D.17 Exocrine pancreatic insufficiency

Item	Details
Key issue in the scope	Management of exocrine pancreatic insufficiency.
Review question in the scope	Gastrointestinal manifestations: What is the effectiveness of enzyme replacement in the treatment of exocrine pancreatic insufficiency?
Review question for the protocol	In people with cystic fibrosis, what is the most effective regimen of enzyme replacement therapy in the treatment of exocrine pancreatic insufficiency?
Objective	Cystic fibrosis is the most common cause of pancreatic insufficiency in children and the reported prevalence within this group is 80% to 90%. The CF gene defect results in a thickening of the pancreatic secretions and accumulation of these causes obstruction eventually leading to pancreatic damage. Pancreatic enzyme insufficiency prevents digestion and absorption of nutrients, resulting in nutrient malabsorption and other symptoms such as diarrhoea. These in turn can affect quality of life and eventually result in malnutrition. Pancreatic enzyme supplementation is the standard of care for fat malabsorption among patients with exocrine pancreatic insufficiency. Treatment is started when clinically significant malabsorption occurs resulting in steatorrhea and weight loss. Treatment failure is addressed in a sequential fashion. Effective therapy has been limited by the ability to replicate the physiologic process of enzyme delivery to the duodenum, at the appropriate time. The challenges include enzyme destruction in the stomach, lack of adequate mixing with the chyme in the duodenum, and failing to deliver and activate at the appropriate time.

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	The aim of this evidence review is to establish the most effective regimen enzyme replacement therapy in the treatment of exocrine pancreatic insufficiency.
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) Exclusions: • Exclude studies which examine PERT for very short duration and do not reflect clinical situation e.g. 1 dose • Exclude studies examining Panzytrat, Pancrease HL and Nutrizym 22 in paediatric populations. • Exclude studies with less than 10 participants (parallel RCT) or 10 observations (crossover RCT).
Population and directness	Children and adults with defined CF (diagnosed clinically and by sweat test or genetic testing) with exocrine pancreatic insufficiency requiring management. Population size and indirectness: • No sample size specification. • Studies with indirect populations will not be included Exclusions: • People with tube feeding excluded
Stratified, subgroup and adjusted analyses	Groups that will be reviewed and analysed separately: • Children • Young people and adults Sensitivity analysis: • In the presence of heterogeneity, sensitivity analysis will conducted including and excluding studies with a high risk of bias.
Intervention	Enteric coated pancreatic enzyme supplementation/replacement therapy. (PERT).
Comparison	• ECT PERT 1 vs ECT PERT 1 + Acid suppression • ECT PERT high dose (Creon® 25 000, Creon® 40 000, Nutrizym 22®, Pancrease HL® or similar) • ECT PERT low dose (for example Creon® 10 000, Creon® Micro, Pancrex®, Pancrex V® or similar)
Outcomes	• Quality of life (CF-QOL, CFQR) • Weight and/or BMI (also %weight for height if available) • Satisfaction • Reduction of steatorrhoea and faecal fat (CFA and FFE specific outcomes and others) • Resolution of symptoms of malabsorption • Drug related side effects/adverse events Time period for outcome measurement: • Quality of Life and symptoms – days • Weight – 1-2 weeks • Nutrition – days • Note: change from baseline will be prioritised over absolute values

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Importance of outcomes	Critical outcomes for decision making: • Reduction of steatorrhoea and faecal fat (CFA and FFE specific outcomes and others) • Weight and/or BMI (also %weight for height if available) • Resolution of symptoms of malabsorption
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 will be used. See appendix E.12 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. • 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): • Health related Quality of Life: CF-QOL = 5; CFQ-R = 4 • Weight and/or BMI (also %weight for height if available): GRADE default • Satisfaction: GRADE default • Reduction of steatorrhoea and faecal fat (CFA and FFE specific outcomes and others): GRADE default • Resolution of symptoms of malabsorption: GRADE default • Drug related side effects/adverse events: 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.

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Notes/additional information	Cochrane reviews: PERT http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008227.pub2/pdf Gastric Acid suppression http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003424.pub3/pdf Systematic review: efficacy and safety of pancreatic enzyme supplements for exocrine pancreatic insufficiency (Taylor 2010) http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2036.2009.04157.x/pdf Guidelines also exist eg Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review http://www.ncbi.nlm.nih.gov/pubmed/18442507 Pancreatic enzyme replacement therapy in cystic fibrosis: Australian guidelines. Pediatric Gastroenterological Society and the Dietitians Association of Australia. J Paediatr Child Health. 1999 Apr;35(2):125-9. http://www.ncbi.nlm.nih.gov/pubmed/10365346