D.11 Mucoactive agents

Item	Details
Key issue in the scope	Management with mucoactive or mucolytic agents.
Review question in the scope	What is the effectiveness of mucoactive or mucolytic agents, including rhDNase, nebulised saline (isotonic and hypertonic) and mannitol?
Review question in the protocol	What is the effectiveness of mucoactive or mucolytic agents, including dornase alpha, nebulised sodium chloride (isotonic and hypertonic) and mannitol?
Objective	Mucolytics are prescribed to facilitate expectoration by reducing sputum viscosity. In some patients with a chronic productive cough, mucolytics can reduce exacerbations; mucolytic therapy should be stopped if there is no benefit after a 5-week trial. The aim of this review is 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.
Language	English
Study design	• Systematic reviews of RCTs • RCTs (including cross over RCTs) • Conference abstracts of RCTs (Only if RCTs unavailable and the quality assessment of abstracts will conducted based on the available information and if necessary the authors of abstracts will be contacted). • Comparative cohort studies (only if RCTs unavailable or limited data to inform decision making)
Population and directness	Children, young people and adults with CF, diagnosed clinically and by sweat test or genetic testing. Population size and indirectness: • Studies with N < 10 will not be included. • Studies with indirect population will not be considered.
Stratified, subgroup and adjusted analyses	Groups that will be reviewed and analysed separately: • Children • Young people and adults Sensitivity analysis: In the presence of heterogeneity, sensitivity analysis will conducted including and excluding studies with a high risk of bias. In the presence of heterogeneity, the following subgroups will be considered for subgroup analysis: • Disease severity

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Intervention	Nebulised and Inhaled Mucolytics • Dornase alfa • Acetylcysteine • Nebulised sodium chloride (saline) (hypertonic and isotonic) • Mannitol (only in children and young people up to the age of 18 years as TA in adults will be included).
Comparison	• Mucoactive agents vs placebo • Mucoactive agent A versus mucoactive agent B
Outcomes	• Lung function: FEV1 • Inflammatory markers (change from baseline) ○ Serum (white blood cell (WBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)) ○ Sputum (IL-8) • Quality of life (CF-QOL, CFQR) • Time to pulmonary exacerbations • Need for intravenous antibiotics for pulmonary exacerbation ○ Number of days of treatment ○ Number of courses • Adverse events ○ alteration in voice ○ haemoptysis ○ bronchospasm Note: change from baseline will be priorised over absolute values
Importance of outcomes	Critical outcomes for decision making: • Lung function: FEV1 • Time to pulmonary exacerbations • Need for intravenous antibiotics for pulmonary exacerbation
Setting	All settings in which NHS-commissioned health and social care is provided.
Search strategy	Sources to be searched: Medline, Medline In-Process, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effectiveness, Health Technology Database, Embase Limits (e.g. date, study design): Apply standard exclusions and English language filters. Limit to RCTs and systematic reviews unless overall return is small Supplementary search techniques: No supplementary search techniques will be used. See appendix E.8 for full strategies
Review strategy	Appraisal of methodological quality: • The methodological quality of each study will be assessed using an appropriate checklist as per NICE guidelines manual (The Cochrane Risk of Bias tool for RCTs and the Newcastle and Ottawa scale for observational studies). • The quality of the evidence will be assessed by GRADE for each outcome according to the process described in the NICE guidelines manual (2014). Synthesis of data: • Meta-analysis will be conducted where appropriate. • Final and change scores will be pooled and if any study reports both, change scores will be used in preference over final scores.

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	• If studies only report p-values from parametric analyses, and 95% CIs cannot be calculated from other data provided, this information will be plotted in GRADE tables, but evidence may be downgraded.
	• If studies only report p-values from non-parametric analyses, this information will be plotted in GRADE tables without downgrading the evidence, as imprecision cannot be assessed for non-parametric analyses
	
	Minimal important differences (MIDs):
	• FEV1: 5 percentage points
	• Inflammatory markers (change from baseline): GRADE default
	• Quality of life: CF-QOL = 5; CFQ-R = 4
	• Time to pulmonary exacerbations: any change will be considered clinically significant
	• Need for intravenous antibiotics for pulmonary exacerbation
	  ○ Number of days of treatment: GRADE default
	  ○ Number of courses: GRADE default
	• Adverse events (alteration in voice, haemoptysis): GRADE default
	• Serious adverse events leading to discontinuation of treatment: any change will be considered clinically significant
	Default MIDs: 0.8 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes.
	
	Review process:
	• This question will be prioritised for dual weeding.
	• A list of excluded studies will be provided following weeding.
	• Evidence tables and an evidence profile will be used to summarise the evidence.

Equalities	• Psychological and behavioural issues are more likely in people with a lower socioeconomic status • Gender- outcomes are worse for women although there is no evidence that this is a consequence of difference in care • Geographical issues – care is given through specialist centres and this may be a problem if a person with CF is living in an isolated location.
Notes/additional information	Relevant Cochrane reviews include: • Dornase alfa for cystic fibrosis • Nebulised hypertonic saline for cystic fibrosis • Nebulized and oral thiol derivatives for pulmonary disease in cystic fibrosis