D.7 Monitoring for pulmonary disease onset in people with CF without clinical signs or symptoms of lung disease

Item	Details
Key issue in the scope	Routine monitoring of lung disease, including microbiological surveillance, radiological imaging and pulmonary function testing.

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Review questions in the scope	What is the effectiveness of the following in monitoring pulmonary disease? • Microbiological investigations, including techniques such as bronchoscopy and lavage • Chest x-ray • CT scan • Lung function testing, including Lung Clearance Index and FEV1.
Review questions for the protocol	What is the value of the following investigative strategies in monitoring the onset of pulmonary disease in people with CF without clinical signs or symptoms of lung disease? (protocol 1) • Non-invasive microbiological investigation- induced sputum samples, cough swab, throat swab, and nasopharangeal aspiration • Invasive microbiological investigation- broncheoalveolar lavage • Lung physiological function tests- Cardiopulmonary exercise testing, Spirometry and Lung Clearance Index • Imaging techniques- Chest x-ray and CT scan
Objective	This is the first of three reviews that aim to determine the most effective strategies for monitoring of pulmonary disease in people with cystic fibrosis, with a view to improving subsequent intervention. This review considers people with CF without clinical signs or symptoms of lung disease and best monitoring strategies to identify the onset of pulmonary disease. This most commonly would inform management in young children, but not exclusively. Young children are often prescribed antibiotics as prophylaxis against S aureus colonisation/subclinical infection, or as acute treatment. Older people are more commonly affected P. aeruginosa. Mucolytics and/or immunomodulatory agents may also be offered to prevent deterioration of health, lung function or tissue architecture. Monitoring using non-invasive microbiological techniques and lung function tests (spirometry) occurs regularly and annual assessment is currently performed. Decisions regarding the need of additional imaging tests are based on the regularly received monitoring results or may occur as part of a formal annual review. This review will compare monitoring strategies or combinations of monitoring strategies • to identify pulmonary disease • to compare their effects on clinical outcomes
Language	English
Study design	• Systematic reviews • Test-and-treat randomised trials (RCTs) • Prospective and retrospective observational studies reporting the prognostic value of monitoring assessments in terms of risk of outcome assessed by multivariate analysis will be included as a first preference. • 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). Exclusion: Observational studies will be excluded if they do not conduct multivariable adjustment for baseline differences between groups.
Population and directness	Children, young people and adults with defined CF, diagnosed clinically and by sweat or genetic testing.

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	Population size and indirectness: • No sample size specification. • Studies with indirect populations will not be included
Stratified, subgroup and adjusted analyses	Groups that will be reviewed and analysed separately: • Children • Adults In the presence of heterogeneity, sensitivity analysis will be conducted including and excluding studies with high and. low risk of bias. To be considered as important confounders if comparative cohort studies are included: • Concurrent treatment with immunomodulatory and/or mucolytic agents. • Age (under 5 years)
Intervention	• Non-invasive microbiological investigation- induced sputum samples, cough swab, throat swab, and nasopharangeal aspiration • Invasive microbiological investigation- broncheoalveolar lavage • Lung physiological function tests- Lung Clearance Index and Spirometry • Imaging tests- Chest X-ray and CT scan
Comparison	Strategy A vs strategy B (*a strategy could be a single or combined interventions.*)

Outcomes	• Lung function
	    o Lung Clearance Index (LCI)
	    o FEV1 (absolute values litres or % predicted or both)
	 • Imaging
	    o CT Scans for under 5s (in lieu of lung function test)
	 • Quality of life (CF-QOL, CFQR)
	 • Nutritional parameters (BMI, weight/ height)
	 • Time to chronic infection using any recognized definition e.g. (Lee 2003)
	    o with P. aeruginosa
	    o with S. aureus
	 • Clearance of the organism from the cultures

Importance of outcomes	Critical outcomes for decision making: • Lung Clearance Index (LCI) • FEV1 (absolute values litres or % predicted or both) • CT Scans for under 5s • Clearance of the organism from the cultures
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. Supplementary search techniques: No supplementary search techniques will be used. See appendix E.6.1 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

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	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.
	• If comparative cohort studies are included, the minimum number of events per covariate to be recorded to ensure accurate multivariate analysis
	• Final and change scores will be pooled and if any study reports both, change scores will be used in preference over final scores.
	• 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):
	• LCI: GRADE default
	• FEV1: deterioration of 5 percentage points
	• CT Scans for under 5s: resolution of all inflammatory scans
	• Clearance of the organism from the cultures: any change will be considered clinically significant
	• Nutritional parameters (BMI, weight/ height): GRADE default
	• Time to chronic infection using any recognized definition (e.g. (Lee 2003) (MID TBC) (with P. aeruginosa, with S. aureus): GRADE default
	• Quality of life: CFQoL, MID = 5; CFQ-R MID = 8.5
	Default MIDs: 0.8 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes.
	Review process:
	• 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	Pulmonary disease: clogging of the airways due to mucus build-up, decreased mucociliary clearance, and resultant inflammation. The inflammation and infection cause injury and structural changes to the lungs, leading to a variety of symptoms.