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Gastro-oesophageal reflux disease in children and young people: Appendices

Gastro-oesophageal reflux disease: recognition, diagnosis and management in children and young people

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Appendices A-E, G-H, K

Draft for Consultation

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Contents

Appendices **6**
Appendix A: Health economics 6
A.1 Feeding changes 6
A.1.1 Health economic question 6
A.1.2 Description of included studies 6
A.1.3 Analysis 7
A.1.4 Resource use and costs 7
A.1.5 Conclusion 8
A.2 Alginates and Antacids 8
A.2.1 Health economic question 8
A.2.2 Description of included studies 8
A.2.3 Analysis 8
A.2.4 Resource use and costs 8
A.2.5 Conclusion 9
A.3 Pharmacological treatment 9
A.3.1 Health economic question 9
A.3.2 Description of included studies 9
A.3.3 Analysis 10
A.3.4 Resource use and costs 10
A.3.5 Conclusion 13
A.4 Fundoplication 13
A.4.1 Health economic question 13
A.4.2 Description of included studies 13
A.4.3 Analysis 13
A.4.4 Resource use and costs 13
A.4.5 Conclusion 14
A.5 Enteral Feeding 14
A.5.1 Health economic question 14
A.5.2 Description of included studies 14
A.5.3 Analysis 14
A.5.4 Resource use and costs 14
A.5.5 Conclusion 15
A.6 Health Economics Discussion 15
A.7 References 16
Appendix B: Scope 18
Appendix C: Stakeholders 26
Appendix D: Declarations of interest 34
Appendix E: Review protocols 36

E.1 Natural course of overt regurgitation ... 36
E.2 Risk Factors ... 37
E.3 Signs and symptoms ... 38
E.4 Infant positioning ... 39
E.5 Feeding changes ... 40
E.6 Alginates and Antacids ... 41
E.7 Pharmacological treatment ... 42
E.8 Fundoplication ... 43
E.9 Enteral Feeding ... 44
Appendix F: Search strategies ... 46
Appendix G: Summary of identified studies ... 47
Appendix H: Excluded studies ... 48
H.1 What is the natural history of overt GOR? ... 48
H.2 What are the risk factors associated with developing GOR/D? ... 52
H.3 What clinical features can be used to assess the presence and severity of gastro-oesophageal reflux disease in children and young people? ... 58
H.4 What is the effectiveness of a clearly described positional intervention in comparison with no positional management and alternative clearly described positional interventions? ... 63
H.5 What is the effectiveness of a managed feeding regimen in comparison with a conventional, age appropriate, regimen in the management of overt GOR? ... 65
H.6 How effective are antacids compared to placebo in alleviating symptoms of GORD, GOR or other GORD related symptoms (e.g. heartburn in older children)? ... 69
H.7 Effectiveness of medical management (H2RAs, PPIs and prokinetics) in GOR/D ... 71
H.8 How effective is fundoplication surgery in the treatment of GOR/D? ... 77
H.9 How effective is enteral tube feeding in the management of GORD? ... 82
Appendix I: Evidence tables ... 93
Appendix J: GRADE tables ... 94
Appendix K: Parent information on administration of medicines ... 95
K.1 Infant Gaviscon ... 95
K.2 Ranitidine ... 95
K.3 PPIs ... 95
K.3.1 Omeprazole ... 95
K.3.2 Lansoprazole ... 96
K.4 Further information ... 96

Appendices

Appendix A: Health economics

There is a clear obligation on healthcare providers to provide treatments that are safe and effective and provide the greatest relief from suffering at the lowest possible cost since, where resources are finite, lower costs of care mean that more people can be treated for this condition or for other health problems. However, treatment with the lowest cost drug does not mean the most cost-effective treatment since the cost of failure associated with drugs that are less effective may outweigh the cost of higher price alternatives. Furthermore, high cost drugs may be cost effective where they provide more health gain at an acceptable additional cost.

Health economic analysis allows decision makers to consider resource use alongside the benefits of a treatment in order to decide if it is good value compared with the next best alternative. Cost effectiveness analysis (with the units of effectiveness expressed in quality adjusted life years [QALYs]) is widely recognised as a useful approach for measuring and comparing different health interventions. Using the QALY as the final outcome allows one to measure the impact of health care in terms of how it extends life as well as how it affects health-related quality of life. Using this generic outcome allows different treatments to be compared using the same threshold for decision making. NICE has a guiding principle that an intervention is cost effective compared to the next best treatment if the additional cost per QALY is less than £20,000.

For almost all the interventions considered in this guideline, published evidence of the cost effectiveness was lacking. Further analysis was undertaken to support the GDG's decision making where health economic input was recognised as useful. None of the analyses presented in this appendix follow NICE's reference case for health economic analysis because of the lack of evidence for effectiveness.

In all topics considered for economic evaluation, resource use and costs were quantified. Details of the methods used in relation to each review question are presented in this chapter. For each question the following are reported: review of published economic literature; description of resource use and costs, and conclusions of the analysis.

For each review question considered in the guideline, this document includes a summary based on evidence and GDG opinion.

A.1 Feeding changes

A.1.1 Health economic question

What is the cost-effectiveness of changes to feeding in infants in GOR/GORD compared to no changes in feeding?

A.1.2 Description of included studies

No published health economic evaluations were identified in the literature search conducted for this review question.

A.1.3 Analysis

The clinical evidence presented in this guideline was limited and could not be used to develop an economic evaluation for this review question. A cost description of four thickened feeds (Aptamil Anti Reflux; Cow & Gate Anti Refulx; Enfamil Anti Reflux and SMA Staydown) and one feed thickener (Instant Carobel) was undertaken for the GDG. This was presented to the GDG to aid consideration of the costs related to providing changes to infant feeds. The feed thickeners and thickened feeds included here were agreed with the GDG members as the most frequently prescribed and appropriate formulae to give their patients. As the GDG did not recommend the routine use of hydrolysed formula, the cost of prescribing these are not presented here.

A.1.4 Resource use and costs

No economic evaluations of thickened feeds or feed thickeners were identified in the literature search conducted for this guideline. The comparative evidence on efficacy is poor. In line with the NICE guidelines manual, the economic evidence focused on the unit costs of the different formulas currently available in England and Wales that can be prescribed or bought over the counter. Even though some of these can be purchased over the counter, and therefore only a cost to the patient , given that all feeds can be prescribed meant it was relevant to include these costs here. To compare costs, a feeding regimen was assumed for cost comparison purposes only. It was assumed that:

- A baby would consume 150ml of infant formula per kilo per day. A 6kg baby would require 900ml per day.
- All standard formulas recommend one scoop of powder added to 30mls water (although scoop sizes vary), therefore 30 scoops of formula are required per day in this case
- For feed thickener, an average consumption of 3g per 100mls of infant formula was assumed, or 27g per day.

The resource use of GP time in prescribing feeding changes is assumed to be the same across all options. Table A1 presents the cost of thickened feeds and feed thickeners for infants suspected to have GORD over the course of a daily feed and a typical monthly cost of continued use. The provision of these feeds are comparable and relatively inexpensive in the short-term, with the cost of a GP 15 minute appointment (£57, Curtis 2013) likely to contribute more expense to the NHS. Cost data were unavailable for thickened feed and feed thickeners from the NHS Drug Tariff, so other sources were used to calculate these costs.

Table A1: Cost comparison of thickened feed and feed thickeners for infants with GORD

Thickened feeds or feed thickeners	Tub size (g)	Scoop size	Price	Cost per day	Cost per month
Aptamil Anti Reflux*	900	4.9	£11.99[1]	£1.96	£59.57
Cow & Gate Anti Reflux*	900	4.4	£10.49[1]	£1.54	£46.80
Enfamil Anti Reflux	400	4.5	£3.52[2]	£1.19	£36.14
SMA Staydown	900	4.3	£7.29[2]	£1.04	£31.78
Instant Carobel	135	n/a	£2.71[2]	£0.54	£16.49

** Not approved by the Advisory Committee on Borderline Substances (ACBS). The ACBS is the committee responsible for advising approved prescribers on the prescribing of certain foodstuffs and toiletries. Borderline substances are mainly foodstuffs, such as enteral feeds and foods that are specially formulated for people with medical conditions.*

[1] Costs obtained from high street retailers, February 2014;

[2] Costs quoted in the Children's BNF April 2014

A.1.5 Conclusion

Cost data for feeding regimens have little use without associated benefits. Therefore, while the costs of prolonged use of thickened feeds or feed thickeners could be significant, without knowing the benefits of food thickeners we cannot know if it will be cost effective. The research recommendation of the GDG to consider the effect of hydrolysed formula in the treatment of GORD would benefit from health economic input to assess the cost-effectiveness of the NHS of providing a comparatively expensive intervention to thickened feeds and feed thickeners.

A.2 Alginates and Antacids

A.2.1 Health economic question

What is the cost-effectiveness of antacids/alginates in the treatment of GOR/GORD?

A.2.2 Description of included studies

No published health economic evaluations were identified in the literature search conducted for this review question.

A.2.3 Analysis

Currently, alginates are widely prescribed and are also available in non-prescription forms although their effectiveness is not well understood. The evidence base for the clinical review is limited, so there is not sufficient evidence to include these treatments in an economic model. A cost description of algintates/antacids for infants (Gaviscon Infant), children and young people (Gaviscon Advance Suspension and Gaviscon Liquid) and children and young people with a neurodisability (Maalox Plus and Altacite Plus) was undertaken for the GDG. This was presented to the GDG to aid consideration of the costs related to alginates/antacids therapy. The alginates/antacids included here were agreed with the GDG members as the most frequently prescribed and appropriate formulae to give their patients.

A.2.4 Resource use and costs

No studies comparing the cost-effectiveness of alginates with other treatments were identified. In line with the NICE guidelines manual, the economic evidence focused on the unit costs of the most common form of alginates. Altacite plus and Maalox plus are prescribed to children with neuro-disability. Table A2 reports the cost of a two-week trial and continued therapy with Gaviscon. Costs are also given for alginates for children and young people. Cost data were taken from the British National Formulary for children (April 2014). As for feeding regimens, we assume that resource use is equivalent across treatments, although the recommendation of a 1-2 week trial is likely to require a considerable amount of more resource use in GP time compared to feeding regimens. As can be seen from Table A2, the antacids/alginates provided over a short time-period are relatively inexpensive, with resource use from GPs the primary contributor to NHS costs (a 15 minute GP appointment = £57 Curtis 2013).

Table A2:Cost comparison of antacids/alginates for children with GORD

Name	tabs or mLs per dose	doses per day	Cost	Packet / bottle size		Cost per day	two-week trial	Cost per month	Notes
<2 years									
Gaviscon Infant	1	6	£3.49	30	sachets	£0.70	£9.77	£21.17	
2-12 year olds									
Gaviscon advance suspension	5	4	£5.21	500	mls	£0.21	£2.92	£6.32	
Maalox Plus	5	3	£3.90	500	mls	£0.12	£1.64	£3.55	2-5 year olds
Maalox Plus	5	4	£3.90	500	mls	£0.16	£2.18	£4.73	5-12 year olds
Gaviscon liquid	10	4	£6.89	600	mls	£0.46	£6.43	£13.93	6-12 year olds
Altacite Plus	5	4	£3.20	500	mls	£0.13	£1.79	£3.88	8-12 year olds
Teenagers									
Gaviscon liquid	20	4	£6.89	600	mls	£0.92	£12.86	£27.87	
Gaviscon advance suspension	10	4	£5.21	500	mls	£0.42	£5.84	£12.64	
Altacite Plus	10	4	£3.20	500	mls	£0.26	£3.58	£7.77	
Maalox Plus	10	4	£3.90	500	mls	£0.31	£4.37	£9.46	

A.2.5 Conclusion

Cost data for antacids/alginates have little use without associated benefits. Therefore, while the costs of prolonged use of antacids/alginates could be significant, without knowing the benefits of food thickeners we cannot know if it will be cost effective.

A.3 Pharmacological treatment

A.3.1 Health economic question

What is the cost-effectiveness of medical management approaches in the treatment of GOR/GORD?

A.3.2 Description of included studies

No published health economic evaluations were identified in the literature search conducted for this review question for the patient population under consideration. A potentially relevant study identified in this review compared medical management of GORD to surgery for the UK adult population (Bojke 2007). This study generated preliminary cost-effective estimates from the REFLUX trial and found that the probability of surgery being more cost-effective than medical management was 0.639 for the NICE WTP threshold of £20,000 per QALY gained. Their cost-effective results were uncertain, but a recent 5 year follow up has found that the probability of laparoscopic surgery being cost-effective is greater than 0.8 in all of their analyses (Grant 2013). Another study identified in the review was a cost minimisation

analysis found that 10mg omeprazole resulted in savings compared to 10mg rabeprazole for South Korean adults (18-75 years old) with severe esophagitis (Park 2013). However, the relevance of this analysis is questionable given the older patient population in this study and that it was conducted in a different healthcare setting than the UK. Therefore, it was excluded this study from the supporting evidence in this guideline. In terms of the UK adult analysis, it was the view of the core GDG members that it would be inappropriate to use clinical evidence from adult studies, because the physiological impact of treatments is different in children compared to adults, and the underlying cause of GORD is different in infants and children compared to adults.

A.3.3 Analysis

PPIs are prescribed to children both to prevent symptoms of GOR and to heal the oesophagus. The literature search found no trials evaluate the effectiveness of PPIs in children and therefore there is not sufficient evidence to include these treatments in an economic model.

Like antacids/alginates, H2 blockers (also sometimes referred to as acid reducers or H2 receptor antagonists) are available in non-prescription and prescription forms. They can be used alone or together with antacids/alginates. The literature search did not find any high quality comparative or placebo-controlled trials evaluating the effectiveness of H2-receptor antagonists in children and therefore there is unlikely to be a good clinical evidence base. Therefore, there is not enough evidence on effectiveness to include these treatments in an economic model.

Prokinetics speed up the emptying of the stomach, so there is less opportunity for acid to irritate the oesophagus. The literature search found little evidence evaluating the effectiveness of prokinetics in children. Therefore, there was insufficient information to include these treatments in an economic model.

A cost description of medical management approaches using PPIs, H2RAs or prokinetics were presented to the GDG. The alginates/antacids included here were agreed with the GDG members as the most frequently prescribed and appropriate formulae to give their patients

A.3.4 Resource use and costs

No studies were identified that looked at the comparative cost-effectiveness of medical therapy for GORD in children, either comparing different drug regimens or comparing medical management with surgical management. The comparative evidence of efficacy is poor. Therefore the economic evidence focused on the unit costs in line with the NICE guidelines manual. The different pharmacological interventions routinely prescribed to children in England and Wales are presented in Table A3, Table A4 and Table A5. respectively. The interventions were agreed with the GDG and represent what might typically be offered in the NHS to children of different age groups. Costs were taken from the NHS Drug Tariff when available and from the BNF for children otherwise. In addition, resource use over a typical month is presented in Table A6 to consider the overall cost of medical management in the initial month of treatment. Unless the patient requires omeprazole, the initial cost of treatment is due to the resource use required in the early stages of medical management.

Table A3:Cost of Proton Pump Inhibitors in the medical management of young people with GORD

NAME	tabs or mls per dose	doses per day	COST	Packet/BOTTLE SIZE		DailY COST	1 MONTH COST
Infants							
Omeprazole 10mg (LOSEC MUPS)	1	1	£7.75	28	tabs	£0.28	£8.40
Omeprazole 10mg	1	1	£1.25	28	caps	£0.04	£1.35
Sodium Biocarbonate	10	1	£62.49	300	mmol per ml	£2.08	£63.18
Omeprazole & Sodium Bicarbonate combined						£2.13	£64.54
Omeprazole liquid 10mg	5	1	£137.24	150	mls	£4.57	£138.76
Lansoprazole Fastab 15mg	0.5	1	£2.99	28	tabs	£0.11	£3.24
18 months up to 12 years							
Omeprazole 20mg (LOSEC MUPS)	1	1	£11.60	28	tabs	£0.41	£12.57
Omeprazole 20mg	1	1	£1.25	28	caps	£0.04	£1.35
Sodium Bicarbonate	10	1	£62.49	300	mmol per ml	£2.08	£63.18
Omeprazole & Sodium Bicarbonate combined						£2.13	£64.54
Omeprazole liquid 20mg	5	1	£159.78	150	mls	£5.33	£161.56
Lansoprazole Fastab 30mg	1	1	£5.50	28	tabs	£0.20	£5.96
Teenagers > 12 years							
Omeprazole 40mg (LOSEC MUPS)	1	1	£5.80	7	tabs	£0.83	£25.13
Omeprazole 10mg	1	1	£4.98	28	caps	£0.18	£5.40
Sodium Bicarbonate	10	1	£62.49	300	mmol per ml	£2.08	£63.18
Omeprazole & Sodium Bicarbonate combined						£2.26	£68.58
Omeprazole 40mg liquid	5	1	£286.48	150	mls	£9.55	£289.66
Lansoprazole Fastab 30mg	1	1	£5.50	28	tabs	£0.20	£5.96

Table A4: Costs of H2 Receptor Antagonists in the medical management of young people with GORD

Name	tabs or MLS per DOSE	DOSES PER DAY	COST	Packet/BOTTLE SIZE		DAILY COST	1 MONTH COST
Infants							
Ranitidine 75mg/5ml (liquid)	2	2	£2.75	100	mLs	£0.11	£3.34
18 months up to 12 years							
Ranitidine 75mg/5ml (liquid)	5	2	£7.61	300	mLs	£0.25	£7.69
Teenagers > 12 years							
Ranitidine 150mg	1	2	1.85	60	tabs	£0.06	£1.87
Ranitidine 75mg/5ml (liquid)	10	2	7.61	300	mLs	£0.51	£15.39

Table A5: Costs of Prokinetic Agents in the medical management of young people with GORD

NAME	tabs or MLS PER DOSE	DOSES PER DAY	COST	PACKET/ BOTTLE size		daily cost	1 month COST
Infants							
Domperidone suspension 5mg/5ml	2	3	12.53	200	mls	£0.38	£11.40
18 months up to 12 years							
Domperidone suspension 5mg/5ml	7.5	3	12.53	200	mls	£1.41	£42.76
Teenagers > 12 years							
Domperidone 10mg tablets	1	3	1.39	30	tabs	£0.14	£4.22
Domperidone 10mg tablets	1	3	4.63	100	tabs	£0.14	£4.21
Domperidone suspension 5mg/5ml	10	3	12.53	200	mls	£1.88	£57.01

Table A6: Estimated resource use in first month of medical management of young people with GORD

HEALTH CARE PROFESSIONAL	TIME(MINUTES)	COST (£)
Nurse	10	8.67
Paediatrician	20	57.33
Paediatrician follow up	25	71.67
Total resource use (month 1)		137.67

[1]*Estimated 2 follow-up visits requiring close supervision commencing medical management. Costs from the PSSRU Curtis et al. (2013)*

A.3.5 Conclusion

Cost data for medical management have little use without associated benefits. Evidence from UK adult population suggests that medical management is not a long-term cost-effective treatment in comparison with surgical management (Bojke 2007, Grant 2013). It was argued by the core GDG members that this evidence was not transferable to the younger UK population, given the different physiological impact of treatments could not be assumed to be comparable. Therefore, no comparison of medical management and surgical management was possible for this guideline.

A.4 Fundoplication

A.4.1 Health economic question

What is the cost-effectiveness of fundoplication surgery in the treatment of GOR/GORD?

A.4.2 Description of included studies

No published health economic evaluations were identified in the literature search conducted for this review question. Three studies compared the resource ulitisation of laparoscopic versus open fundoplication in children and they found in favour of the former approach as a method to contain overall healthcare costs (Blewett 2002, Iglesias 1997, Ostlie 2007). However, all studies are from a US healthcare perspective and make no attempt to compare the effectiveness between the surgical approaches to provide a meaningful outcome to decision-makers as to which approach is cost-effective in a paediatric setting.

As mentioned previously, there is evidence to suggest that the long-term treatment of GORD in adults is cost-effective compared to medical management (Grant 2013). However, the GDG's view was that this evidence was not transferable to the treatment of children suffering from GORD as the physiological impact of treatments is different in children compared to adults, and the underlying cause of GORD is different in children (for example, caused by cerebral palsy) compared to adults (for example, caused by smoking).

A.4.3 Analysis

The surgical management approach (fundoplication) involves wrapping and suturing the stomach to the oesophagus using open or laparoscopic surgical techniques. Surgery is only offered in specialist settings.

A.4.4 Resource use and costs

The short-term efficacy of surgery has not been proven in the published literature. Therefore the economic evidence focussed on the unit costs of surgery in line with the NICE guidelines manual. Evidence on the long-term adverse events, costs and benefits of surgery in terms of future morbidity avoided was also not available. A cost description of surgical management was undertaken for the GDG. This was presented to the GDG to aid consideration of the costs related to providing surgical management of young patients with GORD.

The cost data presented in Table A7 below was obtained from NHS tariff prices (2014/15). Tariffs with top-ups for patients with complications were identified by individual members of the GDG from their hospitals. One hospital charged a tariff top-up for surgery involving children to reflect the additional complexity of the procedure and care requirements. The other hospital did not charge a top-up tariff.

Table A7:Costs of Surgical Management of GORD in children

Procedure	Elective	Tariff including Top-up	Non-elective	Tariff including top-up
Fundoplication -abdominal approach				
<24 months	£5,227		£3,940	
24 months+ without complications	£2,076	£3,028	£3,202	£4,671
24 months+ with complications	£3,482		£5,557	

A.4.5 Conclusion

The costs would need to be considered alongside the benefits to determine value for money and this would require comparative long-term data which are not currently available for children with GORD.

A.5 Enteral Feeding

A.5.1 Health economic question

What is the cost-effectiveness of enteral tube feeding in the management of GOR/GORD?

A.5.2 Description of included studies

No published health economic evaluations were identified in the literature search conducted for this review question. One Canadian study identified compared resource utilisation and morbidity between two different techniques for feeding tube insertion (Baker 2013). They found little differences in the morbidity impacts between an intracorporeal Seldinger technique versus an extracorporeal insertion approach, but the latter was associated with lower resources use. However, as this study makes no attempt to capture the change in patients' improvement from the feeding tubes, it is not possible to account for the changes in effectiveness from this study. Therefore, no economic evaluations can be constructed from this evidence.

A.5.3 Analysis

Enteral tube feeding is a treatment offered in secondary and tertiary care for children with GORD whose coexisting conditions (such as a neurodisability) mean they have problems swallowing and/or ingesting sufficient nutrition leading to failure to thrive. Its use is therefore restricted to a specific group of children. Enteral feeding is not a treatment for GORD but is offered to children who have GORD. Therefore, it is not an alternative treatment to medical management but may be an adjunct to it, or used alone.

A.5.4 Resource use and costs

A cost description of enteral feeding options were presented to the GDG. Costs for the use of enteral feeding are shown in Table A8. Costs are taken from the NHS tariff prices (2014/15). While the costs shown only represent part of the cost of managing GORD for a particular group of patients, it is important that these costs are accounted for in the full cost to the NHS of managing GORD in this subgroup.

Table A8:Costs of enteral feeding in the management of GORD

Procedure	Elective/non-elective
Percutaneous endoscopic gastrostomy	£1,038
Nasogastric tube feeding	£847

Procedure	Elective/non-elective
Permanent temporary gastrostomy	£1,038

A.5.5 Conclusion

Cost data for enteral feeding have little use without associated benefits. Further research would be useful to determine the cost-effectiveness of providing this intervention to the sub-group of GORD patients.

A.6 Health Economics Discussion

No published cost-effectiveness studies evaluating strategies for treating GORD in infants, children and young people were identified in the health economics literature review of 1,791 potential studies identified. A cost-effectiveness model comparing medical management with fundoplication (laparoscopic or open) in adults was recently published but included an adult population study. The study was based on a UK randomised controlled trial with five-year follow-up (Grant 2013). Patient-level cost and EQ-5D data were collected to estimate incremental five-year costs and QALYs. The mean age was 46 years. During the scoping phase, the core GDG members' opinion was that it would be inappropriate to use clinical evidence from adult studies. There were a number of reasons for this, the main ones being that the psychological impact of treatments is different in children compared to adults, and the underlying cause of GORD is different in children (for example cause by cerebral palsy) compared to adults (for example, caused by smoking). The lack of sufficient clinical evidence on the effectiveness of treatment in children identified in the review meant a full economic evaluation could not be conducted for this guideline.

The health economic analysis was limited to reporting of costs and resource use associated with the management of GORD in children. This information can be used in future updates of GORD guidelines when evidence on the effectiveness of alternative treatment options for children can be obtained.

Currently, NICE recommends the use of the generic, preference based measures of health related quality of life to calculate QALYs such as the EuroQol instrument, which also has an adapted version for younger people (Wille 2010). Alternative measures of young person's health-related quality of life that could alternatively be used to generate QALYs are the Health Utilities Index Mark II (Torrance 1996) or the Child Health Utility 9D paediatric quality of life instrument (Stevens 2009). Alternatively, condition-specific questionnaires could be used such as the multidimensional measure for gastroesophageal reflux disease symptoms in children (Malaty 2008), although condition-specific questionnaires are not recommended by NICE for calculating QALYs.

Future research would be useful to investigate if the potential lifelong benefits of surgical intervention compared to medical management for adults are similar for children in GORD. Although continued medical management is less expensive in the short term, the benefits of medical management will only occur for as long as the medication is taken. This kind of comparative research with long term outcomes would likely to be of most benefit for future research. Subgroup analysis of different patient groups (for example, patients with and without neurodisability; severity of GORD) may also be worth pursuing further.

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Appendix B: Scope

1 Guideline title

Gastro-oesophageal reflux disease: recognition, diagnosis and management in children and young people

Short title

Gastro-oesophageal reflux disease in children and young people.

2 The remit

The Department of Health has asked NICE: 'To produce a clinical guideline on the investigation and management of gastro-oesophageal reflux disease in children'.

3 Clinical need for the guideline

3.1 Epidemiology

a) Gastro-oesophageal reflux (GOR) is a normal physiological process. It usually happens after eating in healthy infants, children, young people and adults. In contrast, gastro-oesophageal reflux disease (GORD) is present when GOR causes troublesome symptoms (for example, frequency of regurgitation) and/or complications (for example, oesophagitis) that have a significant effect on the person and require treatment. However, there is no exact distinction of when GOR becomes GORD, and the terms are used to cover a range of severity.

b) All infants, children and young people have a degree of GOR. However, the prevalence of troublesome GOR in children and young people in the UK is uncertain. Data from the USA shows that 'problematic' regurgitation was reported in 23% of infants aged 6 months but decreased to 14% by the age of 7 months.

c) English NHS hospital episode statistics data for 2010–11 show that there were 8943 consultant episodes for GORD with or without oesophagitis in children and young people aged 0–14 years.

d) The prevalence of GORD is higher in certain groups – for example, in children and young people with neurodevelopmental disorders, oesophageal atresia repair, cystic fibrosis, hiatal hernia, or repaired achalasia, in preterm neonates or in people with a family history of complex GORD.

3.2 Current practice

a) Many infants and young children present in primary care with symptoms of GOR. Advice may be sought from midwives, health visitors and GPs about this condition. In cases where symptoms are mild and there is no reason to suspect the presence of GORD, reassurance may be all that is needed. Treatment is often prescribed, including feeding changes or drug therapy with alginates. In addition, some children are referred to a specialist for assessment, investigation and possible treatment. In particular, this includes those with severe symptoms (for example, in a child with overt regurgitation, the presence of blood might indicate erosive oesophagitis, or recurrent respiratory symptoms might be attributed to occult reflux) or those who are receiving specialist care for other conditions, such as preterm neonates or children with neurodevelopmental disorders.

b) In rare situations a specialist might want to carry out diagnostic tests to demonstrate and quantify the presence of reflux or to exclude other serious problems that can present in a similar way. Tests can include:

- oesophageal pH monitoring
- combined use of multiple intraluminal impedance (MII)
- barium meal and other modalities of imaging
- upper gastrointestinal endoscopy and mucosal biopsy
- empirical trial of acid suppression.

c) In addition to the treatments used in primary care, specialists may prescribe drugs to suppress gastric acid production, and some children may also undergo surgery, usually a fundoplication.

4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, ‘Further information’).

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a) Infants, children and young people under 18 years.

b) Specific consideration will be given to children and young people with neurodevelopmental disorders.

4.1.2 Groups that will not be covered

a) People aged 18 years or over.

b) Children and young people with Barrett's oesophagus.

4.2 Healthcare setting

a) All settings where NHS healthcare is provided or commissioned.

4.3 Clinical management

4.3.1 Key clinical issues that will be covered

a) The natural history of overt GOR.

b) The distinction between physiological GOR and GORD.

c) Risk factors associated with developing GORD.

d) Indications for investigations.

e) Indications for treatment.

f) Effectiveness of treatments for GOR/GORD:

- positional management
- changes to feeds (including composition and regimens)
- alginates and antacids
- H_2-receptor antagonists
- proton pump inhibitors
- prokinetic agents
- jejunal feeding
- fundoplication surgery.

Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

4.3.2 Clinical issues that will not be covered

Clinical areas that will not be covered by the guideline are:

a) Diagnosis and management of Barrett's oesophagus.

b) Reflux associated with pregnancy.

c) Technical aspect of undertaking investigations and surgery – for example, assessing results of endoscopy.

4.4 Main outcomes

The following outcomes will be assessed where relevant:

a) Health-related quality of life.

b) Change in symptoms and signs, for example:

- cessation or reduction (volume or frequency) of regurgitation
- reduction in crying and distress

- improved feeding
- improved nutritional status.

c) Improvement in investigative findings, including healing of erosive oesophagitis.

d) Adverse events of interventions (diagnostic or treatment).

e) Resource use and cost.

4.5 Review questions

Review questions guide a systematic review of the literature. They address only the key clinical issues covered in the scope, and usually relate to interventions, diagnosis, prognosis, service delivery or patient experience. Please note that these review questions are draft versions and will be finalised with the Guideline Development Group.

a) What is the clinical course of functional overt reflux in infancy?

b) The distinction between physiological GOR and GORD. For example, what is the association between:

- dental erosion and GOR
- back-arching and GOR
- distressed behaviour and GOR
- apnoea and GOR
- cow's milk protein intolerance and GOR?

c) What are the risk factors for GORD? For example:

- neurodevelopmental impairment
- age (for example, age of onset)
- prematurity
- family history of GORD
- obesity?

d) Which symptoms, signs and risk factors indicate the need for which investigations?

e) Which signs, symptoms and risk factors indicate the need for which treatment?

f) How effective is positional management in infants with GOR/GORD?

g) How effective are changes to feeding in infants with GOR/GORD?

h) How effective are antacids/alginates compared with placebo in the treatment of GOR/GORD?

i) How effective are H_2-receptor antagonists compared with placebo in the treatment of GOR/GORD?

j) How effective are proton pump inhibitors compared with placebo and one another in the treatment of GOR/GORD?

k) How effective are H_2-receptor antagonists compared with proton pump inhibitors in the treatment of GOR/GORD?

l) How effective are prokinetic agents compared with placebo in the treatment of GOR/GORD?

m) How effective is enteral tube feeding in the management of GOR/GORD?

n) How effective is fundoplication surgery in the treatment of GOR/GORD?

4.6 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see ‘Further information’).

4.7 Status

4.7.1 Scope

This is the final scope.

4.7.2 Timing

The development of the guideline recommendations will begin in April 2013.

5 Related NICE guidance

5.1 Published guidance

5.1.1 NICE guidance to be updated

This is a new guideline and will not replace any existing guidance.

5.1.2 NICE guidance to be incorporated

None.

5.1.3 Other related NICE guidance

- Patient experience in adult NHS services. NICE clinical guideline 138 (2011).
- Endoluminal gastroplication for gastro-oesophageal reflux disease. NICE interventional procedure guidance 404 (2011).
- Barrett's oesophagus. NICE clinical guideline 106 (2010).
- Medicines adherence. NICE clinical guideline 76 (2009).
- Catheterless oesophageal pH monitoring. NICE interventional procedure guidance 187 (2006).
- Endoscopic injection of bulking agents for gastro-oesophageal reflux disease. NICE interventional procedure guidance 55 (2004).
- Dyspepsia. NICE clinical guideline 17 (2004).
- Obesity. NICE clinical guideline 43 (2006).

5.2 Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- Dyspepsia and gastro-oesophageal reflux disease (update). NICE clinical guideline. Publication to be confirmed.

6 Further information

Information on the guideline development process is provided in the following documents, available from the NICE website:

- ‘How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS’
- ‘The guidelines manual'.

Information on the progress of the guideline will also be available from the NICE website.

Appendix C: Stakeholders

AbbVie

Airedale NHS Trust

Alder Hey Children's NHS Foundation Trust

Allergy UK

Allocate Software PLC

Association of Anaesthetists of Great Britain and Ireland

Association of British Healthcare Industries

Association of Children's Diabetes Clinicians

Association of Surgeons of Great Britain and Ireland

Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland

Astrazeneca UK Ltd

babyREFLUX

Barnsley Hospital NHS Foundation Trust

Barrett's Oesophagus Campaign

Biohit Healthcare Ltd

Bliss

Boehringer Ingelheim

Bolton Hospitals NHS Trust

Boots

Boston Scientific

Bradford District Care Trust

Breastfeeding Network Scotland

British Association for Community Child Health

British Association for Psychopharmacology

British Association of Paediatric Endoscopic Surgeons

British Association of Perinatal Medicine

British Association of Plastic, Reconstructive and Aesthetic Surgeons)

British Dietetic Association

British Geriatrics Society Gastro enterology and Nutrition Special Interest Group

British Medical Association

British Medical Journal

British National Formulary

British Nuclear Cardiology Society

British Nuclear Medicine Society

British Pain Society

British Psychological Society

British Psychological Society

British Red Cross

British Society for Allergy & Clinical Immunology

British Society for Antimicrobial Chemotherapy

British Society of Paediatric Radiology

British Society of Gastroenterology

British Society of Paediatric Gastroenterology Hepatology and Nutrition

British Specialist Nutrition Association

BSPGHAN

BUPA Foundation

Caduceus Support Limited

Cambridge University Hospitals NHS Foundation Trust

Camden Link

Capsulation PPS

Capsulation PPS

Care Quality Commission

Central London Community Health Care NHS Trust

Children England

Children, Young People and Families NHS Network

Clarity Informatics Ltd

Cochrane Developmental, Psychosocial and Learning Problems

Croydon Clinical Commissioning Group

Croydon Health Services NHS Trust

Croydon University Hospital

Cumbria Partnership NHS Trust

CWHHE Collaborative CCGs

Dako UK Ltd

Department of Health

Department of Health, Social Services and Public Safety Northern Ireland

DNU Health Protection Agency

DO NOT USE NHS Direct

Ealing Public Health

East and North Hertfordshire NHS Trust

East Kent Hospitals University NHS Foundation Trust

Eisai Ltd

Epsom & St Helier University Hospitals NHS Trust

Equalities National Council

Ethical Medicines Industry Group

Faculty of Dental Surgery

Faculty of Public Health

Fighting Oesophageal Reflux Together

Five Boroughs Partnership NHS Trust

gastroenterology specialist group

General Medical Council

George Eliot Hospital NHS Trust

GlaxoSmithKline

Gloucestershire LINk

GP update / Red Whale

Great Western Hospitals NHS Foundation Trust

H & R Healthcare Limited

Hafan Cymru

Health & Social Care Information Centre

Health and Care Professions Council

Healthcare Improvement Scotland

Healthcare Infection Society

Healthcare Quality Improvement Partnership

Healthwatch East Sussex

Heartburn Cancer Awareness support

Hermal

Hertfordshire Partnership NHS Trust

Herts Valleys Clinical Commissioning Group

Hindu Council UK

Hockley Medical Practice

Humber NHS Foundation Trust

Independent Healthcare Advisory Services

Information Centre for Health and Social Care

Institute of Sport and Recreation Management

Janssen

Joint Speciality Committee in Gastroenterology and Hepatology, Royal College of Physicians and British Society of Gastroenterology

KCARE

Lancashire Care NHS Foundation Trust

Leeds Community Healthcare NHS Trust

Leeds North Clinical Commisioning Group

Leeds South and East Clinical Commissioning Group

Living with Reflux

Local Government Association

Luton and Dunstable Hospital NHS Trust

Maidstone and Tunbridge Wells NHS Trust

Mead Johnson Nutritionals

Medicines and Healthcare products Regulatory Agency

Ministry of Defence (MOD)

National Childbirth Trust

National Clinical Guideline Centre

National Collaborating Centre for Cancer

National Collaborating Centre for Mental Health

National Collaborating Centre for Women's and Children's Health

National Deaf Children's Society

National Institute for Health Research Health Technology Assessment Programme

National Institute for Health Research

National Patient Safety Agency

National Public Health Service for Wales

Neonatal & Paediatric Pharmacists Group

Netmums

NHS Ashton, Leigh and Wigan

NHS Barnsley Clinical Commissioning Group

NHS Choices

NHS Connecting for Health

NHS County Durham and Darlington

NHS Cumbria Clinical Commissioning Group

NHS England

NHS England Greater Manchester

NHS Gloucesterhsire & NHS Swindon Cluster

NHS Hardwick CCG

NHS Health at Work

NHS Improvement

NHS Luton CCG

NHS Medway Clinical Commissioning Group

NHS North Somerset CCG

NHS Plus

NHS Sheffield CCG

NHS South Cheshire CCG

NHS Wakefield CCG

NHS Warwickshire North CCG

Norgine Limited

North Essex Mental Health Partnership Trust

North Essex Partnership Foundation Trust

North of England Commissioning Support

North Tees and Hartlepool NHS Foundation Trust

North West London Hospitals NHS Trust

North West London Perinatal Network

Nottingham Children's hospital

Nottingham University Hospitals NHS Trust

Nottinghamshire Healthcare NHS Trust

Novartis Pharmaceuticals

Nursing and Midwifery Council

Oesophageal Patients Association

Oxford Health NHS Foundation Trust

Oxfordshire Clinical Commissioning Group

Pancreatic Cancer Action

Parenteral and Enteral Nutrition Group

Peckforton Pharmaceuticals Ltd

PERIGON Healthcare Ltd

Pfizer

Pharmaceutical Services Negotiating Committee

PHE Alcohol and Drugs, Health & Wellbeing Directorate

PrescQIPP NHS Programme

Primary Care Pharmacists Association

Primary Care Society for Gastroenterology

Primary Care Society for Gastroenterology

Primrose Bank Medical Centre

Proprietary Association of Great Britain

Public Health England

Public Health England Improving Health and Lives Learning Disabilities Observatory

Public Health Wales NHS Trust

Public Health Wales NHS Trust

Royal Berkshire NHS Foundation Trust

Royal College of Anaesthetists

Royal College of General Practitioners

Royal College of General Practitioners in Wales

Royal College of Midwives

Royal College of Midwives

Royal College of Nursing

Royal College of Obstetricians and Gynaecologists

Royal College of Paediatrics and Child Health

Royal College of Paediatrics and Child Health , Gastroenetrology, Hepatology and Nutrition

Royal College of Pathologists

Royal College of Physicians

Royal College of Psychiatrists

Royal College of Radiologists

Royal College of Surgeons of England

Royal Free London NHS Foundation Trust

Royal Pharmaceutical Society

Royal Society of Medicine

Sanofi

Scottish Intercollegiate Guidelines Network

Sheffield Children's Hospital

Sheffield Teaching Hospitals NHS Foundation Trust

SNDRi

Social Care Institute for Excellence

Society and College of Radiographers

South East Coast Ambulance Service

South East Staffordshire and Seisdon Pennisula CCG

South London & Maudsley NHS Trust

South West Yorkshire Partnership NHS Foundation Trust

South Western Ambulance Service NHS Foundation Trust

Southport and Ormskirk Hospital NHS Trust

Spectranetics Corporation

St Mary's Hospital

Staffordshire and Stoke on Trent Partnership NHS Trust

Stockport Clinical Commissioning Group

Stockport Clinical Commissioning Pathfinder

Suffolk County Council

Sutton1in4 Network

Taunton & Somerset NHS Foundation Trust

Teva UK

The Association of the British Pharmaceutical Industry

The British In Vitro Diagnostics Association

The London Centre for Children with Cerebral Palsy

The Patients Association

The Rotherham NHS Foundation Trust

Torax Medical Inc.

UK Clinical Pharmacy Association

UK Pain Society

Unite the Union

Vygon

Walsall Local Involvement Network

Welsh Government

Welsh Scientific Advisory Committee

West London CCG

Western Sussex Hospitals NHS Trust

Wigan Borough Clinical Commissioning Group

Wishaw General Hospital

Worcestershire Acute Hospitals Trust

York Hospitals NHS Foundation Trust

Appendix D: Declarations of interest

All GDG members' interests were recorded on declaration forms provided by NICE. The form covered consultancies, fee-paid work, shareholdings, fellowships and support from the healthcare industry. GDG members' interests are listed in this section. Where conflicts were identified, GDG members were asked not to participate in the relevant discussions. Details are available from the GDG minutes available on the NICE website.

This appendix includes all interests declared between the start of development and submission on 18th June 2014

Table D1:GDG Members' and Expert Adviser's declarations of interest

GDG Member	Interest
Karen Blythe	No Interests declared
Sarah Currell	No Interests declared
Ieuan Davies	Personal non - pecuniary • Member of the council of the British Society of Paediatric Gastroenterology, Hepatology and Nutrition. • Chair of the endoscopy working group for the British Society of Paediatric Gastroenterology, Hepatology and Nutrition. • Member of JAG through other work with the British Society of Paediatric Gastroenterology, Hepatology and Nutrition.
Charlie Fairhurst	Non-personal pecuniary • Department participated in therapeutic trial on pain/spasticity funded by GW Pharma for Sativex.
Rebecca Harmston	Personal family interest • Member of the family is employed by Pharmaceutical Product Development (PPDI). Personal non-pecuniary • Lay Member of Research Ethics Committee Cambridgeshire East (Health Research Authority).
Bruce Jaffray	Personal non-pecuniary • Published research on the subject of survival after fundoplication surgery. • Provided a lecture at The British Society of Paediatric Gastroenterology Hepatology and Nutrition (BSPGHAN) Annual Meeting.
Eleanor Jeans	No Interests declared
Dianne Jones	No Interests declared
John Martin	No Interests declared
Tom McAnea	No Interests declared
Rowena McArtney	No Interests declared
Russell Peek	Personal non-pecuniary • Member if the Royal College of Paediatrics and Child Health. • Member of the British Association of Perinatal Medicine.
Mike Thomson	Personal pecuniary interest • Speaker expenses from Janssen to attend the Australian Gastroenterology week. • Reasonable expenses paid by Nestle to attend the ESPGHAN conference in Jerusalem. • Speaker and chairman for Scientific committee. Attending the World Congress of Paediatric Gastroenterology. Reasonable expenses paid. Personal non –pecuniary

GDG Member	Interest
	• Author of a study which was discussed in the evidence summary during a GDG meeting. • Provided a lecture at The British Society of Paediatric Gastroenterology Hepatology and Nutrition (BSPGHAN) Annual Meeting. • Member of advisory board for a producer of endoscopic diagnostic equipment - Sandhill Scientific. • Member of medical advisory board for a charity supporting families with babies and children with reflux - 'Living with Reflux' • Medical Advisor to a charity providing support to families and individuals with reflux - FORT (Fighting Oesophageal Reflux Together) Non personal pecuniary • Runs endoscopy training courses which benefits department and employer - Sheffield Children's hospital. • Run peer reviewed and ethics approved multi centre and uni centre pharma-funded trials of medication including Prucalopride for constipation. Funding provided by Novatis.
Mark Tighe	Personal non – pecuniary • Lead on the Cochrane review on gastro-oesophageal reflux in children.

Table D2:NCC-WCH staff members' declarations of interest

NCC-WCH staff	Interest
David Bevan	No interests declared
Jiri Chard	No interests declared
Kate Coles	No interests declared
Hannah Rose Douglas	No interests declared
Yelan Guo	No interests declared
Rosalind Lai	No interests declared
Paul Mitchell	No interests declared
Stephen Murphy	No interests declared
Nitara Prasannan	No interests declared

Appendix E: Review protocols

E.1 Natural course of overt regurgitation

	Details	Additional comments
Review question	The natural history of overt GOR	
Objectives	What is the clinical course of overt gastro-oesophageal reflux (GOR)? • What is the usual age of overt gastro-oesophageal reflux onset? • How does the frequency of overt gastro-oesophageal reflux change with age? • At what age is the usual max frequency of overt gastro-oesophageal reflux? • At what age does overt reflux resolve? • Does overt gastro-oesophageal reflux follow an episodic pattern?	At present the divide between GOR and GORD is poorly defined. One aim of the guideline will be to provide a working definition of what is 'normal' so does not require management and 'abnormal' so may require management. The purpose of this review is to provide a description of the onset, progress and eventual recovery in infants and young children with symptoms of overt reflux. The implication may be that an unusual age of onset, pattern or excessive duration beyond that usually observed might be a red flag for either an alternative diagnosis or for complicated reflux (gastro-oesophageal reflux disease).
Language	English	
Study design	Observational studies	
Status		
Population	Children and young people under 18 years • Premature • Cerebral palsy	
Intervention	• What is the usual age of overt gastroesophageal reflux onset? • How does the frequency of overt gastroesophageal reflux change with age? • At what age is the usual max frequency of overt gastroesophageal reflux? • At what age does overt reflux resolve? • Does overt gastroesophageal reflux follow an episodic pattern?	Presenting in a primary care or secondary care setting with a clinical diagnosis of overt reflux or general population consensus.
Comparator	None	This is a descriptive question.
Outcomes	This is the information that needs to be extracted from papers • The median or mean average age (plus range or SD) at which overt reflux was first reported • The median or mean average age (plus range or SD) age at which overt reflux was most frequent • The reported maximum daily frequency of reflux (number of episodes of regurgitation / vomiting) • The median or mean average (plus range or SD) frequency of overt reflux at specific ages (for example, 6, 26, 36 or 52 weeks) • If overt reflux ceased, what was the reported age of cessation	The GDG will have to define the level of overt reflux that is 'abnormal' either frequency or amount. Studies may account for confounding effect of variables, such as prematurity, ethnic group, etc. This needs to be reported.
Other criteria for inclusion/ exclusion of studies	• Cohorts and case series should have at least 50 patients • We are looking for reflux patterns in the general population, so studies including only children with GORD will be excluded.	
Search strategies		
Review strategies		
Equality		

E.2 Risk Factors

	Details	Additional comments
Review question	Risk factors associated with developing GORD.	
Objectives	What are the risk factors for developing gastroesophageal reflux disease The studies will look at 1) In children with proven erosive oesophagitis what was the prevalence of a given risk factor compared to a children without erosive oesophagitis? 2) In children with risk factor what was the prevalence of GORD compared to children without that risk-factor?	Identification of patients who are at increased risk of developing erosive oesophagitis may be important in the identification of those who should undergo upper gastrointestinal endoscopy – the diagnostic test for that condition - or may require more regular follow-up. Identification of patients with erosive oesophagitis is important because this condition may require medical or surgical management. 1) (clinically diagnosed [history, questionnaire, etc] and/or treated) Erosive oesophagitis is a universally recognised and identifiable sign of GORD. Other forms proposed complications of GOR (for example, apnoea or asthma) are unproven (this guideline will examine the evidence). Using erosive oesophagitis as the basis for risk-factors means that they can be linked to an objectively measured sign.
Language	English	
Study design	Cohort studies Case-control studies The studies will look at • In children with proven erosive oesophagitis what was the prevalence of a given risk factor compared to a children without erosive oesophagitis? • In children with risk factor what was the prevalence of GORD compared to children without that risk-factor?	
Status		
Patient Population	Children and young people under 18 years Sub-groups, if data is available • Premature • Cerebral palsy	
Intervention	Risk factors identified by the GDG • Neurodevelopmental disorders • Cerebral palsy • Prematurity • Family history of GORD • Surgical / congenital disorders – hiatal hernia, diaphragmatic hernia, oesophageal atresia • congenital heart disease • chronic lung disease • Obesity Or, • GORD present	
Comparison	• Risk-factor not present, or • GORD not present	
Outcomes	• prevalence of risk-factor (associated condition) • prevalence of GORD	The GDG will need to consider Relationship: • Risk factor causes increased reflux which causes

	Details	Additional comments
	• Measured as RR or OR. Preferably risk-adjusted.	oesophagitis • Risk factors causes susceptible oesophagus and normal reflux causes oesophagitis Not interested in • Oesophagitis causes risk factor, such asthma • Oesophagitis and risk-factor require intensive monitoring There are many potential confounders to relationship between risk-factors and oesophagitis. For example, children with risk-factors are more likely to have endoscope as health professionals already think it is a risk-factor so oesophagitis is more likely to be identified.
Other criteria for inclusion/ exclusion of studies		
Search strategies	One search was conducted to cover all risk factors of interest – see separate document for further details	Potential studies to consider: Total and abdominal obesity are risk factors for gastroesophageal reflux symptoms in children. Quitadamo P, Buonavolontà R, Miele E, Masi P, Coccorullo P, Staiano A
Review strategies		
Equality		

E.3 Signs and symptoms

	Details	Additional comments
Review question	The distinction between physiological gastro-oesophageal reflux and gastro-oesophageal reflux disease.	
Objectives	People seek medical advice due to the presence of symptoms and signs, and health professionals need to be able to use these in order to identify condition, and differentiate serious from non-serious cases. A two stage review is being undertaken: **Stage 1** A review of existing systematic reviews to identify symptoms and signs of GOR/D. **Stage 2** Based on the results of stage 1 the GDG will be asked to identify those symptoms and signs where there is controversy or the association with GOR is unclear. For many of the symptoms and signs it is clinically accepted that these are associated with GORD, so they will not be selected for detailed. The reviews will focus on young children where signs and symptoms are less established compared to older children and young adults. Detailed reviews will be undertaken on each of the selected signs and symptoms. This will include studies that cover combination of symptoms and signs, such as questionnaires. Conclusions and recommendations will be made on	

	Details	Additional comments
	each individual symptoms and sign.	
Language	English	
Study design	RCTs or Observational studies	
Status		
Population	People aged under 18 • Q1. Children presenting with GOR and normal controls • Q2. Children presenting with symptom and normal controls	Sub-group, if available Premature Cerebral palsy
Intervention	GDG identified 11 symptoms for detailed review: • Asthma • Otitis media • Apnea • Dental erosion • Feeding problems • Distressed behavior • Failure to thrive • Heartburn or chest pain • Hoarseness • Recurrent LRTI • Chronic cough	A single protocol has been created for all the symptoms and signs. 'Gold standard' tests for GORD: Endoscopic appearance/ Endoscopic biopsy – oesophagitis Oesophageal pH monitoring Impedance monitoring GOR symptoms scale
Comparator	Symptom not present.	
Outcomes	• Q1. Diagnostic value of symptom (measured as RR or OR or correlation. If diagnostic values [[+/- LR etc] this should be reported) for identify GOR/D • Q2. Diagnostic value of GOR/D (including pH and oesophagitis) (measured as RR or OR or correlation. If diagnostic values [+/- LR etc] this should be reported) for identifying symptom	If data is available the diagnostic value of symptoms will be calculated by the technical team.
Other criteria for inclusion/ exclusion of studies	If the study does not compare symptoms against a final diagnosis then it will not be included.	
Search strategies		
Review strategies		
Equality		

E.4 Infant positioning

	Details	Additional comments
Review question	How effective is positional management in infants with GOR/GORD?	
Objectives	What is the effectiveness of a clearly described positional intervention in comparison with no positional management and alternative clearly described positional interventions?	Positional management is often recommended for the management of GORD. However, it has potential safety implications
Language	English	
Study design	RCT	If no RCT available will consider comparative observational studies (cohort and case control)
Status		
Population	Children and young people under 18 years with GORD • Premature • Cerebral palsy	
Intervention	Positional management	• Positional management can refer to sleeping

	Details	Additional comments
indicators	The use of a clearly described positional intervention aimed at reducing overt regurgitation	position, resting position and feeding/post feed position. • Devices to maintain position or Posture will not be covered by the review
Comparator	• No positional intervention • Other interventions • An alternative clearly described positional intervention	Combinations of treatments will not be examined.
Outcomes	• Reduced frequency of overt regurgitation • Reflux measured using oesophageal pH-metry or impedance monitoring • Resolution of faltering growth • Adverse outcomes (including mortality) • Parent reported reduction in infant distress • Improvement in validated reflux questionnaire • Parent satisfaction with this intervention	• In considering the evidence regarding positional management the GDG will need to take account of "back to sleep" and the issues of safe infant sleep position. • The GDG did not outline an MID
Other criteria for inclusion/ exclusion of studies		
Search strategies		
Review strategies		
Equality		

E.5 Feeding changes

	Details	Additional comments
Review question	Scope question: How effective are changes to feeding in infants with GOR/GORD?	
Objectives	What is the effectiveness of a managed feeding regimen in comparison with a conventional, age appropriate, regimen in the management of overt GOR 1) To determine if smaller feeds can reduce overt reflux in children and young people. 2) To determine if feed thickeners can reduce overt reflux in children and young people. 3) To determine if use of a formula free of cow's milk protein can reduce the frequency of overt reflux in children and young people. 4) To determine if a maternal diet free of cow's milk and/or soya protein can reduce the frequency of overt reflux in children who are being breast fed.	
Language	English	
Study design	RCT Systematic review or meta-analysis of RCTs	
Status		
Population	Children and young people under 18 years diagnosed with GOR/D Premature Cerebral palsy	
Intervention indicators	**Altered feed volume** 1) Any regimen in which the individual feed volume is decreased and the number of feeds is increased to maintain the total daily volume of feed. **Feed thickeners** 2) Milk thickening **Cow's milk protein exclusion**	

	Details	Additional comments
	3) The use of a formula free of cow's milk protein, for example protein hydrolysate, amino acid, or soy protein based formulas. 4) The use of a maternal cow's milk protein free and/or soya free diet in the breast fed baby.	
Comparator	**Altered feed volume** 1) Conventional age appropriate feed volume and frequency maintained. **Feed thickeners** 2) No milk thickening agent used **Cow's milk protein exclusion** 3) Cow's milk protein containing formula 4) Maternal diet including cow's milk protein free and/or soya	Thickening agents may include: • Carobel • Enfamil AR • SMA staydown • Arrowroot • Thick n easy • Multithick • Nutilis • Thixo D • Vitaquick
Outcomes	• Reduced frequency of overt regurgitation – MID could not be defined • Reflux measured using oesophageal pH-metry or impedance monitoring • Resolution of faltering growth • Adverse outcomes • Parent reported reduction in infant distress • Improvement in validated reflux questionnaire • Parent satisfaction with this intervention	No MID outlined by the GDG. If validated questionnaire then look for author reported MID.
Other criteria for inclusion/ exclusion of studies		
Search strategies		
Review strategies		
Equality		

E.6 Alginates and Antacids

	Details	Additional comments
Review question	How effective are antacids and/or alginates compared with placebo in the treatment of GOR/GORD?	
Objectives	How effective are antacids and/or alginates compared with placebo in the treatment of GOR/GORD? 1) To determine if alginates can reduce overt reflux in children and young people. 2) To determine if antacids can overt reflux in children and young people. 3) To determine if antacids and alginates, when used in combination, can reduce overt reflux in children and young people.	
Language	English	
Study design	RCT Systematic reviews or meta-analysis of RCTs	
Status		
Population	Children and young people under 18 years diagnosed with GOR/D • Premature • Cerebral palsy	
Intervention indicators	• Alginates • Antacids	

	Details	Additional comments
	• Antacids and alginates combination	
Comparator	• Placebo • No treatment	
Outcomes	• Cessation (or symptom free days) of overt regurgitation • Reduced frequency of overt regurgitation • Reflux measured using oesophageal pH-metry or impedance monitoring • Resolution of faltering growth • Adverse outcomes • Parent reported reduction in infant distress • Improvement in validated reflux questionnaire • Parent satisfaction with this intervention	MID could not be defined by the GDG
Other criteria for inclusion/ exclusion of studies		
Search strategies		
Review strategies		
Equality		

E.7 Pharmacological treatment

	Details	Additional comments
Review question	Four questions in the scope • How effective are H2-receptor antagonists compared with placebo in the treatment of GOR/GORD? • How effective are proton pump inhibitors compared with placebo and one another in the treatment of GOR/GORD? • How effective are H2-receptor antagonists compared with proton pump inhibitors in the treatment of GOR/GORD? • How effective are prokinetic agents compared with placebo in the treatment of GOR/GORD?	
Objectives	The overarching question “Effectiveness of treatments for GOR/GORD” covers all interventions used for GORD in children. The focus of this review is medical (pharmaceutical) management of GORD. These have been grouped together as the treatments will be compared. • How effective are H2-receptor antagonists compared with placebo in the treatment of GOR/GORD? • How effective are proton pump inhibitors compared with placebo and one another in the treatment of GOR/GORD? • How effective are H2-receptor antagonists compared with proton pump inhibitors in the treatment of GOR/GORD? • How effective are prokinetic agents compared with placebo in the treatment of GOR/GORD?	
Language	English	
Study design	RCTs Systematic reviews or meta-analysis of RCTs	
Status		
Population	Children and young people under 18 years diagnosed with GORD • Premature • Cerebral palsy	Results from adult studies will not be included.

	Details	Additional comments
Intervention indicators	• H2-receptor antagonists • Proton pump inhibitors • Prokinetic	Only examining the use of these treatments for the management of GORD. Combinations of treatments will not be examined.
Comparator	• Placebo • No treatment • Usual treatment	
Outcomes	• Reduced frequency of overt regurgitation – MID could not be defined • Reflux measured using oesophageal pH-metry or impedance monitoring • Resolution of oesophahitis - endoscope • Resolution of faltering growth • Adverse outcomes • Parent reported reduction in infant distress • Improvement in validated reflux questionnaire • Parent satisfaction with this intervention	Adverse outcomes will only be reported as they appear in RCTs. No MIDs was outlined by the GDG.
Other criteria for inclusion/ exclusion of studies		
Search strategies		
Review strategies		
Equality		

E.8 Fundoplication

	Details	Additional comments
Review question	How effective is fundoplication surgery in the treatment of GOR/GORD?	
Objectives	1) To determine if fundoplication surgery can effectively treat GORD in children and young people. 2) To determine if fundoplication surgery can effectively treat specific sub-groups of children and young people with GORD 3) To compare the effectiveness of the following types of fundoplication: • Open fundoplication • Laparoscopic fundoplication	Prioritise 5 year data (follow up) – both for fundoplication and medical management.
Language	English	
Study design	RCT	If no RCT available will consider comparative observational studies (cohort and case control) if case-mix adjustment undertaken
Status		
Population	Children and young people under 18 years diagnosed with GORD Sub-groups, if data is available • Premature • Cerebral palsy	
Intervention indicators	1) Fundoplication (class effect) • Open fundoplication (if available) • Laparoscopic fundoplication (if available)	
Comparator	1) Medical management 2) Comparison between open and laparoscopic fundoplication.	
Outcomes	Resolution of symptoms / disorder for which fundoplication was performed: • Change in frequency of overt regurgitation (for example, complete cessation, numbers of symptom free days per week, number of episodes	Fundoplication might be undertaken for a number of reasons – overt regurgitation, erosive oesophagitis, recurrent apnoea or pneumonia etc. RCTs might focus on fundoplication for such individual problems or they might be contained within subgroups in a

	Details	Additional comments
	per day)* • Resolution of erosive oesophagitis (histologic)* • Resolution of reflux symptoms – for example, heartburn, retrosternal or epigastric pain, waterbrash, • Resolution of faltering growth* • Parent reported reduction in infant distress • Oesophageal reflux measured by oesophageal pH-metry or impedance monitoring • Adverse outcomes • Improvement in validated reflux questionnaire • Parent satisfaction with the intervention	trial.
Other criteria for inclusion/ exclusion of studies		
Search strategies		
Review strategies		
Equality		

E.9 Enteral Feeding

	Details	Additional comments
Review question	How effective is enteral tube feeding in the management of GOR/GORD?	
Objectives	To evaluate the use of enteral tube feeding of any sort (for example, naso-gastric tube, gastrostomy, naso-jejunal or jejunostomy feeding) in the management of gastro-oesophageal reflux disease.	Tube feeding might be employed for a variety of reasons – for example where there is severe overt regurgitation or concern about a risk of pulmonary aspiration. In evaluation evidence of efficacy it will be important to consider the specific complication of reflux for which it is being employed. Sub-groups analysis may be important for those with gastro-oesophageal reflux associated with neurological and developmental conditions.
Language	English	
Study design	RCTs Systematic reviews or meta-analysis of RCTs	
Status		
Population	Children and young people under 18 years diagnosed with GORD Sub-groups, if data is available • Premature • Cerebral palsy	
Intervention indicators	• naso-gastric tube feeding • gastrostomy (tube or button) feeding • naso-jejunal tube feeding • jejunostomy feeding	
Comparator	• Oral feeding • Cross comparisons between any of the four interventions list (above)	
Outcomes	Resolution of gastro-oesophageal reflux complication for which enteral tube feeding was given: • faltering growth • pulmonary aspiration • Overt regurgitation	No MID was outlined by the GDG.

	Details	Additional comments
	• Parent reported reduction in infant distress • Resolution of gastro-oesophageal reflux measured by oesophageal pH-metry or impedance monitoring • Adverse outcomes • Improvement in validated reflux questionnaire • Parent satisfaction with the intervention	
Other criteria for inclusion/ exclusion of studies		
Search strategies		
Review strategies		
Equality		

Appendix F: Search strategies

The search strategies for this guideline are in a separate document “Gastro-oesophageal reflux disease in children and young people: Appendix F ”

Appendix G: Summary of identified studies

Protocol Question	Papers Identified "All"	Duplicates	Weeded out	Abandoned	Excluded	Included
What is the clinical course of overt gastroesophageal reflux (GOR)?	2366	0	2330	0	21	15
The distinction between physiological gastro-oesophageal reflux and gastro-oesophageal reflux disease? **Two stage review**	7630	2	7449	4	130	45
What are the risk factors for developing gastroesophageal reflux disease?	4603	0	4546	2	38	17
What is the effectiveness of a clearly described positional intervention in comparison with no positional management and alternative clearly described positional interventions?	263	0	244	1	11	7
What is the effectiveness of a managed feeding regimen in comparison with a conventional, age appropriate, regimen in the management of overt GOR?	1121	0	1086	1	17	17
Scope question: How effective are changes to feeding in infants with GOR/GORD?	875	0	863	0	8	4
Four questions in the scope: How effective are H2-receptor antagonists compared with placebo in the treatment of GOR/GORD? How effective are proton pump inhibitors compared with placebo and one another in the treatment of GOR/GORD? How effective are H2-receptor antagonists compared with proton pump inhibitors in the treatment of GOR/GORD? How effective are prokinetic agents compared with placebo in the treatment of GOR/GORD?	1381	2	1322	2	38	17
How effective is enteral tube feeding in the management of GOR/GORD?	801	0	731	0	70	0
How effective is fundoplication surgery in the treatment of GOR/GORD?	1682	5	1643	0	30	4

Appendix H: Excluded studies

H.1 What is the natural history of overt GOR?

1. What is the natural history of overt GOR?

Study	Reason for Exclusion
Baker,SusanS, Roach,ChristineM, Leonard,MichaelS, Baker,RobertD, Infantile gastroesophageal reflux in a hospital setting, BMC Pediatrics, 8, 1-8, 2008	Population studied is hospitalized children with reflux (not a general community population)
Chen,J.H., Wang,H.Y., Lin,H.H., Wang,C.C., Wang,L.Y., Prevalence and determinants of gastroesophageal reflux symptoms in adolescents, Journal of Gastroenterology and Hepatology, 29, 269-275, 2014	No relevant data
Corvaglia,L., Mariani,E., Aceti,A., Capretti,M.G., Ancora,G., Faldella,G., Combined oesophageal impedance-pH monitoring in preterm newborn: comparison of two options for layout analysis, Neurogastroenterology and Motility, 21, 1027-1e81, 2009	No relevant data: assessment of the main advantages and limits of combined pH-multichannel intraluminal impedance monitoring in preterm infants
Dalby,K., Nielsen,R.G., Markoew,S., Kruse-Andersen,S., Husby,S., Reproducibility of 24-hour combined multiple intraluminal impedance (MII) and pH measurements in infants and children. Evaluation of a diagnostic procedure for gastroesophageal reflux disease, Digestive Diseases and Sciences, 52, 2159-2165, 2007	No relevant data: investigation of the reproducibility of reflux parameters obtained by 2 times 24 hour consecutive pH/MII monitoring in children and infants with symptoms of GERD
Hegar,B., Vandenplas,Y., Gastroesophageal reflux: Natural evolution, diagnostic approach and treatment, Turkish Journal of Pediatrics, 55, 1-7, 2013	Review article - individual studies checked for inclusion
Kohelet,D., Boaz,M., Serour,F., Cohen-Adad,N., Arbel,E., Gorenstein,A., Esophageal pH study and symptomatology of gastroesophageal reflux in newborn infants, American Journal of Perinatology, 21, 85-91, 2004	No relevant data: assessment of the association between gestational age and esophageal pH monitoring variables

Lin,B.R., Wong,J.M., Yang,J.C., Wang,J.T., Lin,J.T., Wang,T.H., Limited value of typical gastroesophageal reflux disease symptoms to screen for erosive esophagitis in Taiwanese, Journal of the Formosan Medical Association, 102, 299-304, 2003	No relevant data: assessment of the diagnostic sensitivity of a self-administered questionnaire
Lopez-Alonso,M., Moya,M.J., Cabo,J.A., Ribas,J., del Carmen,Macias M., Silny,J., Sifrim,D., Twenty-four-hour esophageal impedance-pH monitoring in healthy preterm neonates: rate and characteristics of acid, weakly acidic, and weakly alkaline gastroesophageal reflux, Pediatrics, 118, e299-e308, 2006	No relevant data: assessment of impedance-pH values for acid, weakly acidic, and weakly alkaline reflux from healthy preterm neonates
Nelson,S.P., Chen,E.H., Syniar,G.M., Christoffel,K.K., Prevalence of symptoms of gastroesophageal reflux during childhood: a pediatric practice-based survey. Pediatric Practice Research Group, Archives of Pediatrics and Adolescent Medicine, 154, 150-154, 2000	Study reports the percentage of children with regurgitation but only at 2 time points
Ng,S.C., Quak,S.H., Gastroesophageal reflux in preterm infants: norms for extended distal esophageal pH monitoring, Journal of Pediatric Gastroenterology and Nutrition, 27, 411-414, 1998	No relevant data: assessment of pH norms for GER
Orenstein,S., Regurgitation & GERD. [10 refs], Journal of Pediatric Gastroenterology and Nutrition, 32 Suppl 1, S16-S18, 2001	General review article
Orenstein,S.R., Shalaby,T.M., Kelsey,S.F., Frankel,E., Natural history of infant reflux esophagitis: symptoms and morphometric histology during one year without pharmacotherapy, American Journal of Gastroenterology, 101, 628-640, 2006	Small sample size: 19 subjects of which only 10 had completed the study
Poddar,U., Diagnosis and Management of Gastroesophageal Reflux Disease (GERD): An Indian Perspective, Indian Pediatrics, 50, 119-126, 2013	General literature review

Sacco,O., Mattioli,G., Girosi,D., Battistini,E., Jasonni,V., Rossi,G.A., Gastroesophageal reflux and its clinical manifestation at gastroenteric and respiratory levels in childhood: physiology, signs and symptoms, diagnosis and treatment, Expert Review of Respiratory Medicine, 1, 391-401, 2007	General literature review
Semeniuk,J., Kaczmarski,M., 24-hour esophageal pH monitoring in children with pathological acid gastroesophageal reflux: primary and secondary to food allergy. Part II. Intraesophageal pH values in proximal channel; preliminary study and control studies--after 1, 2, 4 and 9 years of clinical observation as well as dietary and pharmacological treatment, Advances in Medical Sciences, 52, 206-212, 2007	No relevant data: comparative analysis of parameters of 24-hour intraesophageal pH monitoring with dual-channel probe in children with acid GER
Shepherd,R.W., Wren,J., Evans,S., Gastroesophageal reflux in children. Clinical profile, course and outcome with active therapy in 126 cases, Clinical Pediatrics, 26, 55-60, 1987	No relevant data: evaluation of the effects of active therapy and early recognition of esophagitis on the course and outcome of GER
Stordal,K., Johannesdottir,G.B., Bentsen,B.S., Sandvik,L., Gastroesophageal reflux disease in children: association between symptoms and pH monitoring, Scandinavian Journal of Gastroenterology, 40, 636-640, 2005	No relevant data: assessment of the association between symptoms and pH monitoring
Treem,W.R., Davis,P.M., Hyams,J.S., Gastroesophageal reflux in the older child: Presentation, response to treatment and long-term follow-up, Clinical Pediatrics, 30, 435-440, 1991	No relevant data: assessment of whether the prognosis of GER in older children is different from that in younger ones
Vandenplas,Y., Goyvaerts,H., Helven,R., Sacre,L., Gastroesophageal reflux, as measured by 24-hour pH monitoring, in 509 healthy infants screened for risk of sudden infant death syndrome, Pediatrics, 88, 834-840, 1991	No relevant data: assessment of pH norms for GER

Vandenplas,Y., Sacre-Smits,L., Continuous 24-hour esophageal pH monitoring in 285 asymptomatic infants 0-15 months old, Journal of Pediatric Gastroenterology and Nutrition, 6, 220-224, 1987	No relevant data: assessment of 24 hour pH monitoring in asymptomatic infants
Woodley,F.W., Mousa,H., Acid gastroesophageal reflux reports in infants: a comparison of esophageal pH monitoring and multichannel intraluminal impedance measurements, Digestive Diseases and Sciences, 51, 1910-1916, 2006	No relevant data: comparison of a series of parallel esophageal pH monitoring-derived and pH/multichannel intraluminal impedance monitoring-derived acid GER episode reports

H.2 What are the risk factors associated with developing GOR/D?

2. What are the risk factors associated with developing GOR/D?	
Study	Reason for Exclusion
Blondeau,K., Pauwels,A., Dupont,Lj, Mertens,V., Proesmans,M., Orel,R., Brecelj,J., Lopez-Alonso,M., Moya,M., Malfroot,A., De,Wachter E., Vandenplas,Y., Hauser,B., Sifrim,D., Characteristics of gastroesophageal reflux and potential risk of gastric content aspiration in children with cystic fibrosis, Journal of Pediatric Gastroenterology and Nutrition, 50, 161-166, 2010	Study compares the presence of bile acids in 2 groups of subjects
Bohmer,C.J., Niezen-de Boer,M.C., Klinkenberg-Knol,E.C., Deville,W.L., Nadorp,J.H., Meuwissen,S.G., The prevalence of gastroesophageal reflux disease in institutionalized intellectually disabled individuals, American Journal of Gastroenterology, 94, 804-810, 1999	Study includes both children and adults without a subgroup analysis
Bohmer,C.J., Niezen-de Boer,M.C., Klinkenberg-Knol,E.C., Nadorp,J.H., Meuwissen,S.G., Gastro-oesophageal reflux disease in institutionalised intellectually disabled individuals, Netherlands Journal of Medicine, 51, 134-139, 1997	Study includes both adults and children without a subgroup analysis
Bohmer,C.J.M., Klinkenberg-Knol,E.C., Niezen-de,BoerR, Meuwissen,S.G.M., The prevalence of gastro-oesophageal reflux disease based on non-specific symptoms in institutionalized, intellectually disabled individuals, European Journal of Gastroenterology and Hepatology, 9, 187-190, 1997	Subjects aged 4 to 75 years, no subgroup analysis
Darling,D.B., Hiatal hernia and gastroesophageal reflux in infancy and childhood. Analysis of the radiologic findings, American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, 123, 724-736, 1975	Non-comparative, study focuses on the technique of roentgenologic examination and criteria of diagnosis

Darling,D.B., Fisher,J.H., Gellis,S.S., Hiatal hernia and gastroesophageal reflux in infants and children: analysis of the incidence in North American children, Pediatrics, 54, 450-455, 1974	Comparison groups not of interest to this review question
de Veer,A.J., Bos,J.T., Niezen-de Boer,R.C., Bohmer,C.J., Francke,A.L., Symptoms of gastroesophageal reflux disease in severely mentally retarded people: a systematic review. [26 refs], BMC Gastroenterology, 8, 23-, 2008	Literature review: individual studies checked for inclusion
Di Pace,M.R., Caruso,A.M., Catalano,P., Casuccio,A., Cimador,M., De,Grazia E., Evaluation of esophageal motility and reflux in children treated for esophageal atresia with the use of combined multichannel intraluminal impedance and pH monitoring, Journal of Pediatric Surgery, 46, 443-451, 2011	Outcomes reported in article are continuous and therefore not possible to calculate odds ratios
Gangil,A., Patwari,A.K., Bajaj,P., Kashyap,R., Anand,V.K., Gastroesophageal reflux disease in children with cerebral palsy, Indian Pediatrics, 38, 766-770, 2001	Non-comparative study
Gilger,M.A., El-Serag,H.B., Gold,B.D., Dietrich,C.L., Tsou,V., McDuffie,A., Shub,M.D., Prevalence of endoscopic findings of erosive esophagitis in children: a population-based study, Journal of Pediatric Gastroenterology and Nutrition, 47, 141-146, 2008	Poor reporting of data
Gorenstein,A., Cohen,A.J., Cordova,Z., Witzling,M., Krutman,B., Serour,F., Hiatal hernia in pediatric gastroesophageal reflux, Journal of Pediatric Gastroenterology and Nutrition, 33, 554-557, 2001	Outcomes reported in article are continuous and therefore not possible to calculate odds ratios
Gustafsson,P.M., Tibbling,L., Gastro-oesophageal reflux and oesophageal dysfunction in children and adolescents with brain damage, Acta Paediatrica, 83, 1081-1085, 1994	No comparison group: all children had brain damage

Halac,U., Revillion,M., Michaud,L., Gottrand,F., Faure,C., Functional gastrointestinal disorders induced by esophageal atresia surgery: Is it valid in Humans?, Journal of Neurogastroenterology and Motility, 18, 406-411, 2012	Study examines esophageal atresia as a risk factor for functional gastrointestinal disorders not including GORD
Heimburger,I.L., Alford,W.C., Wooler,G.H., Aylwin,J.A., Hiatal hernia and reflux esophagitis in children, Journal of Thoracic and Cardiovascular Surgery, 50, 463-472, 1965	Non-comparative study
Jadcherl,S.R., Slaughter,J.L., Stenger,M.R., Klebanoff,M., Kelleher,K., Gardner,W., Practice variance, prevalence, and economic burden of premature infants diagnosed with GERD, Hospital Pediatrics, 3, 335-341, 2013	BL unable to supply
James,MartinA, Pratt,N., Declan,KennedyJ, Philip,RyanF, Ruffin,R.E., Miles,H., Marley,J., Natural history and familial relationships of infant spilling to 9 years of age, Pediatrics, 109, 1061-1067, 2002	Not possible to calculate odds ratios based on data reported in the article
Jensen,E.T., Kappelman,M.D., Kim,H.P., Ringel-Kulka,T., Dellon,E.S., Early life exposures as risk factors for pediatric eosinophilic esophagitis, Journal of Pediatric Gastroenterology and Nutrition, 57, 67-71, 2013	Study looks at eosinophilic esophagitis.
Jewett,Jr, Siegel,M., Hiatal hernia and gastroesophageal reflux, Journal of Pediatric Gastroenterology and Nutrition, 3, 340-345, 1984	General review article
Johnsson,F., Joelsson,B., Gudmundsson,K., Determinants of gastro-oesophageal reflux and their inter-relationships, British Journal of Surgery, 76, 241-244, 1989	Non-comparative study in adults

Kallel,L., Bibani,N., Fekih,M., Matri,S., Karoui,S., Mustapha,N.B., Serghini,M., Zouiten,L., Feki,M., Zouari,B., Boubaker,J., Kaabachi,N., Filali,A., Metabolic syndrome is associated with gastroesophageal reflux disease based on a 24-hour ambulatory pH monitoring, Diseases of the Esophagus, 24, 153-159, 2011	Study was undertaken in adults
Kumar,V., Mathai,S.S., Kanitkar,M., Preliminary study in to the incidence of gastroesophageal reflux (GER) in high risk neonates admitted to NICU, Indian Journal of Pediatrics, 79, 1197-1200, 2012	Unclear reporting of results
Lilly,J.R., Randolph,J.G., Hiatal hernia and gastroesophageal reflux in infants and children, Journal of Thoracic and Cardiovascular Surgery, 55, 42-54, 1968	Non-comparative, study focuses on the clinical characteristics and therapeutic management of hiatal hernia
Lin,Y.C., Ni,Y.H., Chang,M.H., Gastroesophageal reflux disease beyond infancy, Pediatrics International, 46, 516-520, 2004	Outcomes reported in article are continuous and therefore not possible to calculate odds ratios
Mendes,T.B., Mezzacappa,M.A., Toro,A.A., Ribeiro,J.D., Risk factors for gastroesophageal reflux disease in very low birth weight infants with bronchopulmonary dysplasia, Jornal de Pediatria, 84, 154-159, 2008	Risk factors vaguely defined as lung disease, abnormal neurological findings and cns disease
Ngerncham,M., Barnhart,D.C., Haricharan,R.N., Roseman,J.M., Georgeson,K.E., Harmon,C.M., Risk factors for recurrent gastroesophageal reflux disease after fundoplication in pediatric patients: a case-control study, Journal of Pediatric Surgery, 42, 1478-1485, 2007	This study looks at 'recurrent' GORD after fundoplication
Peetsold,M.G., Kneepkens,C.M., Heij,H.A., IJsselstijn,H., Tibboel,D., Gemke,R.J., Congenital diaphragmatic hernia: long-term risk of gastroesophageal reflux disease, Journal of Pediatric Gastroenterology and Nutrition, 51, 448-453, 2010	No relevant data

Piccione,J.C., McPhail,G.L., Fenchel,M.C., Brody,A.S., Boesch,R.P., Bronchiectasis in chronic pulmonary aspiration: risk factors and clinical implications, Pediatric Pulmonology, 47, 447-452, 2012	Study examines prior history of GER as risk factor for bronchiectasis
Polat,F.R., Polat,S., The relationship between grade's of the gastroesophageal reflux disease and hiatal hernias, HealthMED, 6, 2226-2228, 2012	Subjects aged 12 to 92 years, no subgroup analysis
Ponz,DeLeonM, Benatti,P., Pedroni,M., Viel,A., Genuardi,M., Percesepe,A., Roncucci,L., Gastroesophageal reflux disease in intellectually disabled individuals: How often, how serious, how manageable?, American Journal of Gastroenterology, 95, 1868-1872, 2000	General review article
Ravelli,A.M., Milla,P.J., Vomiting and gastroesophageal motor activity in children with disorders of the central nervous system, Journal of Pediatric Gastroenterology and Nutrition, 26, 56-63, 1998	No relevant data
Reshetnikov,O.V., Kurilovich,S.A., Gastroesophageal reflux symptoms, H. pylori, and associated factors in adolescents, Helicobacter, 14, 348-, 2009	Conference abstract
Reyes,A.L., Cash,A.J., Green,S.H., Booth,I.W., Gastrooesophageal reflux in children with cerebral palsy, Child: Care, Health and Development, 19, 109-118, 1993	No comparison group: all children had cerebral palsy
Sindel,B.D., Maisels,M.J., Ballantine,T.V., Gastroesophageal reflux to the proximal esophagus in infants with bronchopulmonary dysplasia, American Journal of Diseases of Children, 143, 1103-1106, 1989	Outcomes reported in article are continuous and therefore not possible to calculate odds ratios
Staiano,A., Cucchiara,S., Del,Giudice E., Andreotti,M.R., Minella,R., Disorders of oesophageal motility in children with psychomotor retardation and gastro-oesophageal reflux, European Journal of Pediatrics, 150, 638-641, 1991	No comparison group: all children had brain damage

Stilson,W.L., Sanders,I., Gardiner,G.A., Gorman,H.C., Lodge,D.F., Hiatal hernia and gastroesophageal reflux. A clinicoradiological analysis of more than 1,000 cases, Radiology, 93, 1323-1327, 1969	Non-comparative study
Stringer,D.A., Sprigg,A., Juodis,E., Corey,M., Daneman,A., Levison,H.J., Durie,P.R., The association of cystic fibrosis, gastroesophageal reflux, and reduced pulmonary function, Canadian Association of Radiologists Journal, 39, 100-102, 1988	Outcomes not of interest
Teitelbaum,J.E., Sinha,P., Micale,M., Yeung,S., Jaeger,J., Obesity is related to multiple functional abdominal diseases, Journal of Pediatrics, 154, 444-446, 2009	Data for the comparison group (normal weight children) is not presented
Wu,J.F., Hsu,W.C., Tseng,P.H., Wang,H.P., Hsu,H.Y., Chang,M.H., Ni,Y.H., Combined multichannel intraluminal impedance and pH monitoring assists the diagnosis of sliding hiatal hernia in children with gastroesophageal reflux disease, Journal of Gastroenterology, 48, 1242-1248, 2013	No relevant data, also study focuses on the comparison of sliding vs non-sliding hiatal hernia

H.3 What clinical features can be used to assess the presence and severity of gastro-oesophageal reflux disease in children and young people?

3. What clinical features can be used to assess the presence and severity of gastro-oesophageal reflux disease in children and young people? Restricted to systematic reviews, guidelines and questionnaire development.	
Study	Reason for Exclusion
Aggarwal,S., Mittal,S.K., Kalra,K.K., Rajeshwari,K., Gondal,R., Infant gastroesophageal reflux disease score: reproducibility and validity in a developing country, Tropical gastroenterology : official journal of the Digestive Diseases Foundation, 25, 96-98, 2004	Primary study evaluated use of an outcome score.
Bai,Y., Du,Y., Zou,D., Jin,Z., Zhan,X., Li,Z.S., Yang,Y., Liu,Y., Zhang,S., Qian,J., Zhou,L., Hao,J., Chen,D., Fang,D., Fan,D., Yu,X., Sha,W., Nie,Y., Zhang,X., Xu,H., Lv,N., Jiang,B., Zou,X., Fang,J., Fan,J., Li,Y., Chen,W., Wang,B., Zou,Y., Li,Y., Sun,M., Chen,Q., Chen,M., Zhao,X., Chinese GerdQ Research Group., Gastroesophageal Reflux Disease Questionnaire (GerdQ) in real-world practice: a national multicenter survey on 8065 patients, Journal of Gastroenterology and Hepatology, 28, 626-631, 2013	Based on adults.
Birch,J.L., Newell,S.J., Gastrooesophageal reflux disease in preterm infants: Current management and diagnostic dilemmas, Archives of Disease in Childhood: Fetal and Neonatal Edition, 94, F379-F383, 2009	General literature review
Blondeau,K., Mertens,V., Dupont,L., Pauwels,A., Farre,R., Malfroot,A., De,Wachter E., De,Schutter,I, Hauser,B., Vandenplas,Y., Sifrim,D., The relationship between gastroesophageal reflux and cough in children with chronic unexplained cough using combined impedance-pH-manometry recordings, Pediatric Pulmonology, 46, 286-294, 2011	Can't calculate or - LRs.

Correa,M.C., Lerco,M.M., Cunha,Mde L., Henry,M.A., Salivary parameters and teeth erosions in patients with gastroesophageal reflux disease, Arquivos de Gastroenterologia, 49, 214-218, 2012	Study in Adults
Firouzei,M.S., Khazaei,S., Afghari,P., Savabi,G., Savabi,O., Keshteli,A.H., Adibi,P., Gastroesophageal reflux disease and tooth erosion: SEPAHAN systematic review no. 10, Dental Research Journal, 8, S9-S14, 2011	Study in adults
Fishbein,M., Branham,C., Fraker,C., Walbert,L., Cox,S., Scarborough,D., The incidence of oropharyngeal dysphagia in infants with GERD-like symptoms, Journal of Parenteral and Enteral Nutrition, 37, 667-673, 2013	Definition and outcome included feeding problems, so no use in diagnosing GORD.
Ghezzi,M., Guida,E., Ullmann,N., Sacco,O., Mattioli,G., Jasonni,V., Rossi,G.A., Silvestri,M., Weakly acidic gastroesophageal refluxes are frequently triggers in young children with chronic cough, Pediatric Pulmonology, 48, 295-302, 2013	No comparison group
Greifer,M., Ng,K., Levine,J., Impedance and extraesophageal manifestations of reflux in pediatrics, Laryngoscope, 122, 1397-1400, 2012	Provides no comparative data.
Kelly,E.A., Parakininkas,D.E., Werlin,S.L., Southern,J.F., Johnston,N., Kerschner,J.E., Prevalence of pediatric aspiration-associated extraesophageal reflux disease, JAMA Otolaryngology--Head and Neck Surgery, 139, 996-1001, 2013	Includes adults
Kleinman,L., Revicki,D.A., Flood,E., Validation issues in questionnaires for diagnosis and monitoring of gastroesophageal reflux disease in children. [26 refs], Current Gastroenterology Reports, 8, 230-236, 2006	Patient data not reported

Kleinman,L., Rothman,M., Strauss,R., Orenstein,S.R., Nelson,S., Vandenplas,Y., Cucchiara,S., Revicki,D.A., The infant gastroesophageal reflux questionnaire revised: development and validation as an evaluative instrument, Clinical Gastroenterology and Hepatology, 4, 588-596, 2006	Assessment of a questionnaire
Martigne,L., Delaage,P.H., Thomas-Delecourt,F., Bonnelye,G., Barthelemy,P., Gottrand,F., Prevalence and management of gastroesophageal reflux disease in children and adolescents: a nationwide cross-sectional observational study, European Journal of Pediatrics, 171, 1767-1773, 2012	Individual signs and symptoms not reported
Orenstein,S.R., Symptoms and reflux in infants: Infant Gastroesophageal Reflux Questionnaire Revised (I-GERQ-R)--utility for symptom tracking and diagnosis, Current Gastroenterology Reports, 12, 431-436, 2010	Assessment of I-GERQ questionnaire. List of symptoms and signs not presented.
Orenstein,S.R., Shalaby,T.M., Cohn,J.F., Reflux symptoms in 100 normal infants: diagnostic validity of the infant gastroesophageal reflux questionnaire, Clinical Pediatrics, 35, 607-614, 1996	Does not show how signs and symptoms were identified.
Orenstein,S.R., Shalaby,T.M., Kelsey,S.F., Frankel,E., Natural history of infant reflux esophagitis: symptoms and morphometric histology during one year without pharmacotherapy, American Journal of Gastroenterology, 101, 628-640, 2006	Primary study. Does not list signs and symptoms but uses global score.
Orsi,M., Cohen-Sabban,J., Grandi,C., Donato,M.G., Lifschitz,C., D'Agostino,D., Non acid gastroesophageal reflux episodes decrease with age as determined by multichannel intraluminal impedance-pH monitoring in symptomatic children, Revista de la Facultad de Ciencias Medicas de Cordoba, 68, 8-13, 2011	Primary study of natural history of reflux in infants; no a list of associated signs and symptoms.

Pace,F., Pallotta,S., Tonini,M., Vakil,N., Bianchi,Porro G., Systematic review: gastro-oesophageal reflux disease and dental lesions. [33 refs], Alimentary Pharmacology and Therapeutics, 27, 1179-1186, 2008	Includes adult studies.
Pagliari,A.V., Patti,M., Costa,M.T., Blotta,P., Guadagnini,T., Zambelli,A., Klinger,F., Klinger,M., Atypical extraesophageal symptoms and gastroesophageal reflux in children, International Journal of Pediatric Otorhinolaryngology, 68, 699, 2004-, 2004	Abstract only of a primary study listing signs and symptoms associated with GORD.
Patra,S., Singh,V., Chandra,J., Kumar,P., Tripathi,M., Gastro-esophageal reflux in early childhood wheezers, Pediatric Pulmonology, 46, 272-277, 2011	No comparative data provided.
Rudolph,C.D., Mazur,L.J., Liptak,G.S., Baker,R.D., Boyle,J.T., Colletti,R.B., Gerson,W.T., Werlin,S.L., North American Society for Pediatric Gastroenterology and Nutrition., Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children: recommendations of the North American Society for Pediatric Gastroenterology and Nutrition, Journal of Pediatric Gastroenterology and Nutrition, 32 Suppl 2, S1-31, 2001	Superseded by 2009 guidelines from same organisations
Serra,A., Cocuzza,S., Poli,G., La,Mantia,I, Messina,A., Pavone,P., Otologic findings in children with gastroesophageal reflux, International Journal of Pediatric Otorhinolaryngology, 71, 1693-1697, 2007	This is not a review
Thakkar,K., Boatright,R.O., Gilger,M.A., El-Serag,H.B., Gastroesophageal reflux and asthma in children: a systematic review. [24 refs], Pediatrics, 125, e925-e930, 2010	Review on a single symptom

Valet,R.S., Carroll,K.N., Gebretsadik,T., Minton,P.A., Woodward,K.B., Liu,Z., Hartert,T.V., Gastroesophageal reflux disease increases infant acute respiratory illness severity, but not childhood asthma, Pediatric, Allergy, Immunology, and Pulmonology, 27, 30-33, 2014	Definitions of GERD and Asthma based on retrospective assessment by parent.
Vandenplas,Y., Ashkenazi,A., Belli,D., Boige,N., Bouquet,J., Cadranel,S., Cezard,J.P., Cucchiara,S., Dupont,C., Geboes,K., A proposition for the diagnosis and treatment of gastro-oesophageal reflux disease in children: a report from a working group on gastro-oesophageal reflux disease. Working Group of the European Society of Paediatric Gastro-enterology and Nutrition (ESPGAN). [44 refs], European Journal of Pediatrics, 152, 704-711, 1993	Not a systematic review of signs and symptoms and superseded by updated guidelines.

H.4 What is the effectiveness of a clearly described positional intervention in comparison with no positional management and alternative clearly described positional interventions?

4. What is the effectiveness of a clearly described positional intervention in comparison with no positional management and alternative clearly described positional interventions?

Study	Reason for Exclusion
Button,B.M., Heine,R.G., Catto-Smith,A.G., Phelan,P.D., Olinsky,A., Postural drainage and gastro-oesophageal reflux in infants with cystic fibrosis, Archives of Disease in Childhood, 76, 148-150, 1997	Study examines the effects of different forms of physiotherapy on GOR in infants with cystic fibrosis
Carroll,A.E., Garrison,M.M., Christakis,D.A., A systematic review of nonpharmacological and nonsurgical therapies for gastroesophageal reflux in infants. [47 refs], Archives of Pediatrics and Adolescent Medicine, 156, 109-113, 2002	Systematic review: individual studies checked for inclusion
Chao,H.C., Vandenplas,Y., Effect of cereal-thickened formula and upright positioning on regurgitation, gastric emptying, and weight gain in infants with regurgitation, Nutrition, 23, 23-28, 2007	Study compares positioning versus feeding therapy
Craig,W.R., Hanlon-Dearman,A., Sinclair,C., Taback,S.P., Moffatt,M., WITHDRAWN: Metoclopramide, thickened feedings, and positioning for gastro-oesophageal reflux in children under two years, Cochrane database of systematic reviews (Online), 5, CD003502-, 2010	Cochrane review withdrawn (individual studies checked for inclusion)
Doumit,M., Krishnan,U., Jaffe,A., Belessis,Y., Acid and non-acid reflux during physiotherapy in young children with cystic fibrosis, Pediatric Pulmonology, 47, 119-124, 2012	Study examines the effect of positioning during physiotherapy on GOR in children with cystic fibrosis

Loots,C., Smits,M., Omari,T., Bennink,R., Benninga,M., van,Wijk M., Effect of lateral positioning on gastroesophageal reflux (GER) and underlying mechanisms in GER disease (GERD) patients and healthy controls, Neurogastroenterology and Motility, 25, 222-229, 2013	Study is in adults
Loots,C.M., Kritas,S., van,WijkM, McCall,L., James,J., Peeters,L., Lewindon,P., Bijlmer,R., Haslam,R., Tobin,J.M., Benninga,M.A., Davidson,G.P., Omari,T.I., A randomized sham-controlled trial of left lateral body positioning vs. acid suppression for infantile gastroesophageal reflux, Journal of Pediatric Gastroenterology and Nutrition, 52, E98-E99, 2011	Conference abstract
Orenstein,S.R., Effects on behavior state of prone versus seated positioning for infants with gastroesophageal reflux, Pediatrics, 85, 765-767, 1990	Retrospective analysis of data (this was not an RCT)
Orenstein,S.R., McGowan,J.D., Efficacy of conservative therapy as taught in the primary care setting for symptoms suggesting infant gastroesophageal reflux, Journal of Pediatrics, 152, 310-314, 2008	Retrospective analysis of data obtained for a trial. Study examines the effects of conservative therapy which includes positioning as well as feeding modifications and tobacco smoke exposure avoidance.
Phillips,G.E., Pike,S.E., Rosenthal,M., Bush,A., Holding the baby: head downwards positioning for physiotherapy does not cause gastro-oesophageal reflux, European Respiratory Journal, 12, 954-957, 1998	Study examines the effects of physiotherapy on GOR in infants with cystic fibrosis
Vandenplas,Y., Hachimi-Idrissi,S., Casteels,A., Mahler,T., Loeb,H., A clinical trial with an "anti-regurgitation" formula, European Journal of Pediatrics, 153, 419-423, 1994	Study examines the effect of thickening, positional treatment and parental reassurance versus a group without thickening, positional treatment and parental reassurance.

H.5 What is the effectiveness of a managed feeding regimen in comparison with a conventional, age appropriate, regimen in the management of overt GOR?

5. What is the effectiveness of a managed feeding regimen in comparison with a conventional, age appropriate, regimen in the management of overt GOR?

Study	Reason for Exclusion
Corvaglia,L., Ferlini,M., Rotatori,R., Paoletti,V., Alessandroni,R., Cocchi,G., Faldella,G., Starch thickening of human milk is ineffective in reducing the gastroesophageal reflux in preterm infants: a crossover study using intraluminal impedance, Journal of Pediatrics, 148, 265-268, 2006	Non-randomised study
Craig,Raine William, HanlonDearman,Ana, Sinclair,Chris, Taback,Shayne P., Moffatt,Michael, Metoclopramide, thickened feedings, and positioning for gastro-oesophageal reflux in children under two years, Cochrane Database of Systematic Reviews, -, 2010	Search undertaken in 2003. Several RCTs published since review
Farahmand,F., Najafi,M., Ataee,P., Modarresi,V., Shahraki,T., Rezaei,N., Cow's Milk Allergy among Children with Gastroesophageal Reflux Disease, Gut and Liver, 5, 298-301, 2011	Non-comparative study.
Garzi,A., Messina,M., Frati,F., Carfagna,L., Zagordo,L., Belcastro,M., Parmiani,S., Sensi,L., Marcucci,F., An extensively hydrolysed cow's milk formula improves clinical symptoms of gastroesophageal reflux and reduces the gastric emptying time in infants, Allergologia et Immunopathologia, 30, 36-41, 2002	Study design is a case-control but only reports on cases. Only 10 patients included.
Horvath,A., Dziechciarz,P., Szajewska,H., The effect of thickened-feed interventions on gastroesophageal reflux in infants: systematic review and meta-analysis of randomized, controlled trials. [39 refs][Erratum appears in Pediatrics. 2009 Apr;123(4):1254], Pediatrics, 122, e1268-e1277, 2008	Incorrect analysis of cross-over studies and calculation of SDs.

Horvath,A., Dziechciarz,P., Szajewska,H., The effect of thickened-feed interventions on gastroesophageal reflux in infants: Systematic review and meta-analysis of randomized, controlled trials (Pediatrics (2008) 122, 6, (e1268-e1277) DOI: 10.1542/peds.2008-1900), Pediatrics, 123, 1254-, 2009	Correction to original review
Huang,RaeChi, Forbes,David, Davies,Mark W., Feed thickener for newborn infants with gastro-oesophageal reflux, Cochrane Database of Systematic Reviews, -, 2009	No studies identified for review
Iacono,G., Carroccio,A., Cavataio,F., Montalto,G., Kazmierska,I., Lorello,D., Soresi,M., Notarbartolo,A., Gastroesophageal reflux and cow's milk allergy in infants: a prospective study, Journal of Allergy and Clinical Immunology, 97, 822-827, 1996	Does not investigate if effect of cow's milk elimination on reflux. Shows association between cow's milk allergy and reflux.
Moukarzel,A.A., Akatcherian,C., Effects of a thickened formula on gastric emptying time in infants with GER: a crossover study, Journal of Pediatric Gastroenterology and Nutrition, 37, 386, 2003-, 2003	Conference abstract of later publication
Moya,M., Juste,M., Cortes,E., Auxina,A., Ortiz,I., Clinical evaluation of the different therapeutic possibilities in the treatment of infant regurgitation, Revista Espanola de Pediatria, 55, 219-223, 1999	Written in Spanish
Ramirez-Mayans,J., Palacio-Del,CarmenL, Cervantes-Bustamante,R., Mata-Rivera,N., Pina-Romero,N., Zarate-Mondragon,F., Gelis-Vieitez,P., Mason-Cordero,T., Gutierrez-Castrellon,P., Nutritional Management of Children with Gastroesophageal Reflux: A Comparison of Two Different Formulas, International Pediatrics, 18, 78-83, 2003	Compares different formulas

Tolia,V., Kauffman,R.E., Comparison of evaluation of gastroesophageal reflux in infants using different feedings during intraesophageal pH monitoring, Journal of Pediatric Gastroenterology and Nutrition, 10, 426-429, 1990	Question of interest not examined.
Ummarino,D., Sciorio,E., Crocetto,F., Miele,E., Staiano,A., A prospective, comparative, randomized, controlled study on the efficacy of the treatment with magnesium (Mg-) alginate in infants with gastroesophageal reflux, Digestive and Liver Disease, 45, e299-e300, 2013	Conference abstract only. Data may have been interim as RCT was recruiting patients until December 2013, but abstract was published in September 2013.
van Wijk,M.P., Benninga,M.A., Davidson,G.P., Haslam,R., Omari,T.I., Small volumes of feed can trigger transient lower esophageal sphincter relaxation and gastroesophageal reflux in the right lateral position in infants, Journal of Pediatrics, 156, 744-748, 748	Examines position when reflux occurs
Vandenplas,Y., Grathwohl,D., Steenhout,P., Christens,J., Halut,C., Mulier,S., Marien,P., Veereman,G., Kamoen,K., Peeters,S., Smets,F., Bury,F., Verghote,M., Bollen,P., Beauraind,O., Lenoir,P., Colinet,S., Van,WinckM, Comparison of 2 extensively hydrolyzed formulas for the treatment of children with cow's-milk intolerance, Journal of Pediatric Gastroenterology and Nutrition, 52, E160-E161, 2011	No assessment of GORD
Vandenplas,Y., Leluyer,B., Cazaubiel,M., Housez,B., Bocquet,A., Double-blind comparative trial with 2 antiregurgitation formulae, Journal of Pediatric Gastroenterology and Nutrition, 57, 389-393, 2013	No placebo control group arm.
Xinias,I., Spiroglou,K., Demertzidou,V., Karatza,E., Panteliadis,C., An antiregurgitation milk formula in the management of infants with mild to moderate gastroesophageal reflux, Current Therapeutic Research - Clinical and Experimental, 64, 270-278, 2003	Non-randomised study

H.6 How effective are antacids compared to placebo in alleviating symptoms of GORD, GOR or other GORD related symptoms (e.g. heartburn in older children)?

6. How effective are antacids compared to placebo in alleviating symptoms of GORD, GOR or other GORD related symptoms (e.g. heartburn in older children)?

Study	Reason for Exclusion
Atasay,B., Erdeve,O., Arsan,S., Turmen,T., Effect of sodium alginate on acid gastroesophageal reflux disease in preterm infants: a pilot study, Journal of Clinical Pharmacology, 50, 1267-1272, 2010	Not an RCT
Corvaglia,L., Aceti,A., Mariani,E., De,Giorgi M., Capretti,M.G., Faldella,G., The efficacy of sodium alginate (Gaviscon) for the treatment of gastro-oesophageal reflux in preterm infants, Alimentary Pharmacology and Therapeutics, 33, 466-470, 2011	Not an RCT
Del,Buono R., Ball,G., Thomson,M., The influence of gaviscon infant on gastro-esophageal reflux in infants, Journal of Pediatric Gastroenterology and Nutrition, 35, 441-442, 2002	Abstract of a study published later
Gottlieb,S., Brown,R., Ciccone,P.E., Therapeutic management of gastrointestinal complaints in children including preliminary experience with a new pediatric antacid preparation, American Journal of Therapeutics, 3, 414-418, 1996	Not an RCT (and no data of interest to this review question)
Loots,C.M., Smits,M.J., Wijnakker,R., van,WijkM, Davidson,G., Benninga,M.A., Omari,T.I., Esophageal impedance baselines in infants before and after placebo, antacid and proton pump inhibitor therapy, Journal of Pediatric Gastroenterology and Nutrition, 53, S68-, 2011	Conference abstract

Mandel,K.G., Daggy,B.P., Brodie,D.A., Jacoby,H.I., Review article: alginate-raft formulations in the treatment of heartburn and acid reflux. [106 refs], Alimentary Pharmacology and Therapeutics, 14, 669-690, 2000	Review article: individual studies checked for inclusion
Sweis,R., Kaufman,E., Anggiansah,A., Wong,T., Dettmar,P., Fried,M., Schwizer,W., Avvari,R.K., Pal,A., Fox,M., Post-prandial reflux suppression by a raft-forming alginate (Gaviscon Advance) compared to a simple antacid documented by magnetic resonance imaging and pH-impedance monitoring: Mechanistic assessment in healthy volunteers and randomised, controlled, double-blind study in reflux patients, Alimentary Pharmacology and Therapeutics, 37, 1093-1102, 2013	Comparator is not placebo. This study compares a raft-forming alginate (Gaviscon Advance) against a nonraft-forming antacid.
Weldon,A.P., Robinson,M.J., Trial of gaviscon in the treatment of gastro-oesophageal reflux of infancy, Australian Paediatric Journal, 8, 279-281, 1972	Not an RCT

H.7 Effectiveness of medical management (H2RAs, PPIs and prokinetics) in GOR/D

8. Effectiveness of medical management (H2RAs, PPIs and prokinetics) in GOR/D	
Study	Reason for Exclusion
Baker,R., Tsou,V.M., Tung,J., Baker,S.S., Li,H., Wang,W., Rath,N., Maguire,M.K., Comer,G.M., Clinical results from a randomized, double-blind, dose-ranging study of pantoprazole in children aged 1 through 5 years with symptomatic histologic or erosive esophagitis, Clinical Pediatrics, 49, 852-865, 2010	Dose ranging study; no placebo or no treatment arm.
Bishop,P.R., Soffer,E.F., Comer,G.M., Bishop,P., Blumer,J., Colletti,R., Elitsur,Y., Gremse,D., Gunasekaran,T., Gupta,S., Hammo,A.H., Pohl,J.F., Tolia,V., Tsou,V.M., Winter,H., Multicenter, randomized, double-blind study comparing 10, 20 and 40 mg pantoprazole in children (5-11 years) with symptomatic gastroesophageal reflux disease, Journal of Pediatric Gastroenterology and Nutrition, 42, 384-391, 2006	Dose ranging study; no placebo or no treatment arm
Cucchiara,S., Minella,R., Iervolino,C., Franco,M.T., Campanozzi,A., Franceschi,M., D'Armiento,F., Auricchio,S., Omeprazole and high dose ranitidine in the treatment of refractory reflux oesophagitis, Archives of Disease in Childhood, 69, 655-659, 1993	Included in a separate review of this comparison
Cucchiara,S., Staiano,A., Romaniello,G., Capobianco,S., Auricchio,S., Antacids and cimetidine treatment for gastro-oesophageal reflux and peptic oesophagitis, Archives of Disease in Childhood, 59, 842-847, 1984	Not a comparison specified by the GDG

De,Loore,I, Van,Ravensteyn H., Ameryckx,L., Domperidone drops in the symptomatic treatment of chronic paediatric vomiting and regurgitation. A comparison with metoclopramide, Postgraduate Medical Journal, 55 Suppl 1, 40-42, 1979	Children not defined as having GOR/D
Forbes,D., Hodgson,M., Hill,R., The effects of gaviscon and metoclopramide in gastroesophageal reflux in children, Journal of Pediatric Gastroenterology and Nutrition, 5, 556-559, 1986	Not a comparison specified by the GDG
Gilger,M.A., Tolia,V., Vandenplas,Y., Youssef,N.N., Traxler,B., Illueca,M., Safety and tolerability of esomeprazole in children with gastroesophageal reflux disease, Journal of Pediatric Gastroenterology and Nutrition, 46, 524-533, 2008	Dose response study; no placebo or no treatment arm
Gunasekaran,T., Gupta,S., Gremse,D., Karol,M., Pan,W.J., Chiu,Y.L., Keith,R., Fitzgerald,J., Lansoprazole in adolescents with gastroesophageal reflux disease: pharmacokinetics, pharmacodynamics, symptom relief efficacy, and tolerability, Journal of Pediatric Gastroenterology and Nutrition, 35 Suppl 4, S327-S335, 2002	Dose ranging study
Gunasekaran,T., Tolia,V., Colletti,R.B., Gold,B.D., Traxler,B., Illueca,M., Crawley,J.A., Effects of esomeprazole treatment for gastroesophageal reflux disease on quality of life in 12- to 17-year-old adolescents: an international health outcomes study, BMC Gastroenterology, 9, 84-, 2009	Dose response study; no placebo or no treatment arm.
Gupta,S.K., Tolia,V., Heyman,M.B., Kane III,R.E., Chiu,Y.-L., Pan,W.J., Huang,B., Pilmer,B., Hassall,E., Adolescent patients with gastroesophageal reflux disease: results from a randomized trial of lansoprazole, Journal of Pediatric Gastroenterology and Nutrition, 31, S97-S98, 2000	Conference abstract - liable to change in final publication.

Haddad,I., Kierkus,J., Tron,E., Ulmer,A., Hu,P., Sloan,S., Silber,S., Leitz,G., Efficacy and safety of rabeprazole in children (1-11 years) with gastroesophageal reflux disease, Journal of Pediatric Gastroenterology and Nutrition, 57, 798-807, 2013	Does response study; no placebo data reported.
Hibbs,A.M., Lorch,S.A., Metoclopramide for the treatment of gastroesophageal reflux disease in infants: a systematic review. [34 refs], Pediatrics, 118, 746-752, 2006	Descriptive review; references used in NCC review
Iacono,G., Carroccio,A., Cavataio,F., Montalto,G., Bragion,E., Lorello,D., Balsamo,V., Notarbartolo,A., Severe gastroesophageal reflux in children: Effectiveness of different combinations of drugs, CURR.THER.RES.CLIN.EXP, 50, 474-481, 1991	Combination therapies not specified by GDG
Illueca,M., Wernersson,B., Henderson,C., Lundborg,P., Maintenance treatment with proton pump inhibitors for reflux esophagitis in pediatric patients: a systematic literature analysis, Journal of Pediatric Gastroenterology and Nutrition, 51, 733-740, 2010	Long-term management of GORD.
Jordan,B., Heine,R.G., Meehan,M., Catto-Smith,A.G., Lubitz,L., Effect of antireflux medication, placebo and infant mental health intervention on persistent crying: A randomized clinical trial, Journal of Paediatrics and Child Health, 42, 49-58, 2006	Combination therapy not specified by the GDG; group not defined as having GOR/D
Khoshoo,V., Dhume,P., Clinical response to 2 dosing regimens of lansoprazole in infants with gastroesophageal reflux, Journal of Pediatric Gastroenterology and Nutrition, 46, 352-354, 2008	Dose response study
Lambert,J., Mobassaleh,M., Grand,R.J., Efficacy of cimetidine for gastric acid suppression in pediatric patients, Journal of Pediatrics, 120, 474-478, 1992	Dosage study and mixed patient population including children with pulmonary problems.

Machida,H.M., Forbes,D.A., Gall,D.G., Scott,R.B., Metoclopramide in gastroesophageal reflux of infancy, Journal of Pediatrics, 112, 483-487, 1988	Only 8 children randomised. Authors stated no meaningful comparison could be made.
Monzani,A., Oderda,G., Delayed-release oral suspension of omeprazole for the treatment of erosive esophagitis and gastroesophageal reflux disease in pediatric patients: a review, Clinical and Experimental Gastroenterology, 3, 17-25, 2010	Descriptive review. References used in NCC review.
Omari,T., Davidson,G., Bondarov,P., Naucler,E., Nilsson,C., Lundborg,P., Pharmacokinetics and acid-suppressive effects of esomeprazole in infants 1-24 months old with symptoms of gastroesophageal reflux disease, Journal of Pediatric Gastroenterology and Nutrition, 45, 530-537, 2007	Dosage study
Orenstein,S.R., Gremse,D.A., Pantaleon,C.D., Kling,D.F., Rotenberg,K.S., Nizatidine for the treatment of pediatric gastroesophageal reflux symptoms: an open-label, multiple-dose, randomized, multicenter clinical trial in 210 children, Clinical Therapeutics, 27, 472-483, 2005	Dose response study; no placebo or no treatment arm
Orenstein,S.R., McGowan,J.D., Efficacy of conservative therapy as taught in the primary care setting for symptoms suggesting infant gastroesophageal reflux, Journal of Pediatrics, 152, 310-314, 2008	No intervention of interest examined
Orenstein,S.R., Shalaby,T.M., Devandry,S.N., Liacouras,C.A., Czinn,S.J., Dice,J.E., Simon,T.J., Ahrens,S.P., Stauffer,L.A., Famotidine for infant gastro-oesophageal reflux: A multi-centre, randomized, placebo-controlled, withdrawal trial, Alimentary Pharmacology and Therapeutics, 17, 1097-1107, 2003	Less than 5 children per arm of trial so no meaningful analysis could be undertaken

Orenstein,S.R., Shalaby,T.M., Kosmack,S.N., Liacouras,C., Czinn,S.J., Dice,J.E., Simon,T.J., Ahrens,S.P., Jiang,K., Famotidine for infantile gastroesophageal reflux disease (GERD) Part II: A randomized 4-week double-blind, placebo-controlled withdrawal trial of 2 doses, Journal of Pediatric Gastroenterology and Nutrition, 33, 416-425, 2001	Less than 5 infants per arm of trial and 40% dropout rate.
Pritchard,D.S., Baber,N., Stephenson,T., Should domperidone be used for the treatment of gastro-oesophageal reflux in children? Systematic review of randomized controlled trials in children aged 1 month to 11 years old. [14 refs], British Journal of Clinical Pharmacology, 59, 725-729, 2005	Descriptive review; references from review used in the NCC review.
Tolia,V., Esomeprazole use in pediatrics, Pediatric Health, 2, 687-696, 2008	Descriptive review only
Tolia,V., Ferry,G., Gunasekaran,T., Huang,B., Keith,R., Book,L., Efficacy of lansoprazole in the treatment of gastroesophageal reflux disease in children, Journal of Pediatric Gastroenterology and Nutrition, 35, S308-S318, 2002	Non-randomised, non-comparative study
Tolia,V., Gilger,M.A., Barker,P.N., Illueca,M., Healing of erosive esophagitis and improvement of symptoms of gastroesophageal reflux disease after esomeprazole treatment in children 12 to 36 months old, Journal of Pediatric Gastroenterology and Nutrition, 51, 593-598, 2010	Does ranging study; no placebo or no treatment arm.
Tolia,V., Kuhns,L.R., Calhoun,J.A., Kauffman,R.E., Randomized prospective double-blind study of metoclopramide (MCP) and placebo for gastroesophageal reflux (GER) in infants, Pediatric Research, Vol.23, pp.264A, 1988., -, -32676	Conference abstract - liable to change in final publication.

Tolia,V., Youssef,N.N., Gilger,M.A., Traxler,B., Illueca,M., Esomeprazole for the treatment of erosive esophagitis in children: An international, multicenter, randomized, parallel-group, double-blind (for dose) study, BMC Pediatrics, 10 , 2010. Article Number, -, 2010	Dose response study based on weight.
Tsou,V.M., Baker,R., Book,L., Hammo,A.H., Soffer,E.F., Wang,W., Comer,G.M., Study Group., Multicenter, randomized, double-blind study comparing 20 and 40 mg of pantoprazole for symptom relief in adolescents (12 to 16 years of age) with gastroesophageal reflux disease (GERD), Clinical Pediatrics, 45, 741-749, 2006	Does ranging study; no placebo or no treatment arm.
van der Pol,R.J., Smits,M.J., van Wijk,M.P., Omari,T.I., Tabbers,M.M., Benninga,M.A., Efficacy of proton-pump inhibitors in children with gastroesophageal reflux disease: a systematic review, Pediatrics, 127, 925-935, 2011	Narrative review. Included studies have been included in NCC review, if appropriate.
Winter,H., Kum-Nji,P., Mahomedy,S.H., Kierkus,J., Hinz,M., Li,H., Maguire,M.K., Comer,G.M., Efficacy and safety of pantoprazole delayed-release granules for oral suspension in a placebo-controlled treatment-withdrawal study in infants 1-11 months old with symptomatic GERD, Journal of Pediatric Gastroenterology and Nutrition, 50, 609-618, 2010	Placebo only effect cannot be determined using the data presented.
Winter,H.S., Gunasekaran,T.S., Tolia,V., Gottrand,F., Barker,P.N., Illueca,M., Esomeprazole for the treatment of gastroesophageal reflux disease (GERD) in infants, Gastroenterology, 136, A504-, 2009	Conference abstract - liable to be biased or incomplete

H.8 How effective is fundoplication surgery in the treatment of GOR/D?

9. How effective is fundoplication surgery in the treatment of GOR/D? ALL STUDY TYPES	
Study	Reason for Exclusion
Barsness,K.A., Feliz,A., Potoka,D.A., Gaines,B.A., Upperman,J.S., Kane,T.D., Laparoscopic versus open Nissen fundoplication in infants after neonatal laparotomy, Journal of the Society of Laparoendoscopic Surgeons, 11, 461-465, 2007	Retrospective review, confounding was not addressed.
Bergmeijer,J.H., Hazebroek,F.W., Prospective medical and surgical treatment of gastroesophageal reflux in esophageal atresia, Journal of the American College of Surgeons, 187, 153-157, 1998	No comparison was made
Blewett,C.J., Hollenbeak,C.S., Cilley,R.E., Dillon,P.W., Economic implications of current surgical management of gastroesophageal reflux disease, Journal of Pediatric Surgery, 37, 427-430, 2002	Study outcomes not of interest.
Broeders,J.A., Draaisma,W.A., Rijnhart-de Jong,H.G., Smout,A.J., van Lanschot,J.J., Broeders,I.A., Gooszen,H.G., Impact of surgeon experience on 5-year outcome of laparoscopic Nissen fundoplication, Archives of Surgery, 146, 340-346, 2011	Study on Adults
Broeders,J.A., Rijnhart-de Jong,H.G., Draaisma,W.A., Bredenoord,A.J., Smout,A.J., Gooszen,H.G., Ten-year outcome of laparoscopic and conventional nissen fundoplication: randomized clinical trial, Annals of Surgery, 250, 698-706, 2009	Study on adults
Broeders,J.A., Roks,D.J., Jamieson,G.G., Devitt,P.G., Baigrie,R.J., Watson,D.I., Five-year outcome after laparoscopic anterior partial versus Nissen fundoplication: four randomized trials, Annals of Surgery, 255, 637-642, 2012	Study on adults

Bufo,A.J., Chen,M.K., Lobe,T.E., Shah,R.S., Gross,E., Hixson,S.D., Hollabaugh,R.S., Schropp,K.P., Laparoscopic fundoplication in children: A superior technique, Pediatric Endosurgery and Innovative Techniques, 1, 71-76, 1997	confounding not addressed.
Cheung,K.M., Tse,H.W., Tse,P.W., Chan,K.H., Nissen fundoplication and gastrostomy in severely neurologically impaired children with gastroesophageal reflux, Hong Kong Medical Journal, 12, 282-288, 2006	prospective study, confounding not addressed.
Ciovica,R., Gadenstatter,M., Klingler,A., Lechner,W., Riedl,O., Schwab,G.P., Quality of life in GERD patients: medical treatment versus antireflux surgery, Journal of Gastrointestinal Surgery, 10, 934-939, 2006	Study on adults.
Esposito,C., Garipoli,V., De,Pasquale M., Russo,S., Palazzo,G., Cucchiara,S., Laparoscopic versus traditional fundoplication in the treatment of children with refractory gastro-oesophageal reflux, Italian Journal of Gastroenterology and Hepatology, 29, 399-402, 1997	Retrospective study, confounding not addressed.
Fonkalsrud,E.W., Ashcraft,K.W., Coran,A.G., Ellis,D.G., Grosfeld,J.L., Tunell,W.P., Weber,T.R., Surgical treatment of gastroesophageal reflux in children: a combined hospital study of 7467 patients, Pediatrics, 101, 419-422, 1998	No comparison between ONF and LNF was made.
Iglesias,J.L., Meier,D.E., Thompson,W.R., Cost analysis of laparoscopic and open fundoplication in children, Pediatric Endosurgery and Innovative Techniques, 1, 15-21, 1997	Retrospective study, confounding not addressed.
International Pediatric Endosurgery Group (, IPEG guidelines for the surgical treatment of pediatric gastroesophageal reflux disease (GERD), Journal of Laparoendoscopic and Advanced Surgical Techniques, Part A. 19 Suppl 1, x-xiii, 2009	Discussion paper

Kane,T.D., Brown,M.F., Chen,M.K., Members of the APSA New Technology Committee., Position paper on laparoscopic antireflux operations in infants and children for gastroesophageal reflux disease. American Pediatric Surgery Association, Journal of Pediatric Surgery, 44, 1034-1040, 2009	Discussion paper
Kauer,W.K., Peters,J.H., DeMeester,T.R., Heimbucher,J., Ireland,A.P., Bremner,C.G., A tailored approach to antireflux surgery, Journal of Thoracic and Cardiovascular Surgery, 110, 141-146, 1995	Study on adults.
Kazerooni,N.L., VanCamp,J., Hirschl,R.B., Drongowski,R.A., Coran,A.G., Fundoplication in 160 children under 2 years of age, Journal of Pediatric Surgery, 29, 677-681, 1994	Open fundoplication versus open fundoplication, just different techniques, wrong comparator.
Knatten,C.K., Hviid,C.H., Pripp,A.H., Emblem,R., Bjornland,K., Inflammatory response after open and laparoscopic Nissen fundoplication in children: a randomized study, Pediatric Surgery International, 30, 11-17, 2014	All outcomes examined were inflammatory markers.
Mattioli,G., Repetto,P., Carlini,C., Torre,M., Pini,Prato A., Mazzola,C., Leggio,S., Montobbio,G., Gandullia,P., Barabino,A., Cagnazzo,A., Sacco,O., Jasonni,V., Laparoscopic vs open approach for the treatment of gastroesophageal reflux in children.[Erratum appears in Surg Endosc 2002 Sep;16(9):1381 Note: PiniPrato A [corrected to Pini Prato A]], Surgical Endoscopy, 16, 750-752, 2002	Confounding not addressed.
Mauritz,F.A., van Herwaarden-Lindeboom,M.Y., Stomp,W., Zwaveling,S., Fischer,K., Houwen,R.H., Siersema,P.D., van,der Zee,D.C., The effects and efficacy of antireflux surgery in children with gastroesophageal reflux disease: a systematic review, Journal of Gastrointestinal Surgery, 15, 1872-1878, 2011	Systematic review.

Mousa,H., Caniano,D.A., Alhajj,M., Gibson,L., Di,Lorenzo C., Binkowitz,L., Effect of Nissen fundoplication on gastric motor and sensory functions, Journal of Pediatric Gastroenterology and Nutrition, 43, 185-189, 2006	No comparison was made between intervention groups.
Peters,J.H., Heimbucher,J., Kauer,W.K., Incarbone,R., Bremner,C.G., DeMeester,T.R., Clinical and physiologic comparison of laparoscopic and open Nissen fundoplication, Journal of the American College of Surgeons, 180, 385-393, 1995	Study on adults.
Powers,C.J., Levitt,M.A., Tantoco,J., Rossman,J., Sarpel,U., Brisseau,G., Caty,M.G., Glick,P.L., The respiratory advantage of laparoscopic Nissen fundoplication, Journal of Pediatric Surgery, 38, 886-891, 2003	Confounding not addressed.
Rhee,D., Zhang,Y., Chang,D.C., Arnold,M.A., Salazar-Osuna,J.H., Chrouser,K., Colombani,P.M., Abdullah,F., Population-based comparison of open vs laparoscopic esophagogastric fundoplication in children: application of the Agency for Healthcare Research and Quality pediatric quality indicators, Journal of Pediatric Surgery, 46, 648-654, 2011	Confounding not addressed.
Siddiqui,M.R., Abdulaal,Y., Nisar,A., Ali,H., Hasan,F., A meta-analysis of outcomes after open and laparoscopic Nissen's fundoplication for gastro-oesophageal reflux disease in children, Pediatric Surgery International, 27, 359-366, 2011	Systematic review.
Somme,S., Rodriguez,J.A., Kirsch,D.G., Liu,D.C., Laparoscopic versus open fundoplication in infants, Surgical Endoscopy, 16, 54-56, 2002	Confounding not addressed.
Stanton,M., Andrews,J., Grant,H., Adhesional small bowel obstruction following anti-reflux surgery in children--comparison of 232 laparoscopic and open fundoplications, European Journal of Pediatric Surgery, 20, 11-13, 2010	GERD/GORD was not mentioned as a reason for surgery nor an outcome measure.

Szold,A., Udassin,R., Maayan,C., Vromen,A., Seror,D., Zamir,O., Laparoscopic-modified Nissen fundoplication in children with familial dysautonomia, Journal of Pediatric Surgery, 31, 1560-1562, 1996	Additional surgical procedure in one arm of the study.
Tannuri,A.C., Tannuri,U., Mathias,A.L., Velhote,M.C., Romao,R.L., Goncalves,M.E., Cardoso,S., Gastroesophageal reflux disease in children: efficacy of Nissen fundoplication in treating digestive and respiratory symptoms. Experience of a single center, Diseases of the Esophagus, 21, 746-750, 2008	Confounding not addressed.
Thatch,K.A., Yoo,E.Y., Arthur,L.G.,III, Finck,C., Katz,D., Moront,M., Prasad,R., Vinocur,C., Schwartz,M.Z., A comparison of laparoscopic and open Nissen fundoplication and gastrostomy placement in the neonatal intensive care unit population. [23 refs], Journal of Pediatric Surgery, 45, 346-349, 2010	Confounding not addressed.
Tovar,J.A., Luis,A.L., Encinas,J.L., Burgos,L., Pederiva,F., Martinez,L., Olivares,P., Pediatric surgeons and gastroesophageal reflux, Journal of Pediatric Surgery, 42, 277-283, 2007	Confounding not addressed.

H.9 How effective is enteral tube feeding in the management of GORD?

10. How effective is enteral tube feeding in the management of GORD?

Study	Reason for Exclusion
Akinci,D., Ciftci,T.T., Kaya,D., Ozmen,M.N., Akhan,O., Long-term results of percutaneous radiologic gastrostomy and gastrojejunostomy in children with emphasis on technique: single or double gastropexy?, AJR, American Journal of Roentgenology. 195, 1231-1237, 2010	Non-comparative
Albanese,C.T., Towbin,R.B., Ulman,I., Lewis,J., Smith,S.D., Percutaneous gastrojejunostomy versus Nissen fundoplication for enteral feeding of the neurologically impaired child with gastroesophageal reflux, Journal of Pediatrics, 123, 371-375, 1993	No case-mix adjustment for outcomes. No GORD outcomes reported. Paper is based on data that is 20 years old. Single institution finding. No a comparison outlined by the GDG.
Al-Zubeidi,D., Demir,H., Bishop,W.P., Rahhal,R.M., Gastrojejunal feeding tube use by gastroenterologists in a pediatric academic center, Journal of Pediatric Gastroenterology and Nutrition, 56, 523-527, 2013	Non-comparative
Avitsland,T.L., Birketvedt,K., Bjornland,K., Emblem,R., Parent-reported effects of gastrostomy tube placement, Nutrition in Clinical Practice, 28, 493-498, 2013	Non-comparative
Avitsland,T.L., Kristensen,C., Emblem,R., Veenstra,M., Mala,T., Bjornland,K., Percutaneous endoscopic gastrostomy in children: a safe technique with major symptom relief and high parental satisfaction, Journal of Pediatric Gastroenterology and Nutrition, 43, 624-628, 2006	Non-comparative
Barber,N., Carden,C.A., Mahomed,A.A., Does the placement of a FRECA gastrostomy at the time of laparoscopic fundoplication impact on outcome?, Surgical Endoscopy and Other Interventional Techniques, 23, 598-601, 2009	Non-comparative

Barnhart,D.C., Hall,M., Mahant,S., Goldin,A.B., Berry,J.G., Faix,R.G., Dean,J.M., Srivastava,R., Effectiveness of fundoplication at the time of gastrostomy in infants with neurological impairment, JAMA Pediatrics, 167, 911-918, 2013	Examines feeding tube as a cause of GORD.
Berezin,S., Schwarz,S.M., Halata,M.S., Newman,L.J., Gastroesophageal reflux secondary to gastrostomy tube placement, American Journal of Diseases of Children, 140, 699-701, 1986	Non-comparative and 5 children
Black,T.L., Fernandes,E.T., Ellis,D.G., Hollabaugh,R.S., Hixson,S.D., Mann,C.M., Miller,J.P., Wrenn E Jr., The effect of tube gastrostomy on gastroesophageal reflux in patients with esophageal atresia, Journal of Pediatric Surgery, 26, 168-170, 1991	Does feeding tube cause GORD
Borowitz,S.M., Sutphen,J.L., Hutcheson,R.L., Percutaneous endoscopic gastrostomy without an antireflux procedure in neurologically disabled children, Clinical Pediatrics, 36, 25-29, 1997	Non-comparative
Brant,C.Q., Stanich,P., Ferrari,A.P.,Jr., Improvement of children's nutritional status after enteral feeding by PEG: an interim report, Gastrointestinal Endoscopy, 50, 183-188, 1999	Non-comparative
Burd,R.S., Price,M.R., Whalen,T.V., The role of protective antireflux procedures in neurologically impaired children: a decision analysis, Journal of Pediatric Surgery, 37, 500-506, 2002	Decision analysis. No data comparative data presented.
Cameron,B.H., Blair,G.K., Murphy,J.J.,III, Fraser,G.C., Morbidity in neurologically impaired children after percutaneous endoscopic versus Stamm gastrostomy, Gastrointestinal Endoscopy, 42, 41-44, 1995	Non-comparative

Catto-Smith,A.G., Jimenez,S., Morbidity and mortality after percutaneous endoscopic gastrostomy in children with neurological disability, Journal of Gastroenterology and Hepatology, 21, 734-738, 2006	Non-comparative
Cheung,K.M., Tse,H.W., Tse,P.W., Chan,K.H., Nissen fundoplication and gastrostomy in severely neurologically impaired children with gastroesophageal reflux, Hong Kong Medical Journal, 12, 282-288, 2006	No case-mix adjustment undertaken. Small sample size of 20. Single institution findings. No a comparison outlined by the GDG.
Conway,Steven, Morton,Alison, Wolfe,Susan, Enteral tube feeding for cystic fibrosis, Cochrane Database of Systematic Reviews, -, 2012	No RCTs identified. No information on GRD available.
Craig,G.M., Carr,L.J., Cass,H., Hastings,R.P., Lawson,M., Reilly,S., Ryan,M., Townsend,J., Spitz,L., Medical, surgical, and health outcomes of gastrostomy feeding, Developmental Medicine and Child Neurology, 48, 353-360, 2006	Prospective non-comparative case-series. Does not report on GORD.
Esposito,C., Settimi,A., Centonze,A., Capano,G., Ascione,G., Laparoscopic-assisted jejunostomy: an effective procedure for the treatment of neurologically impaired children with feeding problems and gastroesophageal reflux, Surgical Endoscopy, 19, 501-504, 2005	Non-comparative
Fonkalsrud,E.W., Surgical treatment of the gastroesophageal reflux syndrome in childhood, Zeitschrift fur Kinderchirurgie, 42, 7-11, 1987	Non-comparative
Fortunate,J.E., Darbari,A., Mitchell,S.E., Thompson,R.E., Cuffari,C., The limitations of Gastro-Jejunal (G-J) feeding tubes in children: A 9-year pediatric hospital database analysis, American Journal of Gastroenterology, 100, 186-189, 2005	Non-comparative

Fortunato,J.E., Troy,A.L., Cuffari,C., Davis,J.E., Loza,M.J., Oliva-Hemker,M., Schwarz,K.B., Outcome after percutaneous endoscopic gastrostomy in children and young adults, Journal of Pediatric Gastroenterology and Nutrition, 50, 390-393, 2010	Non-comparative cohort study. Reflux not assessed as a cause or an outcome. Mainly failure to thrive.
Friedman,J.N., Ahmed,S., Connolly,B., Chait,P., Mahant,S., Complications associated with image-guided gastrostomy and gastrojejunostomy tubes in children, Pediatrics, 114, 458-461, 2004	Non-comparative
Gantasala,Sapthagiri, Sullivan,Peter B., Thomas,Adrian G., Gastrostomy feeding versus oral feeding alone for children with cerebral palsy, Cochrane Database of Systematic Reviews, -, 2013	No RCTs identified and no information of GORD.
Godbole,P., Margabanthu,G., Crabbe,D.C., Thomas,A., Puntis,J.W., Abel,G., Arthur,R.J., Stringer,M.D., Limitations and uses of gastrojejunal feeding tubes, Archives of Disease in Childhood, 86, 134-137, 2002	Non-comparative case series
Hament,J.M., Bax,N.M., van,der Zee,D.C., De Schryver,J.E., Nesselaar,C., Complications of percutaneous endoscopic gastrostomy with or without concomitant antireflux surgery in 96 children, Journal of Pediatric Surgery, 36, 1412-1415, 2001	Feeding tube and fundoplication
Heloury,Y., Plattner,V., Mirallie,E., Gerard,P., Lejus,C., Laparoscopic nissen fundoplication with simultaneous percutaneous endoscopic gastrostomy in children, Surgical Endoscopy, 10, 837-841, 1996	Non-comparative
Horn,D., Chaboyer,W., Gastric feeding in critically ill children: a randomized controlled trial, American journal of critical care : an official publication, American Association of Critical-Care Nurses, 12, 461-468, 2003	Type of feeding strategy. Too specific.

Isch,J.A., Rescorla,F.J., Scherer,L.R.,III, West,K.W., Grosfeld,J.L., The development of gastroesophageal reflux after percutaneous endoscopic gastrostomy, Journal of Pediatric Surgery, 32, 321-322, 1997	Developing GERD after surgery
Jawadi,A.H., Casamassimo,P.S., Griffen,A., Enrile,B., Marcone,M., Comparison of oral findings in special needs children with and without gastrostomy, Pediatric Dentistry, 26, 283-288, 2004	Not outcomes of interest
Jones,V.S., La Hei,E.R., Shun,A., Laparoscopic gastrostomy: the preferred method of gastrostomy in children, Pediatric Surgery International, 23, 1085-1089, 2007	Non-comparative
Kawahara,H., Mitani,Y., Nose,K., Nakai,H., Yoneda,A., Kubota,A., Fukuzawa,M., Should fundoplication be added at the time of gastrostomy placement in patients who are neurologically impaired?, Journal of Pediatric Surgery, 45, 2373-2376, 2010	Non-comparative
Khattak,I.U., Kimber,C., Kiely,E.M., Spitz,L., Percutaneous endoscopic gastrostomy in paediatric practice: complications and outcome, Journal of Pediatric Surgery, 33, 67-72, 1998	Non-comparative
Kiely,E., Spitz,L., Is routine gastrostomy necessary in the management of oesophageal atresia?, Pediatric Surgery International, 2, 6-9, 1987	Non-comparative
Langer,J.C., Wesson,D.E., Ein,S.H., Filler,R.M., Shandling,B., Superina,R.A., Papa,M., Feeding gastrostomy in neurologically impaired children: is an antireflux procedure necessary?, Journal of Pediatric Gastroenterology and Nutrition, 7, 837-841, 1988	Non-comparative
Lewis,D., Khoshoo,V., Pencharz,P.B., Golladay,E.S., Impact of nutritional rehabilitation on gastroesophageal reflux in neurologically impaired children, Journal of Pediatric Surgery, 29, 167-169, 1994	Case-series including 10 or fewer.

Lewis,E.C., Connolly,B., Temple,M., John,P., Chait,P.G., Vaughan,J., Amaral,J.G., Growth outcomes and complications after radiologic gastrostomy in 120 children, Pediatric Radiology, 38, 963-970, 2008	Non-comparative
Lintula,H., Antila,P., Kokki,H., Laparoscopic fundoplication in children with a preexisting gastrostomy, Journal of Laparoendoscopic and Advanced Surgical Techniques, Part A. 13, 381-385, 2003	Non-comparative
Lintula,H., Kokki,H., Juvonen,P., Hamynen,I., Heikkinen,M., Eskelinen,M., Severe gastro-oesophageal reflux necessitating fundoplication after percutaneous endoscopic and open gastrostomy in children, Langenbeck's Archives of Surgery, 398, 703-707, 2013	Feeding tube as a cause of GORD rather than a treatment for it.
Mahant,S., Friedman,J.N., Connolly,B., Goia,C., Macarthur,C., Tube feeding and quality of life in children with severe neurological impairment, Archives of Disease in Childhood, 94, 668-673, 2009	Failure to thrive the main reason for intervention. Unclear if this is due to GORD or poor feeding.
Mathus-Vliegen,E.M., Koning,H., Taminiau,J.A., Moorman-Voestermans,C.G., Percutaneous endoscopic gastrostomy and gastrojejunostomy in psychomotor retarded subjects: a follow-up covering 106 patient years, Journal of Pediatric Gastroenterology and Nutrition, 33, 488-494, 2001	Non-comparative
Mathus-Vliegen,L.M., Koning,H., Percutaneous endoscopic gastrostomy and gastrojejunostomy: a critical reappraisal of patient selection, tube function and the feasibility of nutritional support during extended follow-up, Gastrointestinal Endoscopy, 50, 746-754, 1999	Non-comparative

McGuire,W., McEwan,P., Systematic review of transpyloric versus gastric tube feeding for preterm infants, Archives of Disease in Childhood: Fetal and Neonatal Edition, 89, F245-F248, 2004	Summary of Cochrane review. A more recent update is available.
McGuire,W., McEwan,P., Transpyloric versus gastric tube feeding for preterm infants, Cochrane Database of Systematic Reviews, 2007. Article Number, -, 2007	Summary of Cochrane review.
Meert,K.L., Daphtary,K.M., Metheny,N.A., Gastric vs small-bowel feeding in critically ill children receiving mechanical ventilation: a randomized controlled trial, Chest, 126, 872-878, 2004	Not a GORD group
Misra,S., Macwan,K., Albert,V., Transpyloric feeding in gastroesophageal-reflux-associated apnea in premature infants, Acta Paediatrica, International Journal of Paediatrics, 96, 1426-1429, 2007	GORD as a cause of apnoea
Morgan,Angela T., Dodrill,Pamela, Ward,Elizabeth C., Interventions for oropharyngeal dysphagia in children with neurological impairment, Cochrane Database of Systematic Reviews, -, 2012	Not a condition of interest.
Nah,S.A., Narayanaswamy,B., Eaton,S., Coppi,P.D., Kiely,E.M., Curry,J.I., Drake,D.P., Barnacle,A.M., Roebuck,D.J., Pierro,A., Gastrostomy insertion in children: percutaneous endoscopic or percutaneous image-guided?, Journal of Pediatric Surgery, 45, 1153-1158, 2010	Mixed patient population, with GORD examined as an adverse event.
Noble,L.J., Dalzell,A.M., El-Matary,W., The relationship between percutaneous endoscopic gastrostomy and gastro-oesophageal reflux disease in children: a systematic review, Surgical Endoscopy, 26, 2504-2512, 2012	Only includes non-comparative case-series.

Noviski,N., Yehuda,Y.B., Serour,F., Gorenstein,A., Mandelberg,A., Does the size of nasogastric tubes affect gastroesophageal reflux in children?, Journal of Pediatric Gastroenterology and Nutrition, 29, 448-451, 1999	Specific issue
Novotny,N.M., Jester,A.L., Ladd,A.P., Preoperative prediction of need for fundoplication before gastrostomy tube placement in children, Journal of Pediatric Surgery, 44, 173-176, 2009	Feeding tube as a cause of GORD
Park,J.H., Rhie,S., Jeong,S.J., Percutaneous endoscopic gastrostomy in children, Korean Journal of Pediatrics, 54, 17-21, 2011	Non-comparative
Peters,R.T., Balduyck,B., Nour,S., Gastrostomy complications in infants and children: a comparative study, Pediatric Surgery International, 26, 707-709, 2010	Non-comparative
Plantin,I., Arnbjornsson,E., Larsson,L.T., No increase in gastroesophageal reflux after laparoscopic gastrostomy in children, Pediatric Surgery International, 22, 581-584, 2006	Non-comparative and assessing if causes GORD
Ponsky,T.A., Gasior,A.C., Parry,J., Sharp,S.W., Boulanger,S., Parry,R., Ostlie,D.J., St Peter,S.D., Need for subsequent fundoplication after gastrostomy based on patient characteristics, Journal of Surgical Research, 179, 1-4, 2013	Non-comparative need for fundoplication after gastrostomy
Razeghi,S., Lang,T., Behrens,R., Influence of percutaneous endoscopic gastrostomy on gastroesophageal reflux: a prospective study in 68 children, Journal of Pediatric Gastroenterology and Nutrition, 35, 27-30, 2002	Non-comparative
Richards,Robyn, Foster,Jann P., Psaila,Kim, Continuous versus bolus intragastric tube feeding for preterm and low birth weight infants with gastro-oesophageal reflux disease, Cochrane Database of Systematic Reviews, -, 2012	Review protocol only. No review has been undertaken.

Ruangtrakool,R., Ong,T.H., Primary gastrostomy button: a means of long-term enteral feeding in children, Journal of the Medical Association of Thailand, 83, 151-159, 2000	Non-comparative case series
Saavedra,H., Losek,J.D., Shanley,L., Titus,M.O., Gastrostomy tube-related complaints in the pediatric emergency department: identifying opportunities for improvement, Pediatric Emergency Care, 25, 728-732, 2009	Non-comparative case-series
Sjowie,H., Mellberg,M., Arnbjornsson,E., Postoperative complications in children undergoing video-assisted gastrostomy tube placement correlated to their age and diagnosis, Gastroenterology Insights, 4, -, 2012	Non-comparative
Sleigh,G., Brocklehurst,P., Gastrostomy feeding in cerebral palsy: A systematic review, Archives of Disease in Childhood, 89, 534-539, 2004	Descriptive review only.
Srivastava,R., Downey,E.C., O'Gorman,M., Feola,P., Samore,M., Holubkov,R., Mundorff,M., James,B.C., Rosenbaum,P., Young,P.C., Dean,J.M., Impact of fundoplication versus gastrojejunal feeding tubes on mortality and in preventing aspiration pneumonia in young children with neurologic impairment who have gastroesophageal reflux disease, Pediatrics, 123, 338-345, 2009	Focuses on fundoplication to prevent GORD caused by feeding tubes.
Stringel,G., Delgado,M., Guertin,L., Cook,J.D., Maravilla,A., Worthen,H., Gastrostomy and Nissen fundoplication in neurologically impaired children, Journal of Pediatric Surgery, 24, 1044-1048, 1989	Non-comparative case-series combined treatment

Toporowska-Kowalska,E., Gebora-Kowalska,B., Jablonski,J., Fendler,W., Wasowska-Krolikowska,K., Influence of percutaneous endoscopic gastrostomy on gastro-oesophageal reflux evaluated by multiple intraluminal impedance in children with neurological impairment, Developmental Medicine and Child Neurology, 53, 938-943, 2011	Prospective case-series but non-comparative. Examines feeding tube as a cause of GORD.
van der Merwe,W.G., Brown,R.A., Ireland,J.D., Goddard,E., Percutaneous endoscopic gastrostomy in children--a 5-year experience, South African Medical Journal, Suid-Afrikaanse Tydskrif Vir Geneeskunde. 93, 781-785, 2003	Non-comparative case-series
Vervloessem,D., van,Leersum F., Boer,D., Hop,W.C., Escher,J.C., Madern,G.C., de,Ridder L., Bax,K.N., Percutaneous endoscopic gastrostomy (PEG) in children is not a minor procedure: risk factors for major complications, Seminars in Pediatric Surgery, 18, 93-97, 2009	Non-comparative case-series
Wales,P.W., Diamond,I.R., Dutta,S., Muraca,S., Chait,P., Connolly,B., Langer,J.C., Fundoplication and gastrostomy versus image-guided gastrojejunal tube for enteral feeding in neurologically impaired children with gastroesophageal reflux, Journal of Pediatric Surgery, 37, 407-412, 2002	No case-mix adjustment. Based on data that is 20 years old. Single institution findings. No a comparison outlined by the GDG.
Wheatley,M.J., Wesley,J.R., Tkach,D.M., Coran,A.G., Long-term follow-up of brain-damaged children requiring feeding gastrostomy: should an antireflux procedure always be performed?, Journal of Pediatric Surgery, 26, 301-304, 1991	Examines tube feeding as a cause of GORD.
Williams,A.R., Borsellino,A., Sugarman,I.D., Crabbe,D.C., Roux-en-Y feeding jejunostomy in infants and children, European Journal of Pediatric Surgery, 17, 29-33, 2007	Non-comparative

Wilson,G.J.P., van,derZeeD, Bax,N.M.A., Endoscopic gastrostomy placement in the child with gastroesophageal reflux: is concomitant antireflux surgery indicated?, Journal of Pediatric Surgery, 41, 1441-1445, 2006	gastrostomy as a cause of GORD
Yoshida,N.R., Webber,E.M., Gillis,D.A., Giacomantonio,J.M., Roux-en-Y jejunostomy in the pediatric population, Journal of Pediatric Surgery, 31, 791-793, 1996	Specific type of feeding tube

Appendix I: Evidence tables

The evidence tables for this guideline are in a separate document “Gastro-oesophageal reflux disease in children and young people: Appendix I

Appendix J: GRADE tables

The GRADE tables for this guideline are in a separate document “Gastro-oesophageal reflux disease in children and young people: Appendix J ”

Appendix K: Parent information on administration of medicines

K.1 Infant Gaviscon

Breast-fed babies- mix the right amount of powder (as instructed by your doctor or pharmacist) with 5 mL of cooled boiled water to make a smooth paste, then mix in another 10 mL of water. Give this to your baby after the feed, using a syringe or spoon.

Bottle-fed babies - add the right amount of powder (as instructed by your doctor or pharmacist) into the formula feed in the bottle. Shake the bottle well before feeding your baby.

Babies weighing up to 4.5 kg (10 lb) - mix the powder into at least 115 mL of formula feed.

Babies weighing more than 4.5 kg (10 lb) - mix the right amount of powder into at least 225 mL of formula feed.

Any unused milk containing Infant Gaviscon should be thrown away

Infant Gavison should not be used with feed thickeners such as pre-thickened milks or other powders which also thicken the milk

K.2 Ranitidine

Tablets - swallow with a glass of water, milk or juice. Your child should not chew the tablet. Tablets are more suitable for older children.

Dispersible tablets - dissolve in 10 mL of water (two medicine spoons). Gently stir this mixture into a small amount of fruit juice (such as apple, orange or pineapple), or into apple sauce or yoghurt. Do not use milk, fizzy water or other fizzy drinks. Your child should eat/drink all the mixture straight away.

Liquid medicine - measure out the right amount using a medicine spoon or oral syringe. You can get these from your pharmacist. Do not use a kitchen teaspoon as it will not give the right amount.

K.3 PPIs

This group of drugs includes omeprazole and lansoprazole. Information is available on how to how to give these medicines is included in the BNF for Children and the information leaflets provided by the manufacturers. A summary of some of the key points is provided below:

K.3.1 Omeprazole

Dispersible tablet - Losec MUPs ®. This can be dispersed in water, or mixed with fruit juice or yoghurt

Capsule - older children may be able to swallow the capsule whole with some liquid or the capsule contents (granules) mixed with small amount of soft food such as yogurt, honey or jam. Make sure your child swallows it all straight away, without chewing. Some capsules may contain a tablet and these capsules should not be opened

For administration through a feeding tube, use Losec MUPS® or the contents of a capsule which contains granules containing omeprazole, dispersed in a large volume of water, or in

10 mL sodium bicarbonate 8.4% (1 mmol /mL) (allow to stand for 10 minutes before administration). For narrow feeding tubes it may be necessary to use the capsule contents dispersed in sodium bicarbonate as described above to make sure that the feeding tube does not get blocked.

Liquid formulation - omeprazole liquids are available as unlicensed products from Specialist manufacturing companies in the UK. The liquid products can be useful for patients with a feeding tube however the formulations used may vary. These special products usually have short expiry dates.

K.3.2 Lansoprazole

Gastro-resistant capsules - older children may be able to swallow these whole with liquid. For patients with difficulty swallowing; the capsules can be opened and the granules mixed with a small amount of water, apple/tomato juice or sprinkled onto a small amount of soft food (e.g. yoghurt, apple puree) to help administration. For patients with a feeding tube the capsules can be opened and the granules mixed with 40 ml of apple juice.

FasTabs® - this tablet can be placed in the mouth where it will disperse to release gastro-resistant granules which will be swallowed with the saliva. The tablet can also be dispersed in water, leaving microgranules which should be swallowed without being crushed. It can also be administered in apple juice or orange juice. The granules in Fastabs® are smaller than those in the capsules and they are less likely to block feeding tubes.

A proportion of the Fastab® can be used to administer doses to younger children. For example a quarter or half a tablet can be dispersed in water and then administered. This avoids trying to measure part of a dispersed tablet. The remainder of the tablet is usually discarded and a new tablet used for each dose.

K.4 Further information

The following website has information which provides practical advice for parents who need to give medicines to their children and leaflets are available for many of the medicines used for treating GORD in children. http://www.medicinesforchildren.org.uk/search-for-a-leaflet/