D.1 Diagnosis of cystic fibrosis

Item	Details
Key issue in the scope	The clinical manifestations of cystic fibrosis at the time of diagnosis in infants, children, young people and adults.
Review question in the scope	What are the clinical manifestations of cystic fibrosis at the time of diagnosis in infants, children, young people and adults?
Review question for the protocol	In infants, children, young people and adults (including those that have undergone newborn screening) when should cystic fibrosis be suspected? Most children will undergo newborn screening in the UK, and most cases of CF will be picked up that way. However, for those where that did not happen it would be useful for the guideline to raise awareness to HCPs to cases where new born screening was not undertaken and where CF should be suspected.
Objective	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.
Population and directness	Infants, children, young people and adults with suspected symptoms of CF, including those who have been through newborn screening: • Respiratory symptoms (including recurrent pneumonia, chest x-ray evidence of chronic disease) • Failure to thrive • Symptoms of malabsorption • Male infertility Population size and directness: • No minimum sample size. • Indirect populations will not be considered.
Subgroups and sensitivity analyses	The following groups will be assessed separately if possible: • Infants • Children • Young people and adults In the presence of heterogeneity, sensitivity analysis will conducted including and excluding studies with a high risk of bias.
Clinical signs and symptoms	The following clinical manifestations: • Respiratory symptoms (including recurrent infection, chest x-ray evidence of chronic disease) • Faltering growth • Symptoms of malabsorption • Azoospermia • Acute pancreatitis • Meconium ileus Note: DIOS not included in the list, as confirmed DIOS is synonym of CF.
Reference standard	• Sweat test and genetic test for confirmation of CF • Faecal elastase
Outcomes	• Sensitivity • Specificity

Item	Details
	• Positive predictive value • Negative predictive values • Positive likelihood ratios • Negative likelihood ratios] If thresholds are established/pre-defined: • Relative risk (RR) or odds ratio (OR) (and ultimately risk difference) for patient outcomes listed above for those in higher or lower risk groups The expected effect of the classification strategies on clinical outcomes will be extracted if this information is reported.
Importance of outcomes	Critical outcomes: • Clinical diagnosis of CF
Study design	• Prospective cohort studies • Retrospective studies
Setting	Any healthcare setting where NHS care is delivered (primary, secondary, tertiary or community).
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 were used. See appendix E.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 (QUADAS-2 for diagnostic 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 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. • For prognostic studies, multivariate analysis will be used. 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

Item	Details
	• 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	Only tools that are externally validated will be assessed