

We looked for systematic reviews of test and treat RCTs, systematic reviews of cohort studies and prospective and retrospective cohort studies that looked at regular DXA scans or peripheral quantitative computed tomography (pQCT).

For full details see review protocol in Appendix D.

We identified 6 observational studies (Baker 2016, Bhudhikanok 1998, Brenckmann 2003, Haworth 2002, Papaioannou 2008, Schulze 2006).

Three studies were conducted in the USA (Baker 2016, Bhudhikanok 1998, Schulze 2006); 2 in Canada (Brenckmann 2003, Papaioannou 2008) and 1 in the UK (Haworth 2002) and the follow-up ranged from 1 to 4 years.

One study included young people (Schulze 2006); 3 included adults (Baker 2016, Brenckmann 2003, Papaioannou 2008); 1 included young people and adults (Haworth 2002) and 1 included children, young people and adults (Bhudhikanok 1998).

Population size ranged from 18 to 63 people.

With regards to the test, all studies used DXA scans and 1 study also used QCT (Haworth 2002).

Studies reported on change BMD at the lumbar spine (Baker 2016, Brenckmann 2003, Bhudhikanok 1998, Haworth 2002, Papaioannou 2008, Schulze 2006); at the proximal femur (Papaioannou 2008); at the hip (Brenckmann 2003, Haworth 2002); at the femoral neck (Bhudhikanok 1998, Haworth 2002) and change in whole body BMD (Brenckmann 2003, Bhudhikanok 1998, Papaioannou 2008 Schulze 2006). Five studies used z-scores (Baker 2016, Bhudhikanok 1998, Brenckmann 2003, Papaioannou 2008, Schulze 2006), 1 used t-scores for adults (Papaioannou 2008); and 1 study used mg/ml o g/cm2 (Haworth 2002).

Only 1 study (Baker 2016) used a multivariate model adjusting for age, gender, fat-free max index and height.

10.7.3 Summary of included studies

A summary of the studies that were included in this review are presented in Table 166.

Table 166: Summary of included studies

Study	Population	Prognostic indicator	Follow-up	Outcomes	Comments
Baker 2016 USA Retrospective observational study	N=63 adults with CF Mean age (SD): 31.7 (8.0) years (18 to 57) 50.9% male	• Low BMD, defined as z-score ≤ -1 • Very low BMD, defined as z-score ≤ -2 • Standard dual-energy X-ray absorptiometry (DXA) on a QDR4500A model (Hologic Inc, Bedford, MA) •	2 years (data available for n=39)	• Change in posterior-anterior spine BMD • Multivariate model adjusting for: age, gender, fat-free max index and height	Subjects that did not have a repeat PA spine DXA were significantly younger and tended to have lower baseline PA spine z-scores.
Brenckmann 2003 Canada Retrospective observational study	N=40 adults with CF Mean age (SD): 28.7 (8.4) years (19 to 52)	• Hip BMD • Lumbar spine • Total BMD • DXA scan. No details given. •	1 year (data available for n=27)	• Change in hip BMD • Change in lumbar spine • Change in total BMD	Subgroup analysis was not possible as sample size was too small. N=21 participants were receiving oral or IV corticosteroids
Bhudhikanok 1998 USA Prospective observational study	N=47 children, young people and adults with CF Mean age, range: 20.6 years (8.4 to 48.5 years) 30 female, 19 male • Boy and young males n=9 • Adult males n=6 • Girls and young females n=11 • Adult females n=15	• Lumbar spine BMD (QCT) • Femoral neck BMD (DXA) • Whole body BMD (DXA) Dual-energy X-ray (DXA) absorptiometry (QDR 100W, Hologic Corporation, Waltham, Mass)	Mean 17 months (11 to 25 months) (data available for n=41)	• Change in lumbar spine BMD • Change in femoral neck BMD • Change in whole body BMD	
Haworth 2002 UK	N=114 young people and adults with CF Mean (SD) age: 25.1 (6.9)	• Lumbar spine BMD • Femoral neck BMD • Total hip BMD	12 to 13 months	• Change in lumbar spine BMD	

Study	Population	Prognostic indicator	Follow-up	Outcomes	Comments
Prospective observational study	years (15 to 49) • Young cohort ≤ 24 years n=55 • Adult cohort ≥ 25 years n=59	• QCT and DXA • (reported in a previous study)		• Change in femoral neck BMD • Change in total hip BMD	
Papaioannou 2008 Canada Retrospective observational study	N=49 adults with CF Mean age (SD): 25.2 (9.4) years 42.9% male	• Lumbar spine BMD • Proximal femur BMD • Whole body BMD • Standard dual-energy X-ray absorptiometry (DXA) on a QDR4500A model (Hologic Inc, Bedford, MA, USA) •	Mean (SD): 4.03 (1.45) years (data available for n=10)	• Lumbar spine BMD • Proximal femur BMD • Whole body BMD	
Schulze 2006 USA Prospective observational study	N=18 prepubertal and pubertal girls and young females Age range: 7.6 to 17.9 years	• Lumbar spine BMD • Whole body BMD • Standard dual-energy X-ray absorptiometry (DXA) on a QDR4500A model (Hologic Inc, Bedford, MA, USA)	Mean time: 2.13±1.14 years (range 1.6 to 4.10)	• Change in lumbar spine BMD. • Change in whole body BMD.	Although the study reported data stratified by pubertal status, this was not reported in the review as sample size was very low (range 2 to 7) Significant differences were found by pubertal stage at baseline.

10.7.4 Clinical evidence profile

A summary of the results in presented in Table 167.

Table 167: Prognostic indicators for bone mineral density

Study	Prognostic indicator	Effect size	Quality
Baker 2016	• Low baseline BMD, defined as z-score ≤ -1 • Very low baseline BMD, defined as z-score ≤ -2	Change in posterior-anterior spine BMD at 2 years • z-score ≤1 at baseline not significantly and independently associated with greater BMD loss (p-value = 0.81) • z-score ≤2 at baseline not significantly and independently associated with greater BMD loss (p-value = 0.47)	Low
Brenckmnn 2003	• Baseline mean (SD) z-scores: • Left hip BMD: -0.9 (1.1) • Right hip BMD:-1.0 (1.1) • Lumbar spine BMD: -1.1 (1.3) • Baseline mean (SD) gm/cm^2: • Total BMD: 1.2 (0.1)	BMD annual change: • Change in hip BMD: ○ Left hip: -3.01% (95% CI -4.76 to -1.26) ○ Right hip: -3.06% (95% CI -4.69 to -1.43) • Change in lumbar spine BMD: -0.86% (95% CI -2.46 to 0.75) • Change in total body BMD (n=21): 0.0% (SD 1.4%)	Very low
Bhudhikanok 1998	• Baseline lumbar spine BMD (z-score for age and sex) • Males ○ Children and young people < 18 years: -1.0±0.9 ○ Adults ≥ 18 years: -2.5±1.4 • Females ○ Children and young people < 18 years: -1.5±1.5 ○ Adults ≥ 18 years: -1.9±1.6	Change in lumbar spine BMD (z-score for age and sex) at mean 17 months follow-up • Males ○ Children and young people < 18 years: -0.2±0.5; ns ○ Adults ≥ 18 years: 0.1±0.2; ns • Females ○ Children and young people < 18 years: -0.6±0.8; p<0.05 ○ Adults ≥ 18 years: 0.1±0.3; ns	Very low
	• Baseline femoral neck BMD (z-score for age and sex)	Change in femoral neck BMD (z-score for age and sex) at mean 17 months follow-up	

Study	Prognostic indicator	Effect size	Quality
	• Males ○ Children and young people < 18 years: -0.8±0.6 ○ Adults ≥ 18 years: -2.5±0.8 • Females ○ Children and young people < 18 years: -2.0±1.6 ○ Adults ≥ 18 years: -2.2±1.6 •	• Males ○ Children and young people < 18 years: -0.2±0.4; ns ○ Adults ≥ 18 years: -0.2±0.4; ns • Females ○ Children and young people < 18 years: -0.3±0.8; ns ○ Adults ≥ 18 years: 0.1±0.4; ns	
	• Baseline whole body BMD (z-score for age and sex) • Males ○ Children and young people < 18 years: -0.3±0.5 ○ Adults ≥ 18 years: -2.0±1.2 • Females ○ Children and young people < 18 years: -1.3±1.2 ○ Adults ≥ 18 years: -1.3±1.2	Change in femoral neck BMD (z-score for age and sex) at mean 17 months follow-up • Males ○ Children and young people < 18 years: -0.6±0.4; p<0.005 ○ Adults ≥ 18 years: 0.1±0.3; ns • Females ○ Children and young people < 18 years: -0.4±0.3; p<0.005 ○ Adults ≥ 18 years: -0.0±0.2; ns	
Haworth 2002	• Baseline lumbar spine BMD (mg/ml by CQT): • Young cohort ≤ 24 years: 176.1 (166.9 to 185.2) • Adult cohort ≥ 25 years: 170.8 (161.3 to 180.3) • Baseline lumbar spine BMD (g/cm2 by DXA): • Young cohort ≤ 24 years: 0.918 (0.8882 to 0.953) • Adult cohort ≥ 25 years: 0.942 (0.909 to 0.975) • Baseline femoral neck BMD (g/cm2 by DXA): • Young cohort ≤ 24 years: 0.839 (0.801 to 0.877) • Adult cohort ≥ 25 years: 0.781 (0.756 to 0.819) • Baseline total hip BMD (g/cm2 by DXA): • Young cohort ≤ 24 years: 0.917 (0.880 to 0.953 • Adult cohort ≥ 25 years: 0.881 (0.844 to 0.918)	• Annual change in lumbar spine BMD (mg/ml by CQT): • Young cohort ≤ 24 years: -1.7% (-4.4 to 1.1) • Adult cohort ≥ 25 years: 0.7% (-1.5 to 2.8) • Annual change in lumbar spine BMD (g/cm2 by DXA): • Young cohort ≤ 24 years: -0.9% (-2.0 to 0.2) • Adult cohort ≥ 25 years: -0.0% (-1.3 to 1.2) • Annual change in femoral neck BMD (g/cm2 by DXA): • Young cohort ≤ 24 years: -2.5% (-3.8 to -1.2); p-value <0.001 • Adult cohort ≥ 25 years: -1.9% (-2.9 to -0.8); p-value <0.001 • Annual change in total hip BMD (g/cm2 by DXA): • Young cohort ≤ 24 years: -2.2% (-3.3 to -1.0); p-value <0.001 • Adult cohort ≥ 25 years: -1.5% (-2.4 to -0.6); p=0.001	Very low

Study	Prognostic indicator	Effect size	Quality
Papaioannou 2008	• Baseline mean (SD) T-score/ Z-score: • Lumbar spine BMD: -0.80 (1.10) • Proximal femur BMD: -0.57 (0.97) • Whole body BMD: -0.71 (1.11)	Overall rate of bone loss at mean 4.3 years follow-up: • Lumbar spine BMD: -0.73% • Proximal femur BMD: -1.93% • Whole body BMD: -0.40%	Very low
Schulze 2006	Baseline mean±SD gender and age matched z-scores: • Lumbar spine BMD: -0.40±1.13 • Whole body BMD: -0.29±1.01	Change between baseline and follow-up (mean ±SD follow-up 2.13±1.16; range 1.06 to 4.10 years) • Lumbar spine BMD: -0.46±0.94 • Whole body BMD: -0.45±1.16	Very low

BMD: bone mineral density; DXA: dual-energy X-ray absorptiometry; ns: not significant; SD: standard deviation; QCT: quantitative computed tomography

10.7.5 Economic evidence

No economic evaluations of strategies to identify reduced BMD were identified in the literature search conducted for this guideline. Full details of the search economic article selection flow chart can be found in Appendix E and F, respectively.

Diagnostic procedures, including imaging, will not be considered cost-effective if there is not an effective treatment for the condition being diagnosed, or if the person's management is not changed by the results. In other words, if the procedure does not add any additional information to a clinical assessment and does not change the management strategy, those procedures should not be recommended. However, to fully address the cost-effectiveness of strategies (DXA scans and peripheral quantitative computed tomography (pQCT)) to detect reduced BMD would require a model that included the management of reduced BMD which lies outside the scope of this guideline. Moreover, the studies included in the clinical evidence review compared the sites DXA scans could measure, as opposed to the accuracy of DXA scans compared to another imaging procedure. As a result, if the resource use for each site is equivalent, it is evident that the most accurate site should be measured and the economic focus should be on the frequency those scans are performed.

According to the committee, approximately one third of adults with cystic fibrosis have reduced BMD which can lead to osteoporosis and predispose them to bone fractures. Those complications can incur high treatment costs and negatively impact a person's quality of life due to their reduced mobility and ability to perform their usual activities. For these reasons, there are potential cost savings to the NHS if imaging can better identify bone disease related to cystic fibrosis early in its course, resulting in more timely management and the possible prevention of complications associated with reduced BMD.

To assess the risk of reduced BMD in people with cystic fibrosis, the committee advised that most people would receive regular DXA scans, but some may undergo a pQCT scan which is more costly. The cost of those scans, according to NHS Reference Costs 2015, are reported in Table 168.

Table 168: Cost of imaging

Currency code	Currency description	National average cost
DXA Scan		
RD50Z	DXA scan	£59
Computerised tomography scan		
RD20A	one area, without contrast, 19 years and over	£93
RD20B	one area, without contrast, between 6 and 18 years	£93
RD20C	one area, without contrast, 5 years and under	£113
RD21A	one area, with post contrast only, 19 years and over	£104
RD21B	one area, with post contrast only, between 6 and 18 years	£111
RD21C	one area, with post contrast only, 5 years and under	£156
RD22Z	one area, with pre and post contrast	£113
RD23Z	two areas, without contrast	£121
RD24Z	two areas, with contrast	£122
RD25Z	three areas, without contrast	£107
RD26Z	three areas, with contrast	£124
RD27Z	more than three areas	£136
RD28Z	complex	£122

The committee advised that it would be difficult to accurately judge a person's BMD prior to a scan, based on clinical assessment of their risk factors. Therefore, if scans are necessary to determine BMD, the committee should consider when those scans are performed as their frequency could have significant resource implications.

The committee also advised that bone health is strongly linked to the severity of lung disease, body weight and oral corticosteroids use. As a result, the committee should consider if there are populations which should undergo more frequent monitoring because they have a higher risk of reduced BMD compared to the general population, whose downstream costs would escalate much quicker if were are undetected. Finally, if pQCT scans are more costly than DXA scans, the committee should consider when pQCT scans can provide additional information to a DXA scan to justify their additional cost.

10.7.6 Evidence statements

10.7.6.1 Evidence in children and young people

Very low quality evidence from 1 longitudinal study with 18 prepubertal and pubertal girls and young females with CF (age range 7.6 to 17.9 years) suggested that:

- a baseline z-score of -0.40 in lumbar spine BMD (measured by DXA scan) was associated with an overall change in BMD at the spine of -0.07 at 2.13 years follow-up
- a baseline z-score of -0.29 in whole body BMD (measured by DXA scan) was associated with an overall change in whole body BMD of -0.17 at 2.13 years follow-up.

Very low quality evidence from 1 prospective longitudinal study with 20 children and young people with CF (9 males, 11 females; age not reported) suggested that:

- a baseline z-score of -1.0 BMD at the lumbar spine (measured by DXA scan) was not significantly associated with a decrease in BMD at the lumbar spine at 17 months follow-up in boys and young males
- a baseline z-score of -1.5 BMD at the lumbar spine (measured by DXA scan) was significantly associated with a decrease in BMD at the lumbar spine at 17 months follow-up in girls and young females
- a baseline z-score of -0.8 BMD at the femoral neck (measured by DXA scan) was not significantly associated with a decrease in BMD at the femoral neck at 17 months follow-up in boys and young males
- a baseline z-score of -2.0 BMD at the femoral neck (measured by DXA scan) was not significantly associated with a decrease in BMD at the femoral neck at 17 months follow-up in girls and young females
- a baseline z-score of -0.3 in whole body BMD (measured by DXA scan) was significantly associated with a decrease in whole body BMD at 17 months follow-up in boys and young males
- a baseline z-score of -1.3 in whole body BMD (measured by DXA scan) was significantly associated with a decrease in whole body BMD at 17 months follow-up in girls and young females.

10.7.6.2 Evidence in young people and young adults

Very low quality evidence from 1 longitudinal study with 55 young people and young adults with CF (age range 15 to 24 years) suggested that:

- baseline lumbar spine BMD (measured by CQT or DXA) was not significantly associated with a decrease in lumbar spine BMD at 1 year follow-up
- baseline femoral neck BMD (measured by DXA) was significantly associated with a decrease in femoral neck BMD at 1 year follow-up

- baseline total hip BMD (measured by DXA) was significantly associated with a decrease in total hip BMD at 1 year follow-up.

10.7.6.3 Evidence in adults

Moderate quality evidence from 1 longitudinal study with 63 adults with CF (age range 18 to 57 years) suggested that low and very posterior-anterior spine BMD (defined as z-score ≤ -1 and z-score ≤ -2 and measured by DXA scan) were not significantly associated with greater loss of posterior-anterior spine bone mineral density at 2 years follow-up.

Low quality evidence from 1 longitudinal study with 40 adults with CF (age range 18 to 52 years) suggested that:

- a baseline z-score of -0.9 BMD at the left hip (measured by DXA scan) was significantly associated with a decrease in BMD at the left hip at 1 year follow-up
- a baseline z-score of -1.0 BMD at the right hip (measured by DXA scan) was significantly associated with a decrease in BMD at the right hip at 1 year follow-up
- a baseline z-score of -1.1 BMD at the lumbar spine (measured by DXA scan) was not significantly associated with a decrease in BMD at the lumbar spine at 1 year follow-up
- the change in total bone mineral density (measured by DXA scan) from baseline was negligible at 1 year follow-up.

Very low quality evidence from 1 prospective longitudinal study with 21 adults with CF (6 males, 15 females; age not reported) suggested that:

- a baseline z-score of -2.5 BMD at the lumbar spine (measured by DXA scan) was not significantly associated with a decrease in BMD at the lumbar spine at 17 months follow-up in male adults
- a baseline z-score of -1.9 BMD at the lumbar spine (measured by DXA scan) was not significantly associated with a decrease in BMD at the lumbar spine at 17 months follow-up in adult females
- a baseline z-score of -2.5 BMD at the femoral neck (measured by DXA scan) was not significantly associated with a decrease in BMD at the femoral neck at 17 months follow-up in male adults
- a baseline z-score of -2.2 BMD at the femoral neck (measured by DXA scan) was not significantly associated with a decrease in BMD at the femoral neck at 17 months follow-up in adult females
- a baseline z-score of -2.0 in whole body BMD (measured by DXA scan) was not significantly associated with a decrease in whole body BMD at 17 months follow-up in male adults
- a baseline z-score of -1.3 in whole body BMD (measured by DXA scan) was not significantly associated with a decrease in whole body BMD at 17 months follow-up in adult females.

Very low quality evidence from 1 longitudinal study with 59 adults with CF (age ≥ 25 years) suggested that:

- baseline lumbar spine BMD (measured by CQT or DXA) was not significantly associated with a decrease in lumbar spine BMD at 1 year follow-up
- baseline femoral neck BMD (measured by DXA) was significantly associated with a decrease in femoral neck BMD at 1 year follow-up
- baseline total hip BMD (measured by DXA) was significantly associated with a decrease in total hip BMD at 1 year follow-up.

Very low quality from 1 longitudinal study with 49 adults with CF (mean age 25.2 years) suggested that:

- a baseline t-score/ z-score of -0.80 in lumbar spine BMD (measured by DXA scan) was associated with an overall rate of bone loss at lumbar spine was -0.73% at 4.3 years follow-up
- a baseline t-score/ z-score of -0.57 in proximal femur BMD (measured by DXA scan) was associated with an overall rate of bone loss at proximal femur was -1.93% at 4.3 years follow-up
- a baseline t-score/ z-score of -0.71 in whole body BMD (measured by DXA scan) was associated with an overall rate whole body loss was -0.40% at 4.3 years follow-up.

10.7.6.4 Economic evidence statement

No evidence on cost-effectiveness in people with cystic fibrosis was available for this review.

10.7.7 Evidence to recommendations

10.7.7.1 Relative value placed on the outcomes considered

The objective of this review was to determine the most effective strategy to monitor for the identification of reduced mineral density in people with cystic fibrosis.

The committee chose change in bone mineral density as a critical outcome for decision making. Number of fractures and quality of life were rated as important outcomes.

10.7.7.2 Consideration of clinical benefits and harms

The committee acknowledged that most specialist cystic fibrosis centres currently follow the European CF bone mineralisation guidelines (Sermet-Gaudelus 2011). These guidelines recommend that a first bone density scan should be done around age 8 to 10 years and repeated every 1 - 5 years depending on severity (according to BMD t- or z-scores) and risk factors.

The committee discussed the usefulness of conducing regular monitoring for bone mineral density in children as these tests are difficult to interpret in this population. Likewise, the committee discussed whether routine DXA scans should be offered to all adults. They noted that it is unlikely that people over 18 years can build bone mass as this is mostly done during teenage years, therefore, there is limited intervention.

Careful liaison with a bone specialist should occur before commencing children or adults on bisphosphonate therapy. This should include the optimal dose of treatment, duration and monitoring of long-term effects. People should be counselled about the side-effects of bisphosphates before commencing therapy. Careful consideration should also be given to the use of bisphosphates in women of child-bearing age. Vitamin D deficiency and ensuring an optimal calcium intake need to be addressed prior to commencing bisphosphonates. It is important to minimise risk factors for low BMD for example improving nutritional status and encouraging weight bearing exercise.

Even though it was not specifically addressed in the evidence, the committee agreed it is recognised that certain groups across all age groups may benefit from monitoring as they are at a higher risk of reduced bone mineral density. These groups may include people who present with under-nutrition, those using corticosteroids (either frequently of long-term use), those with a history of low impact fracture, those who present exacerbations that require intravenous antibiotics on regular basis, those with poor lung function (low FEV_1), post-menopausal women and following transplants.

The committee noted the available evidence did not provide any clarity in relation to which body sites should be scanned. Therefore, they agreed that a z-score of -2.0 standard

deviations at any body site would be considered abnormal and they recommended to seek expert advice.

The committee agreed z-scores should be used in children, whereas z-scores or t-scores can be used in adults. Although, t-scores are more useful in post-menopausal women and men over 50 years.

10.7.7.3 Consideration of economic benefits and harms

Once presented with the clinical evidence and an outline of the resources scans entail, the committee questioned the value of monitoring for reduced BMD in current clinical practice. They stated that the absence of evidence does not mean current clinical practice should be recommended when the opportunity cost of those resources is high.

The committee noted that scans are useful to compare someone's BMD to the general population as the results can infer if they are at a higher risk of fracture. These results can potentially reduce the number of undiagnosed fractures and downstream costs they entail. Despite this, the committee agreed that management is rarely changed based on the results obtained from a scan as people with cystic fibrosis should always be encouraged to optimise calcium and vitamin D and participate in exercise. Moreover, clinicians are reluctant to prescribe bisphosphonates to maintain BMD in young adults due to their negative effects on fertility, iterating that a low BMD finding from a scan is unlikely to initiate such treatment. For these reasons alone, it was evident to the committee that the use of scans in current clinical practice was not a cost-effective use of resources.

The committee added that DXA scans can overestimate reductions in BMD. If people with reduced BMD are aware of their higher risk of fracture they may stop exercising, resulting in a counterproductive effect. Furthermore, even though the cost of one DXA scan is not substantial, performing a DXA scan every 3 years in everyone with cystic fibrosis under current practice has a substantial resource and cost use when the total is considered.

An alternative to a DXA scan is a pQCT scan. However, the committee advised that the use of pQCT scans to monitor for BMD remains a research area as their interpretation is not fully understood by clinicians in clinical practice. It was noted that pQCT scans can emit radiation and are more expensive to perform than DXA scans due to the extra time and equipment they require.

Overall, the committee agreed that monitoring for reduced BMD would not be considered cost-effective in all cases. They subsequently identified populations deemed to be at a higher risk of reduced BMD who could benefit from a DXA scan.

In those populations, the committee agreed scans could be repeated on an annual basis if the BMD SDS score is less than -2.00. However, the committee did not state the frequency of bone scans in their recommendations as the frequency should be individualised to the person with cystic fibrosis, according to clinical expertise. This would inform if treatment to prevent reduced BMD should to be escalated or stopped or if specialist advice should be sought regarding bisphosphonate treatment.

The committee considered performing a DXA scan after the transition from paediatric to adult services for a baseline BMD measure and then as necessary. However, the committee noted that weight can change BMD quite markedly, this questions the value of a baseline scan that could soon be outdated. As a result, a recommendation was only prioritised to monitor BMD in high risk populations. The committee advised that this would lead to a large change in current practice and result in cost savings, but would not compromise on health benefit as current practice was not a cost-effective use of resources.

10.7.7.4 Quality of evidence

Prospective and retrospective observational studies were included in the review. The quality of the evidence, as assessed per individual studies using a critical appraisal tool for the evaluation of the quality of prognosis studies in systematic reviews (Hayden et al. 2006), was very low. The main sources of bias in the studies were:

- poorly reported sample selection, with unclear inclusion and exclusion criteria,
- the study sample did not fully represent the population of interest with regard to key characteristics, and
- important potential confounders were not appropriately accounted for.

Due to all these limitations, the committee considered that the usefulness of the data reported in the studies is very limited.

10.7.7.5 Other considerations

Due to the scarcity and low quality of the evidence, the recommendations were mainly based on committee members' clinical experience and consensus on good clinical practice.

The committee acknowledge there is a lack of longitudinal studies to evaluate the impact of low BMD on fractures and quality of life. However, it is known that people with cystic fibrosis are at an increased risk of developing osteopenia and osteoporosis (See section on Complications). They were also aware of cross-sectional evidence showing a correlation between low BMD, decreased lung function and poor nutritional status. However, they noted that although the main concern is the risk of fractures, the incidence of fractures in this population is not particularly high.

As discussed previously, the committee agreed the absence of evidence showing a benefit in conducting regular scans, and the fact that people receive treatment anyway, justifies the change in practice. Moreover, conducting routine exams can create anxiety. However, they agreed that people with cystic fibrosis and their carers may feel concerned about a change in practice. They suggested it is important to talk to the families and discuss their concerns.

No equality issues were identified by the committee for this review question.

The committee noted that evidence regarding the impact of low BMD in fractures was mostly conducted in post-menopausal women. They agreed it would be helpful if a study could be conducted looking at people with cystic fibrosis and highlighted the importance in assessing fractures and quality of life. However, it was agreed that this was not a priority research recommendation for the guideline as a whole.

10.7.7.6 Key conclusions

The committee concluded that there is no need to perform routine bone density scans to all children and adults with cystic fibrosis. DXA scans should only be considered in children and adults who are at risk of low bone mineral density. This is because there is little value in routine monitoring as children and young people get treated to help accrue bone mass in spite of the results of the test.

10.7.8 Recommendations

124. Consider dual energy X-ray absorptiometry (DXA) bone density scans for people with cystic fibrosis who have factors that put them at high risk of low bone mineral density, such as:

- frequent or long-term oral corticosteroid use
- frequent intravenous antibiotic use

- severe lung disease
- undernutrition
- previous low-impact fractures
- previous transplants
- post menopause.

125. Seek specialist advice for people with a bone mineral density standard deviation below -2.0 (Z score) or -2.5 (T score).

10.8 Exercise

Review question: What is the effectiveness of programmes of exercise in the management of cystic fibrosis?

10.8.1 Introduction

Physical Exercise programmes are widely recommended as a routine part of the management of cystic fibrosis. In addition to the benefits found by the general population, exercise participation is advised in cystic fibrosis to help maintain and slow the decline in respiratory function, facilitate airway clearance techniques, help improve bone mineral density and to increase and maintain muscle strength, flexibility and posture.

Improving and maintaining cardiovascular fitness is very important for people with cystic fibrosis. Regular education, monitoring and assessment of fitness from the point of diagnosis allows for programmes to be tailored to the individual through the spectrum of cystic fibrosis to meet specific needs

People with cystic fibrosis can experience a number of barriers to full engagement in regular exercise programmes. Some of these barrier can include physical limitations such as fatigue, frequent exacerbations and the treatment burden of medications, nebulisers and physiotherapy. Environmental and socioeconomic factors can limit participation in exercise such as access to appropriate facilities and support both in the community and in the hospital.

Exercise education and prescription has been a routine part of clinical care in cystic fibrosis for many years. However, there is extensive variability in content, supervision and frequency of the intervention. This variation is due to the lack of information about the effectiveness of specific programmes of physical exercise, including supervised and unsupervised programmes, which can lead to improve outcomes and benefits for people with cystic fibrosis.

10.8.2 Description of clinical evidence

The aim of this review was to determine the effectiveness of different exercise programmes in improving health outcomes for people with cystic fibrosis.

The interventions reviewed were: aerobic exercise programme; strength resistance training; high intensity interval training; habitual physical activity; inspiratory muscle training (performed at maximal inspiratory effort of at least 80%) or any combination of these interventions.

We looked for systematic reviews of randomized controlled trials (RCTs) and RCTs. Systematic reviews were assessed for inclusion against the protocol, and if relevant, their quality was assessed using AMSTAR. High-quality systematic reviews were included in our review, and where possible data and quality assessment were taken directly from the review.

Individual studies were retrieved for completeness and accuracy, and were also checked for additional outcomes. Low-quality SR were excluded from our review, but the list of included studies was checked to identify relevant trials.

Given that no evidence was found for high intensity interval training or time to next exacerbation (a critical outcome) in the RCTs, cohort studies were assessed for inclusion and data were reported from these studies only in relation to this intervention or this critical outcome not covered by the RCTs.

Although there were no RCTs on habitual physical activity, cohort studies relating to this intervention were not assessed because the committee thought that the information from RCTs on long term exercise programmes was sufficient to formulate recommendations. Only 1 study on habitual physical activity was included (Cox 2016) because it looked at the outcome need for hospitalization, which was considered appropriate as a proxy outcome for time to next exacerbation.

For full details see review protocol in Appendix D.

Three Cochrane reviews were identified in the search (Cox 2013, Houston 2013, Radtke 2015).

Two reviews were included in the review:

- Radtke (2015) evaluated the effectiveness of physical exercise training compared to no training. 10 RCTs were included from this review (Hebestreit 2010, Hommerding 2015, Klijn 2004, Kriemler 2013, Moorcroft 2004, Rovedder 2014, Santana-Sosa 2012, Santana-Sosa 2014, Schneiderman-Walker 2000, Selvadurai 2002)
- Houston (2013) evaluated the effectiveness of inspiratory muscle training compared to no training. 1 RCT was included from this review (Enright 2004)

One review was excluded:

- Cox (2013) evaluated interventions for promoting physical activity in people with cystic fibrosis. No additional trials were included from this review, as they were included in Radtke (2015).

In addition, 3 RCTs (Beaudoin 2016, Orenstein 2004, Schindel 2015) and 2 cohort studies (Cox 2016, Gruber 2014) were included.

The size of the RCTs or cohort studies ranged from 14 to 67 participants. 5 studies included adults (Beaudoin 2016, Cox 2016, Enright 2004, Gruber 2014, Moorcroft 2004), 1 young people aged ≥ 16 years and adults (Rovedder 2014), 2 young people aged >12 years and adults (Hebestreit 2010, Kriemler 2013), 6 children and young people (Hommerding 2015, Klijn 2004, Orenstein 2004, Santana-Sosa 2012, Santana-Sosa 2014, Selvadurai 2002), 2 children, young people and adults (Schindel 2015; Schneiderman-Walker 2000)

2 studies were conducted in the UK (Enright 2004, Moorcroft 2004), 3 in Brazil (Hommerding 2015, Rovedder 2014, Schindel 2015), 2 in Germany (Hebestreit 2010, Gruber 2014), 2 in Spain (Santana-Sosa 2012, Santana-Sosa 2014), 2 in Canada (Beaudoin 2016, Schneiderman-Walker 2000), 2 in Australia (Cox 2016, Selvadurai 2002), 1 in the Netherlands (Klijn 2004), 1 in Switzerland (Kriemler 2013), 1 in the USA (Orenstein 2004).

6 studies assessed a supervised exercise programme (Gruber 2014, Klijn 2004, Orenstein 2004, Santana-Sosa 2014, Santana-Sosa 2012, Selvadurai 2002). 8 studies assessed a partially supervised or unsupervised exercise programme (Beaudoin 2016, Hebestreit 2010, Hommerding 2015, Kriemler 2013, Moorcroft 2004, Rovedder 2014, Schindel 2015, Schneiderman-Walker 2000). 1 study assessed supervised inspiratory muscle training (Enright 2004). 1 study assessed habitual physical activity (Cox 2016)

1 study compared a supervised aerobic exercise programme for about 19 days to no exercise programme (Selvadurai 2002). 3 studies compared an unsupervised aerobic exercise programme to no exercise programme (Hommerding 2015, Kriemler 2013, Schneiderman Walker 2000). Depending on the study, training lasted 3 months (Hommerding 2015); 6 months (Kriemler 2013) or 3 years (Schneiderman-Walker 2000).

2 studies compared a supervised strength resistance / anaerobic training programme to no exercise programme (Selvadurai 2002, Kllijn 2004). Training lasted either about 19 days (Selvadurai 2002) or 12 weeks (Klijn 2004). 1 study compared an unsupervised strength resistance / anaerobic training programme for 6 months to no exercise programme (Kriemler 2013).

2 studies compared a supervised strength / anaerobic training programme to a supervised aerobic programme (Selvadurai 2002, Orenstein 2004). Training lasted either about 19 days (Selvadurai 2002) or 1 year (Orenstein 2004). One study compared an unsupervised strength / anaerobic training programme for 6 months to an unsupervised aerobic programme for 6 months (Kriemler 2013).

1 study compared a supervised high-intensity interval training for 6 weeks to standard aerobic and anaerobic exercise programme for 6 weeks (Gruber 2014).

1study compared a supervised combined aerobic and anaerobic training programme for 8 weeks to no exercise programme (Santana-Sosa 2012).

5 studies compared an unsupervised combined aerobic and anaerobic training programme to no exercise programme (Beaudoin 2016, Hebestreit 2010, Moorcroft 2004, Rovedder 2014, Schindel 2015). Depending on the study, duration of training was 12 weeks (Beaudoin 2016), 3 months (Rovedder 2014 and Schindel 2015), 6 months (Hebestreit 2010), or 1 year (Moorcroft 2004).

1 study compared a supervised combined inspiratory muscle training, resistance and aerobic training for 8 weeks to no exercise programme (Santana-Sosa 2014).

1 study compared supervised inspiratory muscle training at 80% of maximal effort for 8 weeks to usual care (Enright 2004).

1 study compared a higher amount or longer duration of habitual physical activity to a smaller amount or shorter duration (Cox 2016).

A summary of the included studies is presented in Table 169. See also study selection flow chart in Appendix F, study evidence tables in Appendix G, list of excluded studies in Appendix H, forest plots in Appendix I, and full GRADE profiles in Appendix J.

10.8.3 Summary of included studies

A summary of the studies that were included in this review are presented in Table 169.

Table 169: Summary of included studies

Study	Intervention/Comparison	Population	Outcomes	Comments
Cochrane systematic reviews				
Radtke 2015 Cochrane SR	Comparison 1: Aerobic exercise programme versus no defined exercise programme (Selvadurai 2002, Hommerding 2015, Kriemler 2013, Schneiderman-Walker 2000)	People with cystic fibrosis of any age and any degree of disease severity	Comparison 1: Aerobic training versus no physical training • FEV_1 % predicted • FVC % predicted • VO_2 peak	Santana-Sosa 2014 looks at combined IMT +

Study	Intervention/Comparison	Population	Outcomes	Comments
	Comparison 2: Strength resistance/ anaerobic training versus no defined exercise programme (Selvadurai 2002, Klijn 2004, Kriemler 2013) Comparison 3: Combined aerobic and strength resistance training versus no defined exercise programme (Hebestreit 2010, Moorcroft 2004, Rovedder 2014, Santana-Sosa 2012, Santana-Sosa 2014)		• BMI • Not reported: • Time to next exacerbation • Quality of life • Adverse events • Preference Comparison 2: Anaerobic training versus no physical training • FEV_1 % predicted • FVC % predicted • VO_2 peak • QoL (CFQ) • BMI Not reported: • Time to next exacerbation • Adverse events • Preference Comparison 3: Combined aerobic and anaerobic training versus no physical training • FEV_1 % predicted • FVC % predicted • VO_2 peak • QoL (CFQ-R) • BMI • Adverse events Not reported: • Time to next exacerbation • Preference	resistance + aerobic
Houston 2013 Cochrane SR	Comparison 1. Inspiratory muscle training (80% maximal effort) versus control (Enright 2004)	People with cystic fibrosis of any age	Comparison 1. Inspiratory muscle training (80% maximal effort) versus control • FEV_1 (l) • FVC (l) • Not reported: • VO_2 • Time to next • exacerbation • Body composition • Preference • Quality of life	Only data for IMT80% was included

Study	Intervention/Comparison	Population	Outcomes	Comments
			• Adverse events	
Primary studies included in the SRs				
Enright 2004 (UK) RCT	Intervention: IMT at 80% of "maximal inspiratory effort" • direct supervision at home by designated training • IMT is incremental maximal effort with progressively shorter rest periods • 3 times a week for 8 weeks Control: no training	N=19 adults with cystic fibrosis Age, mean (SD): 22 (4.2) years • IMT group: n=9 • Control group: n=10	• Change in FEV_1 (l) • Change in FVC (l)	Included in Houston 2013 SR
Hebestreit 2010 (Germany) RCT	Intervention: endurance-type and strengthening exercises • Unsupervised programme • Participants agreed to increase their vigorous physical activities by a minimum of 3x 60 min per week in the first 6 months of the study. An individual exercise plan was devised for participants; activity counselling was stopped after the first 6 months and participants were encouraged to maintain or further increase their physical activity level Control: • Participants told to keep their activity level constant during the first 12 months of the study. During the second year (period from 12 - 24 months) they were free to change their activity behaviour	N=38 people with cystic fibrosis >12 years • Exercise group n=23; mean (SD) age: 19.5 (6.4) years • Control group n=15; mean (SD) age: 19.4 (5.3) years	• Change in FEV_1 % predicted • Change in FVC % predicted • Change in VO_2 peak • Change in BMI	Included in Radtke 2015 SR and Cox 2013 SR Data for > 6 months was not considered, as training lasted 6 months
Hommerding 2015 (Brazil) RCT	Intervention: aerobic exercise programme • Unsupervised programme • Included jogging, swimming, walking, ball games and stretching exercises. • based on verbal and written guidelines • twice a week for at least 20 min for 3 months • participants received telephone calls every 2 weeks and instructions were provided by 1 of the authors Control: usual care	N=34 children and young people with cystic fibrosis • Exercise group n=17; mean (SD) age 13.4 (2.8) years • Control group n=17; mean (SD) age 12.7 (3.3) years	• Change in FEV_1 % predicted • Change in FVC % predicted • Change in VO_2 peak	Included in Radtke 2015 SR

Study	Intervention/Comparison	Population	Outcomes	Comments
	• participants were instructed about aerobic exercises once at baseline according to the CF centre routine			
Klijn 2004 (Netherlands) RCT	Intervention: anaerobic training • Supervised programme • 2 days per week for 30 to 45 min • 12 weeks Control: normal daily activities • 12 weeks	N=20 children and young people with cystic fibrosis with stable disease • Intervention group n=11; mean (SD) age 13.6 (1.3) years • Control group n=9; mean (SD) age 14.2 (2.1) years	• Change in VO_2 peak • Change in quality of life	Included in Radtke 2015 SR and Cox 2013 SR 3 participants dropped out; 1 withdrew from the training group for practical reasons
Kriemler 2013 (Switzerland) RCT	Intervention 1: aerobic training • Unsupervised programme • 24-months: 6-month intervention and long-term follow-up period • 3 sessions per week of 30 to 45 minutes for 6 months and received support which was stopped thereafter Intervention 2: strength training • Unsupervised programme • 24-months: 6-month intervention and long-term follow-up period • 3 sessions per week of 30 to 45 minutes for the first 6 months and received support which was stopped thereafter Control: no programme • Participants in the control group were told to keep their activity level constant. • Free access to a fitness centre for 1 year after the first study year	N=39 participants with cystic fibrosis >12 years • Aerobic training group (n=17): mean (95% CI) age 23.8 (21.5 to 26.5) years • Strength training group (n=12): mean (95% CI) age 19.0 (16.0 to 22.0) years • Control group (n=10): mean (95% CI) age 20.3 (17.0 to 23.6) years. • A separate control group from a parallel study (Hebestreit 2010) was added due to an unusual	• Change in FEV_1 % predicted • Change in FVC % predicted • Change in VO_2 peak • Change in BMI	Included in Radtke 2015 SR Long-term exercise study.

Study	Intervention/Comparison	Population	Outcomes	Comments
		deterioration of physical health in the control group in this study (n=15), mean (95% CI) age 19.5 (16.8 to 22.2) years		
Moorcroft 2004 (UK) RCT	Intervention: aerobic exercise • Unsupervised programme • exercise based on individual preferences general aerobic exercises for lower body and weight training for upper body) for 12 months • 3 times per week Control: usual activities • Continue with usual activities	N=51 adults with cystic fibrosis • Exercise group (n=30): mean (SD) age 23.5 (6.4) years. • Control group (n=18): 23.6 (5.5) years.	• Change in BMI	Included in Radtke 2015 SR Long-term study over 1 year. 42 completed the study
Rovedder 2014 (Brazil) RCT	Intervention: aerobic and muscle strengthening exercises • unsupervised programme • 3-month home-based exercise programme. • printed guidance • advised to perform the programme on a daily basis • weekly telephone contacts were Control: no programme • standard follow-up from a physiotherapist without any specific exercise instructions	N=41 people with cystic fibrosis ≥ 16 years • Exercise group n=19; mean (SD) age 23.8 (8.3) years. • Control group n=22; mean (SD) age 25.4 (6.9) years.	• Change in FEV_1 % predicted • Change in FVC % predicted • Change in Quality of life (CFQ-R)	Included in Radtke 2015 SR
Santana-Sosa 2012 (Spain) RCT	Intervention: endurance and strengthening exercises • supervised programme • 8-week intrahospital programme followed by a 4-week detraining period • 3 times per week • same chest physiotherapy Control: no programme • Participants were instructed on the positive effects of regular physical activity	N=22 children and young people with cystic fibrosis. • Exercise group n=11; mean (SEM, range) age 11 years (3 years, 5 - 15 years) • Control group n=11; mean (SEM, range) age 10.0 years (2	• Change in Quality of life (CFQ-R children's and parents' report) • Adverse events	Included in Radtke 2015 SR

Study	Intervention/Comparison	Population	Outcomes	Comments
		years, 6 to 14 years)		
Santana-Sosa 2014 (Spain) RCT	Intervention: aerobic + anaerobic + IMT • supervised programme • 8-week programme followed by a 4-week detraining period • whole body aerobic and weight training 3 times per week • plus 2 daily IMT sessions • same chest physiotherapy Control: low intensity IMT	N=20 children and young people with cystic fibrosis Age: 6 to 17 years • Exercise group n=10; mean (SEM) age 11.1 (1.1) years. • Control group n=10; mean (SEM) age 10.1 (1.1) years.	• Change in FEV_1 (l) • Change in FVC (l) • Change in Quality of life (CFQ-R) • Change in weight (kg) • Adverse events	Included in Radtke 2015 SR
Schneiderman-Walker 2000 (Canada) RCT	Intervention 1: aerobic programme • unsupervised programme • home programme • Minimum of 20 min 3 times per week for 3 years Control: maintained regular activity	N=65 people with cystic fibrosis Age: 7 to 19 years • Exercise group (n=30): mean (SD) age 13.4 (3.9 years). • Control group (n=35): mean (SD) age 13.3 (3.6) years.	• Change in FEV_1 % predicted • Change in FVC % predicted	Included in Radtke 2015 SR and Cox 2013 SR Long-term study 2 groups similar at baseline. 7 dropouts.
Selvadurai 2002 (Australia) RCT	Intervention 1: aerobic training • supervised programme • 30 min, 5 times per week • Training during hospital admission; mean (SD) duration of admission: 18.6 (3.9) days Intervention 2: resistance training • supervised programme • 30 min, 5 times per week • Training during hospital admission; mean (SD) duration of admission: 18.8 (4.1) days Control: no specific training	N=66 children and young people with cystic fibrosis aged 8 to 16 years admitted to hospital due to a pulmonary exacerbation • Aerobic training group (n=22): mean (SD) age 13.2 (2.0) years) • Resistance training group (n=22): mean (SD)	• Change in FEV_1 % predicted • Change in FVC % predicted • Change in VO_2 peak	Included in Radtke 2015 SR and Cox 2013 SR No dropouts.

Study	Intervention/Comparison	Population	Outcomes	Comments
		age 13.1 (2.1) years • Control group (n=22): mean (SD) age 13.2 (2.0) years		
Additional primary studies				
Beaudoin 2016 (Canada) RCT	Intervention: Combined aerobic and resistance training programme • Unsupervised programme • Both aerobic and resistance training: 3 times per week for 12 weeks • Aerobic training: 20 to 40 min; resistance training: 5 to 7 exercises for a progressively increasing number of sets and repetitions Control: no specific training	N= 14 adults with cystic fibrosis aged ≥18 years with glucose abnormality; • Exercise group (n=8): mean age 31.9; age range 24 to 41 • Control group (n=6): mean age 35.5; age range 22 to 57	• Change in FEV_1% predicted • Change in quality of life (measured with CFQ-R) • Change in FVC % predicted • Change in VO_2 peak • Change in BMI • Change in weight	18 adults were recruited; 17 were randomized; 2 dropped out because of pulmonary exacerbations; 1 was excluded because he was noncompliant
Cox 2016 (Australia) Prospective cohort study	Comparison 1. • Intervention: ≥30 minutes daily of habitual moderate-vigorous physical activity • Control: <30 minutes daily of habitual moderate-vigorous physical activity Comparison 2. • Intervention 2: ≥30 minutes daily of habitual moderate-vigorous physical activity accumulated in bouts of > 10 minutes • Control 2: <30 minutes or ≥30 minutes of habitual moderate-vigorous physical activity not accumulated in bouts of > 10 minutes	• N=61 adults with cystic fibrosis aged ≥18 years • Intervention: n=33 • Control: n=28	• Need for hospitalization, n (%) during 12 months	Physical activity was measured over 5-7 days using a portable multi-sensor armband; moderate PA intensity was classified as ≥4.8 metabolic equivalents. People were considered to have reached physical activity in bouts of

Study	Intervention/Comparison	Population	Outcomes	Comments
				at least 10 minutes duration if said bouts were recorded on any 1 day in the monitoring period. 65 adults were recruited; 4 were excluded because they wore the armband for insufficient time at baseline
Gruber 2014 (Germany) Cohort study	Intervention 1: interval-training • supervised programme • interval-training treadmill program • high intensity bouts alternated with active recovery phases • 5 times weekly for 6 weeks Intervention 2: Standard aerobic + anaerobic exercise program • supervised programme • 5 times per week for 45 minutes, for 6 weeks • activities based on participants' fitness level • including prolonged endurance exercise in terms of walking or Nordic-Walking complemented by ball games, stretching, balance training, and resistance training	N=43 rehabilitation clinic cystic fibrosis adult inpatients with FEV_1<40% predicted Age: overall age not reported • Interval training group: n=20. Mean (SD) age: 26.4 (7.5) • Standard exercise group: n=23. Mean (SD) age: 26.3 (9.9)	• Change in FEV_1 % predicted • Change in VC % predicted • Change in VO_2 (ml/kg/min) • Change in BMI	Patients who were unable to participate in standard exercise programme (Subjects who de-saturated (SpO2 < 90%) at very low power (≤0.3 W/kg) or had a SpO2 ≤ 90% at rest) were allocated to high intensity interval training Not stated explicitly if prospective or retrospective, seems

Study	Intervention/Comparison	Population	Outcomes	Comments
				prospective
Orenstein 2004 (USA) RCT	Intervention 1: upper-body strength training • supervised programme • individually tailored to the participants' characteristics • participants were given an upper-body-only-weight-resistance machine • at least 3 times per week, for 1 year • home visits once a week for the first 8 weeks, followed by monthly visits • instructed to perform biceps curls, lateral pull-downs, and military and bench presses • instructed to keep their heart rate <55% of their maximum Intervention 2: aerobic training • supervised programme • each child was given a stair-stepping machine • at least 3 times per week, for 1 year • home visits once a week for the first 8 weeks, followed by monthly visits • instructed to exercise 5 minutes per session, gradually increasing to 30 minutes • taught to gradually increase their target heart rate to 70% of their maximum heart rate	N=67 children and young people with cystic fibrosis Age: 8 to 18 years • Exercise group: n=26) • Control group: n=30	• Change in FEV_1 % predicted • Change in VO_2	
Schindel 2015 (Brazil) RCT	Intervention: aerobic exercise and stretching • supervised programme • 3-month-long exercise programme • instruction handbook • calendar where patients marked the days they performed exercise • at least 3 times per week for a minimum of 20 minutes and perform each stretch 2 times for 20 seconds each • phone calls from the researcher every 2 weeks Control: usual care	N=34 people with cystic fibrosis Age range: 7 to 20 years • Exercise group: n=17. Mean (SD) age: 13.6 (2.8) years • Control group: n=17. Mean (SD) age: 12.9 (3.9) years	• Change in FEV_1 % predicted • Change in FVC % predicted	

Study	Intervention/Comparison	Population	Outcomes	Comments
	• Verbal orientations to perform exercise and stretching			

BMI: body mass index; CF: cystic fibrosis; FVC: forced vital capacity; FEV 1: forced expiratory volume in 1 second; IMT: inspiratory muscle training; RCT: randomised controlled trial; SR: systematic review; VC: vital capacity

10.8.4 Clinical evidence profile

The clinical evidence profiles for this review question (exercise in people with cystic fibrosis) are presented in Table 170 to Table 177.

Table 170: Summary clinical evidence profile: Comparison 1. Aerobic exercise training programme versus no exercise programme

Comparison 1. Aerobic exercise training programme compared to no exercise programme for cystic fibrosis						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No exercise programme	Aerobic exercise training programme				
[Supervised programme] Change in FEV_1 % predicted - Scale from: 0 to 100. Follow-up: at hospital discharge, mean 18.7 days	The mean change in FEV_1 % predicted in the control group was 4.51	The mean change in FEV_1 % predicted in the aerobic exercise training programme groups was 2.03 higher (2.31 lower to 6.37 higher)		44 (Selvadurai 2002)	⊕⊕⊖⊖ low[1,2]	
[Unsupervised programme] Change in FEV_1 % predicted - Scale from: 0 to 100. Follow-up: 3 months	The mean change in FEV_1% predicted in the control group was 1 in 1 study, -7.92 in the other study	The mean change in FEV_1 % predicted in the aerobic exercise training programme groups was MD 5.23 higher (10.06 lower to 20.52 higher)		58 (Hommerding 2015, Kriemler 2013)	⊕⊖⊖⊖ very low[3,4,5]	
[Unsupervised programme] Change in FEV_1 % predicted - Scale from: 0 to 100. Follow-up: 6 months	The mean change in FEV_1% predicted in the control group was -11	The mean change in FEV_1 % predicted in the aerobic exercise training programme groups was 17.17 higher (8.59 to 25.75 higher)		25 (Kriemler 2013)	⊕⊕⊖⊖ low[6]	

Comparison 1. Aerobic exercise training programme compared to no exercise programme for cystic fibrosis						
[Unsupervised programme] Change in FEV_1 % predicted - Scale from: 0 to 100. Follow-up: 3 years	The mean change in FEV_1% predicted in the control group was -3.47	The mean change in FEV_1 % predicted - unsupervised programme in the intervention groups was 2.01 higher (0.06 lower to 4.08 higher)		65 (Schneiderman-Walker 2000)	⊕⊕⊕⊖ moderate 7	
[Supervised programme] Change in FVC % predicted - Scale from: 0 to 100. Follow-up: at hospital discharge, mean 18.7 days	The mean change in FVC1% predicted in the control group was 2.28	The mean change in FVC % predicted in the aerobic exercise training programme groups was 0.06 higher (2.55 lower to 2.67 higher)		44 (Selvadurai 2002)	⊕⊖⊖⊖ very low[1,8]	
[Unsupervised programme] Change in FVC % predicted - Scale from: 0 to 100. Follow-up: 3 months	The mean change in FVC1% predicted in the control group was 2 in 1 study. -5.57 in the other study	The mean change in FVC % predicted in the aerobic exercise training programme groups was 3.99 higher (6.62 lower to 14.61 higher)		58 (Hommerding 2015, Kriemler 2013)	⊕⊖⊖⊖ very low[3,8,9]	
[Unsupervised programme] Change in FVC % predicted - Scale from: 0 to 100. Follow-up: 6 months	The mean change in FVC1% predicted in the control group was -7.85	The mean change in FVC % predicted in the aerobic exercise training programme groups was 12.51 higher (5.9 to 19.12 higher)		25 (Kriemler 2013)	⊕⊕⊖⊖ low[6]	
[Unsupervised programme] Change in FVC % predicted - Scale from: 0 to 100. Follow-up: 3 years	The mean change in FVC1% predicted in the control group was -2.42	The mean change in FVC % in the aerobic exercise training programme in the intervention groups was 2.17 higher (0.47 to 3.87 higher)		65 (Schneiderman-Walker 2000)	⊕⊕⊖⊖ low[7,10]	
[Supervised programme] Change in VO_2 peak - ml/min per kg BW Follow-up: at	The mean change in VO_2 in the control group was -1.22	The mean change in VO_2 peak in the aerobic exercise training programme groups was		44 (Selvadurai 2002)	⊕⊕⊕⊖ moderate [1]	

Comparison 1. Aerobic exercise training programme compared to no exercise programme for cystic fibrosis						
hospital discharge, mean 18.7 days		8.53 higher (4.85 to 12.21 higher)				
[Unsupervised programme] Change in VO_2 peak - ml/min per kg BW Follow-up: 3 months	The mean change in VO_2 in the control group was 2.3 in 1 study, -2.45 in the other study.	The mean change in VO_2 peak in the aerobic exercise training programme groups was MD 3.76 higher (6.89 lower to 14.41 higher)		59 (Hommerding 2015, Kriemler 2013)	⊕⊖⊖⊖ very low[8,11,12]	
[Unsupervised programme] Change in VO_2 peak - ml/min per kg BW Follow-up: 6 months	The mean change in VO_2 in the control group was -11.48	The mean change in VO_2 peak in the aerobic exercise training programme groups was 18.33 higher (8.95 to 27.71 higher)		25 (Kriemler 2013)	⊕⊕⊖⊖ low[6]	
Time to next exacerbation	No evidence was found					
[Unsupervised programme] Change in BMI - kg/m2 Follow-up: 3 months	The mean change in BMI in the control group was -0.3	The mean change in BMI in the aerobic exercise training programme groups was 0.3 higher (0.13 lower to 0.73 higher)		25 (Kriemler 2013)	⊕⊖⊖⊖ very low[6,10]	
[Unsupervised programme] Change in BMI – Kg/ m2 Follow-up: 6 months	The mean change in BMI in the control group was -0.4	The mean change in BMI in the aerobic exercise training programme groups was 0.4 higher (0 to 0.8 higher)		25 (Kriemler 2013)	⊕⊖⊖⊖ very low[6,10]	
[Supervised programme] Change in BMI -	No evidence was found					
Quality of life	No evidence was found					
Preference for training programme	No evidence was found					
Adverse events	No evidence was found					

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: BMI: body mass index; CI: confidence interval; CF: cystic fibrosis; FEV_1: forced expiratory

Comparison 1. Aerobic exercise training programme compared to no exercise programme for cystic fibrosis
volume in 1 second; FVC: forced vital capacity; kg: kilogrammes MD: mean difference; min: minute; ml: millilitres; VO_2 max/ peak: maximal oxygen consumption

1 The quality of the evidence was downgraded by 1 because of unclear risk of bias in relation to random sequence generation, blinding of participants and personnel and blinding of outcome assessment.
2 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 clinical MID
3 The quality of the evidence was downgraded by 2 because of unclear risk of bias in relation to allocation concealment, blinding of participants and personnel and blinding of outcome assessment in 1 study; high risk of bias in relation to random sequence generation and allocation concealment, unclear risk of blinding of personnel, unclear risk of other bias (due to the deterioration of physical health in the control group) in the other study
4 The quality of the evidence was downgraded by 2 due to very serious heterogeneity (chi-squared p<0.1, I-squared inconsistency statistic of 90%) and no plausible explanation was found with sensitivity or subgroup analysis.
5 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 clinical MIDs
6 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to random sequence generation and allocation concealment, unclear risk of bias in relation to blinding of participants and personnel, and unclear risk of other bias (due to the deterioration of physical health in the control group)
7 The quality of the evidence was downgraded by 1 because of unclear risk of bias in relation to allocation concealment, blinding of participants and personnel, incomplete outcome data and other bias (exclusion criteria were not stated)
8 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs
9 The quality of the evidence was downgraded by 2 due to very serious heterogeneity (chi-squared p<0.1, I-squared inconsistency statistic of 84%) and no plausible explanation was found with sensitivity or subgroup analysis.
10 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID
11 The quality of the evidence was downgraded by 2 because of unclear risk of bias in relation to allocation concealment, blinding of participants and personnel, blinding of outcome assessment and other bias (the mean peak heart rate reached during the exercise test is indicative of submaximal effort, which is likely to underestimate the true VO_2 peak of the study participants) in 1 study; high risk of bias in relation to random sequence generation and allocation concealment, unclear risk of blinding of personnel, unclear risk of other bias (due to the deterioration of physical health in the control group) in the other study
12 The quality of the evidence was downgraded by 2 due to very serious heterogeneity (chi-squared p<0.1, I-squared inconsistency statistic of 75%) and no plausible explanation was found with sensitivity or subgroup analysis.

Table 171: Summary clinical evidence profile: Comparison 2.1. Strength resistance/ anaerobic training programme versus no exercise programme

Comparison 2.1. Strength resistance/ anaerobic training programme compared to no exercise programme for cystic fibrosis						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No exercise programme	Strength resistance/ anaerobic training programme				
[Supervised programme] Change in FEV_1 % predicted Scale from: 0 to 100. Follow-up: at hospital discharge, mean 18.7 days	The mean change in FEV_1 % predicted in the control group was 4.51	The mean change in FEV_1 % predicted in the strength resistance/ anaerobic training groups was 5.58 higher (1.34 to 9.82 higher)		44 (Selvadurai 2002)	⊕⊕⊖⊖ low[1,2]	

Comparison 2.1. Strength resistance/ anaerobic training programme compared to no exercise programme for cystic fibrosis						
[Unsupervised programme] Change in FEV_1 % predicted Scale from: 0 to 100. Follow-up: mean 3 months	The mean change in FEV_1 % predicted in the control group was -7.92	The mean change in FEV_1 % predicted in the strength resistance/ anaerobic training groups was 11.11 higher (5.16 to 17.06 higher)		21 (Kriemler 2013)	⊕⊕⊖⊖ low[3]	
[Unsupervised programme] Change in FEV_1 % predicted Scale from: 0 to 100. Follow-up: mean 6 months	The mean change in FEV_1 % predicted in the control group was -11	The mean change in FEV_1 % predicted in the strength resistance/ anaerobic training groups was 19.51 higher (10.57 to 28.45 higher)		21 (Kriemler 2013)	⊕⊕⊖⊖ low[3]	
[Supervised programme] Change in FVC % predicted - Scale from: 0 to 100. Follow-up: at hospital discharge, mean 18.7 days	The mean change in FVC % predicted in the control group was 2.28	The mean change in FVC % predicted in the strength resistance/ anaerobic training groups was 0.17 higher (2.31 lower to 2.65 higher)		44 (Selvadurai 2002)	⊕⊖⊖⊖ very low[1,4]	
[Unsupervised programme] Change in FVC % predicted - Scale from: 0 to 100. Follow-up: mean 3 months	The mean change in FVC % predicted in the control group was -5.57	The mean change in FVC % in the strength resistance/ anaerobic training groups was 7.37 higher (1.89 to 12.85 higher)		21 (Kriemler 2013)	⊕⊖⊖⊖ very low[3,5]	
[Unsupervised programme] Change in FVC % predicted Scale from: 0 to 100. Follow-up: mean 6 months	The mean change in FVC % predicted in the control group was -7.85	The mean change in FVC % predicted in the strength resistance/ anaerobic training groups was 14.05 higher (7.16 to 20.94 higher)		21 (Kriemler 2013)	⊕⊕⊖⊖ low[3]	

Comparison 2.1. Strength resistance/ anaerobic training programme compared to no exercise programme for cystic fibrosis						
[Supervised programme] Change in VO_2 peak ml/min per kg body weight Follow-up: at hospital discharge, mean 18.7 days	The mean change in VO_2 peak in the control group was -1.22	The mean change in VO_2 peak in the strength resistance/ anaerobic training groups was 1.95 higher (1.61 lower to 5.51 higher)		44 (Selvadurai 2002)	⊕⊕⊖⊖ low[1,5]	
[pooled supervised and unsupervised] Change in VO_2 peak at 3 months ml/min per kg body weight Follow-up: mean 3 months	The mean change in VO_2 peak in the control group was -1.84 in 1 study. 2.45 in the other study	The mean change in VO_2 peak in the strength resistance/ anaerobic training groups was 6.36 higher (1.22 to 11.49 higher)		41 (Klijn 2004, Kriemler 2013)	⊕⊖⊖⊖ very low[5,6]	
[Unsupervised programme] Change in VO_2 peak ml/min per kg body weight. Scale from: 0 to 100. Follow-up: mean 3 months	The mean change in VO_2 peak in the control group was -1.84	The mean change in VO_2 peak in the strength resistance/ anaerobic training groups was 9.34 higher (1.66 to 17.02 higher)		21 (Kriemler 2013)	⊕⊖⊖⊖ very low[3,5]	
[Supervised programme] Change in VO_2 peak ml/min per kg body weight. Scale from: 0 to 100. Follow-up: mean 3 months	The mean change in VO_2 peak in the control group was -2.45	The mean change in VO_2 peak in the strength resistance/ anaerobic training groups was 3.95 higher (2.95 lower to 10.85 higher)		20 (Klijn 2004)	⊕⊕⊖⊖ low[5,7]	
[Unsupervised programme] Change in VO_2 peak ml/min per kg body weight Follow-up: mean 6 months	The mean change in VO_2 peak in the control group was -11.48	The mean change in VO_2 peak in the strength resistance/ anaerobic training groups was 17.7 higher (5.98 to 29.42 higher)		18 (Kriemler 2013)	⊕⊖⊖⊖ very low[3,5]	
Time to next exacerbation	No evidence was found					

Comparison 2.1. Strength resistance/ anaerobic training programme compared to no exercise programme for cystic fibrosis						
[Unsupervised programme] Change in BMI Follow-up: mean 3 months	The mean change in BMI in the control group was -0.3	The mean change in BMI in the strength resistance/ anaerobic training groups was 0.5 higher (0.07 to 0.93 higher)		25 (Kriemler 2013)	⊕⊖⊖⊖ very low[3,5]	
[Unsupervised programme] Change in BMI Follow-up: mean 6 months	The mean change in BMI in the control group was -0.4	The mean change in BMI in the strength resistance/ anaerobic training groups was 0.7 higher (0.27 to 1.13 higher)		25 (Kriemler 2013)	⊕⊕⊖⊖ low[3]	
[Supervised programme] Change in BMI	No evidence was found					
[Unsupervised programme] Change in quality of life	No evidence was found					
[Supervised programme] Change in quality of life CFQ - physical function domain. Scale from: 0 to 100. Follow-up: mean 3 months	The mean change in quality of life in the control group was 87.1	The mean change in health-related quality of life in the strength resistance/ anaerobic training groups was 1.3 higher (11.55 lower to 14.15 higher)		20 (Kijn 2004)	⊕⊖⊖⊖ very low[3,8]	
Preference for training programme	No evidence was found					
Adverse events	No evidence was found					

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: BMI: body mass index; CI: confidence interval; CF: cystic fibrosis; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; kg: kilogrammes MD: mean difference; min: minute; ml: millilitres; VO_2 max/ peak: maximal oxygen consumption

1 The quality of the evidence was downgraded by 1 because of unclear risk of bias in relation to random sequence generation, blinding of participants and personnel and blinding of outcome assessment.
2 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 clinical MID
3 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to random sequence generation and allocation concealment, unclear risk of bias in relation to blinding of participants and personnel, and unclear risk of other bias (due to the deterioration of physical health in the control group)

4 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs
5 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID
6 The quality of the evidence was downgraded by 2 because of: high risk of bias in relation to random sequence generation and allocation concealment, unclear risk of bias in relation to blinding of participants and personnel, and unclear risk of other bias (due to the deterioration of physical health in the control group) in 1 study; unclear risk of bias in relation to random sequence generation, blinding of participants and personnel, blinding of outcome assessment, other bias (exclusion criteria were not reported) in the other study.
7 The quality of the evidence was downgraded by 1 because of unclear risk of bias in relation to random sequence generation (described as randomised but no details given), blinding of participants and personnel, blinding of outcome assessment (the primary researcher was blinded but their role in the study is unclear), other bias (exclusion criteria were not reported)
8 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 clinical MIDs

Table 172: Summary clinical evidence profile: Comparison 2.2. Strength/ anaerobic training programme versus aerobic training programme

Comparison 2.2. Strength/ anaerobic training compared to aerobic training for cystic fibrosis						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Aerobic training	Strength/ anaerobic training				
[Supervised programme] Change in FEV_1 % predicted at hospital discharge Scale from: 0 to 100. Follow-up: at hospital discharge, mean 18.7 days	The mean change in FEV_1 % predicted in the aerobic training group was 6.54	The mean change in FEV_1 % predicted in the strength/ anaerobic training groups was 3.55 higher (0.94 lower to 8.04 higher)		44 (Selvadurai 2002)	⊕⊕⊖⊖ low[1,2]	
[Unsupervised programme] Change in FEV_1% predicted Scale from: 0 to 100. Follow-up: 3 months	The mean change in FEV_1 % predicted in the aerobic training group was 4.89	The mean change in FEV_1% predicted in the strength/ anaerobic training groups was 1.7 lower (7.67 lower to 4.27 higher)		25 (Kriemler 2013)	⊕⊖⊖⊖ very low[2,3]	
[Unsupervised exercise] Change in FEV_1 % predicted Scale from: 0 to 100. Follow-up: 6 months	The mean change in FEV_1 % predicted in the aerobic training group was 6.17	The mean change in FEV_1 % predicted in the strength/ anaerobic training groups was 2.34 higher (6.33 lower to 11.01 higher)		26 (Kriemler 2013)	⊕⊖⊖⊖ very low[3,4]	

Comparison 2.2. Strength/ anaerobic training compared to aerobic training for cystic fibrosis						
[Supervised exercise] Change in FEV_1 % predicted Scale from: 0 to 100. Follow-up: 6 months	The mean change in FEV_1 % predicted in the aerobic training group was -2.57	The mean change in FEV_1% predicted in the strength/ anaerobic training groups was 1.66 lower (11.24 lower to 7.92 higher)		56 (Orenstein 2004)	⊕⊖⊖⊖ very low[4,5]	
[Pooled results for supervised and unsupervised programmes] Change in FEV_1 % predicted Scale from: 0 to 100 Follow-up: 6 months	The mean change in FEV_1 % predicted in the aerobic training group was 6.17 in 1 study and -2.57 in the other study	The mean change in FEV_1 % predicted in the strength/ anaerobic training groups was 0.54 higher (5.89 lower to 6.97 higher)		82 (Kriemler 2013, Orenstein 2004)	⊕⊖⊖⊖ very low[4,6]	
[Supervised exercise] Change in FEV_1 % predicted Scale from: 0 to 100. Follow-up: 12 months	The mean change in FEV_1 % predicted in the aerobic training group was -1.19	The mean change in FEV_1 % predicted in the strength/ anaerobic training groups was 0.3 higher (9.21 lower to 9.81 higher)		53 (Orenstein 2004)	⊕⊖⊖⊖ very low4,5	
[Supervised programme] Change in FVC % predicted Scale from: 0 to 100. Follow-up: at hospital discharge, mean 18.7 days	The mean change in FVC % predicted in the aerobic training group was 2.34	The mean change in FVC % predicted in the strength/ anaerobic training groups was 0.11 higher (2.49 lower to 2.71 higher)		44 (Selvadurai 2002)	⊕⊖⊖⊖ very low[1,7]	
[Unsupervised programme] Change in FVC % predicted Scale from: 0 to 100 Follow-up: 3 months.	The mean change in FVC % predicted in the aerobic training group was 3.67	The mean change in FVC % predicted in the strength/ anaerobic training groups was 1.87 lower (7.33 lower to 3.59 higher)		25 (Kriemler 2013)	⊕⊖⊖⊖ very low[3]	
[Unsupervised programme] Change in FVC % predicted	The mean change in FVC % predicted in	The mean change in FVC % predicted in the strength/		26 (Kriemler 2013)	⊕⊖⊖⊖ very low[3,7]	

Comparison 2.2. Strength/ anaerobic training compared to aerobic training for cystic fibrosis						
Scale from: 0 to 100. Follow-up: 6 months	the aerobic training group was 4.66	anaerobic training groups was 1.54 higher (5.12 lower to 8.2 higher)				
[Supervised programme] Change in VO_2 peak Follow-up: at hospital discharge, mean 18.7 days	The mean change in VO_2 peak in the aerobic training group was 7.31	The mean change in VO_2 peak in the strength/ anaerobic training groups was 6.58 lower (10.18 to 2.98 lower)		44 (Selvadurai 2002)	⊕⊕⊖⊖ low[1,8]	
[Unsupervised programme] Change in VO_2 peak Follow-up: 3 months	The mean change in VO_2 peak in the aerobic training group was 7.26	The mean change in VO_2 peak in the strength/ anaerobic training groups was 0.24 higher (6.1 lower to 6.58 higher)		26 (Kriemler 2013)	⊕⊖⊖⊖ very low[3,7]	
[Unsupervised exercise] Change in VO_2 max Follow-up: 6 months	The mean change in VO_2 peak in the aerobic training group was 6.85	The mean change in VO_2 max in the strength/ anaerobic training groups was 0.63 lower (10.94 lower to 9.68 higher)		26 (Kriemler 2013)	⊕⊖⊖⊖ very low3,7	
[Supervised exercise] Change in VO_2 max Follow-up: 6 months	The mean change in VO_2 peak in the aerobic training group was -1.91	The mean change in VO_2 max in the strength/ anaerobic training groups was 0.25 lower (3.35 lower to 2.85 higher)		56 (Orenstein 2004)	⊕⊖⊖⊖ very low[5,8]	
[Pooled results for supervised and unsupervised programmes] Change in VO_2 max Follow-up: 6 months	The mean change in VO_2 max in the aerobic training group was 6.85 in 1 study and -1.91 in the other study	The mean change in VO_2 max in the strength/ anaerobic training groups was -0.28 lower (3.25 lower to 2.69 higher)		82 (Kriemler 2013, Orenstein 2004)	⊕⊕⊖⊖ low[6]	

Comparison 2.2. Strength/ anaerobic training compared to aerobic training for cystic fibrosis						
[Supervised exercise] Change in VO_2 max Follow-up: 12 months	The mean change in VO_2 peak in the aerobic training group was -0.91	The mean change in VO_2 max in the strength/ anaerobic training groups was 0.82 lower (4.32 lower to 2.68 higher)		53 (Orenstein 2004)	⊕⊖⊖⊖ very low[5,8]	
[Unsupervised programme] Change in BMI Follow-up: 3 months	The mean change in BMI in the aerobic training group was 0	The mean change in BMI in the strength/ anaerobic training groups was 0.2 higher (0.23 lower to 0.63 higher)		30 (Kriemler 2013)	⊕⊖⊖⊖ very low[3,8]	
[Unsupervised programme] Change in BMI Follow-up: 6 months	The mean change in BMI in the aerobic training group was 0	The mean change in BMI in the strength/ anaerobic training groups was 0.3 higher (0.1 lower to 0.7 higher)		30 (Kriemler 2013)	⊕⊖⊖⊖ very low[3,8]	
[Supervised programme] Change in BMI -	No evidence available					
Quality of life	No evidence available					
Preference for training programme	No evidence available					
Adverse events	No evidence available					

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: BMI: body mass index; CI: confidence interval; CF: cystic fibrosis; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; kg: kilogrammes MD: mean difference; min: minute; ml: millilitres; VO_2 max/ peak: maximal oxygen consumption

1 The quality of the evidence was downgraded by 1 because of unclear risk of bias in relation to random sequence generation, blinding of participants and personnel and blinding of outcome assessment.
2 The quality of the evidence was downgraded by 1 because the 95% 95% CI crossed 1 clinical MID
3 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to random sequence generation and allocation concealment, unclear risk of bias in relation to blinding of participants and personnel, and unclear risk of other bias (due to the deterioration of physical health in the control group)
4 The quality of the evidence was downgraded by 2 because the 95% 95% CI crossed 2 clinical MIDs
5 The quality of the evidence was downgraded by 2 due to high risk of bias in relation to blinding of participants and personnel and unclear risk of bias in relation to random sequence generation and allocation concealment.
6 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to random sequence generation and allocation concealment in 1 study, and unclear risk of bias in relation to the same domains in the other study; high risk of bias in relation to blinding of participants and personnel in 1 study and unclear risk of bias in relation to the same domains in the other study; and unclear risk of other bias in 1 study (due to the deterioration of physical health in the control group)
7 The quality of the evidence was downgraded by 2 because the 95% 95% CI crossed 2 default MIDs
8 The quality of the evidence was downgraded by 1 because the 95% 95% CI crossed 1 default MID

Table 173: Summary clinical evidence profile: Comparison 3. High-intensity interval training versus standard aerobic and anaerobic exercise programme

Comparison 3. High intensity interval training programme compared to standard combined aerobic and anaerobic exercise programme for cystic fibrosis						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Standard combined aerobic and anaerobic exercise programme	High intensity interval training programme				
[Unsupervised programme] Change in FEV_1%	No evidence was found					
[Supervised programme] Change in FEV_1% predicted - Scale from: 0 to 100. Follow-up: 6 weeks	The mean change in FEV_1 % predicted in the control group was 2.8	The mean change in FEV_1% predicted in the high intensity interval training groups was 3.9 lower (7.61 to 0.19 lower)		43 (Gruber 2014)	⊕⊖⊖⊖ very low[1,2]	
[Unsupervised programme] Change in vital capacity (VC) % predicted	No evidence was found					
[Supervised programme] Change in vital capacity (VC) % predicted Scale from: 0 to 100. Follow-up: 6 weeks	The mean change in VC % predicted in the standard exercise group was 3.9	The mean change in vital capacity (VC) % predicted in the high intensity interval training groups was 5.1 lower (11.05 lower to 0.85 higher)		43 (Gruber 2014)	⊕⊖⊖⊖ very low[1,3]	
[Unsupervised programme] Change in VO_2 peak	No evidence was found					
[Supervised programme] Change in VO_2 peak Follow-up: 6 weeks	The mean change in VO_2 peak in the control standard exercise was 3.3	The mean change in VO_2 peak in the high intensity interval training groups was 0.8 lower (4.59 lower to 2.99 higher)		43 (Gruber 2014)	⊕⊖⊖⊖ very low[1,3]	

Comparison 3. High intensity interval training programme compared to standard combined aerobic and anaerobic exercise programme for cystic fibrosis						
Time to next exacerbation	No evidence was found					
[Unsupervised programme] BMI	No evidence was found					
[Supervised programme] BMI Follow-up: 6 weeks	The mean change in BMI in the standard exercise group was 0.4	The mean BMI in the high intensity interval training groups was 0 higher (1.34 lower to 1.34 higher)		44 (Gruber 2014)	⊕⊖⊖⊖ very low[1,4]	
Quality of life	No evidence was found					
Preference for training programme	No evidence was found					
Adverse events	No evidence was found					

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: BMI: body mass index; CI: confidence interval; CF: cystic fibrosis; FEV_1: forced expiratory volume in 1 second; VC: vital capacity; kg: kilogrammes MD: mean difference; min: minute; ml: millilitres; VO_2 max/ peak: maximal oxygen consumption

1 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to the selection of the participants for each group and the comparability of the groups
2 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 clinical MID
3 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID
4 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs

Table 174: Summary clinical evidence profile: Comparison 4. Inspiratory muscle training (IMT) at 80% of maximal effort versus usual care

Comparison 4. Inspiratory muscle training (80% of maximal effort) programme compared to usual care for cystic fibrosis						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Usual care	Inspiratory muscle training (IMT) (80% of maximal effort) programme				
Change in FEV_1% (litres) Scale from: 0 to 100. Follow-up: 2 to 6 months	The mean change in FEV_1 (litres) in the control group was 2	The mean change in FEV_1% (litres) in the IMT groups was 0 higher (0.9 lower to 0.9 higher)		19 (Enright 2004)	⊕⊕⊖⊖ low[1]	

Comparison 4. Inspiratory muscle training (80% of maximal effort) programme compared to usual care for cystic fibrosis						
Change in FVC (litres) Scale from: 0 to 100. Follow-up: 2 to 6 months	The mean change in FEV_1 (litres) in the control group was 3	The mean change in FVC (litres) in the IMT groups was 0.1 higher (0.9 lower to 1.1 higher)		19 (Enright 2004)	⊕⊖⊖⊖ very low[1,2]	
VO_2 peak	No evidence was found					
Time to next exacerbation	No evidence was found					
Body composition	No evidence was found					
Quality of life	No evidence was found					
Preference for training programme	No evidence was found					
Adverse events	No evidence was found					
**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).* *Abbreviations: CI: confidence interval; CF: cystic fibrosis; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; IMT: inspiratory muscle training; MD: mean difference*						

1 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to blinding (performance bias and detection bias), and unclear risk of bias in relation to random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other bias.
2 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs

Table 175: Summary clinical evidence profile: Comparison 5. Combined aerobic and anaerobic training programme versus no exercise programme

Comparison 5. Combined aerobic and anaerobic training programme compared to no exercise programme for cystic fibrosis						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No exercise programme	Combined aerobic and anaerobic training programme				
[Unsupervised programme] Change in FEV_1 % predicted Scale from: 0 to 100.	The mean change in FEV_1 % predicted in the control group was	The mean change in FEV_1 % predicted in the combined aerobic and anaerobic training groups		89 (Beaudoin 2016, Rovedder 2014, Schindel 2015)	⊕⊕⊖⊖ low[1,2]	

Comparison 5. Combined aerobic and anaerobic training programme compared to no exercise programme for cystic fibrosis						
Follow-up: 3 months	-0.5 in 1 study; -2 in another study; 2.7 in the third study.	was 4.27 lower (9.63 lower to 1.09 higher)				
[Unsupervised programme] Change in FEV_1 % predicted Scale from: 0 to 100. Follow-up: 3-6 months	The mean change in FEV_1 % predicted in the control group was -4.1	The mean change in FEV 1 % predicted in the combined aerobic and anaerobic training groups was 2 higher (5.31 lower to 9.31 higher)		35 (Hebestreit 2010)	⊕⊖⊖⊖ very low[3,4]	
[Unsupervised programme] Change in FVC % predicted Scale from: 0 to 100. Follow-up: 3 months	The mean change in FVC % predicted in the control group was: -3.68 in 1 study; -3.5 in 1 study; 1.8 in 1 study	The mean change in FVC % predicted in the combined aerobic and anaerobic training groups was 1.47 lower (6.21 lower to 3.27 higher)		89 (Beaudoin 2016, Rovedder 2014, Schindel 2015)	⊕⊕⊖⊖ low[1,5]	
[Unsupervised programme] Change in FVC % predicted Scale from: 0 to 100. Follow-up: 3-6 months	The mean change in FVC % predicted in the control group was not calculable	The mean change in FVC % predicted in the combined aerobic and anaerobic training groups was 0.5 higher (4.3 lower to 5.3 higher)		35 (Hebestreit 2010)	⊕⊖⊖⊖ very low[3,6]	
[Unsupervised programme] Change in VO_2 peak Follow-up: 3 months	The mean change in VO_2 peak in the control group was 2.37	The mean change in VO_2 peak in the combined aerobic and anaerobic training groups was 2.13 lower (7.06 lower to 2.80 higher)		14 (Beaudoin 2016)	⊕⊖⊖⊖ very low[6,7]	
[Unsupervised programme] Change in VO_2 peak Follow-up: 3-6 months	The mean change in VO_2 peak in the control group was not calculable	The mean change in VO_2 peak in the combined aerobic and anaerobic training groups		38 (Hebestreit 2010)	⊕⊕⊖⊖ low[3]	

Comparison 5. Combined aerobic and anaerobic training programme compared to no exercise programme for cystic fibrosis						
		was 2.04 higher (0.08 to 4 higher)				
[Unsupervised programme] Change in weight (kg) Follow-up: 3 months	The mean change in weight (kg) in the control groups was 0.07	The mean change in weight (kg) in the combined aerobic and anaerobic training groups was 0.27 lower (12.95 lower to 12.41 higher)		14 (Beaudoin 2016)	⊕⊖⊖⊖ very low[6,7]	
[Unsupervised programme] Change in BMI Follow-up: 3 months	The mean change in BMI in the control groups was -0.15	The mean change in BMI in the combined aerobic and anaerobic training groups was 0.06 higher (2.68 lower to 2.80 higher)		14 (Beaudoin 2016)	⊕⊖⊖⊖ very low[6,7]	
[Unsupervised programme] Change in BMI Follow-up: 3 to 6 months	The mean change in BMI in the control groups was not calculable	The mean change in BMI in the combined aerobic and anaerobic training groups was 0.4 higher (0.17 lower to 0.97 higher)		35 (Hebestreit 2010)	⊕⊖⊖⊖ very low[3,5]	
[Unsupervised programme] Change in BMI Follow-up: 12 months	The mean change in BMI in the control groups was not calculable	The mean change in BMI in the combined aerobic and anaerobic training groups was 0.54 higher (0.09 lower to 1.17 higher)		48 (Moorcroft 2004)	⊕⊖⊖⊖ very low[5,8]	
[Unsupervised programme] Change in QOL: CFQ-R physical - Scale from: 0 to 100. Follow-up: 3 months	The median (IQR) CFQ-R physical in the control group was 2.4 (--1.0 to 13)	Not calculable.	P=0.742	41 (Rovedder 2014)	⊕⊕⊕⊖ moderate[9,10]	
[Unsupervised programme]	The mean change in CFQ-R	The mean change in CFQ-R physical in the		14 (Beaudoin 2016)	⊕⊖⊖⊖	

Comparison 5. Combined aerobic and anaerobic training programme compared to no exercise programme for cystic fibrosis						
Change in QOL: CFQ-R physical Follow-up: 3 months	physical in the control group was 6.92	combined aerobic and anaerobic training in the intervention groups was 0.60 higher (17.56 lower to 18.76 higher)			very low[4,7]	
[Unsupervised programme] Change in QOL: CFQ-R body image Scale from: 0 to 100. Follow-up: 3 months	The median (IQR) CFQ-R body image in the control group was 3.0 (-2 to 11)	Not calculable.	P=0.915	41 (Rovedder 2014)	⊕⊕⊖ moderate[9,10]	
[Unsupervised programme] Change in QOL: CFQ-R body image) Follow-up: 3 months	The mean change in CFQ-R body image in the control group was 1.87	The mean change in CFQ-R body image in the combined aerobic and anaerobic training groups was 6.03 lower (18.89 lower to 6.83 higher)		14 (Beaudoin 2016)	⊕⊖⊖ ⊖ very low[2,7]	
[Unsupervised programme] Change in QOL: CFQ-R digestive - Scale from: 0 to 100. Follow-up: 3 months	The median (IQR) CFQ-R digestive in the control group was -0.5 (0 to 0)	Not calculable.	P=0.953	41 (Rovedder 2014)	⊕⊕⊖ moderate[9,10]	
[Unsupervised programme] Change in QOL: CFQ-R digestive Follow-up: 3 months	The mean change in CFQ-R digestive in the control group was -9.25	The mean change in CFQ-R in the combined aerobic and anaerobic training groups was 14.80 higher (0.43 to 29.17 higher)		14 (Beaudoin 2016)	⊕⊖⊖ ⊖ very low[2,7]	
[Unsupervised programme] Change in QOL: CFQ-R respiratory - Scale from: 0 to 100.	The median (IQR) CFQ-R respiratory in the control group was -4.7 (-1 to 7)	Not calculable.	P=0.925	41 (Rovedder 2014)	⊕⊕⊖ moderate[9,10]	

Comparison 5. Combined aerobic and anaerobic training programme compared to no exercise programme for cystic fibrosis						
Follow-up: 3 months						
[Unsupervised programme] Change in QOL: CFQ-R respiratory Follow-up: 3 months	The mean change in CFQ-R respiratory in the control group was 4.63	The mean change in CFQ-R respiratory in the combined aerobic and anaerobic training groups was 4.63 lower (16.88 lower to 7.62 higher)		14 (Beaudoin 2016)	⊕⊖⊖⊖ very low[2,7]	
[Unsupervised programme] Change in QOL: CFQ-R emotional - Scale from: 0 to 100. Follow-up: 3 months	The median (IQR) CFQ-R emotional in the control group was -4.3 (-13 to 6)	Not calculable.	P=0.458	41 (Rovedder 2014)	⊕⊕⊕⊖ moderate[9,10]	
[Unsupervised programme] Change in QOL: CFQ-R emotional Supervised programme Scale from: 0 to 100. Follow-up: 3 months	The mean change in CFQ-R emotional in the control group was 1.11	The mean change in CFQ-R emotional in the combined aerobic and anaerobic training groups was 7.78 lower (18.65 lower to 3.09 higher)		14 (Beaudoin 2016)	⊕⊖⊖⊖ very low[2,7]	
[Unsupervised programme] Change in QOL: CFQ-R social - Scale from: 0 to 100. Follow-up: 3 months	The median (IQR) CFQ-R social in the control group was -1.7 (5 to 11)	Not calculable.	P=0.953	41 (Rovedder 2014)	⊕⊕⊕⊖ moderate[9,10]	
[Unsupervised programme] Change in QOL: CFQ-R social Scale from: 0 to 100. Follow-up: 3 months	The mean change in CFQ-R social in the control group was 2.79	The mean change in CFQ-R social in the combined aerobic and anaerobic training groups was 5.29 lower (18.10 lower to 7.52 higher)		14 (Beaudoin 2016)	⊕⊖⊖⊖ very low[2,7]	
[Unsupervised programme]	The median (IQR) CFQ-R eating	Not calculable.	P=0.913	41 (Rovedder 2014)	⊕⊕⊕⊖	

Comparison 5. Combined aerobic and anaerobic training programme compared to no exercise programme for cystic fibrosis						
Change in QOL: (CFQ-R eating disturbances - Scale from: 0 to 100. Follow-up: 3 months	disturbances in the control group was -2.0 (-11 to 0)				moderate[9,10]	
[Unsupervised programme] Change in QOL: CFQ-R eating disturbances Follow-up: 3 months	The mean change in CFQ-R food in the control group was 0	The mean change in CFQ-R eating disturbances in the combined aerobic and anaerobic training groups was MD -1.39 (4.91 lower to 2.13 higher)		14 (Beaudoin 2016)	⊕⊕⊖⊖ low[7]	
[Unsupervised programme] Change in QOL: CFQ-R treatment at 3 months - u	The median (IQR) CFQ-R treatment in the control group was -2.0 (-11 to 0)	Not calculable.	P=0.850	41 (Rovedder 2014)	⊕⊕⊕⊖ moderate[9,10]	
[Unsupervised programme] Change in QOL: CFQ-R treatment Scale from: 0 to 100. Follow-up: 3 months	The mean change in CFQ-R treatment in the control group was 0	The mean change in CFQ-R treatment in the combined aerobic and anaerobic training groups was 5.56 lower (26.03 lower to 14.91 higher)		14 (Beaudoin 2016)	⊕⊖⊖⊖ very low[4,7]	
[Unsupervised programme] Change in QOL: CFQ-R vitality Scale from: 0 to 100. Follow-up: 3 months	The median (IQR) CFQ-R vitality in the control group was 2.6 (-8 to 10)	Not calculable.	P=0.579	41 (Rovedder 2014)	⊕⊕⊕⊖ moderate9,10	
[Unsupervised programme] Change in QOL: CFQ-R vitality Follow-up: 3 months	The mean change in CFQ-R vitality in the control group was 0	The mean change in CFQ-R vitality in the combined aerobic and anaerobic training in the intervention groups was 3.13 higher		14 (Beaudoin 2016)	⊕⊖⊖⊖ very low[4,7]	

Comparison 5. Combined aerobic and anaerobic training programme compared to no exercise programme for cystic fibrosis						
		(13.45 lower to 19.71 higher)				
[Unsupervised programme] Change in QOL: CFQ-R health - Scale from: 0 to 100. Follow-up: 3 months	The median (IQR) CFQ-R health in the control group was -3.0	Not calculable.	P=0.382	41 (Rovedder 2014)	⊕⊕⊕⊖ moderate[9,10]	
[Unsupervised programme] Change in QOL: CFQ-R health Scale from: 0 to 100. Follow-up: 3 months	The mean change in CFQ-R health in the control group was 16.68	The mean change in CFQ-R health at 3 months in the combined aerobic and anaerobic training groups was 5.57 lower (21.75 lower to 10.61 higher)		14 (Beaudoin 2016)	⊕⊖⊖⊖ very low[4,7]	
[Unsupervised programme] Change in QOL: CFQ-R weight Scale from: 0 to 100. Follow-up: 3 months	The median (IQR) CFQ-R weight in the control group was 4.6 (0 to 33)	Not calculable.	P=0.410	41 (Rovedder 2014)	⊕⊕⊕⊖ moderate[9,10]	
[Unsupervised programme] Change in QOL: CFQ-R weight Follow-up: 3 months	The mean change in CFQ-R weight in the control group was 0	The mean change in CFQ-R weight in the combined aerobic and anaerobic training groups was 8.34 lower (36.73 lower to 20.05 higher)		14 (Beaudoin 2016)	⊕⊖⊖⊖ very low[4,7]	
[Unsupervised programme] Change in QOL: CFQ-R role limitations Follow-up: 3 months	The mean change in CFQ-R role limitations in the control group was -5.56	The mean change in CFQ-R role limitations in the combined aerobic and anaerobic training groups was 4.52 higher (13.37 lower to 22.41 higher)		14 (Beaudoin 2016)	⊕⊖⊖⊖ very low[4,7]	
[Supervised programme]	In the control group the median pre-intervention	Not calculable.	P=0.257	22 (Santana-	⊕⊕⊖⊖ low[10,11]	

Comparison 5. Combined aerobic and anaerobic training programme compared to no exercise programme for cystic fibrosis						
Change in QOL: CFQ-R children's Scale from: 0 to 100. Follow-up: 2 months	was 696 (495 to 741); the median post-intervention was 719 (550 to 734)			Sosa 2012)		
[Supervised programme] Change in QOL: CFQ-R parents' Scale from: 0 to 100. Follow-up: 2 months	In the control group the median pre-intervention was 896 (688 to 1011); the median post-intervention was 889 (811 to 973)	Not calculable.	P=0.143	22 (Santana-Sosa 2012)	⊕⊕⊖⊖ low[10,11]	
Preference for training programme	No evidence available					
[Supervised programme] Adverse events Follow-up: 2 months	No data reported for the control group	Not calculable. No adverse events occurred during exercise training		22 (Santana-Sosa 2012)	⊕⊕⊖⊖ low[10,11]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: BMI: body mass index; CI: confidence interval; CF: cystic fibrosis; CFQ-R: cystic fibrosis questionnaire revised; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; kg: kilogrammes MD: mean difference; min: minute; ml: millilitres; VO_2 max/ peak: maximal oxygen consumption

1 The quality of the evidence was downgraded by 1 because of unclear risk of bias in relation to the allocation concealment and blinding of participants and personnel across the 3 studies; high risk of bias in relation to incomplete outcome data and unclear risk of bias in relation to blinding of outcome assessors and selective reporting in 1 study
2 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 clinical MID
3 The quality of the evidence was downgraded by 2 because of high risk of bias for the random sequence generation and allocation concealment domains and unclear risk of bias for the blinding, outcome assessment and reporting domains
4 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 clinical MIDs
5 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID
6 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs
7The quality of the evidence was downgraded by 2 because of high risk of bias in relation to incomplete outcome data, unclear risk of bias in relation to allocation concealment, selective reporting, blinding of participants and personnel and outcome assessors8 The quality of the evidence was downgraded by 2 due to unclear risk of bias for the random sequence generation, allocation concealment, blinding and incomplete outcome data domains
9 The quality of the evidence was downgraded by 1 because of unclear risk of bias for the domains allocation concealment and blinding
10 Imprecision could not be calculated, as results are provided as medians
11 The quality of the evidence was downgraded by 2 because of high risk of bias for incomplete outcome data, and unclear risk of bias for random sequence generation, allocation concealment and blinding

Table 176: Summary clinical evidence profile: Comparison 6. Combined inspiratory muscle training (IMT), resistance and aerobic training

Comparison 6. Combined inspiratory muscle training resistance and aerobic training compared to no exercise programme for cystic fibrosis						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No exercise programme	Combined inspiratory muscle training (IMT) resistance and aerobic training				
[Unsupervised programme] Change in FEV_1 (litres)	No evidence was found.					
[Supervised programme] Change in FEV_1 (litres) Scale from: 0 to 100. Follow-up: 2 months	The mean change FEV_1 (litres) in the control group was 0.02	The mean change in FEV_1 (litres) in the combined inspiratory muscle training (IMT) resistance and aerobic training group was 0.07 higher (0.54 lower to 0.68 higher)		20 (Santana-Sosa 2014)	⊕⊕⊖⊖ low[1]	
[Unsupervised programme] Change in FVC	No evidence was found.					
Change in FVC (litres) Supervised programme Scale from: 0 to 100. Follow-up: 2 months	The mean change FVC (litres) in the control group was -0.05	The mean change in forced vital capacity (litres) in the combined inspiratory muscle training (IMT) resistance and aerobic training group was 0.16 higher (0.68 lower to 1 higher)		20 (Santana-Sosa 2014)	⊕⊖⊖⊖ very low[1,2]	
Change in VO_2 peak	No evidence was found.					
Time to next exacerbation	No evidence was found.					
[Unsupervised programme] Change in weight	No evidence was found.					

Comparison 6. Combined inspiratory muscle training resistance and aerobic training compared to no exercise programme for cystic fibrosis						
[Supervised programme] Change in weight (kg) Follow-up: 2 months	The mean change weight in the control group was 0.9	The mean change in weight at 2 months in the intervention group was 0.50 higher (10.51 lower to 11.51 higher)		20 (Santana-Sosa 2014)	⊕⊖⊖⊖ very low[1,2]	
[Unsupervised programme] Change in QOL (CFQ-R) Follow-up: 2 months	No evidence was found.					
[Supervised programme] Change in QOL (CFQ-R) Scale from: 0 to 100. Follow-up: 2 months	Not reported	The median QOL (CFQ-R) at 2 months in the intervention group was 688 (609 to 791); whereas the median pre-intervention: 629 (505 to 701) (p=0.071)		20 (Santana-Sosa 2014)	⊕⊕⊖⊖ low[1,3]	
Preference for training programme	No evidence was found.					
[Unsupervised programme] Adverse events	No evidence was found.					
[Supervised programme] Adverse events Follow-up: 2 months	Not reported	No adverse events occurred during exercise training.	Not estimable	20 (Santana-Sosa 2014)	⊕⊕⊖⊖ low[1,3]	
**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).* *Abbreviations: CI: confidence interval; CF: cystic fibrosis; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; kg: kilogrammes MD: mean difference; VO_2 max/ peak: maximal oxygen consumption*						

1 The quality of the evidence was downgraded by 2 due to high risk of bias for outcome reporting, and unclear risk of bias for randomisation, allocation concealment and blinding
2 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs
3 Imprecision could not be calculated, as data was reported narratively only

Table 177: Summary clinical evidence profile: Comparison 7. Physical activity: higher amount or longer duration versus lower amount or shorter duration

Comparison 7. Physical activity: higher amount or longer duration compared to physical activity for lower amount or shorter duration for cystic fibrosis						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence	Comments
	Assumed risk	Corresponding risk				

Comparison 7. Physical activity: higher amount or longer duration compared to physical activity for lower amount or shorter duration for cystic fibrosis						
					(GRADE)	
	Physical activity for lower amount or shorter duration	Physical activity for higher amount or longer duration				
Lung function: FEV_1% predicted	No evidence available					
Lung function: FVC% predicted	No evidence available					
VO_2 peak	No evidence available					
Body composition	No evidence available					
Quality of life	No evidence available					
Preference for training programme	No evidence available					
Adverse events	No evidence available					
[≥30 mins daily versus < 30 mins] Need for hospitalization Follow-up: 12 months	679 per 1000	482 per 1000 (312 to 746)	RR 0.71 (0.46 to 1.1)	61 (Cox 2016)	⨁⊖⊖⊖ very low[1,2]	
[≥30 mins for ≥10 mins bouts daily versus lower amount or shorter duration] Need for hospitalization Follow-up: 12 months	650 per 1000	383 per 1000 (208 to 689)	RR 0.59 (0.32 to 1.06)	61 (Cox 2016)	⨁⊖⊖⊖ very low[1,2]	
**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).* *Abbreviations: CI: confidence interval; RR: risk ratio*						

1 The quality of the evidence was downgraded by 2 due to high risk of bias in relation to the selection of the study population and the comparability of the 2 groups
2 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID

10.8.5 Economic evidence

No economic evaluations of exercise programmes were identified in the literature search conducted for this guideline. Full details of the search and economic article selection flow chart can be found in Appendix E and F, respectively.

This review question was not prioritised for de novo economic modelling. However, the exercise programmes under consideration vary in the resources and costs required, for example habitual exercise programmes could be incorporated into daily activities, whereas programmes monitored and facilitated by exercise psychologists, therapy technical instructors or physiotherapists can entail high staff costs, especially if they are performed regularly.

According to NHS Reference Costs 2015/16 the cost per attendance with a sport and exercise therapist is £94 (WF02A, Non-Admitted Face to Face Attendance, Follow-up, Non-consultant led, 325, Sport and Exercise Medicine) and the cost per attendance with a physiotherapist is £45 (WF02A, Non-Admitted Face to Face Attendance, Follow-up, Non-consultant led, 650, Physiotherapy). Consequently, supervised programmes that incur high staff costs will need to provide additional benefits, in relation to unsupervised programmes to be considered cost-effective.

10.8.6 Evidence statements

10.8.6.1 Aerobic exercise programmes

10.8.6.1.1 Comparison 1. Aerobic exercise training programme versus no exercise programme

Lung function: FEV_1

Low quality evidence from 1 RCT with 44 children and young people with cystic fibrosis admitted to hospital due to a pulmonary exacerbation showed no clinically significant difference in lung function (measured as change in FEV_1 % predicted) between the group of participants attending a *supervised* hospital training programme – consisting of aerobic exercise – and those who received usual care at hospital discharge (mean follow-up ≈ 19 days).

Very low quality evidence from 2 RCTs showed conflicting results in relation to the difference in lung function (measured as change in FEV_1 % predicted) between the group of participants receiving an *unsupervised* training programme – consisting of aerobic exercise – and the participants in the control group at 3 months follow-up. One RCT with 34 children and young people with cystic fibrosis showed no clinically significant difference between the groups. One RCT with 24 participants with cystic fibrosis aged >12 years showed a clinically significant improvement in the group of participants receiving an *unsupervised* training programme –consisting of aerobic exercise- compared to the participants in the control group.

Likewise, low quality evidence from 1 RCT with 25 people with cystic fibrosis >12 years showed a clinically significant improvement in lung function (measured as change in FEV_1 % predicted) in the group of participants receiving an *unsupervised* training programme – consisting of aerobic exercise – compared to the participants in the control group at 6 months follow-up.

However, moderate quality evidence from 1 RCT with 65 people with cystic fibrosis showed no clinically significant difference in lung function (measured as change in FEV_1 % predicted) between the group of participants receiving an *unsupervised* home exercise programme – consisting of aerobic training – and the participants in the control group at 3 years follow-up.

Lung function: FVC

Low quality evidence from 1 RCT with 44 children and young people with cystic fibrosis admitted to hospital due to a pulmonary exacerbation showed no clinically significant difference in forced vital capacity (measured as change in FVC % predicted) between the group of participants attending a *supervised* hospital training programme – consisting of aerobic exercise – and those who received usual care at hospital discharge (mean follow-up ≈ 19 days).

Very low quality evidence from 2 RCTs showed conflicting results in relation to the difference in forced vital capacity (measured as change in FVC % predicted) between the group of participants receiving an *unsupervised* training programme – consisting of aerobic exercise – and the participants in the control group at 3 months follow-up. One RCT with 34 children

and young people with cystic fibrosis showed no clinically significant difference between the groups. One RCT with 24 participants with cystic fibrosis aged >12 years showed a clinically significant improvement in the group of participants receiving an *unsupervised* training programme –consisting of aerobic exercise- compared to the participants in the control group.

Likewise, low quality evidence from 1 RCT with 25 people with cystic fibrosis >12 years showed a clinically significant improvement in forced vital capacity (measured as change in FVC % predicted) in the group of participants receiving an *unsupervised* training programme – consisting of aerobic exercise – compared to the participants in the control group at 6 months follow-up.

Low quality evidence from 1 RCT with 65 people with cystic fibrosis showed a clinically significant improvement in forced vital capacity (measured as change in FVC % predicted) in the group of participants receiving an *unsupervised* home exercise programme – consisting of aerobic training – compared to the participants in the control group at 3 years follow-up.

VO_2 max

Moderate quality evidence from 1 RCT with 44 children and young people with cystic fibrosis admitted to hospital due to a pulmonary exacerbation showed a clinically significant improvement in the maximum volume of oxygen (measured as change in VO_2 max) in the group of participants attending a *supervised* hospital training programme – consisting of aerobic exercise – compared those who received usual care at hospital discharge (mean follow-up ≈ 19 days).

Very low quality evidence from 2 RCTs showed conflicting results in relation to the difference in the maximum volume of oxygen (measured as change in VO_2 max) between the group of participants receiving an *unsupervised* training programme – consisting of aerobic exercise – and the participants in the control group at 3 months follow-up. One RCT with 34 children and young people with cystic fibrosis showed no clinically significant difference between the groups. One RCT with 25 participants with cystic fibrosis aged >12 years showed a clinically significant improvement in the group of participants receiving an *unsupervised* training programme –consisting of aerobic exercise- compared to the participants in the control group.

However, low quality evidence from 1 RCT with 25 people with cystic fibrosis >12 years showed a clinically significant improvement in the maximum volume of oxygen (measured as change in VO_2 max) in the group of participants receiving an *unsupervised* training programme – consisting of aerobic exercise – compared to the participants in the control group at 6 months follow-up.

Time to next exacerbation

No evidence was found for this critical outcome.

Body composition

Very low quality evidence from 1 RCT with 25 people with cystic fibrosis >12 years showed no clinically significant difference in weight (measured as change in BMI) between the participants receiving an *unsupervised* training programme – consisting of aerobic exercise – and the participants in the control group at 3 and 6 months follow-up.

No evidence was found for *supervised* training programmes.

Quality of life

No evidence was found for this critical outcome.

Preference for training programme

No evidence was found for this important outcome.

Adverse events

No evidence was found for this important outcome.

10.8.6.2 Strength resistance training/ anaerobic training

10.8.6.2.1 Comparison 2.1. Strength resistance / anaerobic training programme versus no exercise programme

Lung function: FEV_1

Low quality evidence from 1 RCT with 44 children and young people with cystic fibrosis admitted to hospital due to a pulmonary exacerbation showed a clinically significant improvement in lung function (measured as change in FEV_1 % predicted) in the group of participants attending a *supervised* hospital training programme – consisting of anaerobic exercise – compare to those who received usual care at hospital discharge (mean follow-up ≈ 19 days).

Low quality evidence from 1 RCT with 21 people with cystic fibrosis >12 years showed a clinically significant improvement in lung function (measured as change in FEV_1 % predicted) in the group of participants attending an *unsupervised* anaerobic programme – consisting of strength training sessions – compared to the control group at 3 and 6 months follow-up.

Lung function: FVC

Very low quality evidence from 1 RCT with 44 children and young people with cystic fibrosis admitted to hospital due to a pulmonary exacerbation showed no clinically significant difference in forced vital capacity (measured as change in FVC % predicted) between the group of participants attending a *supervised* hospital training programme – consisting of anaerobic exercise – and those who received usual care at hospital discharge (mean follow-up ≈ 19 days).

However, low to very low quality evidence from 1 RCT with 21 people with cystic fibrosis >12 years showed a clinically significant improvement in forced vital capacity (measured as change in FVC % predicted) in the group of participants attending an *unsupervised* anaerobic programme – consisting of strength training sessions – compared to the control group at 3 and 6 months follow-up.

VO_2 max

Very low quality evidence from 1 RCT with 44 children and young people with cystic fibrosis admitted to hospital due to a pulmonary exacerbation showed no clinically significant difference in maximum volume of oxygen (measured as change in VO_2 max) between the group of participants attending a *supervised* hospital training programme – consisting of anaerobic exercise – and those who received usual care at hospital discharge (mean follow-up ≈ 19 days).

Low quality evidence from 1 RCT with 20 children and young people with cystic fibrosis with stable disease showed no clinically significant difference in the maximum volume of oxygen (measured as change in VO_2 max) between the participants attending a supervised anaerobic training programme and the control group at 3 months follow-up. However, very low quality evidence from 1 RCT with 21 people with cystic fibrosis >12 years showed a clinically significant improvement between the group of participants attending an *unsupervised* anaerobic programme – consisting of strength training sessions – and the

control group at the same follow-up. Very low quality evidence from the pooled results of both *supervised and unsupervised* training programmes showed a clinically significant beneficial effect in VO_2 max in the group of participants attending the training programme at 3 months follow-up-.

Very low quality evidence from 1 RCT with 18 people with cystic fibrosis >12 years showed a clinically significant improvement in the maximum volume of oxygen (measured as change in VO_2 max) in the group of participants attending an *unsupervised* anaerobic programme – consisting of strength training sessions – compared to the control group at 6 months follow-up.

Time to next exacerbation

No evidence was found for this critical outcome.

Body composition: BMI

Low quality evidence from 1 RCT with 25 people with cystic fibrosis >12 years showed a clinically significant improvement in weight (measured as change in BMI) in the group of participants attending an *unsupervised* anaerobic programme – consisting of strength training sessions – compared to the control group at 3 and 6 months follow-up.

Quality of life

Very low quality evidence from 1 RCT with 20 children and young people with cystic fibrosis with stable disease showed no clinically significant difference in health related quality of life (measured with the CFQ-R tool, physical domain) between the participants attending a supervised anaerobic training programme and the control group at 3 months follow-up.

No evidence was found for *supervised* training programmes.

Preference for training programme

No evidence was found for this important outcome.

Adverse events

No evidence was found for this important outcome.

10.8.6.2.2 Comparison 2.2. Strength/ anaerobic training programme versus aerobic training programme

Lung function: FEV_1

Low quality evidence from 1 RCT with 44 children and young people with cystic fibrosis admitted to hospital due to a pulmonary exacerbation showed no clinically significant difference in lung function (measured as change in FEV_1 % predicted) between the group of participants attending a *supervised* hospital anaerobic exercise training programme and those attending a *supervised* hospital aerobic exercise training programme at hospital discharge (mean follow-up ≈ 19 days).

Very low quality evidence from 1 RCT with 26 people with cystic fibrosis >12 years showed no clinically significant difference in lung function (measured as change in FEV_1 % predicted) between the group of participants attending an *unsupervised* anaerobic programme – consisting of strength training sessions –and those attending an *unsupervised* aerobic programme at 3 and 6 months follow-up. Likewise, very low quality evidence from 1 RCT with 56 children and young people with cystic fibrosis showed no clinically significant difference in lung function (measured as change in FEV_1 % predicted) between the group of

participants attending a *supervised* anaerobic training programme - consisting of upper-body strength regime – and the participants attending an aerobic training programme at 6 months follow-up. Very low quality evidence from pooled results of both *supervised and unsupervised* training programmes showed no clinically significant difference in lung function (measured as change in FEV_1 % predicted) between the group of participants attending an anaerobic training programme and those attending an aerobic training programme at 6 months follow-up.

Very low quality evidence from 1 RCT with 56 children and young people with cystic fibrosis showed no clinically significant difference in lung function (measured as change in FEV_1 % predicted) between the group of participants attending a *supervised* anaerobic training programme - consisting of upper-body strength regime – and the participants attending an aerobic training programme at 12 months follow-up.

Lung function: FVC

Very low quality evidence from 1 RCT with 44 children and young people with cystic fibrosis admitted to hospital due to a pulmonary exacerbation showed no clinically significant difference in lung function (measured as change in FVC % predicted) between the group of participants attending a *supervised* hospital anaerobic exercise training programme and those attending a *supervised* hospital aerobic exercise training programme at hospital discharge (mean follow-up ≈ 19 days).

Very low quality evidence from 1 RCT with 26 people with cystic fibrosis >12 years showed no clinically significant difference in lung function (measured as change in FVC % predicted) between the group of participants attending an *unsupervised* anaerobic programme – consisting of strength training sessions –and those attending an *unsupervised* aerobic programme at 3 and 6 months follow-up.

VO_2 max

Low quality evidence from 1 RCT with 44 children and young people with cystic fibrosis admitted to hospital due to a pulmonary exacerbation showed a clinically significant lower improvement in the maximum volume of oxygen (measured as change in VO_2 max) in the group of participants attending a *supervised* hospital anaerobic exercise training programme compared to those attending a *supervised* hospital aerobic exercise training programme at hospital discharge (mean follow-up ≈ 19 days).

Very low quality evidence from 1 RCT with 26 people with cystic fibrosis >12 years showed no clinically significant difference in the maximum volume of oxygen (measured as change in VO_2 max) between the group of participants attending an *unsupervised* anaerobic programme – consisting of strength training sessions –and those attending an *unsupervised* aerobic programme at 3 months follow-up.

Very low quality evidence from 1 RCT with 26 people with cystic fibrosis >12 years showed no clinically significant difference in the maximum volume of oxygen (measured as change in VO_2 max) between the group of participants attending an *unsupervised* anaerobic programme – consisting of strength training sessions –and those attending an *unsupervised* aerobic programme at 6 months follow-up. Likewise, very low quality evidence from 1 RCT with 56 children and young people with cystic fibrosis showed no clinically significant difference in the maximum volume of oxygen (measured as change in VO_2 max) between the group of participants attending a *supervised* anaerobic training programme - consisting of upper-body strength regime – and the participants attending a *supervised* aerobic training programme at 6 months follow-up. Low quality evidence from the pooled results of both *supervised and unsupervised* training programmes showed no clinically significant difference in in the maximum volume of oxygen (measured as change in VO_2 max) between the group

of participants attending an anaerobic training programme and those attending an aerobic training programme at 6 months follow-up.

Very low quality evidence from 1 RCT with 56 children and young people with cystic fibrosis showed no clinically significant difference in the maximum volume of oxygen (measured as change in VO_2 max) between the group of participants attending a *supervised* anaerobic training programme - consisting of upper-body strength regime – and the participants attending a *supervised* aerobic training programme at 12 months follow-up.

Time to next exacerbation

No evidence was found for this critical outcome.

Body composition

Very low quality evidence from 1 RCT with 30 people with cystic fibrosis >12 years showed no clinically significant difference in BMI between the group of participants attending an *unsupervised* anaerobic programme – consisting of strength training sessions –and those attending an *unsupervised* aerobic programme at 3 and 6 months follow-up.

No evidence was found for *supervised* exercise programmes.

Quality of life

No evidence was found for this critical outcome.

Preference for training programme

No evidence was found for this important outcome.

Adverse events

No evidence was found for this important outcome.

10.8.6.3 High intensity interval training

10.8.6.3.1 Comparison 3. High intensity interval training versus standard aerobic and anaerobic exercise programme

Lung function: FEV_1

Very low quality evidence from 1 cohort study with 43 adult inpatients with cystic fibrosis with severe disease (FEV_1 <40% predicted) showed no clinically significant difference in lung function (measured as change in FEV_1 % predicted) between the group of participants performing supervised high intensity interval training and the participants performing a *supervised* standardised exercise programme at 6 week follow-up.

No evidence was found for *unsupervised* training programmes.

Lung function: vital capacity (VC)

Very low quality evidence from 1 cohort study with 43 adult inpatients with cystic fibrosis with severe disease (FEV_1 <40% predicted) showed no clinically significant difference in vital capacity (measured as change in VC % predicted) between the group of participants performing *supervised* high intensity interval training and the participants performing a *supervised* standardised exercise programme at 6 week follow-up.

No evidence was found for *unsupervised* training programmes.

VO_2 max

Very low quality evidence from 1 cohort study with 43 adult inpatients with cystic fibrosis with severe disease (FEV_1 <40% predicted) showed no clinically significant difference in the maximum volume of oxygen (VO_2 max) between the group of participants performing *supervised* high intensity interval training and the participants performing a *supervised* standardised exercise programme at 6 week follow-up.

No evidence was found for *unsupervised* training programmes.

Time to next exacerbation

No evidence was found for this critical outcome.

Body composition: BMI

Very low quality evidence from 1 cohort study with 43 adult inpatients with cystic fibrosis with severe disease (FEV_1 <40% predicted) showed no clinically significant difference in BMI between the group of participants performing *supervised* high intensity interval training and the participants performing a *supervised* standardised exercise programme at 6 week follow-up.

No evidence was found for *unsupervised* training programmes.

Quality of life

No evidence was found for this critical outcome.

Preference for training programme

No evidence was found for this important outcome.

Adverse events

No evidence was found for this important outcome.

10.8.6.4 Inspiratory muscle training

10.8.6.4.1 Comparison 4. Inspiratory muscle training (IMT) at 80% of maximal effort versus usual care

Lung function: FEV_1

Low quality evidence from 1 RCT with 19 adults with cystic fibrosis showed no clinically significant difference in lung function (measured as change in FEV_1 % predicted) between the group of participants receiving IMT at home at 80% of maximal inspiratory effort and the participants receiving usual care at 2 to 6 months follow-up.

Lung function: FVC

Low quality evidence from 1 RCT with 19 adults with cystic fibrosis showed no clinically significant difference in lung function (measured as change in FVC % predicted) between the group of participants receiving IMT at home at 80% of maximal inspiratory effort and the participants receiving usual care at 2 to 6 months follow-up.

VO_2 max

No evidence was found for this important outcome.

Time to next exacerbation

No evidence was found for this critical outcome.

Body composition

No evidence was found for this important outcome.

Quality of life

No evidence was found for this critical outcome.

Preference for training programme

No evidence was found for this important outcome.

Adverse events

No evidence was found for this important outcome.

10.8.6.5 Combined programmes

10.8.6.5.1 Comparison 5. Combined aerobic and anaerobic training versus no exercise programme

Lung function: FEV_1

Low quality evidence from 3 RCTs with 89 people with cystic fibrosis aged ≥7 years showed no clinically significant difference in lung function (measured as change in FEV_1 % predicted) between the participants attending an *unsupervised* training programme - consisting of a combination of aerobic and anaerobic exercises - and the participants in the control group at 3 months follow-up.

Likewise, very low quality evidence from another RCT with 35 people with cystic fibrosis >12 years showed no clinically significant difference in change in FEV_1 % predicted between the participants attending an *unsupervised* training programme - consisting of a combination of endurance-type and strengthening exercises - and the control group at 3 to 6 months follow-up.

No evidence was found for *supervised* training programmes.

Lung function: FVC

Likewise, low quality evidence from 3 RCTs with 89 people with cystic fibrosis >7 years old showed no clinically significant difference in forced vital capacity (measured as change in FVC % predicted) between the participants attending an *unsupervised* training programme - consisting of a combination of aerobic and anaerobic or resistance training exercises - and the participants in the control group at 3 months follow-up.

Likewise, very low quality evidence from another RCT with 35 people with cystic fibrosis >12 years showed no clinically significant difference in change in FVC % predicted between the participants attending an *unsupervised* training programme - consisting in a combination of endurance-type and strengthening exercises - and the control group at 3 to 6 months follow-up.

No evidence was found for *supervised* training programmes.

VO_2 max

Very low quality evidence from 1 RCT with 14 adults with cystic fibrosis showed no clinically significant difference in maximum volume of oxygen (measured as change in VO_2 max) between the participants attending an *unsupervised* training programme - consisting of a combination of aerobic and resistance training exercise- and the participants in the control group at 3 months follow-up.

Low quality evidence from 1 RCT with 38 people with cystic fibrosis >12 years showed no clinically significant difference in the maximum volume of oxygen (measured as change in VO_2 max) between the participants attending an *unsupervised* training programme - consisting in a combination of endurance-type and strengthening exercises - and the participants in the control group at 3 to 6 months follow-up.

No evidence was found for *supervised* training programmes.

Time to next exacerbation

No evidence was found for this critical outcome.

Body composition: weight and BMI

Very low quality evidence from 1 RCT with 14 adults with cystic fibrosis showed no clinically significant difference in weight (measured as change in kg) between the participants attending an *unsupervised* training programme - consisting of a combination of aerobic and resistance training exercise- and the participants in the control group at 3 months follow-up.

Very low quality evidence from 1 RCT with 14 adults with cystic fibrosis showed no clinically significant difference in weight (measured as change in BMI) between the participants attending an *unsupervised* training programme - consisting of a combination of aerobic and resistance training exercise- and the participants in the control group at 3 months follow-up.

Very low quality evidence from 1 RCT with 35 people with cystic fibrosis >12 years showed no clinically significant difference in weight (measured at change in BMI) between the participants attending an *unsupervised* training programme - consisting of a combination of endurance-type and strengthening exercises - and the participants in the control group at 3 to 6 months follow-up.

Likewise, very low quality evidence from another RCT with 48 adults with cystic fibrosis showed no clinically significant difference between the participants attending an *unsupervised* training programme – consisting of general aerobic exercises and weight training – and the participants in the control group at 12 months follow-up.

No evidence was found for *supervised* training programmes.

Quality of life

Low to very low quality evidence from 1 RCT with 14 adults with cystic fibrosis showed no clinically significant difference in the following quality of life domains (measured as change in the scores obtained with CFQ-R questionnaire) between the participants attending an *unsupervised* training programme - consisting of a combination of aerobic and resistance training exercise- and the participants in the control group at 3 months follow-up: physical functioning, vitality, emotional state, eating disturbances, treatment burden, health perception, social limitations, body image, role limitations, weight problems, respiratory symptoms. The same evidence showed a clinically significant improvement in the quality of life domain digestion symptoms among the participants attending the training programme compared to the control group at 3 months follow-up.

Low quality evidence from 1 RCT with 22 children and young people with cystic fibrosis showed no significant difference in quality of life (measured with CFQ-R children's and parents' scales) between the participants attending a *supervised* intra-hospital exercise programme – consisting of endurance and strengthening exercises - and the control group at 2 months follow-up. The clinical significance of these outcomes could not be calculated.

Likewise, moderate quality evidence from 1 RCT with 41 participants with cystic fibrosis >16 years showed no significant difference in quality of life (measured with CFQ-R questionnaire, all domains) between the participants attending an *unsupervised* home-based exercise programme – consisting of aerobic and muscle strengthening exercises – and the control group at 3 months follow-up. The clinical significance of these outcomes could not be calculated.

Preference for training programme

No evidence was found for this important outcome.

Adverse events

Low quality evidence from 1 RCT with 22 children with cystic fibrosis showed that none of the participants attending a *supervised* training programme - consisting of endurance and strengthening exercises – experienced an adverse event at 2 months follow-up.

No evidence was found for *unsupervised* training programmes.

10.8.6.5.2 Comparison 6. Combined inspiratory muscle training, resistance and aerobic training versus no exercise programme

Lung function: FEV_1

Low quality evidence from 1 RCT with 20 children and young people with cystic fibrosis showed no clinically significant difference in lung function (measured as change in FEV_1 litres) between the participants attending a *supervised* training programme - consisting of a combination of inspiratory muscle training, resistance and aerobic training - and the participants in the control group at 2 months follow-up.

No evidence was found for *unsupervised* training programmes.

Lung function: FVC

Very low quality evidence from 1 RCT with 20 children and young people with cystic fibrosis showed no clinically significant difference in forced vital capacity (measured as change in FVC litres) between the participants attending a *supervised* training programme - consisting of a combination of inspiratory muscle training, resistance and aerobic training - and the participants in the control group at 2 months follow-up.

No evidence was found for *unsupervised* training programmes.

VO_2 max

No evidence was found for this important outcome.

Time to next exacerbation

No evidence was found for this critical outcome.

Body composition: weight

Very low quality evidence from 1 RCT with 20 children and young people with cystic fibrosis showed no clinically significant difference in weight change (measured in kg) between the participants attending a *supervised* training programme - consisting of a combination of inspiratory muscle training, resistance and aerobic training - and the participants in the control group at 2 months follow-up.

No evidence was found for *unsupervised* training programmes.

Quality of life

Low quality evidence from 1 RCT with 20 children and young people with cystic fibrosis showed no significant difference in quality of life (measured with CFQ-R questionnaire) between the participants attending a *supervised* training programme – consisting of a combination of inspiratory muscle training, resistance and aerobic training - at 2 months follow-up. The clinical significance of this outcome could not be calculated.

No evidence was found for *unsupervised* training programmes.

Preference for training programme

No evidence was found for this important outcome.

Adverse events

Low quality evidence from 1 RCT with 20 children and young people with cystic fibrosis showed that none of the participants attending a *supervised* training programme - consisting of a combination of inspiratory muscle training, resistance and aerobic training – experienced an adverse event at 2 months follow-up.

No evidence was found for *unsupervised* training programmes.

10.8.6.6 Habitual physical activity

10.8.6.6.1 Comparison 7. Physical activity: higher amount or longer duration versus lower amount or shorter duration

Lung function: FEV_1

No evidence was found for this critical outcome.

Lung function: FVC

No evidence was found for this important outcome.

VO_2 **max**

No evidence was found for this important outcome.

Need of hospitalization (proxy outcome for time to next exacerbation)

Very low quality evidence from a cohort study with 61 adults with cystic fibrosis showed no clinically significant difference in need for hospitalization between the group of people doing at least 30 minutes daily of moderate-vigorous physical activity compared to those doing less physical activity at 12 months follow-up. The same evidence showed that there was no clinically significant difference in need for hospitalization between the group that did at least 30 minutes of moderate-vigorous physical activity per day accumulated in bouts of more than

10 minutes and those who did less than 30 minutes daily or did more than 30 minutes but in shorter bouts at 12 months follow-up.

Body composition

No evidence was found for this important outcome.

Quality of life

No evidence was found for this critical outcome.

Preference for training programme

No evidence was found for this important outcome.

Adverse events

No evidence was found for this important outcome.

10.8.6.7 Economic evidence statements

No evidence on cost-effectiveness in people with cystic fibrosis was available for this review.

10.8.7 Evidence to recommendations

10.8.7.1 Relative value placed on the outcomes considered

The aim of this review was to determine the effectiveness of different exercise programmes in improving health outcomes for people with cystic fibrosis.

The committee chose lung function (FEV_1), quality of life and time to next exacerbation as critical outcomes for decision making. Forced vital capacity (FVC), maximum volume of oxygen (VO_2), body composition, preference for training programme and adverse events were rated as important.

10.8.7.2 Consideration of clinical benefits and harms

The committee reviewed the evidence on the effectiveness of aerobic exercise programmes compared to no exercise programme. The evidence was of moderate to very low quality. The evidence showed that these programmes were mostly effective in relation to FVC % predicted and VO_2 max, results were mixed in relation to FEV_1 % predicted or the evidence showed no benefits in relation to BMI. No evidence was found in relation to the other outcomes including adverse events. The committee concluded that the evidence showed some benefit of aerobic exercise programmes and there was no evidence of harm.

The committee reviewed the evidence on programmes of strength resistance or anaerobic training compared to no exercise programme. The evidence was of low to very low quality. The evidence showed that these programmes were mostly effective in relation to FEV_1% predicted, VO_2 max and body composition. Results were mixed in relation to FVC% predicted, the evidence showed no benefits in relation to quality of life. No evidence was found in relation to the other outcomes of interest including adverse events. The committee concluded that the evidence showed some benefit of strength resistance or anaerobic exercise programmes and there was no evidence of harm.

The committee reviewed the evidence on programmes of combined aerobic and anaerobic training compared to no exercise programme. The evidence was of moderate to very low quality and showed no benefits of training in relation to FEV_1% predicted, FVC% predicted, VO_2 max, BMI or quality of life. This kind of training did not lead to an increase in adverse events.

Overall, the committee noted that the evidence showed some benefits for lung function and no harm of aerobic, strength resistance or anaerobic training. In addition to these benefits for lung function, the committee agreed that people with cystic fibrosis would also gain the same kind of fitness benefits from exercise that would be gained by the general population. Therefore, the committee decided to recommend to advise people with cystic fibrosis of the benefits of regular exercise in relation to lung function in addition to the expected fitness benefits.

The committee reviewed the evidence on the effectiveness of a strength resistance or anaerobic training programme compared to an aerobic training programme. The evidence was of very low quality and showed no differences in relation to FEV_1 % predicted and VO_2 max. No evidence was found in relation to the other outcomes. Therefore, the committee decided not to recommend one type of exercise over another. Rather, they decided to recommend to offer all people with cystic fibrosis individualised exercise programmes which take into account the capability and preferences of the person. The committee noted that taking someone's preferences into account is key to increase the likelihood of adherence to a training programme.

The committee reviewed the evidence on high intensity interval training compared to a standard exercise programme. The evidence was of very low quality and was based on a population of inpatients with FEV_1 <40% predicted. The evidence showed no benefits in relation to FEV_1% predicted, VC% predicted, VO_2 max or BMI. No evidence was found in relation to the other outcomes including adverse events.

The committee reviewed the evidence on inspiratory muscle training (IMT) at 80% of maximal effort compared to usual care. The evidence was of low quality and showed no benefits in relation to FEV_1% predicted and FVC% predicted. No evidence was found in relation to the other outcomes including adverse events.

The committee reviewed the evidence on a programme of combined IMT, resistance and aerobic training compared to no exercise programme. The evidence was of low to very low quality. The evidence showed no benefits in relation to FEV_1, FVC, weight or quality of life. This kind of training did not lead to an increase in adverse events.

Given that the evidence on the 3 aforementioned training programmes did not show benefits or harm, and was of low to very low quality, the committee chose not to make a recommendation specific to these kinds of training.

The committee agreed that they could not draw a clear conclusion from the evidence on whether supervised programmes were more effective than unsupervised programmes. Therefore, they decided not to make a recommendation on this. They recommended, however, to regularly monitor exercise programmes at clinic visits so that they can be adapted as necessary. They noted that regular exercise testing is an important part of monitoring.

The committee noted that there was no evidence on what intensity or frequency of exercise would be the most effective. Therefore, they decided not to make a recommendation specific to this.

10.8.7.3 Consideration of economic benefits and harms

People with cystic fibrosis are encouraged to participate in activity and exercise that is available to the general population, leading to no additional resource or cost use. However, the committee noted that there may be individuals who would benefit from more specialised advice.

According to the committee, exercise programmes for individuals with cystic fibrosis should be developed along with support of physiotherapy teams that specialise in cystic fibrosis who

can provide regular monitoring and support. This enables exercise to complement existing airway clearance techniques and treatment regimens in order to maximise and support adherence. In turn, this will improve treatment effects which the committee believed would subsequently outweigh the cost of developing and maintaining those programmes.

From the clinical review, there was no strong evidence supervised programmes were more effective than unsupervised programmes or no programme. In light of this, the committee agreed that not all people with cystic fibrosis require supervised programmes. However, there may be times when supervision is important such as to help teach technique. In those cases, such as strength and resistance training, supervision is key to ensure the exercise is performed correctly to minimise injuries and maximise benefits. The committee stated that such initial costs would be negligible compared to the potential downstream costs from injuries and inactivity.

Given that not every person would benefit from supervised programmes, the committee agreed that physiotherapists must consider the opportunity cost of their time to supervise individuals. For those reasons, the committee agreed not to recommend supervised programmes as the level of supervision would be individualised.

The committee stated that patient preference is paramount to the success and sustainability of a programme. Therefore, despite higher costs, a programme could be considered cost-effective if it provides them with greater benefits than a cheaper programme. However, the committee noted that freely available activities would be trialled first. Following this, the committee did not want to specify the type or duration of exercise as this should be tailored to someone's preferences and capabilities.

The committee agreed that offering all people with cystic fibrosis individualised exercise programmes would not lead to a change in clinical practice as physiotherapists and dietitians regularly review participation in exercise at each review. Therefore, recommendations to offer exercise programmes were prioritised to enforce the importance of exercise. Moreover, the committee advised the cost to create an individualised programme would be negligible compared to the benefits sustained exercise can provide.

Following this, the committee highlighted the importance of maintaining an exercise programme, even during inpatient care, to prevent any additional deteriorations in their health that could lead to additional costs, such as longer hospital stays. As a result, the committee prioritised a recommendation to offer inpatients the opportunity to exercise. The committee agreed that inpatients usually have poorer health than outpatients and, in their experience, are more at risk of adverse events. Therefore, supervised exercise would be more appropriate for some inpatients in order to prevent the downstream costs from unsupervised exercise that is potentially unsafe or ineffective.

The committee agreed that an assessment upon hospital admission by a physiotherapist, and any subsequent supervision, would not deviate from current clinical practice. However, the committee were concerned that not all hospitals have sufficient exercise facilities for people with cystic fibrosis or space to store exercise equipment. Their solution was not to build a "second" gym, but to provide a schedule that promotes cross-infection control measures for people with cystic fibrosis to access the facilities. Achieving those schedules may incur additional cleaning and equipment, and reduce the time facilities are available for patient use. For these reasons, hospitals should consider if their strategies to prevent cross-infection using existing exercise facilities outweighs the cost to provide additional space and equipment devoted to people with cystic fibrosis.

Overall, the committee advised that their recommendations were within the remit of specialist cystic fibrosis physiotherapy teams. However, they noted that staffing levels and exercise facilities during episodes of inpatient care need to be prioritised to allow exercise programmes to be continued.

10.8.7.4 Quality of evidence

The quality of the evidence presented in this review ranged from very low to moderate as assessed by GRADE.

For the domain risk of bias, the studies were assigned the same risk of bias as in the Cochrane reviews and were not individually reviewed. The main biases that led to downgrading the quality of the evidence were randomisation, allocation concealment, attrition, and reporting bias. It is important to note that it was not possible to blind participants to the exercise intervention in RCTs thus increasing the risk of performance bias.

In studies on unsupervised programmes it was not possible to independently assess if the participants actually performed the exercise programmes as prescribed.

Another factor which led to downgrading the quality of the evidence was the imprecision, as confidence intervals crossed 1 or 2 MIDs. The committee noted that many trials were underpowered to detect a clinically important difference.

No serious issues were found regarding inconsistency (heterogeneity), as most outcomes were reported by a single study. Where heterogeneity was identified, and sensitivity or sub-group analysis did not explain the source of inconsistency, the results were explained to the committee.

No serious issues were found regarding indirectness of the population or the interventions.

10.8.7.5 Other considerations

The committee noted the NHS service specifications for cystic fibrosis do not cover exercise in detail, although they mention that inpatients should have access to facilities for exercise.

No equality issues were identified by the committee for this review question.

The committee felt a research recommendation was not needed as there is enough available evidence to show that regular exercise is beneficial for people with cystic fibrosis.

10.8.7.6 Key conclusions

The committee concluded that regular exercise is especially beneficial for people with cystic fibrosis due to the benefits to lung function and other health benefits. Exercise programmes should be individualised to take into account personal circumstances and preferences given there is no evidence that a specific programme may be better than another. There is no evidence to indicate whether a supervised exercise programme may be better than an unsupervised programme, however, the programme should be regularly monitored and adapted if necessary. Inpatient stays should be used as opportunities to promote regular exercise. Appropriate supervision should be offered, if necessary, depending on individual circumstances. Moreover, access to appropriate exercise facilities should be guaranteed in the inpatient setting while taking into account local infection control guidelines.

10.8.8 Recommendations

126. Advise people with cystic fibrosis and their family members or carers (as appropriate) that regular exercise improves both lung function and overall fitness.

127. Offer people with cystic fibrosis an individualised exercise programme, taking into account their capability and preferences.

128. Regularly review exercise programmes to monitor the person's progress and ensure that the programme continues to be appropriate for their needs.

129. Provide people with cystic fibrosis who are having inpatient care with:

- an assessment of their exercise capacity
- the facilities and support to continue their exercise programme (as appropriate), taking into account the need to prevent cross-infection (see Prevention of cross infection) and local infection control guidelines.

10.9 Psychological assessment

Review question: What strategies are effective at identifying people with cystic fibrosis for the presence of a psychological and behavioural problem?

10.9.1 Introduction

The emotional impact of a diagnosis of cystic fibrosis is significant. Without appropriate psychological guidance, people with cystic fibrosis, their families and carers can find the impact extends to their interpersonal relationships, health and quality of life. It is known that physical health outcomes can be improved if psychological distress is prevented or reduced.

Clinical psychologists with expert knowledge of cystic fibrosis can offer strategies to identify psychological and behavioural problems. They can provide interventions to prevent mental health symptoms from developing into intractable mental health diagnoses.

Clinical psychologists, as members of the specialist cystic fibrosis multidisciplinary team, can hold in mind any likely impact of cystic fibrosis treatments on emotional functioning and the key triggers for potential distress. Vice versa, emotional difficulties for other reasons can impact on cystic fibrosis treatments. Clinical psychologists can offer a preventative model of working, by offering strategies to colleagues, people with cystic fibrosis or family and carers to explore their emotional wellbeing. If necessary the clinical psychologist can offer further assessment and intervention, or facilitate onward referral for severe mental health conditions which may, or may not, be attributable to the diagnosis of cystic fibrosis.

The role of the psychologist is to promote psychological health and likely psychological and behavioural issues are; adherence, procedural-anxiety and phobias, difficulties with engagement with health care team, adjustment to diagnosis or deteriorated function, self-esteem problems, anger management, relationship difficulties, sleep problems, body image or eating issues, medical trauma, substance misuse, generalised anxiety disorders, low mood and depression. The clinical psychologist can also play a role in identifying whether other challenges of a psychological nature (for example school absence or tics) may be wholly or partially attributable to having a chronic health condition or not.

10.9.2 Description of clinical evidence

The aim of this review was to determine which assessment strategies are effective at identifying psychological, behavioural and adherence problems in children, young people and adults with cystic fibrosis.

The committee identified the following tools as relevant for this review (See Table 178 for full a description of the tools).

- Generalised Anxiety Disorder 7-item scale (GAD-7)
- Patient Health Questionnaire 2-item scale (PHQ-2)
- Patient Health Questionnaire 9-item primary care scale (PHQ-9)
- Hospital Anxiety and Depression Scale (HADS)
- Paediatric Index of Emotional Distress (PI-ED)
- Centre for Epidemiologic Studies Depression Scale (CES-D)

- Eating Disorders Examination (EDE)
- Child Eating Disorders Examination (CEDE, ChEDE)
- Eating Attitudes Test (EAT)
- Child Eating Attitude Test (ChEAT)

For the diagnostic accuracy data, the following reference standards were considered.

For psychological problems (including anxiety, depression, mood disorders, emotional distress, adjustment disorders and eating disorders), the reference standard diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD). Studies that did not clearly state the comparator to be DSM or ICD diagnosis of depression, or that did not provide sufficient diagnostic accuracy data, were excluded.

For adherence, electronic monitoring was considered the gold standard. Alternatively, pharmacy collection records were also considered a reference standard.

For other behavioural problems listed in the protocol (such as school phobia), the reference standard was considered as reported by the study.

We also included validation studies that looked at the validity and reliability of the tools.

We looked for systematic reviews of diagnostic studies, and prospective and retrospective cohort studies.

For this review, quality appraisal of the evidence has been conducted by study.

For full details see review protocol in Appendix D.

Table 178: Description of tools assessed

Tool name	Key features
Centre for Epidemiologic Studies Depression Scale (CES-D)	• The CES-D is a self-report measure and screens for depression and depressive disorders. It measures symptoms defined by the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-V) for a major depressive episode. • Designed for use with the general adult population and young people aged 13 and over. • The questionnaire is comprised of 20 items and measures symptoms of depression in nine different groups as defined by the DSM-V: sadness (dysphoria), loss of interest (anhedonia), appetite, sleep, thinking/ concentration, guilt (worthlessness), tired (fatigue), movement (agitation) and suicidal ideation. • The response values for each item ask the individual to indicate the frequency of symptoms in the past week.
Child eating attitudes test (ChEAT)	• The ChEAT is a modified version of the Eating Attitudes Test (EAT) by Garner and Garfinkle (1979) and provides an assessment of attitudes towards eating and dietary behaviours. • The ChEAT is a self-report measure for children aged between 8 to 14 years. • The questionnaire comprises 26 items that are rated on a 6-point scale with responses: 'always', 'very often', 'often', 'sometimes', 'rarely' and 'never'. • The items of the ChEAT are mostly scored and interpreted according to total score. However, factor analysis supported three factors – subscales derived from these factors are: dieting, restricting and purging and food preoccupation.
Child eating disorders examination	• The ChEDE was adapted from the Eating Disorder Examination (EDE) for recommended use with children and young people aged 8 to 14 years to assess psychopathology associated with the diagnosis of an eating disorder.

Tool name	Key features
(CEDE, ChEDE)	• The measure is a semi-structured interview, with 2 main administrative modifications compared with the EDE. Ideas about weight and shape are assessed via a sort task rather than through questioning, and some of the questions assessing actual behaviour in adults, were reformulated to assess intent in children and young people. • The interview provides an overall global score and a score for 4 subscales: restraint, eating concern, shape concern and weight concern.
Eating attitudes test (EAT)	• The EAT is a self-report measure designed adults and young people aged 15 and over which screens for symptoms and concerns characteristic of eating disorders. • The questionnaire was originally developed in 1979 and called EAT-40, containing 40 questions. The EAT-26 is used more commonly nowadays, which is a refined version of the questionnaire developed following factor analysis. • There are three parts to the 26-item version: part A asks for the age, weight and other physical attributes of the respondent, part B screens for the respondent's attitude towards their weight, height and shape and part C asks about behavioural tendencies of the respondent over the past 6 months. • Total scores are interpreted in relation to BMI norms for the individual's age. Items are also divided to produce scores for 2 areas: dieting, bulimia and food preoccupation and oral control.
Eating disorders examination (EDE)	• The EDE is a semi-structured interview to assess psychopathology associated with the diagnosis of an eating disorder, including range and severity of eating disorder features. • It is intended for use in adults but has been used in young people aged 13 and over. • It is described as an assessment and diagnostic tool which provides operationally defined eating disorder diagnoses. • Questions address the frequency in which an individual engages in behaviours indicative of an eating disorder over a 28-day period. • The interview provides an overall global score and a score for 4 subscales: restraint, eating concern, shape concern and weight concern. • The Eating Disorders Examination Questionnaire (EDE-Q) has been developed from the EDE, which provides a 41-item self-report questionnaire that retains the 4 subscales and global score.
Generalised Anxiety Disorder 7-item scale (GAD-7)	• The GAD-7 is a self-report questionnaire which provides a screening measure for generalised anxiety disorder (GAD). • It is intended for use in adults but has been used in young people aged 13 and over. • The questionnaire has 7 items which measure the severity of symptoms associated with GAD, according to DSM-IV criteria. The individual is asked to consider how often, in the past 2 weeks, they were bothered by each symptom. • Items are scored on a 4 point scale with responses: 'not at all', 'several days', 'more than half the days' and 'nearly every day'.
Hospital Anxiety and Depression scale (HADS)	• The HADS is a self-rating scale for use with adults and young people aged 13 and over; it screens for anxiety and depression in both hospital and community settings. • The measure assesses symptom severity of anxiety and depression in people with illness and the general population. • The questionnaire contains 14 items, 7 of which assess anxiety, and the remaining 7, depression.
Patient Health Questionnaire 2-item scale (PHQ-2)	• The PHQ-2 is a self-report screening tool for depression, which enquires about the frequency of depressed mood and anhedonia over the past 2 weeks. • For use with adults and young people aged 13 and over.

Tool name	Key features
	• The questionnaire contains only 2 items, which are the first 2 questions from the PHQ-9. • It is recommended that individuals who screen positive should be evaluated further with the PHQ-9 to determine whether they meet criteria for depressive disorder.
Patient Health Questionnaire 9-item scale (PHQ-9)	• The PHQ-9 is a self-report tool for screening, diagnosing, monitoring and measuring the severity of depression. • For use with both adults and young people aged 13 and over. • It contains 9 items, which incorporate DSM-IV depression diagnostic criteria. • Individuals are required to rate how frequently over the past 2 weeks they are bothered by the 9 statements presented. • Items are scored on a 4 point scale with responses: 'not at all', 'several days', 'more than half the days' and 'nearly every day'.
Paediatric Index of Emotional Distress (PI-ED)	• The PI-ED is based on the HADS and is a self-rating scale which screens for emotional distress in children and young people aged 8 to 16 years. • The measure is designed for use with both children that have physical health problems and children in a normal population. • It contains 14 questions which ask about symptoms of anxiety and depression.

Four studies were identified for inclusion in this review.

One study (Shearer 2014) aimed to evaluate the CEDE for the assessment of eating disorders in children with cystic fibrosis. The study was conducted in the UK and included 55 children and young people.

Three studies (Daniels 2011, Siracusa 2015, White 2014) aimed to determine what assessments are effective in measuring adherence to treatment in children, young people and adults with cystic fibrosis. These studies were conducted in the UK and the USA. Sample sizes ranged from 12 to 250.

None of the studies looked at tools assessing anxiety, depression, mood and emotional distress or adjustment disorders.

A summary of the included studies is presented in Table 159 and Table 180. See also study selection flow chart in Appendix F, study evidence tables in Appendix G, and list of excluded studies in Appendix H.

10.9.3 Summary of included studies and results

A summary of the included studies and results for this review is presented in Table 159 and Table 180.

Table 179: Summary of included studies and results for psychological problems

Study	Psychological disorder	Tool assessed	Participants	Results	Comments
Shearer 2004 (UK)	Eating disorder	CEDE	N=55 children and young people with CF not undergoing psychological therapy Age: 11 to 17 years	Reliability • Inter-rater reliability = 0.69 to 1 Validity Not reported	Overall quality: moderate

CF: cystic fibrosis; CEDE: Child eating disorders examination: UK: United Kingdom

Table 180: Summary of included studies and results for adherence to treatment

Study	Treatment	Method assessed	Participants	Results	Comments
Daniels 2011 (UK)	Nebulizers	Index: • Self-report • Clinician-report Gold standard: • Electronic monitoring (I-neb nebulizer system)	N=78 adults with CF on nebulizer therapy. Median age (IQR): 26 (21 to 31) years	Adherence according to self-report: • Median (IQR) = 80% (57.5% to 95%) of treatment prescribed Adherence according to electronic monitoring: • Median (IQR) = 36% (5% to 84.8%) of treatment prescribed Clinician agreement: • ICC = 0.95 (95% CI 0.44 to 0.66) • Agreement between clinician report and electronic monitoring: • ICC dietitian = 0.36 (95% CI 0.11 to 0.55) • ICC liaison/ home nurse = 0.36 (95% CI 0.15 to 0.54) • ICC physician = 0.42 (95% CI 0.21 to 0.59) • ICC ward nurse = 0.34 (95% CI 0.11 to 0.54) • ICC pharmacist = 0.28 (95% CI 0.07 to 0.47)	• Overall quality: moderate • Extreme inaccuracy was observed for individual participants by clinicians and self-report adherence.

Study	Treatment	Method assessed	Participants	Results	Comments
				• ICC physiotherapist = 0.54 (95% CI 0.36 to 0.68)	
Siracusa 2015 (USA)	Ivacaftor	Index: • Self-report • Pharmacy refill history Gold standard: • Electronic monitoring (Medication Event Monitoring System (MEMS)) • Mean monitoring duration: 118 days (SD=35)	N=12 children, young people and adults with CF previously prescribed Ivacaftor Mean age (range): 20.8 years (6 to 48 years)	Adherence rates according to (mean, SD, range): • self-report: 100% (14% to 100%) • pharmacy refill history: 84% (31) (13% to 124% • electronic monitoring: 61% (28) (4% to 99%) Electronic monitoring versus self-report • r_s=0.40; p=0.22 • ICC=0.14; p=0.23 Electronic monitoring versus pharmacy refill history • r_s=0.26; p=0.42 • ICC-=0.26; p=0.14	Overall quality: low Individuals demonstrated wide variability in regards to the different measures of adherence.
White 2014 (UK)	• Aerosol to open air • Aerosol to thin mucus • Inhaler • PERT • Oral nutritional supplements • Oral antibiotics • Nebulised antibiotics	Index: • Self-report (CFQ-R) Index: • Pharmacy script data collection	N=250 young people and adults with CF Mean (SD) age: 29.7 (9.2)	Correlation between pharmacy script collection and self-report: • Aerosol to open air: r=0.34; p<0.005 • Aerosol to thin mucus: r=0.51; p<0.001 • Inhaler: r=0.51; p<0.001 • PERT: r=0.45; p<0.001 • Oral nutritional supplements: r=0.51; p<0.001 • Oral antibiotics: r=0.46; p<0.001 • Nebulised antibiotics: r=0.55; p<0.001 • Total: r=0.61; p<0.001	Overall quality: cannot be assessed Conference abstract

CI: confidence interval; CF: cystic fibrosis; CFQ-R: cystic fibrosis questionnaire revised; ICC: intraclass correlation coefficient; IQR: inter-quartile range; PERT: pancreatic exocrine replacement therapy; SD: standard deviation

10.9.4 Clinical evidence profile

See summary of results in Table 159 and Table 180 in Summary of included studies and results.

10.9.5 Economic evidence

No economic evaluations of psychological and behavioural assessments were identified in the literature search conducted for this guideline and this review question was not prioritised for de novo economic modelling.

Full details of the search and economic article selection flow chart can be found in Appendix E and F, respectively.

10.9.6 Evidence statements

10.9.6.1 Psychological disorders

10.9.6.1.1 Anxiety

Generalised Anxiety Disorder 7-item scale (GAD-7)

No evidence was found for this tool.

Hospital Anxiety and Depression scale (HADS)

No evidence was found for this tool.

10.9.6.1.2 Depression, mood disorders and emotional distress

Centre for Epidemiologic Studies Depression Scale (CES-D)

No evidence was found for this tool.

Hospital Anxiety and Depression scale (HADS)

No evidence was found for this tool.

Patient Health Questionnaire 2-item scale (PHQ-2)

No evidence was found for this tool.

Patient Health Questionnaire 9-item scale (PHQ-9)

No evidence was found for this tool.

Paediatric Index of Emotional Distress (PI-ED)

No evidence was found for this tool.

10.9.6.1.3 Adjustment disorders

No evidence was found for this disorder.

10.9.6.1.4 Eating disorders and feeding issues

Eating attitudes test (EAT)

No evidence was found for this tool.

Child eating attitudes test (ChEAT)

No evidence was found for this tool.

Eating disorders examination (EDE)

No evidence was found for this tool.

Child eating disorders examination (CEDE)

One study reported on the usefulness of the CEDE scale in a population of 55 children and young people with cystic fibrosis not receiving psychological treatment. Inter-rater reliability ranged from 0.69 to 1. No measures of validity were reported. This overall quality of this study was moderate.

10.9.6.2 Non adherence to treatment

One study reported on the usefulness of self-report and clinician-report as measures of adherence in a population of 78 adults with cystic fibrosis on nebulizer therapy:

- there was an overestimation of adherence by the participants. No measures of reliability were reported;
- there was an overestimation of adherence by the clinicians. The intra-class correlation agreement ranged between 0.28 and 0.54.

No measures of validity were reported. It is important to note that extreme inaccuracy was observed for individual participants by clinicians and self-report adherence. This overall quality of this study was moderate.

One study reported on the usefulness of self-report and pharmacy refill history as measures of adherence in a population of 12 children, young people and adults with cystic fibrosis receiving Ivacaftor:

- there was an overestimation of adherence by the participants. There was no statistically significant correlation between overall electronic-monitoring adherence and self-report (intra-class correlation coefficient was 0.14);
- there was an overestimation of adherence by the pharmacy records. There was also no statistically significant correlation between overall electronic-monitoring adherence and pharmacy refill history (intra-class correlation coefficient was 0.26).
- No measures of validity were reported. It is important to note that individuals demonstrated wide variability in regards to the different measures of adherence. The overall quality of this study was low, mainly because it was underpowered.

One study reported on the usefulness of self-report (using the CFQ-R tool) as a measure of adherence to treatment in a population of 250 young people and adults with cystic fibrosis:

- there was a statistically significant correlation between pharmacy script collection and self-report adherence to aerosol to open air (r=0.34);
- there was a statistically significant correlation between pharmacy script collection and self-report adherence to aerosol to thin mucus (r=0.51);
- there was a statistically significant correlation between pharmacy script collection and self-report adherence to inhalers (r=0.51);

- there was a statistically significant correlation between pharmacy script collection and self-report adherence to PERT (r=0.45);
- there was a statistically significant correlation between pharmacy script collection and self-report adherence to oral nutritional supplements (r=0.51);
- there was a statistically significant correlation between pharmacy script collection and self-report adherence to oral antibiotics (r=0.51).
- there was a statistically significant correlation between pharmacy script collection and self-report adherence to nebulised antibiotics (r=0.55).

The overall quality of this study could not be assessed, as the information was extracted from a conference abstract. Full publication not available.

10.9.6.3 Economic evidence statements

No evidence on cost-effectiveness in people with cystic fibrosis was available for this review.

10.9.7 Evidence to recommendations

10.9.7.1 Relative value placed on the outcomes considered

The aim of this review was to determine which assessment strategies are effective at identifying psychological, behavioural and adherence problems in children, young people and adults with cystic fibrosis.

Sensitivity and specificity of the tools were prioritised as critical outcomes for decision making. Positive likelihood ratio, negative likelihood ratio, AUROC, and reliability or validity were rated as important outcomes.

10.9.7.2 Consideration of clinical benefits and harms

The committee agreed the limited available evidence was not helpful in guiding them to make recommendations.

The committee discussed the issue of adherence at length. They noted adherence is an overarching issue in this guideline and should not fall under the category of psychological or behavioural disorder or problem. To reflect this, results for adherence were presented separately in this review.

The results from this review showed that there is poor correlation between what participants or professionals report, and what is actually taken. Likewise, there was poor correlation between what it is collected and what it is actually taken. According to the committee, these results are consistent with clinical practice. The committee noted that adherence is extremely difficult to measure in both clinical practice and research, unless a particular objective measuring tool is employed (for example electronic monitoring or pharmacy records), which is rare in routine clinical practice. The evidence used 2 different methods for electronic monitoring as reference standards to measure adherence: the I-neb was used in one study and the Medication Event Monitoring System (MEMS) was used in another study; however the committee noted that the I-neb is by far the commonest in the UK. The committee stressed that adherence problems are common in people with chronic conditions, and those with a number of concurrent treatments, and are not specific to cystic fibrosis. They agreed that the overarching principles from the NICE guidance on Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence [CG76] is applicable to people with cystic fibrosis. Therefore, the committee decided not to make a recommendation specific to measuring adherence in cystic fibrosis care. The committee felt no specific recommendations could be made regarding assessment tools as no evidence was found. They highlighted there are no available tools specific to people with cystic

fibrosis. They noted that, although assessment tools are helpful to assess the severity of the psychological or behavioural disorder, in practice psychologists are able to intervene without a formal diagnosis. Therefore, although a case findingtool for psychological problems in cystic fibrosis would help, all people and families should be seen regularly by a psychologist..

The committee noted that routine psychological support is important to improve outcomes in a chronic and life-threatening illness. Early psychological support can improve adherence to long-term medications in adolescence, which is a major determinant of life expectancy. Following this discussion, the committee agreed a psychologist with expertise in cystic fibrosis should be an integral member of the multi-disciplinary team. They agreed people with cystic fibrosis should be seen by the psychologist as part of the annual review. However, all members in the multidisciplinary team should be aware of how to identify psychological and behavioural problems.

The committee agreed that people with cystic fibrosis should have a specialist clinical psychologist review as part of the annual review to identify psychological and behavioural problems and offer advice. Moreover, the specialist clinical psychologist should assess and advise people with cystic fibrosis, and their families and carers, at cystic fibrosis clinical visits, inpatient admissions and for further outpatient consultations (such as community visits, school or social care meetings) or telephone calls when required.

The clinical psychologist should assess the needs of family members or carers (as appropriate) in relation to the impact of cystic fibrosis to support their psychological wellbeing and to facilitate onward referral. The committee noted that if psychological needs were more of an individual nature rather than related to cystic fibrosis, the clinical psychologist would refer the person to the GP who would then provide onward referral to a mental health practitioner, who would be part of the local mental health team. The clinical psychologist should also consider (in discussion with the family) Tier 2 referral or onward referral to local psychological wellbeing services for further support (for example with the school counsellor or CAMHS).The annual review should be individualised depending on the circumstances of the person. But as a general guidance it should cover aspects such as general mental health and quality of life, behavioural problems impacting on health outcomes, adherence to treatment, school attendance, friendship and social life. The annual review should also include assessment of any emerging indicators of psychosocial problems such as poor school attendance, family break up, anxious thoughts, low mood, missing treatments, financial or home management difficulties, safeguarding concerns, employment support needs or criminality. If a severe mental health condition is identified as part of the annual assessments such as psychosis, high level of risk of self-harm or need for psychiatric care, the person should be referred to a mental health practitioner, who would be part of the local mental health team. This would normally involve a “stepping up” of care into specialist mental health services. This is already consistent with current practice. Detailed guidance on identification and management for specific mental health conditions can be found at other NICE guidelines (For example, the following guidelines on common mental health problems: Identification and pathways to care [CG123], Depression in children and young people [CG28], Depression in adults [CG90], Depression in adults with a chronic physical health problem: recognition and management [CG91], Generalised anxiety disorder and panic disorder in adults [CG113], Eating disorders in over 8s: management [CG9]; the following guidelines on social and emotional wellbeing: Social and emotional wellbeing: early years [PH40], Social and emotional wellbeing in primary education [PH12], Social and emotional wellbeing in secondary education [PH20]).

10.9.7.3 Consideration of economic benefits and harms

There will be a cost attached to the administration and interpretation of questionnaires such as the PI-ED. But the committee agreed that cost of the assessment would be negligible and outweighed if the assessment can improve identification and subsequent management. However, the committee stated that psychological and behavioural assessment tools are not

validated for people with cystic fibrosis, who have a multi-system disorder and a lifetime of complex treatment schedules. Following this, the committee noted that the cost-effectiveness of a treatment can depend on adherence and provided examples when regimens become cost-ineffective, such as unused treatments which are followed with additional supplies, or treatments prescribed at higher doses, when the former was considered to be too low. To reduce those occurrences, the committee agreed that the overarching principles from the NICE guidance on Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence [CG76] should be followed.

The committee stated that the number of people with cystic fibrosis with psychological and behavioural problems is growing. One reason for this is the limited time psychologists have to take preventative measures. To reduce the high risk of missing emerging problems, the committee agreed psychologists should be available to see people with cystic fibrosis, and their family members or carers, at outpatient clinic visits and during inpatient admissions. The committee also agreed that the frequency of visits to the psychologist should be based on individual needs as it would be cost-ineffective to monitor each individual using the same schedule when the opportunity cost of the psychologist's time is high.

Overall, the committee agreed that monitoring in addition to the annual review would promote a cost-effective use of resource as changes to a management strategy can occur sooner to reduce the negative effects psychological and behavioural problems entail. The committee also agreed that their recommendations would reinforce best practice and reduce geographical variation.

10.9.7.4 Quality of evidence

The studies included in the review aimed to establish the reliability and validity of assessment tools. The following were considered as the main criteria for assessing the quality of each study, as reported by Jerosch-Herold (2005).

- Sample size
- Sampling methodology
- Blinding of raters
- Statistical analysis

Main risk of bias in the included studies was little information given on whether observer or tester were appropriately trained or certified.

One study was only available as conference abstract and the quality could not be assessed.

In one study extreme inaccuracy was observed for individual participants by clinicians and self-report adherence. In another study, individuals demonstrated wide variability in regards to the different measures of adherence.

10.9.7.5 Other considerations

The committee discussed whether the cystic fibrosis psychologist should be available to meet people with cystic fibrosis and their families or carers at every cystic fibrosis clinic if necessary. They highlighted it is not happening in current practice. This is particularly the case in adult clinics because the number of psychologists have remained the same. This is despite the number of adult people with cystic fibrosis increasing. While this may lead to a resource impact, it was noted that early identification and intervention can help prevent more serious issues in the future.

The committee stated that when a psychologist is introduced at diagnosis stage as a natural member of the team (for example a nurse) people with cystic fibrosis and their carers are more likely to be accepting of this role.

The committee suggested some strategies effective at identifying the presence of psychological or behavioural problems.

- Informal but frequent assessments by the psychologist and multidisciplinary team members by regularly asking questions about emotional wellbeing as well as physical health.
- The team clinical psychologist can support the rest of the team in this by holding psychological wellbeing in mind, and supporting staff if they would like to think through the responses they get from patients (or family members), or provide training to staff on delivery of basic emotional support.
- Ensure team clinical psychologist presence at patient case discussions of outpatients, inpatients, complex case meetings and annual review reports.
- Annual assessment by clinical psychologist using face to face professional assessment and standardised measures of psychological wellbeing and mental health functioning.
- Providing information to people with cystic fibrosis, and their family or carer, regarding psychology services and support available including easy access to services, including self-referral.
- Increased access to clinical psychology and review of vulnerable groups and people at particularly complicated stages of cystic fibrosis. For example, newly diagnosed, mental health problems in parents or carers, substance misuse, pre- and post-transition, end stage illness, pregnancy and assisted conception, secondary diagnosis and referral for transplant.
- Provide support for people with cystic fibrosis and training for staff around sensitive issues that may be difficult to discuss. In particular, anxieties relating to transplant decisions and people's wishes for end-of-life care.

The committee discussed potential equality issues. They noted psychological problems may be more likely in people from lower socio-economic groups. However, they agreed care is available to all people so there was no need to draft additional recommendations.

The committee agreed there was a lack of evidence to determine the best objective measures of adherence. Difficulties with full adherence to all components of the cystic fibrosis daily treatment regimen were well documented and directly resulted in poor health outcomes. Studies indicated that reports of rates of adherence varied and so subjective measures were unreliable. The committee noted that the reference standards for measuring adherence are electronic monitoring or pharmacy records, and noted that the I-neb is the most commonly used method of electronic monitoring in the UK. There needed to be further research to understand the occasions when people with cystic fibrosis do and don't follow prescribed recommendations, and which types of treatment are more likely to be taken than others. This would help adapt prescribed treatments to support increased likelihood of compliance. This would lead to better health outcomes. The area was not prioritised for a research recommendation but the committee wanted it noted.

The committee agreed a research recommendation around psychological assessment. As noted previously, there are no validated tools to assess psychological and behavioural problems in people with cystic fibrosis. The committee thought it would be useful to validate generic measures, for example for depression and anxiety. They noted that people with a long term physical health condition are more likely to present with psychological and mental health difficulties than people without. NHSE recommendations state that prevention of psychological problems is the most cost-effective service provision. This means that all people with cystic fibrosis must be routinely and regularly assessed for their physical health status and their mental health status. People with cystic fibrosis would benefit, therefore, in having a routine screen which would indicate those who require further psychological intervention. This would allow early intervention by a team psychologist to support maintenance of good quality of life, prevention of the development of mental health disorders and improvement in health outcomes as a result of improved wellbeing.

10.9.7.6 Key conclusions

The committee concluded that the cystic fibrosis psychologist should be an integral member of the multidisciplinary team and should be available to people with cystic fibrosis and their families or carers. A psychological and behavioural assessment should be part of the annual review. People should be referred to a mental health practitioner, who would be part of the local mental health team, if a severe mental health condition is identified.

10.9.8 Recommendations

130. At the annual review, the specialist clinical psychologist should include assessments of:

- general mental health and wellbeing
- quality of life
- any factors that are making treatment adherence difficult
- indicators of emerging psychosocial problems
- behaviours that affect health outcomes.

131. If a severe mental health condition is identified at any assessment performed by the cystic fibrosis clinical psychologist, refer the person with cystic fibrosis to a mental health practitioner. For guidance on treating mental health conditions, refer to the relevant NICE guideline.

132. For family members or carers of people with cystic fibrosis, the specialist clinical psychologist should

- assess any cystic-fibrosis-related needs they have
- support their psychological wellbeing
- refer them to mental health practitioners as needed.

10.9.9 Research recommendations

6. What is the most effective measure of psychological functioning to use as a test for thresholds of concern in people with cystic fibrosis?

Table 181: Research recommendations rationale

Research question	What is the most effective measure of psychological functioning to use as a test for thresholds of concern in people with cystic fibrosis?
Why this is needed	
Importance to 'patients' or the population	People with a long term physical health condition are more likely to present with psychological and mental health difficulties than people without a physical health condition. NHSE recommendations are that prevention of psychological problems is the most cost-effective service provision. This means that all people with cystic fibrosis must be routinely and regularly assessed not just for their physical health status but also their mental health status. People with cystic fibrosis would benefit therefore in having a routine screen which would indicate those who require further psychological intervention. This would allow early intervention by a team psychologist to enable maintenance of good quality of life, prevention of the development of mental health disorders and improvement in health outcomes as a result of improved wellbeing.
Relevance to NICE guidance	High: There is a need to understand the particular psychological and mental health needs of people with cystic fibrosis. Mental health difficulties decrease physical health outcomes and so understanding the extent of psychological

Research question	What is the most effective measure of psychological functioning to use as a test for thresholds of concern in people with cystic fibrosis?
	needs of the cystic fibrosis population especially as an expanding population with diagnosis now in infancy and longer lifespan, NICE guidance might have to change to accommodate the psychological health as well as physical health needs. Recommendations to treat psychological health could reduce drug costs by improving attitude to health management and improving likelihood of being able to contribute economically to the workforce.
Relevance to the NHS	Early intervention to prevent psychological and mental health diagnosis will save NHS money.
National priorities	Yes: Future in Mind, NHSE, 2015; Five Year Forward View for Mental health, NHSE, 2016
Current evidence base	Research questions the evidence base is sparse. Though a few papers have moderate quality, the research has not been done.
Equality	Yes, it is anecdotally reported that those children and adults with cystic fibrosis who are most likely to suffer from mental health difficulties and be less likely to manage a complicated daily treatment regimen are over-represented in the most vulnerable societal groups.
Feasibility	Yes, though it would need to be a large scale study but potential use of the national cystic fibrosis registry for this research question
Other comments	Highlighted as an area for research development by Guideline committee, no existing literature in this area, of benefit for clinical assessment, direction of appropriate treatment resource, research and national registry data.

Table 182: Research recommendation statements

Criterion	Explanation
Population	Children and young people with cystic fibrosis aged 6 years and over, and their parents or carers. Adults with cystic fibrosis.
Index test	Administration of existing outcome and screening measures of psychological wellbeing and mental health.
Reference standard	For diagnostic: • Diagnosis statistical manual (DSM) or International Classification of diseases (ICD) diagnosis for anxiety, depression, mood disorders, emotional distress and eating disorders
Reference population	For validation: • Other physical health condition population • Nominated well participants (for example siblings, schools, colleges)
Outcomes	• Diagnostic outcomes: • Sensitivity • Specificity • Positive likelihood ratio • Negative likelihood ratio • Psychometric properties • Reliability • Validity
Study design	Diagnostic cohort study (to conduct logistical regression analyses to look for predictors of wellbeing, co-morbidities, agreement between measures and concordance between psychological symptoms and physical symptoms)
Timeframe	Two years

11 Prevention of cross infection

Review questions:

- **What is the effectiveness of cohorting on the basis of pathogen status versus not cohorting on the basis of pathogen status in reducing transmission of CF pathogens?**
- **What is the effectiveness of different models of segregating patients in reducing transmission of CF pathogens?**
- **What is the effectiveness of individual protective equipment in reducing transmission of CF pathogens?**
- **What is the effectiveness of the combination of cohorting, segregating and protective equipment in reducing transmission of CF pathogens?**

11.1 Introduction

Measures to reduce the risk of cross infection with transmissible pathogens are widely accepted as good or optimum clinical practice in the care of people with cystic fibrosis. Prior to the 1990's it was not unusual for people with cystic fibrosis to attend social events together and share hospital waiting areas. However, landmark evidence of the transmission of bacterial lung infection between people treated at the same hospital, and the emergence of new bacteria, has led to care providers adopting increasingly stringent infection control strategies.

Segregation in single rooms on a ward or in a clinic, cohorting clinics by pathogen status, discouraging social contact and the use of personal protective equipment are all strategies employed in isolation or combination in cystic fibrosis care in the UK. Despite acknowledgement that it is essential to use these measures to reduce the risk of cross infection, people with cystic fibrosis, families and carers can express feelings of anxiety and social isolation as a result, especially where such measures are employed in a varied or inconsistent manner.

11.2 Description of clinical evidence

The aim of this review was to determine the effectiveness of the different strategies (such as cohorting, segregation, or protective equipment) in reducing the transmission of cystic fibrosis pathogens.

The interventions that are reviewed are either cohort segregation by time (for example by clinic schedule), cohort segregation by location (for example separate clinics or separate wards), individual segregation by location (for example patients in separate rooms with en-suite facilities), use of protective equipment, or any combination of these interventions.

One single literature search was run for the review questions. We looked for systematic reviews, RCTs and prospective and retrospective comparative cohort studies that were conducted in Western countries. Studies based on registry and audit data from the UK were also eligible for inclusion. Conference abstracts of RCTs were considered if RCTs were unavailable. However, given that only 1 RCT and no cohort studies were identified for inclusion, before-and-after implementation studies were also considered eligible for inclusion where no data for critical outcomes was available from higher quality studies. Evidence from questionnaires conducted within cross sectional studies was also considered (for example for quality of life or patient satisfaction).

For full details see review protocol in Appendix D.

In total 16 studies were included in this review. There was 1 RCT (Hayes 2010), 3 surveys (Griffiths 2004, Russo 2006, Waine 2007) and 12 retrospective before-and-after studies (Chen 2001, France 2008, Frederiksen 1999, Griffiths 2005, Griffiths 2012, Hoiby & Pedersen 1989, Jones 2005, Lee 2004, McKay 2009, Savant 2014, Thomassen 1986, Whiteford 1995)

Depending on the study, interventions were implemented in the following setting: either outpatient, inpatient or mixed (both outpatient and inpatient) settings. For the purpose of structuring the review, interventions implemented in the same setting are grouped together.

In the outpatient setting, the following comparisons were assessed:

- Comparison 1. Cohort segregation by clinic times versus no cohort segregation (2 studies: Hayes 2010, McKay 2009)
- Comparison 2. Cohort segregation by location versus no cohort segregation (1 study: Lee 2004)
- Comparison 3. Combination of protective equipment + individual segregation versus incomplete protective equipment + incomplete individual segregation (1 study: Savant 2014).

In the inpatient setting, the following comparisons are assessed:

- Comparison 4. Cohort segregation by location versus no cohort segregation (2 studies: Chen 2001, Thomassen 1986)
- Comparison 5. Individual segregation by location versus usual care (1 study: Russo 2006).

When interventions were implemented both in the inpatient and outpatient setting, the following comparisons were assessed:

- Comparison 6. Cohort segregation versus no cohort segregation (7 studies: France 2008, Frederiksen 1999, Griffiths 2005, Griffiths 2012, Hoiby & Pedersen 1989, Jones 2005, Whiteford 1995)
- Comparison 7. Complete cohort segregation versus incomplete cohort segregation (1 study: France 2008)
- Comparison 8. Individual segregation versus usual care (1 study: Waine 2007)
- Comparison 9. Cohort segregation + individual segregation versus cohort segregation (2 studies: Chen 2001, France 2008)
- Comparison 10. Cohort segregation + individual segregation + protective equipment versus usual care. (1 study: Chen 2001)
- Comparison 11. Cohort segregation + individual segregation versus usual care (1 study: Griffiths 2004).

The reported size of the studies ranged from 39 to 232 participants with cystic fibrosis, however for some studies the total size was not reported. 3 studies included adults (France 2008, Jones 2005, Waine 2007), 2 included children and young people and their parents (Griffiths 2004, Russo 2006), 2 included infants and children (Hayes 2010, McKay 2009), 1 included infants, children and young people (Whiteford 1995), 1 included infants, children, young people and adults (Savant 2014). 4 included people receiving paediatric care, however the age range was not reported (Griffiths 2005, Griffiths 2012, Lee 2004, Thomassen 1986). In 3 studies age of the study population was not reported (Chen 2001, Frederiksen 1999, Hoiby & Pedersen 1989).

6 studies were conducted in the UK (France 2008, Jones 2005, Lee 2004, Russo 2006, Waine 2007, Whiteford 1995), 4 in the USA (Chen 2001, Hayes 2010, Savant 2014, Thomassen 1986), 2 in Denmark (Frederiksen 1999, Hoiby & Pedersen 1989), 4 in Australia (Griffiths 2004, Griffiths 2005, Griffiths 2012, McKay 2009)

A summary of the included studies is presented in Table 159. See study selection flow chart in Appendix F, study evidence tables in Appendix G, list of excluded studies in Appendix H, forest plots in Appendix I, and full GRADE profiles in Appendix J.

11.3 Summary of included studies

A summary of the studies that were included in this review are presented in Table 183.

Table 183: Summary of included studies

Study	Intervention/ Comparison	Population	Outcomes	Comments
OUTPATIENT SETTINGS				
Cohorting into different pathogens by clinic times				
Hayes 2010 USA RCT	Intervention: Cohort segregation • Segregated clinics free of patients with PA held on a separate day in the same clinic space used for mixed clinics; • Large clinics and waiting rooms, and hygienic precautions. Comparison: No cohort segregation • Mixed clinics that included PA positive patients; • Large clinics and waiting rooms, and hygienic precautions.	Infants and children with cystic fibrosis. N=39 intervention group: n=21 comparison group: n=18 Age: not reported	Incidence of PA infection over 10 years	Study dates 1996-2005
McKay 2009 Australia Retrospective before and after study	Intervention: Cohort segregation by age. • Outpatients clinics were designated by colour as "red" (children 5 and under who were PA-free), "blue" (primary school age or children under 5 already colonised with PA) or "green" (secondary school age). • Additional infection measures (for example removal of toys from the waiting room and hand cleansing). Comparison: No cohort segregation • One all age (0-18) clinic • Free mixing of patients in waiting area	Infants and children with cystic fibrosis. N=Between 72 and 90 were seen in each year of the study The results of 2837 sputum cultures were analysed for the study Age: ≤5 years	Prevalence of culture results (MRSA, non-mucoid PA, mucoid PA) Staff compliance	Segregation policy introduced in April and May 2003 and outcome data for 1999-2002 versus 2004-2007 The paper also mentions that all inpatients were treated in single rooms or in rooms shared with children without cystic fibrosis. However it is unclear if this policy started in 2003.
Cohorting into different pathogens by location				

Study	Intervention/ Comparison	Population	Outcomes	Comments
Lee 2004 UK Retrospective before and after study	Intervention: Cohort segregation. • Separate clinics for patients chronically infected with PA and uninfected patients. • Improved hygienic measures in a purpose-built cystic fibrosis centre Comparison: No cohort segregation • Various management strategies over the years to reduce the prevalence of chronic PA, including regular microbiological monitoring	People with cystic fibrosis receiving paediatric care. N=232 people 1990: n=966 patient months (mean age: 7.73) 2000: n=1803 patient months; (mean age: 9.42)	Incidence of PA infection Prevalence of chronic PA infection Prevalence of intermittent PA infection	Patients receiving full-time care at the Leeds Paediatric CF Centre. Separate clinics at the Leeds Regional CF Unit. Intervention implemented in 1991, outcome data provided for 1990 and 2000. Incidence reported narratively. Prevalence data calculated based on patient months
Combination strategies				
Savant 2014 USA Retrospective before and after study	Intervention: Protective equipment and individual segregation • Contact precautions for all patients in the outpatient clinic, regardless of respiratory tract culture results: gowning and gloving and hand hygiene by all providers; requesting that all patients use hand gel and mask when entering the facility or when outside of the exam room • Abolishing the designated communal area for taking vital sign measurements and converting to exam rooms. • Re-enforcement of the "no-waiting" room policy (Immediate placement within the examination room) • Education of patients and families; cleaning rooms thoroughly. Comparison: Incomplete use of protective equipment and incomplete individual separation	People with cystic fibrosis receiving paediatric care. N= ranged from 126 to 177 during the study years. Age range: 0 to 21.	Prevalence (% of patients cultured each quarter with positive tract cultures) of PA infections Prevalence (% of patients cultured each quarter with positive tract cultures) of MRSA infections	Mean no. of respiratory tract cultures per quarter = 169

Study	Intervention/ Comparison	Population	Outcomes	Comments
	• Any patient with respiratory tract cultures revealing a multi-resistant pathogen had a flag placed on the chart to indicate the need for contact precautions. However a consistent process for the use of this indicator was not systematic or routine. • Vital signs were performed in a common station in the hallway close to the exam rooms, without specific cleaning between patients. • "No-waiting" room policy			
INPATIENT SETTINGS				
Cohorting into different pathogens by location				
Chen 2001 USA Retrospective before and after study	Intervention 1. Cohort segregation. • Cohorting of hospitalized patients with cystic fibrosis on the basis of *B cepacia* colonization status Comparison 1: No cohort segregation No details	People with cystic fibrosis. N not reported Age not reported.	Incidence of *B cepacia* complex infection	Intervention introduced in early 1990, incidence data for 1988, 1989, 1990 and 1991. We compare 1989 and 1991 (the closest pre-intervention full year and the closes post-intervention full year)
Thomassen 1986 USA Retrospective before and after study	Intervention: Incomplete cohort segregation • All patients with *Pseudomonas cepacia* recovered from sputum or throat culture were admitted to 1 floor of the hospital - other patients with cystic fibrosis were not admitted to this floor. • The patients on this ward were not permitted to visit other inpatient wards but were not isolated in any other way. They had free access to the elevators, hospital cafeteria, and other common areas. No special precautions were taken to totally avoid chance meetings of the 2 groups of patients in the radiology department, outpatient areas, pulmonary function laboratory, or other hospital areas.	People with cystic fibrosis receiving paediatric care admissions pre-segregation: n=453 admissions post-segregation: n=389 Age: not reported	Incidence of hospital-associated colonisation of *P cepacia* Serotyping	Intervention introduced in August 1983. Data on 1 year and 5 months before the intervention compared to 1 year and 5 months afterwards

Study	Intervention/ Comparison	Population	Outcomes	Comments
	• Equipment in pulmonary function lab was sterilized or changed between patients. Handwashing was emphasised. • Masks or other isolation equipment were not used by patients or hospital personnel. • Summer camp facility was reserved for patients free of P. cepacia, another camp site was provided for colonized patients. Comparison: No cohort segregation in hospital • Basic infection control procedures (no details) • No segregation in camp facility			
Individual segregation				
Russo 2006 UK Survey. Questionnaire with both closed-ended and open-ended questions	Intervention: individual segregation. • Policy of segregation requiring all patients to remain in their individual rooms for the duration of their hospital stay Comparison: Usual care	Children and young people with cystic fibrosis and their parents N= 192 parents, 101 people with cystic fibrosis. Mean age of eligible participants: 13 (range 10 to 17)	Patient and carer satisfaction: % of parents and children who supported segregated treatment	Views were elicited in preparation for the process of implementing a formal policy of segregation
MIXED POPULATIONS (BOTH OUTPATIENT AND INPATIENT SETTINGS)				
Cohorting into different pathogens				
France 2008 UK Retrospective before and after study	Intervention 2. Complete cohort segregation. • Patients with Burkholderia species infection were cohorted into separate wards to non-Bcc infected patients and each inpatient has their own single room. • Patients with Burkholderia species infection have also continued to attend a different outpatient clinic. • Isolation policy for patients with B. species not yet implemented Intervention 1: Incomplete cohort segregation.	Adults with cystic fibrosis. N not reported. Age not reported.	Incidence of Burkholderia species infection	Incomplete inpatient and complete outpatient A lot of graphic reporting, some numbers are mentioned, see below: Intervention 1 versus comparison 1: Intervention 1 implemented in 1991, range of incidence of

Study	Intervention/ Comparison	Population	Outcomes	Comments
	• Patients with Burkholderia species infection were admitted to inpatient beds on the opposite side of the corridor to non-Burkholderia species infected patients. • There was continued patient mixing within a day-room facility on the ward and within areas such as the radiology department. • Patients with Burkholderia species infection attended separate outpatient clinics to other cystic fibrosis patients. Comparison 1. No infection control measures to prevent *B cepacia* complex cross-infection No details			Burkholderia species infection for 1983-1990, incidence 1992. Intervention 2 versus intervention 1: Intervention 2 implemented from November 1993 onwards. Incidence 1992 and incidence "following complete cohort segregation"
Frederikse n 1999 Denmark Retrospect ive before and after study	Intervention: Cohort segregation: • The cystic fibrosis centre was reconstructed, separating the wards and the outpatient clinic • Patients with PA in their sputum were separated from patients without PA in the wards, in the outpatient clinic, and during social events. Comparison: No cohort segregation • The wards with inpatients receiving iv treatment were near the outpatient clinic visited by all cystic fibrosis patients • Cystic fibrosis patients were not segregated according to presence or absence of PA in their sputum	People with cystic fibrosis. 1974: n=107. Median age: 9.0 1995: n=256. Median age: 18.5	Incidence of intermittent PA infection Incidence of chronic PA infection	Cohort segregation introduced in 1981. Incidence given for each year from 1974 and 1995, we compare 1980 and 1982.
Griffiths 2005 and 2012 Australia Retrospect ive before and after study	Intervention: Cohort segregation • Cohorts: PA (negative, positive non-epidemic, epidemic PA (AES-1)) • Separation of cohorts was maintained at outpatient visits and during hospital admissions. • Standard infection control measures were reinforced, and education seminars were arranged for staff and families.	People with cystic fibrosis receiving paediatric care. 1999: n=325 Sputum producers: n=153 2002: n=291 Sputum producers: n=149	Prevalence of AES-1 (PA epidemic strain)	Cohort segregation in 2000, outcome data for 1999 and 2002

Study	Intervention/ Comparison	Population	Outcomes	Comments
	Comparison: No cohort segregation. • No segregation based on PA. • Standard infection control measures, *B cepacia* complex and MRSA strict individual segregation	Age range: from <10 to ≥16 years, exact age range not reported.		
Hoiby & Pedersen 1989 Denmark Retrospective before and after study	Intervention 2: Cohort segregation (by multiply resistant PA strain) • Three groups: Patients with multiply resistant PA strain; cohort with normally sensitive strains of chronic PA infection; PA negative patients • Improved hygiene precautions Intervention 1. Cohort segregation (by PA infection, but not multiply resistant PA strain) • Two cohorts, cohort with chronic PA infection separated from PA negative patients • Segregated from each other in different wards and seen on different days in the outpatient clinic.	People with cystic fibrosis. N (range): 54 to 226 (between 1970 and 1987). Subgroup of people with PA infection in 1983: n=119 Age: Not reported	Incidence of multiply resistant PA strain Prevalence of multiply resistant PA strain	Intervention 2 (compared to intervention 1) was implemented in April 1983. Incidence and prevalence of multiply resistant PA is provided for Jan, Feb, Mar, Apr, May, June 1983
Jones 2005 UK Retrospective before and after study	Intervention 1: Incomplete cohort segregation. • Patients without chronic PA infection attended outpatient clinic appointments on a different day than other patients with cystic fibrosis. • Inpatients without chronic PA infection were housed on the same cystic fibrosis ward as patients with chronic PA infection, but in rooms with en-suite facilities, and were advised not to socialise with other patients on the ward. However there was still some social mixing between patients on the ward. Comparison: No cohort segregation. • Purpose-built facilities: all inpatients had their own bedroom, although only 2 of 11 rooms had en-suite facilities. • Treatments with door closed • Practice of strict hygiene. Rooms are cleaned between patients, equipment not shared	People with cystic fibrosis who attend an adult centre. 1999: n= 216 2000: n=221 2001: n=228 Age not reported	Prevalence of chronic PA infection Prevalence of transmissible PA infection Prevalence of chronic infection with transmissible PA strain	Outpatient policy of segregation instituted in 2000. Outcome data provided for 1999, 2000, 2001, 2002 and 2003. We compare 1999 to 2001

Study	Intervention/ Comparison	Population	Outcomes	Comments
	between patients, hand hygiene for staff.			
Whiteford 1995 UK Retrospective Before and after study	Intervention. Cohort segregation. • Children with *B cepacia* were admitted to a separate ward • Children with *B cepacia* were moved to a different waiting area and given appointment times at the end of the clinic. • Recommendations to parents to avoid close physical contact outside the hospital Comparison: no cohort segregation • No cohort segregation for children with *B cepacia* • Children with cystic fibrosis needing inpatient care were admitted to 1 ward where they had complete freedom to play together and socialise • Each child had an individual peak flow meter and nebuliser for use throughout the admission • Children colonised with PA had their chest physiotherapy separately from children without PA	Infants, children and young people with cystic fibrosis. N=115. Mean (range) age: 7.6 years (0.6 to 15.8 year)	Incidence of *B cepacia* infection	Intervention introduced in June 1992; number of cases given for each month of 1992. , 114 at risk in Jan 1992
Individual segregation				
Waine 2007 UK Survey	Intervention: Individual separation Not mixing with others with cystic fibrosis Comparison: no separation Mixing with others with cystic fibrosis	Adults with cystic fibrosis. N=94 respondents (184 invited to participate) Mean (SD age: 27.2 (8.5) years	Patient satisfaction % of those who mixed with others who said that if they avoided others with cystic fibrosis, their quality of life would be: significantly or greatly affected / not suffer	All patients attending a clinic appointment/inpatients at the West Midlands Adult CF Centre were offered a questionnaire. Questionnaires were posted to 8 patients colonized with the *B cepacia* complex who attended a separate clinic.
Combination of strategies				

Study	Intervention/ Comparison	Population	Outcomes	Comments
Chen 2001 USA Retrospective before and after study	Intervention 2: Individual segregation in addition to cohort segregation • Hospitalized non-colonized patients were prohibited from sharing rooms, then this policy was expanded so that all patients with cystic fibrosis irrespective of *B cepacia* colonization were in separate rooms. • Separate waiting rooms were established for outpatients. Intervention 1. Cohort segregation. • Cohorting of hospitalized patients with cystic fibrosis on the basis of *B cepacia* colonization status Intervention 3: Cohort segregation combined with individual segregation and with protective equipment. • Cohorting of hospitalized patients on the basis of *B cepacia* colonization status. • Furthermore inpatients colonized with *B cepacia* were placed in contact isolation and were required to wear mask and gloves when out of their rooms. • In the outpatient setting, patients infected with *B cepacia* were restricted to separate clinic days during which no non-colonized patients were seen. • Patients were required to wear masks while in the waiting room. • A hospital-wide educational program regarding infection control measures was introduced • Particular attention was given to disinfection of clinic rooms and equipment Comparison 3: Usual care No details	People with cystic fibrosis. N not reported. Age not reported.	Annual incidence of *B cepacia* complex infection. Prevalence of *B cepacia* complex infection	Intervention 2 versus intervention 1: Progressive isolation measures in mid-1996, 1997, 1998, and prevalence data for 1992 and 1999 Intervention 3 versus comparison 3: Measures introduced in early 1997, annual incidence given for 1996, 1997 and “since time of implementation”
France 2008 UK	• Intervention 3. Cohort segregation combined with individual segregation.	Adults with cystic fibrosis. N not reported.	Prevalence of Burkholderia species	Policy of isolation in 2000

Study	Intervention/ Comparison	Population	Outcomes	Comments
Retrospective before and after study	• A policy of isolation was introduced for patients infected with all Burkholderia species. This policy involves patients not having any contact with other patients, either at an inpatient or outpatient level. • Patients being admitted to single rooms during admissions and attending outpatient appointments and being immediately isolated within their own clinic room. • Patients with Burkholderia species infection were cohorted into separate wards to non-Bcc infected patients and attended a different outpatient clinic. Intervention 2. Cohort segregation. • Patients with Burkholderia species infection were cohorted into separate wards to non-Bcc infected patients and each inpatient had their own single room. • Patients with Burkholderia species infection attended a different outpatient clinic. • Isolation policy for patients with Burkholderia species not yet implemented	Age not reported.	Prevalence of transmissible *B cepacia* complex infection.	Peak prevalence of Burkholderia species infection 1994 and prevalence 2005. Prevalence of *B cepacia* complex transmissible infections for 1993/94 and for 2005.
Griffiths 2004 Australia Survey	Intervention: Combination of cohort and individual segregation. • Cohort segregation was based on five separate groups: PA positive; epidemic strain PA; *B cepacia*; MRSA; and PA negative. • Inpatients were nursed in separate sections and attended physiotherapy sessions at different times. • Children infected with epidemic strain PA, MRSA or BC were isolated from each other and all other patients • Those within the other groups were allowed to mix within their cohort groups. Comparison: Usual care	People with cystic fibrosis receiving paediatric care and their parents N= 190 questionnaires were completed (291 people were sent the questionnaire) 114 parents alone 75 parents completed the questionnaire together with a person with cystic fibrosis aged >=12 years	Patient and carer satisfaction: Children's and parents' overall response to segregation measures: positive / negative / unsure	Survey was conducted 2 years after the introduction of the intervention. Royal Children's Hospital, Melbourne, not clear if both inpatient and outpatient

Study	Intervention/ Comparison	Population	Outcomes	Comments
		1 questionnaire completed by child only. Mean age: unclear		

PA: P aeruginosa; B *cepacia:* B *cepacia; MRSA: Meticillin-resistant* S *aureus*

11.4 Clinical evidence profile

The summary clinical evidence profiles for this review question (cross-infection control) are presented in Table 184 to Table 194.

11.4.1 Outpatient care

Table 184: Summary clinical evidence profile: Comparison 1. Cohort segregation by clinic times versus no cohort segregation

Outpatient care: Comparison 1. Cohort segregation by clinic times versus no cohort segregation						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No cohort segregation	Cohort segregation into different pathogens by clinic times				
10-year incidence of *P aeruginosa* infections. Follow-up: 10 years	778 per 1000	622 per 1000 (404 to 941)	RR 0.8 (0.52 to 1.21)	39 (Hayes 2010)	⊕⊕⊖⊖ low[1,2]	
4-year prevalence of MRSA (percentages) Follow-up: 4 years	1%	1.3%	ns	≈2,837 sputum cultures (McKay 2009)[4]	⊕⊖⊖⊖ very low[3]	
4-year prevalence of non-mucoid *P aeruginosa* (percentages) Follow-up: 4 years	22.3%	22.7%	ns	≈2,837 sputum cultures (McKay 2009)[4]	⊕⊖⊖⊖ very low[3]	
4-year prevalence of mucoid *P aeruginosa* (percentages) Follow-up: 4 years	5.9%	1.0%	P=0.001	≈2,837 sputum cultures (McKay 2009)[4]	⊕⊖⊖⊖ very low[3]	

Outpatient care: Comparison 1. Cohort segregation by clinic times versus no cohort segregation						
Staff compliance (percentages) Follow-up: 4 years	-	Adherence to the "coloured" clinic booking scheme: % of children attending the red clinic who were 5 and under: 2004: 96.8%; 2005: 97.5%; 2006: 94.4%; 2007: 95.9%	Not estimable	N not reported (McKay 2009)[4]	⊕⊖⊖⊖ very low[3]	Narrative data

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: CI: confidence interval; MRSA: methicillin-resistant S aureus; ns: not significant; RR: risk ratio

1 The quality of the evidence was downgraded by 1 due to unclear randomisation, allocation concealment, blinding, incomplete data outcome and selective reporting
2 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID
3 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to sample selection, comparability between groups and outcome reporting
4 Intervention group: data for the period 2004 to 2007; comparison group: data for the period 1999 to 2002. Intervention introduced in 2003.

Table 185: Summary clinical evidence profile: Comparison 2. Cohort segregation by location versus no cohort segregation

Outpatient care: Comparison 2. Cohort segregation by location versus no cohort segregation						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No cohort segregation	Cohort segregation into different pathogens by location				
Annual incidence of new growths of *P aeruginosa*. Follow-up: 9 years	-	The annual incidence of new growths of *P aeruginosa*, while fluctuating, showed no downward trend, despite segregation	Not estimable	232 (Lee 2004)[3]	⊕⊖⊖⊖ very low[1,2]	Narrative data
Yearly prevalence of chronic *P aeruginosa* infection Follow-up: 9 years	245 per 1000	181 per 1000 (154 to 210)	OR 0.68 (0.56 to 0.82)	2769 patient months (Lee 2004)[3]	⊕⊖⊖⊖ very low[1,4]	
Yearly prevalence of intermittent *P*	262 per 1000	574 per 1000 (528 to 620)	OR 3.8 (3.15 to 4.59)	2769 patient months	⊕⊖⊖⊖ very low[1]	

Outpatient care: Comparison 2. Cohort segregation by location versus no cohort segregation						
aeruginosa infection Follow-up: 9 years				(Lee 2004)[3]		

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: CI: confidence interval; OR: odds ratio

1 The quality of the evidence was downgraded by 2 because high risk of bias in relation to sample selection, comparability between groups, and outcome assessment and reporting
2 Imprecision cannot be calculated with the data provided
3 Intervention group: data from 2000; comparison group: data from 1990. Intervention implemented in 1991.
4 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 default MID

Table 186: Summary clinical evidence profile: Comparison 3. Combination of protective equipment + individual segregation versus incomplete protective equipment + incomplete individual segregation

Outpatient care: Comparison 3. Combination of protective equipment + individual segregation versus incomplete protective equipment + incomplete individual segregation						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Incomplete protective equipment + incomplete individual segregation	Protective equipment + individual segregation				
4-month prevalence of *P aeruginosa* infections (percentages). Follow-up: 5 years	The 4-month prevalence of *P aeruginosa* infections in the control group was: 29.79%	The 4-month prevalence of *P aeruginosa* infections in the intervention group was: 21.78%	p<0.0001	N varied from 126 to 177 during the study years (Savant 2014) [3]	⊕⊖⊖⊖ very low[1,2]	
4-month prevalence of MRSA infections (percentages) Follow-up: 5 years	The 4-month prevalence of MRSA infections in the control group was: 10.76%	The 4-month prevalence of MRSA infections in the intervention group was: 8.68%	p=0.008	N varied from 126 to 177 during the study years (Savant 2014) [3]	⊕⊖⊖⊖ very low[1,2]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: CI: confidence interval; MRSA: methicillin-resistant S aureus

1 The quality of the evidence was downgraded by 2 because of high risk bias in relation to sample selection, comparability between groups and outcome assessment.
2 Imprecision cannot be assessed with the reported data.
3 Intervention group: mean data for the period 2008 to 2012; comparison group: mean data for the period 2005 to 2007. Intervention implemented in 2007.

11.4.2 Inpatient care

Table 187: Summary clinical evidence profile: Comparison 4. Cohort segregation by location versus no cohort segregation

Inpatient care: Comparison 4. Cohort segregation by location versus no cohort segregation						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No cohort segregation	Cohort segregation into different pathogens by location				
Annual incidence of *B cepacia* complex (percentages) Follow-up: 1 year	The annual incidence of *B cepacia* complex infections in the control group was: 5.8%	The annual incidence of *B cepacia* complex infections in the intervention group was: 3.7%	Not estimable	N not reported (Chen 2001) [3]	⊕⊖⊖⊖ very low[1,2]	
5-month incidence of hospital-associated colonisation of *P. Cepacia* Follow-up: 5 months	78 per 1000	26 per 1000 (10 to 61)	OR 0.31 (0.12 to 0.77)	N of people unclear. N of admissions: ≈842 (Thomassen 1986)[5]	⊕⊖⊖⊖ very low[4]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: CI: confidence interval; OR: odds ratio

1 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to sample selection, comparability between groups and outcome assessment
2 Imprecision cannot be calculated with the data reported
3 Intervention group: data from 1991; comparison group: data from 1989. Intervention implemented in early 1990.
4 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to the comparability between groups and outcome assessment
5 Intervention group: data for the period 1 Aug 1983 to 31 Dec 1984; comparison group: data for the period 1 Mar 1982 to 31 Jul 1983. Intervention introduced in August 1983.

Table 188: Summary clinical evidence profile: Comparison 5. Individual segregation by location versus usual care

Inpatient care: Comparison 5. Individual segregation by location versus usual care						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Usual care	Individual segregation				

Inpatient care: Comparison 5. Individual segregation by location versus usual care						
Patient satisfaction (narrative)		92% of children supported segregated treatment	na	101 (Russo 2006)	⊕⊖⊖⊖ very low[1,2]	Narrative results only
Parents' satisfaction (narrative)		91% of parents supported segregated treatment	na	192 (Russo 2006)	⊕⊖⊖⊖ very low[1,2]	Narrative results only

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: CI: confidence interval

1 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to sample selection, the comparability between groups and outcome assessment.
2 The imprecision cannot be calculated with the data reported

11.4.3 Combined inpatient and outpatient care

Table 189: Summary clinical evidence profile: Comparison 6. Cohort segregation versus no cohort segregation

Inpatient/ outpatient care: Comparison 6. Cohort segregation versus no cohort segregation						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Cohort segregation into pathogens				
Monthly incidence of multiply resistant *P aeruginosa* strain Follow-up: 1 month	206 per 1000	65 per 1000 (25 to 161)	OR 0.27 (0.1 to 0.74)	119 (Hoiby & Pedersen 1989)[2]	⊕⊖⊖⊖ very low[1]	
Annual incidence of intermittent *P aeruginosa* Follow-up: 1 year	333 per 1000	225 per 1000 (99 to 433)	OR 0.58 (0.22 to 1.53)	Total N unclear (Frederiksen 1999) [5]	⊕⊖⊖⊖ very low[3,4]	
Annual incidence of chronic *P aeruginosa* Follow-up: 1 year	200 per 1000	101 per 1000 (41 to 229)	OR 0.45 (0.17 to 1.19)	Total N unclear (Frederiksen 1999) [5]	⊕⊖⊖⊖ very low[3,6]	
6-month incidence *B cepacia* Follow-up: 6 months	46 per 1000	11 per 1000 (1 to 87)	OR 0.23 (0.03 to 1.97)	115 (Whiteford 1995)[8]	⊕⊖⊖⊖ very low[4,7]	
Annual incidence of *Burkholderia* species infection (percentages) Follow-up: 1 year	3-5%	16.3%	Not estimable	N not reported (France)[11]	⊕⊖⊖⊖ very low[9,10]	
Monthly prevalence of multiple resistant	328 per 1000	332 per 1000 (226 to 462)	OR 1.02 (0.60 to 176)	119 (Hoiby 1989)[2]	⊕⊖⊖⊖ very low[1,4]	

Inpatient/ outpatient care: Comparison 6. Cohort segregation versus no cohort segregation						
P aeruginosa strain (percentages) Follow-up: 1 month						
Prevalence of AES-1 (*P aeruginosa* epidemic strain) Follow-up: 2 years	-	-	aRR 0.64 (0.47 to 0.87)	Total N unclear (Griffiths 2005) [12]	⊕⊖⊖⊖ very low[6]	
Annual prevalence of chronic *P aeruginosa* infection Follow-up: 1 year	722 per 1000	807 per 1000 (728 to 867)	OR 1.61 (1.03 to 2.51)	Total N unclear (Jones 2005)[13]	⊕⊖⊖⊖ very low[6]	
Annual prevalence of transmissible *P aeruginosa* infection Follow-up: 1 year	130 per 1000	154 per 1000 (96 to 237)	OR 1.22 (0.71 to 2.08)	Total N unclear (Jones 2005) [13]	⊕⊖⊖⊖ very low[4]	
Annual prevalence of chronic infection with transmissible *P aeruginosa* strain (percentages) Follow-up: 1 year	13%	15.4%	Not estimable	Total N unclear (Jones 2005) [13]	⊕⊖⊖⊖ very low[10]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: adjRR: adjusted risk ratio; ASUSP-1: Australian epidemic strain, type 1; CI: confidence interval; MRSA: methicillin-resistant S aureus; OR: odds ratio

1 The quality of the evidence was downgraded by 1 because of high risk of bias in relation to comparability of the groups, and outcome reporting
2 Intervention group: data from May 1983; comparison group: data from March 1983. Intervention implemented in April 1983.
3 The quality of the evidence was downgraded by 1 because of high risk of bias in relation to comparability between groups, and outcome assessment
4 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs
5 Intervention group: data from 1982; comparison group: data from 1980. Intervention implemented in 1981
6 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID
7 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to the comparability between groups, outcome assessment and unclear sample selection
8 Intervention group: data from December 1992; comparison group: data from May 1992. Intervention implemented in June 1992.
9 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to sample selection, comparability between groups and outcome assessment
10 Imprecision cannot be calculated with the data reported
11 Intervention group: data from 1992; comparison group: data from 1983-1990. Intervention implemented in November 1991.Intervention was incomplete cohort segregation.
12 Intervention group: data from 2002; comparison group: data from 1999. Intervention implemented in January 2000.
13 Intervention group: data from 2001; comparison group: data from 1999. Intervention implemented in 2000.

Table 190: Summary clinical evidence profile: Comparison 7. Complete cohort segregation versus incomplete cohort segregation

Inpatient/ outpatient care: Comparison 7. Complete cohort segregation versus incomplete cohort segregation						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Incomplete cohort segregation 3	Complete cohort segregation3				
Annual incidence of Burkholderia species (percentages). Follow-up: unclear	The annual incidence of Burkholderia species for the control group was: 16.3%	The annual incidence of Burkholderia species for the intervention group was : < 3% (for all but 1 year)	Not estimable	N not reported (France 2008)3	very low1,2	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: CI: confidence interval

1 The quality of the evidence was downgraded by 2 because high risk of bias in relation to sample selection, the comparability between the groups and the outcome reporting and assessment.
2 Imprecision cannot be calculated with the data reported
3 Intervention group: data after 1993; comparison group: data from 1992. Intervention implemented in November 1993.

Table 191: Summary clinical evidence profile: Comparison 8. Individual segregation versus usual care

Inpatient/ outpatient care: Comparison 8. Individual segregation versus usual care						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Usual care	Individual segregation				
Patient satisfaction (narrative results)	23.3% of patients said that their quality of life would suffer a 'significant amount' or 'a great deal' if they were to begin avoiding others	62.5% of patients said that their quality of life did not suffer as a result.	Not estimable	94 (Waine 2007)	vey low1,2	Narrative results only

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: CI: confidence interval

1 The quality of the evidence was downgraded by 2 because high risk of bias in relation to sample selection, the comparability between the groups and the outcome reporting and assessment.
2 Imprecision cannot be calculated with the data reported

Table 192: Summary clinical evidence profile: Comparison 8. Individual segregation versus usual care

Inpatient/ outpatient care: Comparison 8. Individual segregation versus usual care						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Cohort segregation	Cohort segregation + individual segregation				
Yearly prevalence of *B cepacia* complex infection (percentages) Follow-up: 1 year	The annual incidence of *B cepacia* complex infections in the control group was: 15%	The annual incidence of *B cepacia* complex infections in the intervention group was: 7%	Not estimable	N not reported (Chen 2001)3	very low1,2	
Yearly prevalence of *Burkholderia* species (percentages) Follow-up: 1 year	The annual incidence of *Burkholderia* species for the control group was: 31.2%	The annual incidence of *Burkholderia* species for the intervention group was : 9.3%	Not estimable	N not reported (France 2008)5	very low2,4	
**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).* *Abbreviations: CI: confidence interval*						

1 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to sample selection, comparability between groups and outcome assessment
2 Imprecision cannot be calculated with the data reported
3 Intervention group: data from 1999; comparison group: data from 1992. Intervention introduced in 1996.
4 The quality of the evidence was downgraded by 2 because high risk of bias in relation to sample selection, the comparability between the groups and the outcome reporting and assessment.
5 Intervention group: data from 2005; comparison group: data from 1994. Intervention implemented in 2000.

Table 193: Summary clinical evidence profile: Comparison 10. Cohort segregation + individual segregation + protective equipment versus usual care

Inpatient/ outpatient care: Comparison 10. Cohort segregation + individual segregation + protective equipment versus usual care						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Usual care	Cohort segregation + individual segregation +				

Inpatient/ outpatient care: Comparison 10. Cohort segregation + individual segregation + protective equipment versus usual care						
		protective equipment				
Annual incidence of *B cepacia* complex infection (percentages) Follow-up: 1 year	The annual incidence of *B cepacia* complex infections in the control group was: 8.8%	The annual incidence of *B cepacia* complex infections in the intervention group was: < 1%	Not estimable	N not reported (Chen 2001)[3]	vey low[1,2]	
**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).* *Abbreviations: CI: confidence interval*						

1 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to sample selection, comparability between groups and outcome assessment
2 Imprecision cannot be calculated with the data reported
3 Intervention group: data after implementation; comparison group: data from 1996. Intervention implemented in early 1997.

Table 194: Summary clinical evidence profile: Comparison 11. Cohort segregation + individual segregation versus usual care

Inpatient/ outpatient care: Comparison 11. Cohort segregation + individual segregation versus usual care						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Cohort segregation into pathogens				
Patient satisfaction	-	Positive: 63%: Negative: 12%: Unsure: 25% (p<0.001)	Not estimable	190 (Griffiths 2004)	⊕⊖⊖⊖ very low[1,2]	Narrative results only
Carer satisfaction	-	Positive: 85%: Negative: 4%: Unsure: 11% (p<0.001)	Not estimable	190 (Griffiths 2004)	⊕⊖⊖⊖ very low[1,2]	Narrative results only
**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).* *Abbreviations: CI: confidence interval*						

1 The quality of the evidence was downgraded by 1 because of high risk of bias in relation to sample selection and outcome reporting
2 Imprecision cannot be calculated with the data reported

11.5 Economic evidence

No economic evaluations of strategies to prevent cross-infection were identified in the literature search conducted for this guideline. Full details of the search and economic article selection flow chart can be found in Appendix E and F, respectively.

This area was prioritised for de novo economic modelling, subsequently a cost-utility model was developed. The decision analytic model took the form of a decision tree (Figure 15) where the outcome (probability of transmissible pathogen) is associated with a treatment cost and utility value. The methods used to construct the model and the results of all analyses are reported in Appendix K. A summary of cost-effectiveness estimates are provided in Table 195 for ease of reference.

Figure 15: Decision tree

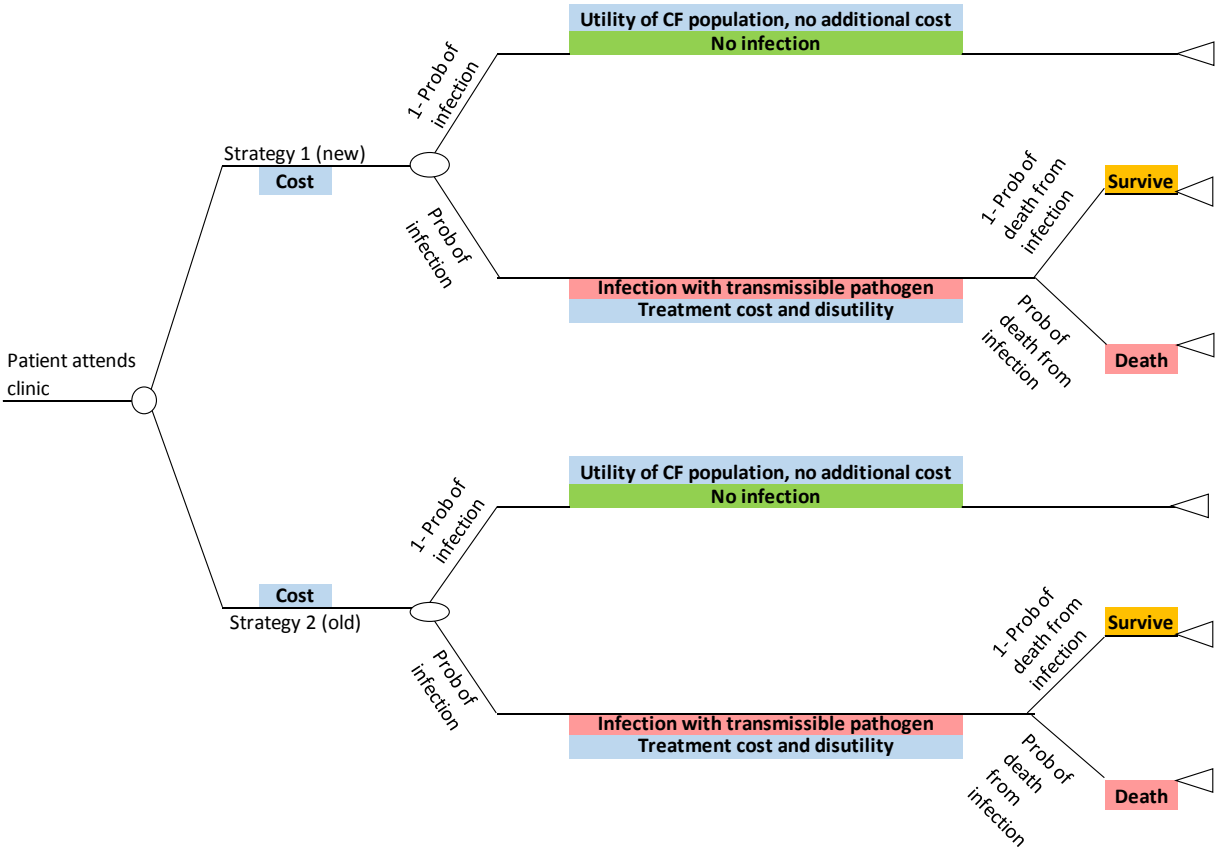


Table 195: Summary of cost-effectiveness estimates

Strategy	Infection with transmissible pathogen			
	Intermittent BCC	Intermittent PA	Chronic PA	Super infection with chronic PA
Cohort segregation	Cost-effectiveness uncertain (dominant to dominated)	Not Cost-Effective (ICER £241,185 to dominated)	Cost-effective (dominant)	NC
Protective equipment	Cost-effective (dominant)	Cost-effective (dominant)	NC	NC
Single inpatient rooms versus beds in shared rooms	Cost-effective (dominant)	NC	NC	NC

Strategy	Infection with transmissible pathogen			
	Intermittent BCC	Intermittent PA	Chronic PA	Super infection with chronic PA
Incomplete cohort segregation including en suite bathroom facilities versus no cohort segregation including shared bathroom facilities	NC	Cost-effective if en suite facilities cost less than an additional £21,600/ clinic /year	NC	Cost-effectiveness uncertain

BCC, B cepacia complex; ICER, incremental cost-effectiveness ratio; NC, not calculable; PA, P aeruginosa

11.6 Evidence statements

11.6.1 Outpatient care

11.6.1.1 Cohorting into different pathogens by clinic times

11.6.1.1.1 Comparison 1. Cohort segregation by clinic times versus no cohort segregation

Incidence of patients infected with transmissible pathogens

Low quality evidence from 1 RCT with 39 infants and children with cystic fibrosis showed no clinically significant difference in the incidence of *P aeruginosa* infections between cohorting patients into different pathogens by clinic times and no cohort segregation at 10 years follow-up.

Prevalence of patients infected with transmissible pathogens

Very low quality evidence from 1 observational study with ≈2,837 sputum cultures showed no significant difference in the prevalence of MRSA and non-mucoid *P aeruginosa* infections among infants and children with cystic fibrosis after segregation measures (consisting in segregating patients by age using a booking system) were put in place during the 4-year follow-up. However, a significant lower prevalence of mucoid *P aeruginosa* was observed during the same study period. The uncertainty for these outcomes could not be calculated.

Quality of life

No evidence was found.

Emotional function including anxiety and depression

No evidence was found.

Carer satisfaction

No evidence was found.

Patient satisfaction

No evidence was found.

Staff experience

No evidence was found.

Staff and patient compliance

Very low quality evidence from 1 observational study with staff looking after infants and children with cystic fibrosis, showed that the staff adherence to the segregation programme (using a clinic booking system) was over 90% during the 4-year follow-up period. This result is provided narratively. The total number of people included in the study was not reported.

11.6.1.2 Cohorting into different pathogens by location

11.6.1.2.1 Comparison 2. Cohort segregation by location versus no cohort segregation

Incidence of patients infected with transmissible pathogens

Very low quality evidence from 1 observational study with people with 232 people with cystic fibrosis receiving paediatric care suggested that the annual incidence of new growths of *P aeruginosa*, while fluctuating, showed no downward trend 9 years after segregation measures (consisting of separate clinics) were put in place, compared to previous usual care. This outcome was reported narratively only.

Prevalence of patients infected with transmissible pathogens

Very low quality evidence from 1 observational study with 2,769 patient months showed a clinically significant lower yearly prevalence of chronic *P aeruginosa* infections among people with cystic fibrosis receiving paediatric care 9 years after segregation measures (consisting of separate clinics) were put in place, compared to previous usual care. However, a clinically significant higher yearly prevalence of intermittent *P aeruginosa* infections was observed.

Quality of life

No evidence was found.

Emotional function including anxiety and depression

No evidence was found.

Carer satisfaction

No evidence was found.

Patient satisfaction

No evidence was found.

Staff experience

No evidence was found.

Staff and patient compliance

No evidence was found

11.6.1.3 Individual segregation

No studies have been identified.

11.6.1.4 Protective equipment

No studies have been identified.

11.6.1.5 Combination of strategies

11.6.1.5.1 Comparison 3. Combination of protective equipment + individual segregation versus incomplete protective equipment + incomplete individual segregation

Incidence of patients infected with transmissible pathogens

No evidence was found.

Prevalence of patients infected with transmissible pathogens

Very low quality evidence from 1 observational study with people with cystic fibrosis receiving paediatric care and aged 0 to 21 showed a significantly lower prevalence of *P aeruginosa* and MRSA infections calculated as average prevalence for 4 month intervals over a 5 year period after an infection prevention and control policy (consisting in a combination of individual segregation and protective equipment) was put in place, compared to the previous strategy (that consisted in a combination of incomplete protective equipment + incomplete individual segregation). The uncertainty for these outcomes could not be calculated. The total number of people included in the study was not reported.

Quality of life

No evidence was found.

Emotional function including anxiety and depression

No evidence was found.

Carer satisfaction

No evidence was found.

Patient satisfaction

No evidence was found.

Staff experience

No evidence was found.

Staff and patient compliance

No evidence was found.

11.6.2 Inpatient care

11.6.2.1 Cohorting into pathogen by location

11.6.2.1.1 Comparison 4. Cohort segregation by location versus no cohort segregation

Incidence of patients infected with transmissible pathogens

Very low quality evidence from 1 observational study with people with cystic fibrosis showed a lower annual incidence of *B cepacia complex* infection over 1 year after infection control measures (consisting in cohorting hospitalised patients on the basis of *B cepacia* colonisation status) were put in place, compared to the previous situation (no cohorting segregation). The significance and the uncertainty of this result could not be calculated. The age range and the total number of people in the study was not reported.

Very low quality evidence from 1 observational study with people with cystic fibrosis receiving paediatric care showed a clinically significant lower incidence of hospital-associated colonisation of *P cepacia* over 5 months after precautionary measures were implemented (consisting in admitting all patients with *P cepacia* to the same ward), compared to the previous situation (where only basic infection prevention measures were in place). The total number of people in the study was not reported

Prevalence of patients infected with transmissible pathogens

No evidence was found.

Quality of life

No evidence was found.

Emotional function including anxiety and depression

No evidence was found.

Carer satisfaction

No evidence was found.

Patient satisfaction

No evidence was found.

Staff experience

No evidence was found.

Staff and patient compliance

No evidence was found.

11.6.2.1.2 Comparison 5. Individual segregation by location versus usual care.

Incidence of patients infected with transmissible pathogens

No evidence was found.

Prevalence of patients infected with transmissible pathogens

No evidence was found.

Quality of life

No evidence was found.

Emotional function including anxiety and depression

No evidence was found.

Patient and carer satisfaction

Very low quality from a cross-sectional study with 101 children and young people with cystic fibrosis and their parents suggested that a high percentage of children and parents support having segregated treatment (92% and 91% respectively).

Staff experience

No evidence was found.

Staff and patient compliance

No evidence was found.

11.6.2.2 Inpatient room with ensuite facilities

No studies have been identified.

11.6.2.3 Inpatient recreational facilities

No studies have been identified.

11.6.3 Combined inpatient and outpatient care

11.6.3.1 Cohorting into pathogens

11.6.3.1.1 Comparison 6. Cohort segregation versus no cohort segregation

Incidence of patients infected with transmissible pathogens

Very low quality evidence from 1 observational study with 119 people with cystic fibrosis showed a clinically significant lower monthly incidence of multiply resistant *P aeruginosa* strain 1 month after control measures (consisting in segregating patients based on PA strains), compared to the previous policy (where patients were separated on the basis of the PA status). The age of the people included in the study was not reported.

Very low quality evidence from 1 observational study with people with cystic fibrosis showed no clinically significant difference in the annual incidence of intermittent and chronic *P aeruginosa* 1 year after cohort isolation was introduced, compared to previous usual care. The age range and the total number of people in the study was not reported.

Very low quality evidence from 1 observational study with 115 infants, children and young people with cystic fibrosis showed no clinically significant difference in the incidence of *B cepacia* during the 6-month study period after segregation measures were introduced,

compared to previous usual care. The total number of people included in the study was not reported.

Very low evidence from 1 observational study with adults with cystic fibrosis showed a higher annual incidence of *Burkholderia* species infections after changing infection control practices (consisting in partially segregating patients with *Burkholderia* species infection), compared to previous usual care. The significance and the uncertainty of this result could not be calculated. The total number of people in the study was not reported.

Prevalence of patients infected with transmissible pathogens

Very low quality evidence from 1 observational study with 119 people with cystic fibrosis showed no clinically significant difference in monthly prevalence of multiply resistant *P aeruginosa* strain 1 month after control measures (consisting in segregating patients based on PA strains), compared to the previous policy (where patients were separated on the basis of the PA status). The age of the people included in the study was not reported.

Very low quality evidence from 1 observational study with people with cystic fibrosis receiving paediatric care who were able to produce sputum showed a clinically significant lower prevalence of *P aeruginosa* epidemic strain 2 years after cohort segregation measures based on PA status were put in place, compare to previous usual care. The total number of people included in the study was unclear.

Very low quality evidence from 1 observational study with adults with cystic fibrosis showed a clinically significant higher annual prevalence of chronic *P aeruginosa* infection 1 year after simple segregation measures were put in place, compared to previous usual care. However, no clinically significant differences were found in the annual prevalence of transmissible *P aeruginosa* infection. In addition, a slightly higher annual prevalence of chronic infection with transmissible *P aeruginosa* strain was also observed, but the significance and the uncertainty of this outcome could not be calculated. The total number of people included in the study was unclear.

Quality of life

No evidence was found.

Emotional function including anxiety and depression

No evidence was found.

Patient and carer satisfaction

No evidence was found.

Staff experience

No evidence was found.

Staff and patient compliance

No evidence was found

11.6.3.1.2 Comparison 7. Complete cohort segregation versus incomplete cohort segregation

Incidence of patients infected with transmissible pathogens

Very low evidence from 1 observational study with adults with cystic fibrosis showed a lower annual incidence of *Burkholderia* species infections after changing infection control practices (consisting in cohorting patients with *Burkholderia* species infection), compared to the previous situation (partial cohort segregation). The significance and the uncertainty of this result could not be calculated. The follow-up and the total number of people included in the study were unclear.

Prevalence of patients infected with transmissible pathogens

Quality of life

No evidence was found.

Emotional function including anxiety and depression

No evidence was found.

Carer satisfaction

No evidence was found.

Patient satisfaction

No evidence was found.

Staff experience

No evidence was found.

Staff and patient compliance

No evidence was found.

11.6.3.1.3 Comparison 8. Individual segregation versus usual care

Incidence of patients infected with transmissible pathogens

No evidence was found.

Prevalence of patients infected with transmissible pathogens

No evidence was found.

Quality of life

No evidence was found.

Emotional function including anxiety and depression

No evidence was found.

Carer satisfaction

No evidence was found.

Patient satisfaction

Very low quality evidence from 1 observational study with 94 adults with cystic fibrosis indicated that the majority of the people (62.5%) who did not mix with others with cystic fibrosis felt that their quality of life did not suffer as a result of this prevention control strategy; whereas almost a quarter of the people (23.3%) who mixed with others with cystic fibrosis were concerned that their quality of life would suffer a 'significant amount' or 'a great deal' if they were to begin avoiding others. These results are provided narratively only.

Staff experience

No evidence was found.

Staff and patient compliance

No evidence was found.

11.6.3.2 Protective equipment

No studies have been identified.

11.6.3.3 Combination of strategies

11.6.3.3.1 Comparison 9. Cohort segregation + individual segregation versus cohort segregation

Incidence of patients infected with transmissible pathogens

No evidence was found.

Prevalence of patients infected with transmissible pathogens

Very low quality evidence from 1 observational study with people with cystic fibrosis showed a lower annual prevalence of *B cepacia complex* infection 3 years after infection control measures (consisting in cohorting hospitalised patients on the basis of *B cepacia* colonisation status and individual isolation) were put in place, compared to the previous situation (cohort segregation on the basis of *B cepacia* colonisation status only). The significance and the uncertainty of this result could not be calculated. The age and the total number of people included in the study was unclear.

Very low evidence from 1 observational study with adults with cystic fibrosis showed a lower annual prevalence of *Burkholderia* species infections 5 years after changing infection control practices (consisting in isolating patients with *Burkholderia* species infection in addition to cohort segregation), compared to the previous situation (cohorting patients with *Burkholderia* species infection). The significance and the uncertainty of this result could not be calculated. The total number of people included in the study was unclear.

Quality of life

No evidence was found.

Emotional function including anxiety and depression

No evidence was found.

Carer satisfaction

No evidence was found.

Patient satisfaction

No evidence was found.

Staff experience

No evidence was found.

Staff and patient compliance

No evidence was found.

11.6.3.3.2 Comparison 10. Cohort segregation + individual segregation + protective equipment versus usual care

Incidence of patients infected with transmissible pathogens

Very low quality evidence from 1 observational study with people with cystic fibrosis showed a lower annual incidence of *B cepacia complex* infection after a combination of infection control measures (consisting in cohorting hospitalised patients on the basis of *B cepacia* colonisation status, in addition to isolation and use of protective equipment) were put in place, compared to the previous situation (usual care). The significance and the uncertainty of this result could not be calculated. The follow-up, age and total number of people included in the study were not reported.

Prevalence of patients infected with transmissible pathogens

No evidence was found.

Quality of life

No evidence was found.

Emotional function including anxiety and depression

No evidence was found.

Carer satisfaction

No evidence was found.

Patient satisfaction

No evidence was found.

Staff experience

No evidence was found.

Staff and patient compliance

No evidence was found.

11.6.3.3.3 Comparison 11. Cohort segregation + individual segregation versus usual care

Incidence of patients infected with transmissible pathogens

No evidence was found

Prevalence of patients infected with transmissible pathogens

No evidence was found.

Quality of life

No evidence was found.

Emotional function including anxiety and depression

No evidence was found.

Patient and carer satisfaction

Very low quality evidence from 190 people with cystic fibrosis receiving paediatric care or their parents or carers indicated that both patients and carers showed an overall positive response to segregation measures. This results are provided narratively only.

Staff experience

No evidence was found.

Staff and patient compliance

No evidence was found.

11.6.4 Economic evidence statements

No published evidence on cost-effectiveness in people with cystic fibrosis was available for this review.

The economic model found that cohort segregation according to chronic *P aeruginosa* was cost-effective compared to no cohort segregation (3 studies).

The economic model found that cohort segregation according to intermittent *P aeruginosa* was not cost-effective compared to no cohort segregation (2 studies).

The economic model found that cohort segregation according to intermittent *B cepacia* complex was cost-effective compared to no cohort segregation in 1 study and cost-ineffective in 1 study.

The economic model found that the addition of protective equipment was cost-effective to prevent cross-infection with intermittent *B cepacia* complex (1 study) and intermittent *P aeruginosa* (1 study).

The economic model found that individual inpatient segregation (single inpatient rooms) according to intermittent *B cepacia* complex would be cost-effective compared to no individual inpatient segregation (shared ward) (2 studies).

11.7 Evidence to recommendations

11.7.1 Relative value placed on the outcomes considered

The aim of this review was to determine the effectiveness of the different strategies, such as cohorting, segregation, or protective equipment, in reducing the transmission of cystic fibrosis pathogens.

The committee identified incidence and prevalence of patients infected with transmissible pathogens as critical outcomes for decision making. Quality of life, emotional function, patient satisfaction, staff experience and staff and patient compliance were rated as important outcomes.

11.7.2 Consideration of clinical benefits and harms

The committee noted that there were existing NICE guidelines on preventing and controlling infection. Therefore, they incorporated a reference to these guidelines and focussed their recommendations on cross-infection concerns specific to people with cystic fibrosis.

The committee noted that the evidence showed mixed results with regards to whether incidence and prevalence of people infected with transmissible pathogens decreased after cohort segregation was implemented across the inpatient and outpatient setting or in the outpatient setting alone. There was some evidence that the incidence of *B cepacia* complex and hospital-associated *P cepacia* infections decreased after cohort segregation was implemented in the inpatient setting alone. Moreover, there was some evidence that prevalence of *B cepacia* complex infection decreased after individual segregation was added to cohort segregation across the inpatient and outpatient setting. The committee noted the lack of evidence assessing individual segregation as an intervention on its own in the outpatient setting alone. The committee noted that feelings of isolation may be a potential disadvantage of individual or cohort segregation. However, there was some evidence that people with cystic fibrosis and carers supported both cohort and individual segregation.

The committee noted that infection control would have to be implemented both in the inpatient and outpatient setting at the same time. Therefore, the committee recommended that arrangements to prevent cross-infection among people with cystic fibrosis should be based on a local infection control strategy that covers both outpatient and inpatient care. This strategy would cover interventions such as cleaning of rooms and equipment, closing the doors of rooms in the hospital or the outpatient clinic and effective ventilation in gyms to remove exposure of airborne cross-infection. Moreover, the committee recommended that arrangements to prevent cross-infection should also be based on a microbiological surveillance programme.

The committee noted that segregation interventions would be ineffective if people did not adhere to segregation rules or they met with each other outside of the health care setting. Therefore, a recommendation was prioritised to inform people with cystic fibrosis, their family members or carers and staff involved in their care about the risk of cross-infection and how to avoid it.

The committee agreed that a combination of cohort segregation and individual segregation is likely to be more effective than cohort segregation alone. Cross-infection can occur between people with cystic fibrosis who are designated as having the same pathogen but have different strains which may have differing virulence characteristics. For example, superinfection with different, more virulent epidemic strains of *P aeruginosa*, potentially as a result of cross-infection, can occur in people who already have *P aeruginosa*. Similarly, patients with less virulent species of *B cepacia* complex, for example *Burkholderia multivorans*, could become infected with the more virulent *B cenocepacia* if cohorting is based on *B cepacia* complex status without species differentiation or if patients have as yet

undetected infection. If people were to be cohorted based on different pathogen strains, cohort interventions would become complex due to a relatively high number of different cohorts which may increase as understanding of individual pathogen virulence develops. Moreover, any information on a person's infection status refers to the last sputum culture that was performed. Therefore, after acquisition of an infection there would be a time interval until the next sputum culture. During this period someone would be cohorted with people who are free of infection. Therefore, the committee concluded that separating all people with cystic fibrosis, regardless of their infection status, from each other was very important both in the outpatient and inpatient setting.

The committee agreed that each specialist cystic fibrosis clinic should be organised as to ensure that contact between people with cystic fibrosis is prevented both during the use of communal areas such as waiting areas, cafes and restrooms, and during attendance at diagnostic, treatment and pharmacy facilities. The committee noted that there were multiple options to separate people; for example, placing the person directly into a room, where the multidisciplinary team can go to conduct the visit.

The committee agreed that even if a clinic separates all people from each other, casual contact may still occur. Therefore, the committee agreed that a combination of cohorting and individual segregation was more effective than individual segregation alone and recommended that the local infection control strategy that covers outpatient and inpatient care should include cohorting. The committee noted casual contact might be more likely to happen in the outpatient setting because the whole patient journey would need to be taken into account. Additionally, it is more common that people attend for the use of diagnostic or treatment facilities without a prior booking in the outpatient setting.

Therefore, in addition to individual segregation, the committee agreed to prioritise a recommendation to keep people with transmissible or chronic *P aeruginosa* or *B cepacia* complex infection separate from people who do not have these infections, for example by using separate outpatient clinics. The committee noted that one way of cohorting would be to have separate buildings for separate patients, another way of cohorting would be to book appointments with people with a specific pathogen on one day of the week and for people with a different pathogen on a different day of the week.

Intermittent *P aeruginosa* infection is harder to diagnose given that tests with positive results would alternate with tests with negative results. Therefore, the committee noted that it would be difficult to cohort people with intermittent *P aeruginosa* infection from those who do not have this infection. Moreover, some evidence showed a higher prevalence of intermittent *P aeruginosa* infection after cohort segregation in the outpatient setting. However a lower prevalence of chronic *P aeruginosa* infection was observed in the same setting. Therefore, these trends may be due to treatment strategies rather than to cohort segregation because treatment may prevent the intermittent pathogen from becoming chronic. With regards to this point, the committee agreed that changes in prevalence and incidence may be due, not only to cross-infection, but also to other factors such as acquisition of infection from environmental sources and advances in treatment. Moreover, prevalence relates to survival. The evidence also showed no clinically significant difference in the incidence of intermittent *P aeruginosa* after cohort segregation across the inpatient and outpatient setting. Given the lack of evidence supporting segregation and considering the difficulties involved in diagnosing intermittent *P aeruginosa*, the committee decided not to be overly prescriptive and recommended to consider keeping people who have intermittent isolation of *P aeruginosa* separate from people who do not have this infection, for example by using separate outpatient clinics.

The committee noted that no evidence was identified on non-tuberculous mycobacteria. Therefore, no recommendation was drafted specific to this pathogen. However, the committee noted that all recommendations on cross-infection except for those two that refer to *P aeruginosa* and *B cepacia* complex should apply to all people with cystic fibrosis,

irrespective of their pathogen status. Cohorting could be done based on any pathogen that a local cross-infection control strategy may deem relevant.

The committee noted that the inpatient setting is where people would be more likely to come into close contact with each other as they may spend days or weeks in the hospital. Therefore, the committee prioritised a recommendation to give people with cystic fibrosis individual rooms with en-suite facilities. This recommendation is consistent with the NHS service specifications for cystic fibrosis. The committee noted that, in practice, people with cystic fibrosis are sometimes segregated into individual rooms but have contact in communal areas, this is to be avoided. Therefore, the committee recommended to help inpatients with cystic fibrosis plan their attendance to avoid contact with each other, for example when they use hospital restaurants, schools, recreational areas (such as the gym) and diagnostic, treatment and pharmacy facilities. The committee noted that a timetable could be used for school and gym attendance. Moreover, for diagnostic and treatment procedures there could be a computerised system suggesting who should enter specific areas at what time. Finally, systems should be in place to ensure that if someone with cystic fibrosis comes to the hospital, contact with the inpatients is prevented.

There was some evidence that prevalence of people infected with transmissible pathogens decreased after a combination of individual segregation with protective equipment was implemented in the outpatient setting alone. Incidence of infection decreased after a combination of cohort and individual segregation and protective equipment was implemented across the inpatient and outpatient settings. However, there was no evidence on the use of protective equipment alone. The committee noted that the use of protective equipment is difficult to implement. People's motivation is limited because of stigma and because it protects other people but not themselves, as a result they tend to take it off. Therefore, the committee decided not to make a recommendation on protective equipment.

11.7.3 Consideration of economic benefits and harms

11.7.3.1 Cohort segregation

P aeruginosa

The economic model showed that cohort segregation was cost-effective to reduce the transmission of chronic *P aeruginosa* compared to no cohort segregation, but was not cost-effective to reduce the transmission of intermittent *P aeruginosa*. This difference was driven by Lee 2004 who found that a fall in the number of cases with chronic infection was associated with a rise in those classified as intermittent. Following this, the committee noted that it is difficult to define an intermittent infection, adding that the distinction is even more difficult in children who cannot produce sputum.

Based on the evidence presented to them, and their clinical expertise, the committee agreed they could justify a recommendation to cohort people with transmissible *P aeruginosa* and chronic *P aeruginosa* as most clinics implement this as a cost-effective measure.

The committee wanted to enable clinics that had the ability to differentiate pathogens for intermittent *P aeruginosa* to do so, although they agreed that the findings from Lee 2004 were limited. This was because Lee 2004 did not genotype the participants' *P aeruginosa* isolates in order to infer if their strains were transmissible and potentially acquired from the clinic. Given that the findings from Lee 2004 can produce an unreliable estimate of cost-effectiveness, and cohort segregation depends on the ability of the clinic to identify intermittent *P aeruginosa*, the committee reduced the strength of their recommendation to consider cohorting people with cystic fibrosis who have intermittent *P aeruginosa* to reflect the weaker evidence compared to chronic *P aeruginosa*.

The committee discussed the potential harms of seeing less people with cystic fibrosis using cohorted clinics. They advised that waiting times could increase in the short term, but in the longer term the number of people with a transmissible pathogen would decrease. This decrease would subsequently increase the number of people that could be seen during "usual" clinics. The committee referred to their recommendations on service delivery. People with cystic fibrosis, and their family members or carers, can contact the MDT at any them when they have urgent enquiries, to minimise delays in identification and management.

The committee stated that genotyping is currently used by cystic fibrosis clinics to keep a track on the number of epidemic strains. This identification can prompt further investigation when there is a significant increase in numbers. Cystic fibrosis clinics currently follow CF Trust laboratory standards and infection control guidelines that advise surveillance should be performed on all new isolates and annually on those from people infected with *P aeruginosa*. Therefore, genotyping all isolates of *P aeruginosa,* in order to provide more up to date information for accurate clinic segregation, as a means to reduce cross-infections with transmissible pathogens could not be achieved with existing laboratory resources. The committee advised that it would be relatively easy to set up in-house polymerase chain reaction (PCR) methods for detecting the presence, or otherwise, of known epidemic strains. However, this work would require dedicated project budget and recruitment of technical and scientific staff to deliver it. Moreover, to achieve the required level of discriminatory power, more complex typing methodologies such as variable number of tandem repeats (VNTR) typing or whole genome sequencing (WGS) would be necessary, but would raise costs and workloads even further. Overall, the committee considered a recommendation was needed to ensure microbiological surveillance and local infection control strategies were in place. The committee were reluctant to specify how such arrangements should be achieved as this would depend on the expertise and prevalence of pathogens within each clinic.

In addition, there is insufficient evidence to enable full understanding of the results regarding detailed genotyping. This is especially so as there is data suggesting significant intra-patient, and intra-isolate, variability when detailed methods are used referring to the study by Darch 2015. Therefore, a recommendation in favour of regular, detailed genotyping was not prioritised by the committee. As a result, the committee wanted to make a research recommendation to define optimal microbiological methods and their role to inform infection control strategies, to assess if the benefits of regular genotyping could justify the additional resources. However, this was later deprioritised as it was considered a public health issue for local areas to devise their own policies.

***B cepacia* complex**

One study (Whitford 1995) found cohort segregation according to *B cepacia* complex to be cost-effective compared to no cohort segregation. Conversely, the second study (France 2008) found no cohort segregation to dominate cohort segregation according to *B cepacia* complex, as no cohort segregation was less expensive and more effective than cohort segregation. However, given that complete cohort segregation, with the addition of single inpatient rooms, dominated (less expensive and more effective) incomplete cohort segregation. The committee agreed that people infected with *B cepacia* complex also should be cohorted at outpatient clinics and inpatient care. Following this, the committee noted that the species of *B cepacia* complex must be determined otherwise those with *B cenocepacia* could be cohorted with *multivorans,* which would be inappropriate and hazardous. The committee noted that the prevalence of *B cepacia* complex is decreasing (circa 3%) according to UK registry data, indicating that current infection control measures to cohort these people with cystic fibrosis are working.

11.7.3.2 Individual segregation

The committee advised that, unlike cohort segregation, individual segregation acts as a preventative measure as there is less need to worry about the specific pathogen. The

committee added that individual segregation is a strategy currently applied in cystic fibrosis clinics in order to reduce the risk of cross-infection with transmissible pathogens.

The committee agreed that the additional cost of single rooms, compared to beds in shared rooms, was best reflected by NHS Estates 2005 (an additional £10.61/day in 2016 prices) and potentially overestimated when an additional 25% was assumed.

The clinical evidence was not meta-analysed as the studies were too heterogeneous. Consequently, the committee considered the cost-effective results produced by each of the studies and concluded that France 2008 was the study most reflective of UK clinical practice today. Based on France 2008, the dominant strategy (less expensive and more effective strategy) was to admit people with cystic fibrosis to single rooms when an additional £10.61/bed/day or 25%/bed/day compared to beds in shared rooms was assumed. As a result, the committee prioritised a recommendation for all inpatients to have their own single room as the economic model provided additional justifications for current practice to be followed.

The committee considered the acceptable additional cost given the additional QALY gain, based on the study by Jones 2005 who compared incomplete cohort segregation to no cohort segregation. Incomplete cohort segregation provided inpatient rooms with en-suite facilities, whereas only 2 of the 11 rooms in no cohort segregation strategy included en-suite facilities. Incomplete cohort segregation also meant people without chronic *P aeruginosa* attended different outpatient clinic appointments to other people with cystic fibrosis. The committee acknowledged that the incidence of superinfection by transmissible strains among trial participants (Jones 2005) already infected with chronic *P aeruginosa* was sporadic, potentially resulting in a dominated (more expensive and less effective) strategy.

However, incomplete cohort segregation produced more QALYs than no cohort segregation, with a fall in the incidence of intermittent *P aeruginosa* from 9.7% to 0% each year, following the new strategy. Based on this benefit, the committee believed that incomplete cohort segregation could be cost-effective. The committee added that the majority of single rooms include en-suite facilities and referred to the NHS Commissioning document on service specifications that states “Every CF patient will be in their own room, with en-suite facilities to minimise the risk of cross infection and to enable them to continue life as normally as possible”. Given that the majority of centres follow this, the committee agreed a recommendation in favour of en-suite facilities that would not lead to substantial increase from current resource use.

11.7.3.3 Protective equipment

The new strategies implemented by Savant 2014 and Chen 2001 that included protective equipment to prevent intermittent infections were cost-effective (dominant). However, it is important to note that the effect of protective equipment alone could not be disaggregated into a separate effect measure from the combination of strategies applied. Following this, the committee agreed that a dominant result was unlikely to be driven by the protective equipment as Chen 2001 also cohorted their participants according to *B cepacia* complex infection and Savant 2014 applied a “no-waiting” room policy. The committee believed this cohorting to be the true cost-effective strategies.

Despite the low cost of protective equipment, the committee agreed, based on their knowledge and expertise, that there was not enough evidence to support the use of protective equipment as compliance outside of a trial setting would be low, due to the negative impact the equipment has on social interaction.

11.7.3.4 Other considerations

The committee agreed that communal areas in cystic fibrosis clinics promote patient contact and increase the risk of infection from transmissible pathogens. The acknowledged the

opportunity cost of the space would be of greater value in other areas of the hospital. For these reasons, the committee made a recommendation to manage the use of communal waiting areas in outpatient clinics. The committee considered the benefits from closing clinic room doors. This is a very simple, quick and costless way to prevent transmissions that can be overlooked, or stopped, by reluctant parents. However, a recommendation was not prioritised.

11.7.4 Quality of evidence

All the evidence included in the review was of very low quality as assessed by GRADE.

One RCT was included. This study had unclear risk of selection bias, performance bias, detection bias, attrition bias and outcome reporting bias.

Most included studies were retrospective uncontrolled before-after studies. In some of these studies, the intervention and comparison groups were drawn from years, or time intervals, that were considerably distant in time. These time intervals increased the likelihood that the intervention group may have been exposed to additional interventions affecting incidence or prevalence. Moreover, in some studies the frequency of cultures performed to detect relevant infections was unclear or only annual. Therefore, people that were considered “at risk” when the intervention started may have already had the infection. Consequently, there was a high risk of selection bias. Most studies did not control for any factor, therefore, there was a high risk of comparability bias. Furthermore, many studies looked at changes in prevalence and incidence without making a distinction between transmissible strains and unique strains. Most studies did not use genotyping in order to understand whether changes in incidence or prevalence were related to cross-infection. Therefore, there was high risk of bias in relation to the outcomes of incidence and prevalence.

Three surveys were included. Only 1 study assessed comparability between respondents and non-respondents and all 3 studies had high risk of selection bias. None of the 3 studies controlled the analysis for possible confounders, therefore, there was high risk of comparability bias.

11.7.5 Other considerations

There was some evidence that staff adherence to cohort segregation was high. This indicated that cohort segregation was feasible.

No equality issues were identified by the committee for this review question.

The committee discussed the need for a research recommendation in this area, but they agreed it was not needed. They noted it is the responsibility of local areas to devise their own policies and is primarily a public health issue. They acknowledged there is a NICE guideline on infection.

11.7.6 Key conclusions

The committee concluded that people with cystic fibrosis should avoid contact with each other irrespective of their infection status. Moreover, cohorting should be implemented in addition to individual segregation, to reduce chances of casual contact between people with different infection status. The minimum requirement in terms of cohorting is that people with transmissible or chronic *P aeruginosa* or *B cepacia* complex infection should be kept separate from people who do not have these infections, for example by using separate outpatient clinics. Additionally, outpatient and inpatient care facilities should follow their local infection control strategy to prevent cross-infection.

11.8 Recommendations

133. For recommendations on preventing and controlling infection, see the NICE guidelines on infection control in primary and community care and healthcare-associated infections, and the NICE quality standard on infection prevention and control.

134. To prevent cross-infection among people with cystic fibrosis in outpatient and inpatient care, use microbiological surveillance and a local infection control strategy that includes cohorting.

135. Inform people with cystic fibrosis, their family members or carers (as appropriate) and staff involved in their care about the risk of cross-infection and how to avoid it.

136. Each specialist cystic fibrosis clinic should be organised to prevent cross-infection. Separate people individually during the clinic, including by organising:

- the use of communal areas
- attendance at diagnostic, treatment and pharmacy facilities.

137. Keep people with transmissible or chronic *Pseudomonas aeruginosa* or *Burkholderia cepacia* complex infection separate from people who do not have these infections, for example by using separate outpatient clinics.

138. Consider keeping people with cystic fibrosis who have intermittent isolation of *Pseudomonas aeruginosa* separate from people who do not have this infection, for example by using separate outpatient clinics. Help people with cystic fibrosis plan their inpatient attendance to avoid contact with each other, for example when they use:

- hospital restaurants, schools and recreation areas
- diagnostic, treatment and pharmacy facilities (see Information and Support).

139. During inpatient care, give people with cystic fibrosis individual rooms with en-suite facilities.

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13 Glossary and abbreviations

Term	Definition
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
ACT	Airway clearance techniques help to clear mucous from the lungs reducing the risk of infection and improve lung function.
Allocation concealment	The process used to prevent advance knowledge of group assignment in a randomised controlled trial (RCT). The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Alveolus (Alveoli)	The specialised part of the lung where oxygen enters the blood and carbon dioxide can leave.
Antimicrobial prophylaxis	Antimicrobial drugs administered to those without symptoms or positive cultures with the intention of preventing future infection/colonisation.
Applicability	How well the results of a study or NICE evidence review can answer a clinical question or be applied to the population being considered.
APRI	AST to platelet ratio index (APRI) is a liver fibrosis test.
Arm (of a clinical study)	Subsection of individuals within a study who receive one particular intervention, for example placebo arm.
Association	Statistical relationship between 2 or more events, characteristics or other variables. The relationship may or may not be causal.
Attrition bias	Systematic differences between comparison groups in withdrawals or exclusion of participants from a study.
Available case analysis	Analysis of data that is available for participants at the end of follow-up.
BAL	Bronchoalveolar lavage. The bronchi and alveoli are washed via bronchoscope with a small amount of fluid which is then collected for analysis.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable) with which subsequent results are compared.
Before-and-after study	A study that investigates the effects of an intervention by measuring particular characteristics of a population both before and after taking the intervention, and assessing any change that occurs.
Bias	Influences on a study that can make the results look better or worse than they really are. (Bias can even make it look as if a treatment works when it does not.) Bias can occur by chance, deliberately or as a result of systematic errors in the design and execution of a study. It can also occur at different stages in the research process, for example during the collection, analysis, interpretation, publication or review of research data. For examples see selection bias, performance bias, information bias, confounding factor and publication bias.
Bilirubin	A substance formed in liver by the breakdown of haemoglobin and excreted in bile.
Bronchus (Bronchi)	Small airways in the lung.
Cardiopulmonary exercise testing	Measurement of the function of the heart and lungs at rest and during exercise.
Carer (caregiver)	Someone who looks after family, partners or friends in need of help because they are ill, frail or have a disability.
Case series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.

Term	Definition
Case-control study	A study to find out the cause(s) of a disease or condition. This is done by comparing a group of patients who have the disease or condition (cases) with a group of people who do not have it (controls) but who are otherwise as similar as possible (in characteristics thought to be unrelated to the causes of the disease or condition). This means the researcher can look for aspects of their lives that differ to see if they may cause the condition. For example, a group of people with lung cancer might be compared with a group of people the same age that do not have lung cancer. The researcher could compare how long both groups had been exposed to tobacco smoke. Such studies are retrospective because they look back in time from the outcome to the possible causes of a disease or condition.
CFRD	Cystic fibrosis related diabetes.
Chronic pulmonary infection	Presence of pathogens on culture (colonisation) in the absence of worsening clinical symptoms/signs of respiratory disease. Antimicrobials may be administered to suppress or eradicate such pathogens with the intention of reducing future acute pulmonary exacerbations.
Cirrhosis	Progressive fibrous tissue overgrowth in an organ.
Clinical audit	A systematic process for setting and monitoring standards of clinical care. Whereas 'guidelines' define what the best clinical practice should be, 'audit' investigates whether best practice is being carried out. Clinical audit can be described as a cycle or spiral. Within the cycle there are stages that follow a systematic process of establishing best practice, measuring care against specific criteria, taking action to improve care and monitoring to sustain improvement. The spiral suggests that as the process continues, each cycle aspires to a higher level of quality.
Clinical effectiveness	How well a specific test or treatment works when used in the 'real world' (for example when used by a doctor with a patient at home), rather than in a carefully controlled clinical trial. Trials that assess clinical effectiveness are sometimes called management trials. Clinical effectiveness is not the same as efficacy.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinician	A healthcare professional who provides patient care; for example a doctor, nurse or physiotherapist.
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence based medicine databases including the Cochrane Database of Systematic Reviews (reviews of RCTs prepared by the Cochrane Collaboration).
Cohort study	A study with 2 or more groups of people – cohorts – with similar characteristics. One group receives a treatment, is exposed to a risk factor or has a particular symptom and the other group does not. The study follows their progress over time and records what happens.
Cohorting (cross-infection)	Grouping patients with positive cultures of the same pathogen(s).
Colonisation	Presence of pathogens on culture without signs of infection. See chronic pulmonary infection.
Community care	Care provided by community nurses, health visitors or school nurses of the region who look after people with CF and will administer treatments such as home IV antibiotics. It can include palliative services.
Comorbidity	A disease or condition that someone has in addition to the health problem being studied or treated.
Concealment of allocation	The process used to ensure that the person deciding to enter a participant into a randomised controlled trial does not know the comparison group into which that individual will be allocated. This is distinct from blinding and is aimed at preventing selection bias. Some attempts at concealing

Term	Definition
	allocation are more prone to manipulation than others, and the method of allocation concealment is used as an assessment of the quality of a trial.
Confidence interval (CI)	There is always some uncertainty in research. This is because a small group of patients is studied to predict the effects of a treatment on the wider population. The confidence interval is a way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. The CI is usually stated as '95% CI', which means that the range of values has a 95 in 100 chance of including the 'true' value. For example, a study may state that “based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110”. In such a case the 95% CI would be 110 to 150. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment – often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example if a large number of patients have been studied).
Confounding factor	Something that influences a study and can result in misleading findings if it is not understood or appropriately dealt with. For example, a study of heart disease may look at a group of people who exercise regularly and a group who do not exercise. If the ages of the people in the 2 groups are different, then any difference in heart disease rates between the 2 groups could be because of age rather than exercise. Therefore age is a confounding factor.
Consensus methods	Techniques used to reach agreement on a particular issue. Consensus methods may be used to develop NICE guidance if there is not enough good quality research evidence to give a clear answer to a question. Formal consensus methods include Delphi and nominal group techniques.
Continuous outcome	Data with a potentially infinite number of possible values within a given range. Height, weight and blood pressure are examples of continuous variables.
Control group	A group of people in a study who do not receive the treatment or test being studied. Instead, they may receive the standard treatment (sometimes called 'usual care') or a dummy treatment (placebo). The results for the control group are compared with those for a group receiving the treatment being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the treatment group, to make it as easy as possible to detect any effects due to the treatment.
Corticosteroids	Anti-inflammatory medicines.
Cost–benefit analysis (CBA)	Cost-benefit analysis is one of the tools used to carry out an economic evaluation. The costs and benefits are measured using the same monetary units (for example UK pounds) to see whether the benefits exceed the costs.
Cost–consequence analysis (CCA)	Cost–consequence analysis is one of the tools used to carry out an economic evaluation. This compares the costs (such as treatment and hospital care) and the consequences (such as health outcomes) of a test or treatment with a suitable alternative. Unlike cost–benefit analysis or cost-effectiveness analysis, it does not attempt to summarise outcomes in a single measure (like the quality adjusted life year) or in financial terms. Instead, outcomes are shown in their natural units (some of which may be monetary) and it is left to decision-makers to determine whether, overall, the treatment is worth carrying out
Cost-effectiveness analysis (CEA)	Cost-effectiveness analysis is one of the tools used to carry out an economic evaluation. The benefits are expressed in non-monetary terms related to health, such as symptom-free days, heart attacks avoided, deaths avoided or life years gained (that is, the number of years by which life is extended as a result of the intervention).

Term	Definition
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost–utility analysis (CUA)	Cost–utility analysis is one of the tools used to carry out an economic evaluation. The benefits are assessed in terms of both quality and duration of life, and expressed as quality adjusted life years (QALYs).
COX proportional hazard model	In survival analysis, a statistical model that asserts that the effect of the study factors (for example the intervention of interest) on the hazard rate (the risk of occurrence of an event) in the study population is multiplicative and does not change over time.
Credible interval (CrI)	The Bayesian equivalent of a confidence interval.
CT scan	Computerised tomography scan; computer-processed combinations of x-ray images producing cross-sectional images.
Decision analysis	An explicit quantitative approach to decision-making under uncertainty based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Dichotomous outcomes	Outcome that can take 1 of 2 possible values, such as dead/alive, smoker/non-smoker, present/not present (also called binary data).
DIOS	Distal Intestinal Obstruction Syndrome. A blockage of the gut which occurs in older children and adults with cystic fibrosis.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Dominance	A health economics term. When comparing tests or treatments, an option that is both less effective and costs more is said to be 'dominated' by the alternative.
Drop-out	A participant who withdraws from a trial before the end.
Economic evaluation	An economic evaluation is used to assess the cost effectiveness of healthcare interventions (that is, to compare the costs and benefits of a healthcare intervention to assess whether it is worth doing). The aim of an economic evaluation is to maximise the level of benefits – health effects – relative to the resources available. It should be used to inform and support the decision-making process; it is not supposed to replace the judgement of healthcare professionals. There are several types of economic evaluation: cost–benefit analysis, cost consequence analysis, cost-effectiveness analysis, cost-minimisation analysis and cost–utility analysis. They use similar methods to define and evaluate costs, but differ in the way they estimate the benefits of a particular drug, programme or intervention.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	A measure that shows the magnitude of the outcome in 1 group compared with that in a control group. For example, if the absolute risk reduction is shown to be 5% and it is the outcome of interest, the effect size is 5%. The effect size is usually tested, using statistics, to find out how likely it is that the effect is a result of the treatment and has not just happened incidentally.
Effectiveness	How beneficial a test or treatment is under usual or everyday conditions, compared with doing nothing or opting for another type of care.
Efficacy	How beneficial a test, treatment or public health intervention is under ideal conditions (for example in a laboratory), compared with doing nothing or opting for another type of care.
Enteric coated	Covered with a coating which protects against acid in the stomach.

Term	Definition
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (for example infection, diet) and interventions.
EQ-5D (EuroQol 5 dimensions)	A standardised instrument used to measure health-related quality-of-life. It provides a single index value for health status.
Equivalence study	A trial designed to determine whether the response to 2 or more treatments differs by an amount that is clinically unimportant. This is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.
Eradication regimen, antibiotic	An antibiotic regimen aimed at eliminating a specific pulmonary pathogen such as *S aureus* or *P aeruginosa* in people with cystic fibrosis
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals or patients).
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect when both are compared with a do-nothing alternative, then Option A is said to have extended dominance over Option B. Option A is therefore more cost effective and should be preferred, other things remaining equal.
Extrapolation	An assumption that the results of studies of a specific population will also hold true for another population with similar characteristics.
Fibroscan	See Transient elastography
Fixed-effect model	In meta-analysis, a model that calculates a pooled effect estimate using the assumption that all observed variation between studies is caused by the play of chance. Studies are assumed to be measuring the same overall effect.
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Forest plot	A graphical representation of the individual results of each study included in a meta-analysis together with the combined meta-analysis result. The plot also allows readers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centred on each study's point estimate. A horizontal line runs through each square to show each study's confidence interval. The overall estimate from the meta-analysis and its confidence interval are shown at the bottom, represented as a diamond. The centre of the diamond represents the pooled point estimate, and its horizontal tips represent the confidence interval.
Forns score	A non-invasive marker of liver fibrosis.
Generalisability	The extent to which the results of a study hold true for groups that did not participate in the research. See also external validity.
Gold standard	A method, procedure or measurement that is widely accepted as being the best available to test for or treat a disease.
GRADE, GRADE profile	A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.

Term	Definition
Haemophilus influenzae	A bacterium which is a common cause of respiratory infection in cystic fibrosis.
Haemoptysis	Coughing up blood.
Harms	Adverse effects of an intervention.
Hazard ratio	A hazard is the rate at which events happen, so that the probability of an event happening in a short time interval is the length of time multiplied by the hazard. Although the hazard may vary with time, the assumption in proportional hazard models for survival analysis is that the hazard in one group is a constant proportion of the hazard in the other group. This proportion is the hazard ratio.
Health economics	Study or analysis of the cost of using and distributing healthcare resources.
Health related quality of life (HRQoL)	A measure of the effects of an illness to see how it affects someone's day-to-day life.
Heterogeneity	The term is used in meta-analyses and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ.
HFCWO	High frequency chest wall oscillation; technique aimed at improving airway clearance
Home care (e.g. hospital at home)	Giving care at home instead of a hospital, provided by the relevant cystic fibrosis specialist (such as a specialist nurse, dietitian or psychologist).
Immunomodulatory dose	The use of a drug such as azithromycin prescribed at a lower dose than the minimum inhibitory dose.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental cost	The extra cost linked to using one test or treatment rather than another. Or the additional cost of doing a test or providing a treatment more frequently.
Incremental cost effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000×QALYs gained) minus incremental cost.
Indirectness	The available evidence is different to the review question being addressed, in terms of population, intervention, comparison and outcome (PICO).
Intention-to-treat analysis (ITT)	An assessment of the people taking part in a clinical trial, based on the group they were initially (and randomly) allocated to. This is regardless of whether or not they dropped out, fully complied with the treatment or switched to an alternative treatment. Intention-to-treat analyses are often used to assess clinical effectiveness because they mirror actual practice: that is, not everyone complies with treatment and the treatment people receive may be changed according to how they respond to it.
Intervention	In medical terms this could be a drug treatment, surgical procedure, diagnostic or psychological therapy. Examples of public health interventions could include action to help someone to be physically active or to eat a more healthy diet.
Kappa statistic	A statistical measure of inter-rater agreement that takes into account the agreement occurring by chance.

Term	Definition
LCI	Lung Clearance Index. A measure of lung function.
Length of stay	The total number of days a participant stays in hospital.
Licence	See 'Product licence'.
Life years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Likelihood ratio	The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by (1 minus specificity).
Loss to follow-up	Patients who have withdrawn from a clinical trial at the point of follow-up.
Malabsorption	A failure to absorb nutrients from the intestine. In cystic fibrosis this is due to the common occurrence of exocrine pancreatic insufficiency, so that there is a deficiency or absence of the pancreatic enzymes necessary to digest complex carbohydrates, proteins and fats (maldigestion) resulting in an inability to absorb these and other nutrients
Maldigestion	See malabsorption.
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
MDT	Multi-disciplinary team. A patient care team comprised of healthcare professionals of various specialties.
Mean	An average value, calculated by adding all the observations and dividing by the number of observations.
Mean difference	In meta-analysis, a method used to combine measures on continuous scales (such as weight), where the mean, standard deviation and sample size in each group are known. The weight given to the difference in means from each study (for example how much influence each study has on the overall results of the meta-analysis) is determined by the precision of its estimate of effect.
Meconium ileus	An obstruction of the small intestine at birth due to inspissated material in the gut lumen in infants with cystic fibrosis.
Meconium Ileus Equivalent	See DIOS
Median	The value of the observation that comes half-way when the observations are ranked in order.
Meta-analysis	A method often used in systematic reviews. Results from several studies of the same test or treatment are combined to estimate the overall effect of the treatment.
Microspheres	Enzyme granules contained within a pancreatin capsule.
Minimal important difference (MID)	Thresholds for clinical importance, which represent minimal important differences for benefit or for harm; for example the threshold at which drug A is less effective than drug B by an amount that is clinically important to patients.
MRI	Magnetic Resonance Imaging. Diagnostic imaging using magnetic fields and radio waves.
Mucoactive agent	See mucolytic agent.
Mucolytic agent	Drug affecting the viscosity of mucus, typically administered with the intention of making the removal of mucus through coughing easier.
Multivariate model	A statistical model for analysis of the relationship between 2 or more predictor (independent) variables and the outcome (dependent) variable.
Nebuliser	A small machine which converts liquid medication to a fine mist which can be breathed in to work directly in the lungs.

Term	Definition
Net monetary benefit (NMB)	The value (usually in monetary terms) of an intervention net of its cost. The NMB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the NMB is calculated as: (£20,000×QALYs gained) minus cost.
Network meta-analysis	Meta-analysis in which multiple treatments (that is, 3 or more) are being compared using both direct comparisons of interventions within RCTs and indirect comparisons across trials based on a common comparator.
Number needed to treat (NNT)	The average number of patients who need to be treated to get a positive outcome. For example, if the NNT is 4, then 4 patients would have to be treated to ensure 1 of them gets better. The closer the NNT is to 1, the better the treatment. For example, if you give a stroke prevention drug to 20 people before 1 stroke is prevented, the number needed to treat is 20.
Observational study	Individuals or groups are observed or certain factors are measured. No attempt is made to affect the outcome. For example, an observational study of a disease or treatment would allow 'nature' or usual medical care to take its course. Changes or differences in 1 characteristic (for example whether or not people received a specific treatment or intervention) are studied without intervening. There is a greater risk of selection bias than in experimental studies.
Odds ratio (OR)	Odds are a way to represent how likely it is that something will happen (the probability). An odds ratio compares the probability of something in 1 group with the probability of the same thing in another. An odds ratio of 1 between 2 groups would show that the probability of the event (for example a person developing a disease or a treatment working) is the same for both. An odds ratio greater than 1 means the event is more likely in the first group. An odds ratio less than 1 means that the event is less likely in the first group. Sometimes probability can be compared across more than 2 groups - in this case, 1 of the groups is chosen as the 'reference category', and the odds ratio is calculated for each group compared with the reference category. For example, to compare the risk of dying from lung cancer for non-smokers, occasional smokers and regular smokers, non-smokers could be used as the reference category. Odds ratios would be worked out for occasional smokers compared with non-smokers and for regular smokers compared with non-smokers. See also confidence interval, relative risk, risk ratio.
Odds ratio (OR)	Odds are a way to represent how likely it is that something will happen (the probability). An odds ratio compares the probability of something in 1 group with the probability of the same thing in another. An odds ratio of 1 between 2 groups would show that the probability of the event (for example a person developing a disease, or a treatment working) is the same for both. An odds ratio greater than 1 means the event is more likely in the first group. An odds ratio less than 1 means that the event is less likely in the first group. Sometimes probability can be compared across more than 2 groups – in this case, 1 of the groups is chosen as the 'reference category' and the odds ratio is calculated for each group compared with the reference category. For example, to compare the risk of dying from lung cancer for non-smokers, occasional smokers and regular smokers, non-smokers could be used as the reference category. Odds ratios would be worked out for occasional smokers compared with non-smokers and for regular smokers compared with non-smokers.
Opportunity cost	The loss of other healthcare programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Outcomes from interventions to improve the public's health could include changes in knowledge and behaviour related to health, societal changes (for example a reduction in

Term	Definition
	crime rates) and a change in people's health and wellbeing or health status. In clinical terms, outcomes could include the number of patients who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone's health, functional ability, symptoms or situation. Researchers should decide what outcomes to measure before a study begins.
Outreach care	A model of care in which the specialist multidisciplinary cystic fibrosis team provide outpatient clinics in local hospitals.
P value	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance) it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Pancreatin	An extract of animal pancreas; the general name for all pancreatic enzymes.
PEP	Positive expiratory pressure; a technique aimed at improving airway clearance.
Performance bias	Systematic differences between intervention groups in care provided apart from the intervention being evaluated. Blinding of study participants (both the recipients and providers of care) is used to protect against performance bias.
PERT	Pancreatic enzyme replacement therapy.
Placebo	A fake (or dummy) treatment given to participants in the control group of a clinical trial. It is indistinguishable from the actual treatment (which is given to participants in the experimental group). The aim is to determine what effect the experimental treatment has had – over and above any placebo effect caused because someone has received (or thinks they have received) care or attention.
Placebo effect	A beneficial (or adverse) effect produced by a placebo and not due to any property of the placebo itself.
Post-hoc analysis	Statistical analyses that are not specified in the trial protocol and are generally suggested by the data.
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Primary care	Healthcare delivered outside hospitals. It includes a range of services provided by GPs, nurses, health visitors, midwives and other healthcare professionals and allied health professionals such as dentists, pharmacists and opticians.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prophylactic antibiotics	Antibiotics used for the prevention of infection complications.

Term	Definition
Prospective study	A research study in which the health or other characteristic of participants is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
Pseudomonas aeruginosa	A bacterial infection which affects the lungs.
Publication bias	Publication bias occurs when researchers publish the results of studies showing that a treatment works well and don't publish those showing it did not have any effect. If this happens, analysis of the published results will not give an accurate idea of how well the treatment works. This type of bias can be assessed by a funnel plot.
Pulmonary exacerbation	The sudden or recent worsening of clinical symptoms or signs. This is frequently caused by an acute pulmonary infection.
Pulmonary infection	In people with cystic fibrosis, this can be diagnosed based on symptoms or signs, or by identifying pathogens in respiratory secretion samples.
Pyrexia	A fever.
Sepsis	A whole-body inflammation caused by an infection.
Shared-care (Network CF Clinic)	When a local hospital cares for people with cystic fibrosis, with oversight, support and direct involvement from members of a specialist cystic fibrosis multidisciplinary team.
Specialist centre	This is a centre for the diagnosis and management of cystic fibrosis, and working with a multidisciplinary team approach. Cystic fibrosis specialist centres are commissioned by NHS England.
Spirometry	A lung function test measuring the volume and/or speed of air that can be inhaled and exhaled.
Stakeholder	An organisation with an interest in a topic that NICE is developing a NICE guideline or piece of public health guidance on. Organisations that register as stakeholders can comment on the draft scope and the draft guidance. Stakeholders may be:
Standard deviation (SD)	A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.
Staphylococcus aureus	A bacterial infection that can affect the lungs.
Steatorrhoea	Abnormal amount of fat in faeces due to malabsorption.
Subgroup analysis	An analysis in which the intervention effect is evaluated in a defined subset of the participants in a trial, or in complementary subsets.
Suppression regimen, antibiotic	An antibiotic regimen aimed at reducing the level of infection with a specific pulmonary pathogen such as *S aureus* or *P aeruginosa* in people with cystic fibrosis
Systematic review (SR)	A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. It may include a meta-analysis.
Telemedicine	Providing clinical services remotely, using phone and video messaging to communicate with the patient.
Time horizon	The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.
Transient elastography	An ultrasound technique to measure tissue stiffness.
Treatment allocation	Assigning a participant to a particular arm of a trial.
UDCA	Ursodeoxycholic acid; drug administered with the intention of preventing progression of liver disease.
Ultrasound	Imaging technique using ultrasound (high frequency sound waves).
Univariate	Analysis which separately explores each variable in a data set.

Term	Definition
Utility	In health economics, a 'utility' is the measure of the preference or value that an individual or society places upon a particular health state. It is generally a number between 0 (representing death) and 1 (perfect health). The most widely used measure of benefit in cost–utility analysis is the quality adjusted life year (QALY), but other measures include disability adjusted life years (DALYs) and healthy year equivalents (HYEs).