D.15 Immunomodulatory agents

Item	Details
Key issue in the scope	Immunomodulatory management in chest disease.
Review question in the scope	What is the effectiveness of immunomodulatory agents in the management of lung disease (for example corticosteroids, azithromycin)?
Review question	What is the effectiveness of immunomodulatory agents in the management of lung disease?
Objective	The aim of this review is to determine the clinical and cost effectiveness of immunomodulatory agents in reducing pulmonary inflammation in children and young people and adults with cystic fibrosis.
Language	English
Study design	• Systematic reviews of RCTs • 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 and young people with cystic fibrosis (diagnosed clinically and by sweat test or genetic testing) with lung disease. Population size and indirectness: • Studies where N<20 will not be included. • Studies with indirect populations will not be considered.
Stratified, subgroup and adjusted analyses	Groups that will be reviewed and analysed separately, if possible: • Children • Young people and adults • People with chronic lung disease • People with acute exacerbations • People with allergic bronchopulmonary aspergillosis (ABPA) In the event of heterogeneity, analysis will be conducted excluding studies with high-risk of bias. In the presence of heterogeneity, the following subgroups will be considered for sensitivity analysis: • Chronic Pseudomonas • Duration of treatment

Intervention	• Inhaled corticosteroids
	  ○ Beclamethozone
	  ○ Budesimide
	  ○ Fluticazone
	• Oral and IV Corticosteroids
	  ○ IV Methylprednisolone
	  ○ Oral Prednisolone
	• Macrolide antibiotics
	  ○ Azithromycin
	• NSAIDs
	  ○ Ibuprofen
	• Monoclonal antibody

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Item	Details
	○ Omalizumab
Comparison	• Placebo • Treatment A vs treatment B
Outcomes	• Lung function: ○ forced expiratory volume in one second (FEV1) • Quality of life measures (CF-QOL, CF-QR) • Nutritional status as noted by weight gain, body mass index, z score or other indices of nutritional state • Time to next pulmonary exacerbation • Adverse effects: ○ Growth retardation ○ Reduction in bone mineral density ○ Cataracts ○ Renal failure ○ Diabetes ○ Deafness ○ Cardiac arrhythmia ○ Abdominal pain (for ibuprofen use) • Mortality Note: change from baseline will be priorised over absolute values
Importance of outcomes	Critical outcomes for decision making: • Forced expiratory volume in one second (FEV1) • Time to next exacerbation • Adverse events (particularly growth retardation in children)
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.10 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. • 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.

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Item	Details
	• 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: 2 percentage points • Change in number of respiratory exacerbations: any difference will be considered clinically significant • Quality of life measures: CF-QOL = 5; CFQ-R = 8.5 • Nutritional status as noted by weight gain, body mass index, z score or other indices of nutritional state = GRADE default • Time to next pulmonary exacerbation: any difference will be considered clinically significant • Adverse effects: GRADE default • Adverse events that lead to discontinuation of treatment: any difference will be considered clinically significant • Mortality: any difference 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. • This question will be prioritised for data extraction. • 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: • Oral steroids for long-term use in cystic fibrosis • Oral non-steroidal anti-inflammatory drug therapy for lung disease in cystic fibrosis • Macrolide antibiotics for cystic fibrosis Anti-IgE therapy for allergic bronchopulmonary aspergillosis in people with cystic fibrosis. Cochrane Database of Systematic Reviews 2013, Issue 9. Art. No.: CD010288.) but it includes only one unpublished trial.

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