D.20 Ursodeoxycholic acid for cystic fibrosis-related liver disease

Item	Details
Key issue in the scope	Surveillance for cystic-fibrosis-related liver disease and prevention of progression.
Review question in scope	Liver disease: What is the effectiveness of ursodeoxycholic acid for preventing liver disease progression in people with cystic fibrosis?
Review question for the protocol	What is the effectiveness of ursodeoxycholic acid for preventing the development or progression of liver disease in people with cystic fibrosis?
Objective	To assess the clinical and cost effectiveness of ursodeoxycholic acid for the development or prevention of liver disease progression in people 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	Infants, children, young people and adults with defined CF, diagnosed clinically and by sweat test or genetic testing. Population size and indirectness: • Studies where N<10 will not be included. • Studies with indirect populations will not be considered.
Stratified, subgroup and adjusted analyses	Sensitivity analysis: In the presence of heterogeneity, sensitivity analysis will conducted including and excluding studies with a high risk of bias.

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	In the presence of heterogeneity, subgroup analyses will be conducted examining patients with evidence of liver disease at randomisation separately from those without liver disease.
Intervention	UDCA administered orally, at any dose, given for a period of at least three months.
Comparison	• Placebo • No additional therapy (i.e. both groups receiving usual CF therapy)

Outcomes	• Quality of life (CF-QOL, CFQR)
	• Hepatocellular enzymes or bilirubin level
	• Liver failure
	• Liver transplantation
	• Liver related mortality
	• Development of portal hypertension indicated by an:
	  ○ Enlarged spleen (increased by at least 15%)
	  ○ Development of varices
	  ○ Ultrasound evidence of portal hypertension
	• No development of liver disease
	• Note: change from baseline will be prioritised over absolute values

Importance of outcomes	Critical outcomes for decision making:
	• Change of hepatocellular enzymes
	• Liver failure
	• Development of portal hypertension indicated by an:
	  ○ Enlarged spleen (increased by at least 15%)
	  ○ Development of varices
	  ○ Ultrasound evidence of portal hypertension
	Outcomes to be measured at 6 months and 12 months

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): Limit to English language only where possible (Medline and Embase). Limit to RCTs and systematic reviews unless overall return is small Supplementary search techniques: No supplementary search techniques were used. See appendix E.15 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.

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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): • Health related quality of life: CF-QOL = 5; CFQ-R = 8.5 • Change of hepatocellular enzymes or bilirubin level: GRADE default • Liver failure: any change will be considered clinically significant • Liver transplantation: any change will be considered clinically significant • Liver related mortality: any change will be considered clinically significant • Development of portal hypertension: any change will be considered clinically significant • No development of liver disease: 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: • 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	Based on a Cochrane Review http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000222.pub3/full There have been no RCTs investigating UDCA for preventing the development of liver disease in people with CF. This review has shown the absence of any significant effects of UDCA treatment on people with CF, apart from a slight effect on the surrogate endpoint of reduction of raised liver enzymes to normal.