D.8 Monitoring for evolving pulmonary disease in people with CF with established 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?
Review question for the protocol	What is the value of the following investigative strategies in monitoring evolving pulmonary disease in people with established lung disease? (protocol 2) • 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 Evolving pulmonary disease defined as decline in lung function (based on FEV1), increased exacerbations and/or infections, (symptom based?) and CT changes.
Objective	This is the second 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 with established lung disease and the added value of monitoring strategies to monitor evolving pulmonary disease. People are likely to be receiving a mucolytic, and/or an immunomodulatory agent and/or a prophylactic antibiotic. Monitoring helps inform initiation of or changes to treatment (e.g. if there are issues of adherence to treatment). Monitoring using non-invasive microbiological techniques and lung function tests 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 assess the added value of imaging in addition to the above listed monitoring strategies or combinations of monitoring tests: • to identify evolving pulmonary disease • to compare their effects on prioritised outcomes
Language	English
Study design	• Systematic reviews • Test-and-treat randomised trials (RCTs) • Conference abstracts of RCTs (only if fully published RCTs are not available) • Observational (prospective and retrospective) 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. To exclude studies if they do not conduct multivariable adjustment for baseline differences between groups.
Population and directness	Children, young people and adults with defined cystic fibrosis, diagnosed clinically and by sweat test or genetic testing. Population size and indirectness: • No sample size specification. • Studies with indirect populations will not be included
Stratified, subgroup and adjusted analyses	Stratified analysis: groups that will be reviewed and analysed separately: • Children • Adults

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	In the presence of heterogeneity sensitivity analysis will be conducted including and excluding studies with a high 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)
Monitoring techniques	• 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 • Imaging tests in addition to any of the other strategies.
Comparison	• Any of techniques above
Outcomes	• Lung function ○ Lung Clearance Index (LCI) ○ FEV1 (absolute values litres or % predicted or both) ○ VO2 max (CPEX testing) ○ CT Scans for under 5s (in lieu of lung function test) • Time to next exacerbation • Time to chronic infection using any recognized definition e.g. (Lee 2003) ○ with P. aeruginosa ○ with S. aureus • Mortality • Nutritional parameters (BMI, weight/ height • Quality of life (CF-QOL, CFQR)
Importance of outcomes	Critical outcomes for decision making: • Lung function ○ Lung Clearance Index (LCI) ○ FEV1 (absolute values litres or % predicted or both) ○ VO2 max (CPEX testing) ○ High-resolution computed tomography (CT) appearances using a recognised scoring system (e.g. Brody 2004; Loeve 2009) • Time to next 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. Supplementary search techniques: No supplementary search techniques will be used. See appendix E.6.2 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).

Item	Details
	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, the method used in the majority of studies will be analysed. • If studies only report p-values, this information will be plotted in GRADE tables without an assessment of imprecision possible to be made. MIDs: • Lung function o Lung Clearance Index (LCI): GRADE default o FEV1: deterioration of 5 percentage points o VO2 max: GRADE default o High-resolution computed tomography (CT) appearances using a recognised scoring system (e.g. Brody 2004; Loeve 2009): resolution of all inflammatory scans • Time to next exacerbation: any difference will be considered clinically significant • Quality of life: CFQoL MID = 5; CFQ-R MID = 8.5 • Mortality: any difference will be considered clinically significant • • Nutritional parameters (BMI, weight/ height): GRADE defaut • Time to chronic infection using any recognized definition e.g. (Lee 2003) o with P. aeruginosa: GRADE default o with S. aureus: GRADE default 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	None.