National Institute for Health and Care Excellence

Final

Barrett's oesophagus and stage 1 oesophageal adenocarcinoma

[N] Evidence review for anti-reflux surgery to reduce progression to dysplasia or cancer

NICE guideline NG231

Evidence review underpinning recommendation 1.8.1 in the NICE guideline

February 2023

Final

National Institute for Health and Care Excellence

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1.1 Review question

For adults with Barrett's oesophagus, what is the clinical and cost effectiveness of anti-reflux surgery to reduce progression to dysplasia or cancer?

1.1.1 Introduction

In adults with Barrett's oesophagus, anti-reflux surgery (laparoscopic fundoplication) can be used to try and prevent progression to dysplasia and or cancer. This review aims to assess how clinically and cost-effective anti-reflux surgery is for those with Barrett's.

1.1.2 Summary of the protocol

Table 1: PICO characteristics of review question

Population	Adults, 18 years and over, with non-dysplastic Barrett's oesophagus, indefinite for dysplasia or low-grade dysplasia
Intervention	Anti-reflux surgery (any type of fundoplication)
Comparison	No treatment Pharmacological treatment (including PPI, Antacids etc.)
Outcomes	• Mortality (disease specific mortality, treatment related mortality and all cause) • Health related quality of life • Dysphagia • Progression to/of dysplasia • Progression to cancer • Adverse events (including failure of procedure, rate of re-operation, sedation related, bleeding, pain, perforation) • Reintroduction of regular medication • Rate of re-introduction of PPI
Study design	RCTs • If no RCT data is available, non-randomised studies will be considered only if there is an active comparator within the study Published NMAs and IPDs will be considered for inclusion.

For full details see the review protocol in Appendix A.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

Two randomized controlled trials were included in the review [1, 3] these are summarised in Table 2 below. Both studies included people with Barrett's oesophagus.

One study compared long-term medical treatment (esomeprazole) with Laparoscopic Nissen fundoplication (LARS). The study included Gastro oesophageal reflux disease (GERD) patients with or without Barrett's oesophagus. For the purpose of this review only data relevant to people with Barrett's oesophagus have been extracted.

The other study compared LARS (Anti-reflux surgery) with esomeprazole. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

1.1.4.2 Excluded studies

See the excluded studies list in Appendix H.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Attwood 2008 [1] (LOTUS trial)	Laparoscopic Nissen fundoplication (N=32) Vs Medical treatment with esomeprazole 20 mg od for their disease (N=28)	Adults aged 18–70 years with confirmed GERD, with or without Barrett's oesophagus. Only results relevant to people with Barrett's oesophagus (N=60) have been extracted in the present review. Mean age: 47 years (Surgical arm) and 50 years (Medical arm) Europe	Treatment failure (Protocol outcome: adverse events) During a 3-year follow-up	Long-Term Usage of Acid Suppression Versus Anti-Reflux Surgery trial (LARS)
Parrilla 2003 [3]	Anti-reflux surgery (N=58) short Nissen fundoplication (1.5–3 cm) over a 48 to 50 French bougie through a laparotomy. Vs Medical treatment for all patients (N= 43) consisted of hygiene, diet, and postural measures as well as antisecretory drugs: H2 antagonists (150 mg twice daily)	Patients diagnosed with Barrett's oesophagus (including short Barrett's segment with intestinal metaplasia) (N=101) Median age(range): Surgical arm: 43 years (10–71) Medical arm: 50 years (12–78) Spain	Progression to high-grade dysplasia Dysplasia de novo (Progression to any grade dysplasia from non-dysplastic Barrett's oesophagus Complications (Splenectomy. inability to belch or vomit, and mild and transitory postoperative dysphagia)	N=91 had intestinal metaplasia; N=8 had low-grade dysplasia. Low grade dysplasia: Medical treatment: n=3 (7%) Anti-reflux surgery: n=5 (9%) Intestinal metaplasia: Medical treatment: n=39 (91%) Anti-reflux surgery: n= 52 (90%)

Study	Intervention and comparison	Population	Outcomes	Comments
	initially and omeprazole (20 mg twice daily) from 1992 onward for all patients.		Median (range) 5 years follow-up (range 1–18)	Downgraded for indirectness as children are included in the study participants.

See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Table 3: Clinical evidence summary: Anti reflux surgery vs Medical treatment

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No treatment/Pharmacological treatment	Risk difference with Anti reflux surgery
Progression to High-grade dysplasia	101 (1 RCT)	⨁⨁◯◯ Lowa,[b]	RR 0.74 (0.11 to 5.06)	47 per 1,000	12 fewer per 1,000 (41 fewer to 189 more)
Dysplasia De novo	93 (1 RCT)	⨁⨁◯◯ Lowa,[b]	RR 0.28 (0.08 to 1.00)	200 per 1,000	144 fewer per 1,000 (184 fewer to 0 fewer)
Complications	101 (1 RCT)	⨁⨁⨁◯ Moderate [a]	OR 12.03 (5.14 to 28.18)	0 per 1,000	530 more per 1,000 (400 more to 670 more) c
Treatment failure (protocol outcome: adverse events)	60 (1 RCT)	⨁⨁◯◯ Low[b]	RR 0.29 (0.03 to 2.65)	107 per 1,000	76 fewer per 1,000 (104 fewer to 177 more)

a. Downgraded by 1 increment due to population indirectness as children were included in the study participants
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs (default MIDs for dichotomous outcomes: 0.8 and 1.25)
c. Calculated using the Risk difference: 0.53 (95% CI 0.40 to 0.67) due to zero events in the control group.

See Appendix F for full GRADE tables

1.1.7 Economic evidence

1.1.7.1 Included studies

No health economic studies were included.

1.1.7.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G.

1.1.8 Summary of included economic evidence

This area was not prioritised for new cost-effectiveness analysis.

1.1.9 Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.1.10 Unit costs

Table 4: Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Resource	Unit costs	Source
Very complex, mouth or throat procedures, with CC scores 0-5+ (CA80A-C)	£17,822*	NHS reference costs 2019-20
Complex, mouth or throat procedures, 19 years and over, with CC scores 0-2+ (CA81A-B)	£4,058*	
Very major, mouth or throat procedures, 19 years and over, with CC scores 0-2+ (CA82A-B)	£3,764*	
Major, mouth or throat procedures, 19 years and over, with CC scores 0-2+ (CA83A-B)	£3,435*	
Intermediate, mouth or throat procedures, 19 years and over, with CC scores 0-2+ (CA84A-B)	£2,964*	
Minor, mouth or throat procedures, 19 years and over (CA85A)	£514	
Minor, mouth or throat procedures, 19 years and over (CA86A)	£338	
Proton pump inhibitors	£2.31*	Prescription Cost Analysis 2020/21
H2 receptor antagonists	£15.62*	
Antacids	£30.75*	

*Weighted average unit cost

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

The outcomes considered for this review were mortality (disease specific mortality, treatment related mortality and all cause), health related quality of life, dysphagia, progression to/of dysplasia, progression to cancer, adverse events (including failure of procedure, rate of re-operation, sedation related, bleeding, pain, perforation), reintroduction of regular medication and rate of re-introduction of PPI. For purposes of decision making, all outcomes were considered equally important and were therefore rated as critical by the committee.

Evidence was identified for the outcomes of progression to dysplasia (including dysplasia de novo) and adverse events (treatment failure and complications). No other relevant outcome was identified.

1.1.12.2 The quality of the evidence

Two small RCTs comparing anti-reflux surgery (Nissen fundoplication) with Esomeprazole were included. One RCT on treatment failure addressing the protocol outcome of adverse events, and one RCT on progression to high-grade dysplasia, dysplasia de novo (progression to any grade of dysplasia from non-dysplastic Barrett's oesophagus) and complications such as splenectomy, inability to belch or vomit and transitionary postoperative dysphagia.

The quality of the evidence varied across outcomes ranging from low to moderate. The quality of the evidence was low for progression to high-grade dysplasia and dysplasia de novo as it was downgraded for population indirectness due to the inclusion of an unclear proportion of children in the study sample, and serious imprecision based on the confidence interval of the effect estimates. The quality of evidence was low for the outcome of treatment

failure as it was downgraded for very serious imprecision in the effect estimate with confidence intervals being very wide. The quality of the evidence was moderate for the outcome of complications as, similarly to the evidence for dysplasia outcomes, it was downgraded for population indirectness.

1.1.12.3 Benefits and harms

Included studies examined different outcomes and thus pooling of data was not possible. The evidence showed a clinically important benefit of medical treatment for the outcome of complications and no clinically important difference for the outcomes of progression to high-grade dysplasia and treatment failure. The committee agreed, the findings were in line with their clinical experience that anti-reflux surgery does not offer any advantage over medical treatment with PPI for progression to dysplasia or cancer.

For the outcome of dysplasia de novo, the evidence showed a clinically important benefit of anti-reflux surgery. Dysplasia de novo was defined as progression to any grade of dysplasia from non-dysplastic Barrett's. The committee noted that this outcome came from a study that was conducted between 1982 and 2000, and that in the years before 2000, the diagnosis of low-grade dysplasia was not reliable due to the use of different diagnostic criteria. The committee also noted that the patients in the study were on H2 receptor antagonists for the first 10 years of the study which are now considered inferior to PPI for chemoprevention. The committee concluded that the evidence reported for dysplasia de novo was not reliable to base recommendations on.

The committee agreed, based on the current limited and low quality of evidence that anti-reflux surgery cannot be recommended for chemoprevention for people with Barrett's oesophagus.

The committee discussed that although PPI is widely used in current practice for symptom control in people with Barrett's oesophagus, there are a number of people who express concerns about being on high dose PPI medication over the long-term, or who are intolerant to the medication. The committee agreed that anti-reflux surgery provides an alternative option to long-term medical treatment for this group of people.

One study showed anti-reflux surgery results in a greater number of complications compared to medical treatment and that the difference is clinically important, but the committee noted the evidence was very limited and the safety of anti-reflux surgery has improved since the study was conducted.

Based on the available evidence and their experience the committee agreed anti-reflux surgery should not be offered to prevent progression to dysplasia or cancer but could be considered as an alternative to acid suppressant medication, such as PPI, for people who are intolerant or unwilling to take the medication. The committee decided to refer to the recommendations on Laprascopic fundoplication in the Gastro-osophageal reflux disease and dyspepsia in adults NICE guideline.

The committee considered making a research recommendation, but concluded it is unlikely there would be any support for a trial comparing anti-reflux surgery with medical treatment, based on the results of the Aspect trial which did not support a change in current practice for symptom control with acid suppression medication such as PPI.

1.1.12.4 Cost effectiveness and resource use

Surgery has a high up-front cost, but this could be potentially offset by improved health outcome and reduced use of medicine. No economic evaluations were identified for this question.

The committee therefore discussed the clinical evidence presented to them. They noted that surgery is much more costly than medical treatment. The committee concluded that anti-

reflux surgery does not offer any advantage over medical treatment with PPI for progression to dysplasia or cancer and therefore, given the cost and complications, did not recommend surgery.

The committee's recommendations are in line with current practice and should not significantly alter NHS resource use.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendation 1.8.1.

1.1.14 References

1. Attwood SE, Lundell L, Hatlebakk JG, Eklund S, Junghard O, Galmiche JP et al. Medical or surgical management of GERD patients with Barrett's esophagus: The LOTUS trial 3-year experience. Journal of Gastrointestinal Surgery. 2008; 12(10):1646-1654

2. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [updated January 2022]. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

3. Parrilla P, Martinez de Haro LF, Ortiz A, Munitiz V, Molina J, Bermejo J et al. Long-term results of a randomized prospective study comparing medical and surgical treatment of Barrett's esophagus. Annals of Surgery. 2003; 237(3):291-298

Appendices

Appendix A – Review protocols

Review protocol for anti-reflux surgery to reduce progression to dysplasia or cancer

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	Anti-reflux surgery to reduce progression to dysplasia or cancer
2.	Review question	For adults with Barrett's oesophagus, what is the clinical and cost effectiveness of anti-reflux surgery to reduce progression to dysplasia or cancer?
3.	Objective	To determine the clinical and cost effectiveness of anti-reflux surgery to reduce progression to dysplasia or cancer, in adults with Barrett's oesophagus
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • English language studies • Human studies • Letters and comments are excluded

		Other searches: • Inclusion lists of systematic reviews will be checked by the reviewers The searches will be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Barrett's Oesophagus
6.	Population	Inclusion: Adults, 18 years and over, with non-dysplastic Barrett's Oesophagus, indefinite for dysplasia or low-grade dysplasia Exclusion: Adults with high-grade dysplasia or any stage of adenocarcinoma; people who have received endoscopic treatment (resection or ablations)
7.	Intervention	Anti-reflux surgery: • Any type of fundoplication
8.	Comparator	• No treatment

		• Pharmacological treatment (including PPI, Antacids etc.)
9.	Types of study to be included	• RCT • If no RCT data is available, non-randomised studies will be considered only if there is an active comparator within the study Published NMAs and IPDs will be considered for inclusion.
10.	Other exclusion criteria	Non-English language studies. Non comparative cohort studies Before and after studies Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	In adults with Barrett's Oesophagus, anti-reflux surgery can be used to try and prevent progression to dysplasia and or cancer. This review aims to assess how clinically and cost effective anti-reflux surgery is for those with Barrett's.
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Mortality (disease specific mortality, treatment related mortality and all cause) • Health related quality of life • Dysphagia • Progression to/of dysplasia • Progression to cancer • Adverse events (including failure of procedure, rate of re-operation, sedation related, bleeding, pain, perforation) • Reintroduction of regular medication • Rate of re-introduction of PPI

		Time points: any time point available; no minimum follow-up
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. This review will make use of the priority screening functionality within the EPPI-reviewer software. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Randomised Controlled Trial: Cochrane RoB (2.0) Nonrandomised study, including cohort studies: Cochrane ROBINS-I

		Case control study: CASP case control checklist
16.	Strategy for data synthesis	Where available, outcome data from new studies will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome. If insufficient data is available, WinBUGS will be used for network meta-analysis, if possible, given the data identified.
17.	Analysis of sub-groups	Stratification: Non-dysplastic Barrett's oesophagus. Barrett's oesophagus with indefinite dysplasia. Barrett's oesophagus with low-grade dysplasia.

		Subgrouping: If serious or very serious heterogeneity (I2>50%) is present, sub-grouping will occur according to the following strategies: Comparator treatment: Pharmacological treatment (e.g. PPI vs no PPI, any pharma treatment) vs no pharma treatment		
18.	Type and method of review	☒	Intervention	
		☐	Diagnostic	
		☐	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date			
22.	Anticipated completion date			
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐

		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail @nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Norma O Flynn Gill Ritchie Amy Crisp Lina Gulhane Muksitar Rahman Maheen Qureshi		

		Melina Vasileiou Stephen Deed
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.
29.	Other registration details	
30.	Reference/URL for published protocol	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Barrett's oesophagus

33.	Details of existing review of same topic by same authors		
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information		
36.	Details of final publication	www.nice.org.uk	

Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken for all years using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2006, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published in 2006 or later, that were included in the previous guidelines, will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014). [2] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2006 or later (including any such studies included in the previous guidelines) but that depend on unit costs and resource data entirely or predominantly from before 2006 will be rated as ‘Not applicable’.
- Studies published before 2006 (including any such studies included in the previous guidelines) will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B – Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[2]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve.

Table 5: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 28 April 2022	Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 28 April 2022	Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
The Cochrane Library (Wiley)	Cochrane Database of Systematic Reviews to Issue 4 of 12, April 2022 Cochrane Central Register of Controlled Trials to Issue 4 of 12, April 2022	Exclusions (clinical trials, conference abstracts)
Epistemonikos (The Epistemonikos Foundation)	Inception to 28 April 2022	Systematic review Exclusions (Cochrane reviews)

Medline (Ovid) search terms

1.	exp Barrett esophagus/
2.	barrett*.ti,ab.
3.	(speciali* adj3 (epithel* or oesophag* or esophag* or mucos*)).ti,ab.
4.	(column* adj3 (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)).ti,ab.
5.	(intestin* adj2 metaplas*).ti,ab.
6.	or/1-5
7.	Precancerous conditions/
8.	(dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or

	carcinoma* or adenocarcinom* or adenoma* or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*).ti,ab.
9.	7 or 8
10.	exp Esophagus/
11.	Esophageal Mucosa/
12.	(oesophag* or esophag* or intramucosal* or intra-mucosal*).ti,ab.
13.	or/10-12
14.	9 and 13
15.	exp Esophageal Neoplasms/
16.	6 or 14 or 15
17.	letter/
18.	editorial/
19.	news/
20.	exp historical article/
21.	Anecdotes as Topic/
22.	comment/
23.	case report/
24.	(letter or comment*).ti.
25.	or/17-24
26.	randomized controlled trial/ or random*.ti,ab.
27.	25 not 26
28.	animals/ not humans/
29.	exp Animals, Laboratory/
30.	exp Animal Experimentation/
31.	exp Models, Animal/
32.	exp Rodentia/
33.	(rat or rats or mouse or mice or rodent*).ti.
34.	or/27-33
35.	16 not 34
36.	limit 35 to English language
37.	Fundoplication/
38.	Gastroesophageal Reflux/su [Surgery]
39.	(fundoplicat* or fundo plicat* or fundalplicat* or fundal plicat* or fundic wrap*).ti,ab,kf.
40.	(nissen or rossetti or toupet or lind or watson or belsey or thal or dor).ti,ab,kf.
41.	(antireflux or anti reflux).ti,ab,kf.
42.	or/37-41
43.	36 and 42

Embase (Ovid) search terms

1.	exp Barrett esophagus/
2.	barrett*.ti,ab.
3.	(speciali* adj3 (epithel* or oesophag* or esophag* or mucos*)).ti,ab.
4.	(column* adj3 (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)).ti,ab.
5.	(intestin* adj2 metaplas*).ti,ab.
6.	or/1-5
7.	Precancer/

8.	(dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma* or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*).ti,ab.
9.	7 or 8
10.	exp Esophagus/
11.	Esophagus Mucosa/
12.	(oesophag* or esophag*).ti,ab.
13.	or/10-12
14.	9 and 13
15.	exp Esophagus Tumor/
16.	6 or 14 or 15
17.	letter.pt. or letter/
18.	note.pt.
19.	editorial.pt.
20.	case report/ or case study/
21.	(letter or comment*).ti.
22.	(conference abstract or conference paper).pt.
23.	or/17-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animal/ not human/
27.	nonhuman/
28.	exp Animal Experiment/
29.	exp Experimental Animal/
30.	animal model/
31.	exp Rodent/
32.	(rat or rats or mouse or mice or rodent*).ti.
33.	or/25-32
34.	16 not 33
35.	limit 34 to English language
36.	exp stomach fundoplication/
37.	gastroesophageal reflux/su [Surgery]
38.	(fundoplicat* or fundo plicat* or fundalplicat* or fundal plicat* or fundic wrap*).ti,ab,kf.
39.	(nissen or rossetti or toupet or lind or watson or belsey or thal or dor).ti,ab,kf.
40.	(antireflux or anti reflux).ti,ab,kf.
41.	or/36-40
42.	35 and 41

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Barrett Esophagus] explode all trees
#2.	barrett*:ti,ab
#3.	speciali* near/3 (epithel* or oesophag* or esophag* or mucos*):ti,ab
#4.	column* near/3 (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*):ti,ab
#5.	(intestin* near/2 metaplas*):ti,ab
#6.	(or #1-#5)

#7.	MeSH descriptor: [Precancerous Conditions] explode all trees
#8.	(dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma* or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*):ti,ab
#9.	#7 or #8
#10.	MeSH descriptor: [Esophagus] explode all trees
#11.	MeSH descriptor: [Esophageal Mucosa] explode all trees
#12.	(oesophag* or esophag* or intramucosal* or intra-mucosal*):ti,ab
#13.	(or #10-#12)
#14.	#9 and #13
#15.	MeSH descriptor: [Esophageal Neoplasms] explode all trees
#16.	#6 or #14 or #15
#17.	MeSH descriptor: [Fundoplication] this term only
#18.	MeSH descriptor: [Gastroesophageal Reflux] this term only and with qualifier(s): [surgery - SU]
#19.	(fundoplicat* or fundo plicat* or fundalplicat* or fundal plicat* or fundic wrap*):ti,ab,kw
#20.	(nissen or rossetti or toupet or lind or watson or belsey or thal or dor):ti,ab,kw
#21.	(antireflux or anti reflux):ti,ab,kw
#22.	(or #17-#21)
#23.	#16 and #22
#24.	conference:pt or (clinicaltrials or trialsearch):so
#25.	#23 not #24

Epistemonikos search terms

1.	(title:(Barrett* OR "oesophageal adenocarcinoma*" OR "esophageal adenocarcinoma*" OR "oesophageal cancer*" OR "esophageal cancer*" OR "oesophageal carcinoma*" OR "esophageal carcinoma*" OR "oesophageal metaplas*" OR "esophageal dysplas*" OR "column* epithel*" OR "intestin* metaplas*" OR "intestin* dysplas*") OR abstract:(Barrett* OR "oesophageal adenocarcinoma*" OR "esophageal adenocarcinoma*" OR "oesophageal cancer*" OR "esophageal cancer*" OR "oesophageal carcinoma*" OR "esophageal carcinoma*" OR "oesophageal metaplas*" OR "esophageal dysplas*" OR "column* epithel*" OR "intestin* metaplas*" OR "intestin* dysplas*")) AND (title:(fundoplicat* OR "fundo plicat*" OR fundalplicat* OR "fundal plicat*" OR "fundic wrap*" OR nissen OR rossetti OR toupet OR lind OR watson OR besley OR thal OR dor OR antireflux OR "anti reflux") OR abstract:(fundoplicat* OR "fundo plicat*" OR fundalplicat* OR "fundal plicat*" OR "fundic wrap*" OR nissen OR rossetti OR toupet OR lind OR watson OR besley OR thal OR dor OR antireflux OR "anti reflux")

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Barrett's Oesophagus population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies.

Table 6: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 29 April 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
	Quality of Life 1946 – 29 April 2022	
Embase (OVID)	Health Economics 1 January 2014 – 29 April 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
	Quality of Life 1974 – 29 April 2022	
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 29 April 2022	English language

Medline (Ovid) search terms

1.	exp Barrett esophagus/
2.	barrett*.ti,ab.
3.	(speciali* adj3 (epithel* or oesophag* or esophag* or mucos*)).ti,ab.
4.	(column* adj3 (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)).ti,ab.
5.	or/1-4
6.	Precancerous conditions/
7.	(dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma* or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*).ti,ab.
8.	6 or 7
9.	exp Esophagus/
10.	Esophageal Mucosa/

11.	(oesophag* or esophag* or intramucosal* or intra-mucosal*).ti,ab.
12.	or/9-11
13.	8 and 12
14.	exp Esophageal Neoplasms/
15.	5 or 13 or 14
16.	letter/
17.	editorial/
18.	news/
19.	exp historical article/
20.	Anecdotes as Topic/
21.	comment/
22.	case report/
23.	(letter or comment*).ti.
24.	or/16-23
25.	randomized controlled trial/ or random*.ti,ab.
26.	24 not 25
27.	animals/ not humans/
28.	exp Animals, Laboratory/
29.	exp Animal Experimentation/
30.	exp Models, Animal/
31.	exp Rodentia/
32.	(rat or rats or mouse or mice or rodent*).ti.
33.	or/26-32
34.	15 not 33
35.	limit 34 to English language
36.	economics/
37.	value of life/
38.	exp "costs and cost analysis"/
39.	exp Economics, Hospital/
40.	exp Economics, medical/
41.	Economics, nursing/
42.	economics, pharmaceutical/
43.	exp "Fees and Charges"/
44.	exp budgets/
45.	budget*.ti,ab.
46.	cost*.ti.
47.	(economic* or pharmaco?economic*).ti.
48.	(price* or pricing*).ti,ab.
49.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
50.	(financ* or fee or fees).ti,ab.
51.	(value adj2 (money or monetary)).ti,ab.

52.	or/36-51
53.	quality-adjusted life years/
54.	sickness impact profile/
55.	(quality adj2 (wellbeing or well being)).ti,ab.
56.	sickness impact profile.ti,ab.
57.	disability adjusted life.ti,ab.
58.	(qal* or qtime* or qwb* or daly*).ti,ab.
59.	(euroqol* or eq5d* or eq 5*).ti,ab.
60.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
61.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
62.	(hui or hui1 or hui2 or hui3).ti,ab.
63.	(health* year* equivalent* or hye or hyes).ti,ab.
64.	discrete choice*.ti,ab.
65.	rosser.ti,ab.
66.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
67.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
68.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
69.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
70.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
71.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
72.	or/53-71
73.	35 and (52 or 72)

Embase (Ovid) search terms

1.	exp Barrett esophagus/
2.	barrett*.ti,ab.
3.	(speciali* adj3 (epithel* or oesophag* or esophag* or mucos*)).ti,ab.
4.	(column* adj3 (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)).ti,ab.
5.	or/1-4
6.	Precancer/
7.	(dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma* or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*).ti,ab.
8.	6 or 7
9.	exp Esophagus/
10.	Esophagus Mucosa/
11.	(oesophag* or esophag*).ti,ab.
12.	or/9-11
13.	8 and 12
14.	exp Esophagus Tumor/
15.	5 or 13 or 14
16.	letter.pt. or letter/

17.	note.pt.
18.	editorial.pt.
19.	case report/ or case study/
20.	(letter or comment*).ti.
21.	(conference abstract or conference paper).pt.
22.	or/16-21
23.	randomized controlled trial/ or random*.ti,ab.
24.	22 not 23
25.	animal/ not human/
26.	nonhuman/
27.	exp Animal Experiment/
28.	exp Experimental Animal/
29.	animal model/
30.	exp Rodent/
31.	(rat or rats or mouse or mice or rodent*).ti.
32.	or/24-31
33.	15 not 32
34.	limit 33 to English language
35.	health economics/
36.	exp economic evaluation/
37.	exp health care cost/
38.	exp fee/
39.	budget/
40.	funding/
41.	budget*.ti,ab.
42.	cost*.ti.
43.	(economic* or pharmaco?economic*).ti.
44.	(price* or pricing*).ti,ab.
45.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
46.	(financ* or fee or fees).ti,ab.
47.	(value adj2 (money or monetary)).ti,ab.
48.	or/35-47
49.	quality-adjusted life years/
50.	"quality of life index"/
51.	short form 12/ or short form 20/ or short form 36/ or short form 8/
52.	sickness impact profile/
53.	(quality adj2 (wellbeing or well being)).ti,ab.
54.	sickness impact profile.ti,ab.
55.	disability adjusted life.ti,ab.
56.	(qal* or qtime* or qwb* or daly*).ti,ab.
57.	(euroqol* or eq5d* or eq 5*).ti,ab.
58.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
59.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
60.	(hui or hui1 or hui2 or hui3).ti,ab.
61.	(health* year* equivalent* or hye or hyes).ti,ab.
62.	discrete choice*.ti,ab.

63.	rosser.ti,ab.
64.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
65.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
66.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
67.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
68.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
69.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
70.	or/49-69
71.	34 and (48 or 70)

NHS EED and HTA (CRD) search terms

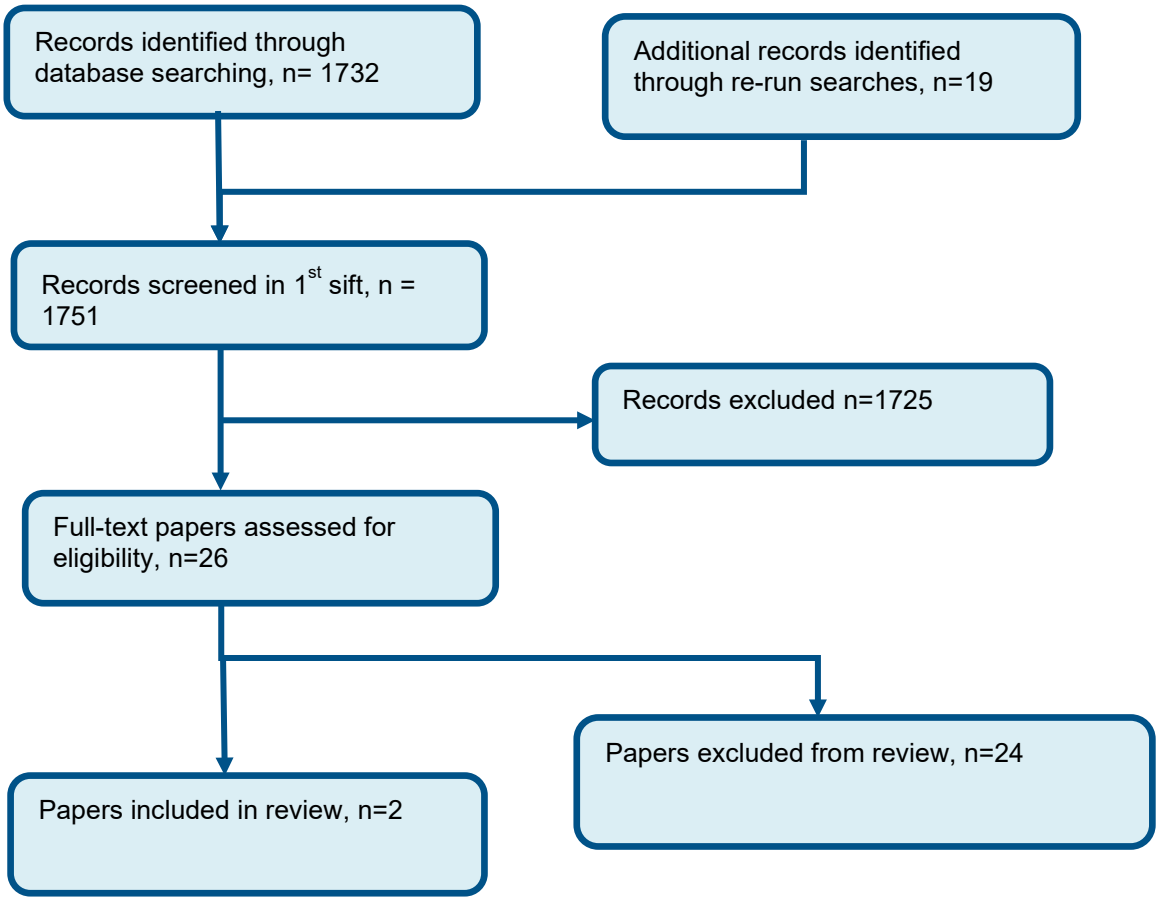
#1.	MeSH DESCRIPTOR Barrett Esophagus EXPLODE ALL TREES
#2.	(barrett*)
#3.	(speciali*) AND (epithel* or oesophag* or esophag* or mucos*)
#4.	(column*) AND (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)
#5.	#1 OR #2 OR #3 OR #4
#6.	MeSH DESCRIPTOR Precancerous Conditions EXPLODE ALL TREES
#7.	((dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma*or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*))
#8.	#6 OR #7
#9.	MeSH DESCRIPTOR Esophagus EXPLODE ALL TREES
#10.	MeSH DESCRIPTOR Esophageal Mucosa EXPLODE ALL TREES
#11.	(oesophag* or esophag* or intramucosal* or intra-mucosal*)
#12.	#9 OR #10 OR #11
#13.	#8 AND #12
#14.	#5 OR #13
#15.	MeSH DESCRIPTOR Esophageal Neoplasms EXPLODE ALL TREES
#16.	#14 OR #15

INAHTA search terms

1.	("Barrett Esophagus"[mh]) OR (Barrett*) OR (Esophageal Neoplasms)[mh]

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of anti-reflux surgery to reduce progression



Appendix D – Effectiveness evidence

Attwood, 2008

Bibliographic Reference	Attwood, S. E.; Lundell, L.; Hatlebakk, J. G.; Eklund, S.; Junghard, O.; Galmiche, J. P.; Ell, C.; Fiocca, R.; Lind, T.; Medical or surgical management of GERD patients with Barrett's esophagus: the LOTUS trial 3-year experience; Journal of Gastrointestinal Surgery; 2008; vol. 12 (no. 10); 1646-54; discussion 1654

Study details

Secondary publication of another included study- see primary study for details	Primary study
Other publications associated with this study included in review	None
Trial name / registration number	Trial name: Long term usage of Acid suppression versus Anti-reflux surgery (LOTUS)
Study type	Randomised controlled trial (RCT)
Study location	Multicentre study in Europe
Study setting	
Sources of funding	This study was funded by AstraZeneca, Mölndal, Sweden

Inclusion criteria	• Adults aged 18-70 with confirmed GERD, with or without BE
Exclusion criteria	• Any patient who had a primary need for surgery (e.g., for paraesophageal hernia or failure of medical therapy to control symptoms adequately) was not eligible to be recruited. • Patients who required PPI treatment for diseases other than GERD • Patients who had a history of oesophageal, gastric, or duodenal surgery or who had other diseases that might have a negative impact on their subsequent treatment within the study
Recruitment / selection of participants	Patients meeting inclusion criteria; recruitment method not specified
Intervention(s)	• Patients were randomized to receive Anti-reflux surgery • A laparoscopic Nissen fundoplication was recommended to be performed in all patients, according to a standardized technique agreed upon by the surgeons at the beginning of the study. • Follow-up clinic visits took place every 6 months (with surgical patients having extra visits for the operation and a 1-month postsurgical check-up). • Before randomization, the protocol mandated a 12-week run-in period, which allowed baseline recordings to be made and medical treatment with esomeprazole 40 mg od to facilitate healing of the esophagitis. • An investigational week was then scheduled without therapy to allow endoscopy, assessment of esophagitis according to the Los Angeles classification,13 biopsy sampling, laboratory screening, and 24-h pH metry with manometry and symptom association probability (SAP).
Comparator	Patients were randomized to receive medical treatment Medical treatment was started at 20 mg od but could be dose adjusted, not to exceed 20 mg bid
Number of participants	N=60

Duration of follow-up	3 years
Indirectness	None
Additional comments	The main analyses were conducted using the intention to treat population that included all randomized patients.

Study arms

Anti reflux surgery (N = 32)
Laproscopic Anti-reflux surgery (LARS)

Medical treatment (N = 28)
Esomeprazole

Characteristics

Arm-level characteristics

Characteristic	Anti-reflux surgery (N = 32)	Medical treatment (N = 28)
Age (years (mean)) Nominal	47	50
Male Sample size	n = 28 ; % = 87.5	n = 21 ; % = 75

Characteristic	Anti-reflux surgery (N = 32)	Medical treatment (N = 28)
Female Sample size	n = 4 ; % = 12.5	n = 7 ; % = 25
Esophagitis grade: None Sample size	n = 14 ; % = 43.7	n = 20 ; % = 71.4
Esophagitis grade: Grade A Sample size	n = 7 ; % = 21.8	n = 1 ; % = 3.5
Esophagitis grade: Grade B Sample size	n = 9 ; % = 28.1	n = 4 ; % = 14.2
Esophagitis grade: Grade C Sample size	n = 1 ; % = 3.1	n = 3 ; % = 10.7
Esophagitis grade: Grade D Sample size	n = 1 ; % = 3.1	n = 0 ; % = 0

Outcomes

Primary outcome

Outcome	Anti reflux surgery, , N = 32	Medical treatment, , N = 28
Adverse event Treatment failure	n = 1 ; % = 3.1	n = 3 ; % = 10.7

Outcome	Anti reflux surgery, , N = 32	Medical treatment, , N = 28
No of events		

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Primary outcome-Adverse events -No Of Events -Anti-reflux surgery-Medical treatment

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Parrilla, 2003

Bibliographic Reference	Parrilla, P.; Martinez de Haro, L. F.; Ortiz, A.; Munitiz, V.; Molina, J.; Bermejo, J.; Canteras, M.; Long-term results of a randomized prospective study comparing medical and surgical treatment of Barrett's esophagus; Annals of Surgery; 2003; vol. 237 (no. 3); 291-8

Study details

Secondary publication of another included	Primary study

study- see primary study for details	
Other publications associated with this study included in review	None
Trial name / registration number	
Study type	Randomised controlled trial (RCT)
Study location	
Study setting	
Study dates	1982 to 2000
Sources of funding	Supported by a grant from the FISS (Fondo de Investigaciones de la Seguridad Social)
Inclusion criteria	Patients diagnosed with Barrett's oesophagus (presence of columnar epithelium over 3cm in length continuing to the cardia and confirmed histologically; from 1997 onward, patients with short Barrett's segment with intestinal metaplasia were also included)
Exclusion criteria	Patients with stenosis of more than 1 cm in length and/or less than 1.2 cm in diameter (n=25) and patients who rejected randomization (n=8)
Intervention(s)	Surgical treatment (n=58), short Nissen fundoplication (1.5–3 cm) over a 48 to 50 French bougie through a laparotomy
Population subgroups	
Comparator	• Medical treatment for all patients (n=43) consisted of anti-secretory drugs: H2 antagonists (150 mg twice daily) initially and omeprazole (20 mg twice daily) from 1992 onward for all patients, and periodic dilatations in patients with stenosis. • Hygiene, diet, and postural measures as well

Number of participants	N=101
Duration of follow-up	Median follow-up= 5 years (range 1-18)
Additional comments	

Study arms

Anti-reflux surgery (N = 58)

Medical treatment (N = 43)
Anti-secretory drugs: H2 antagonists (150 mg twice daily) initially and omeprazole (20 mg twice daily) 1992 onwards in all patients

Characteristics

Arm-level characteristics

Characteristic	Anti-reflux surgery (N = 58)	Medical treatment (N = 43)
Age (years) Median (range)	43 (10 to 71)	50 (12 to 78)
Male Sample size	n = 39 ; % = 67.2	n = 33 ; % = 76.7

Characteristic	Anti-reflux surgery (N = 58)	Medical treatment (N = 43)
Female Sample size	n = 19 ; % = 32.7	n = 10 ; % = 23.2
Esophagitis Sample size	n = 32	n = 25 ; % = 58
Stricture Sample size	n = 16 ; % = 28	n = 18 ; % = 42
Barrett's ulcer Sample size	n = 8 ; % = 14	n = 5 ; % = 12
Intestinal metaplasia Sample size	n = 52 ; % = 90	n = 39 ; % = 91
Low-grade dysplasia Sample size	n = 5 ; % = 9	n = 3 ; % = 7

Outcomes

Primary outcome

Outcome	Anti-reflux surgery, , N = 58	Medical treatment, , N = 43
Progression to high grade dysplasia (n (%)) No of events	n = 2 ; % = 3.4	n = 2 ; % = 4.6

Outcome	Anti-reflux surgery, , N = 58	Medical treatment, , N = 43
Complications (n (%)) No of events	n = 31 ; % = 53.4	n = 0 ; % = 0

Progression to dysplasia - Polarity - Lower values are better
Complications - Polarity - Lower values are better

Primary outcome

Outcome	Anti-reflux surgery, , N = 53	Medical treatment, , N = 40
Dysplasia de novo No of events	n = 3 ; % = 6	n = 8 ; % = 20

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Primary outcome-Progression to dysplasia-No Of Events-Anti-reflux surgery-Medical treatment

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Primary outcome-Dysplasia de novo-No Of Events-Anti-reflux surgery-Medical treatment

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Primary outcome-Complications-No Of Events-Anti-reflux surgery-Medical treatment

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Appendix E – Forest plot

Figure 2: **Progression to High grade Dysplasia**

Study or Subgroup	Anti reflux surgery Events	Total	Medical treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Parrilla 2003	2	58	2	43	100.0%	0.74 [0.11, 5.06]
Total (95% CI)		**58**		**43**	**100.0%**	**0.74 [0.11, 5.06]**
Total events	2		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.31 (P = 0.76)

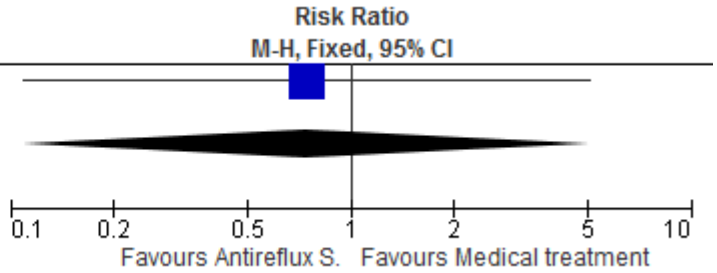


Figure 3: Dysplasia De Novo

Study or Subgroup	Anti reflux surgery Events	Total	Medical treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Parrilla 2003	3	53	8	40	100.0%	0.28 [0.08, 1.00]
Total (95% CI)		**53**		**40**	**100.0%**	**0.28 [0.08, 1.00]**
Total events	3		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.96 (P = 0.05)

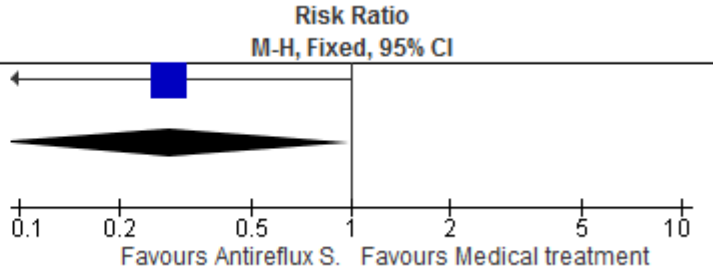


Figure 4: **Complications**

Study or Subgroup	Anti reflux surgery Events	Total	Medical treatment Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Parrilla 2003	31	58	0	43	100.0%	12.03 [5.14, 28.18]
Total (95% CI)		**58**		**43**	**100.0%**	**12.03 [5.14, 28.18]**
Total events	31		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 5.73 (P < 0.00001)

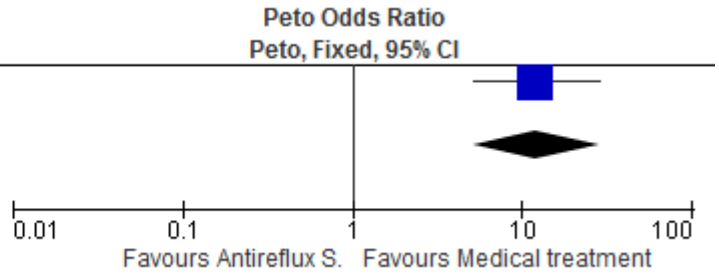
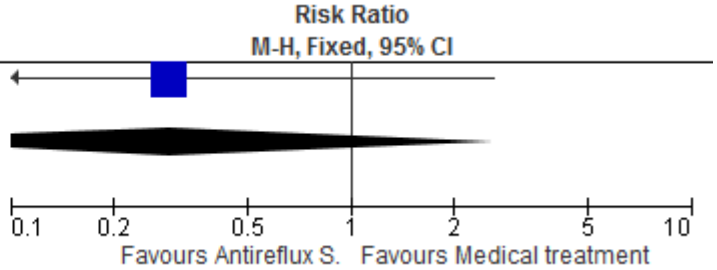


Figure 5: Treatment failure

Study or Subgroup	Anti reflux surgery Events	Total	Medical treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Attawood 2008	1	32	3	28	100.0%	0.29 [0.03, 2.65]
Total (95% CI)		**32**		**28**	**100.0%**	**0.29 [0.03, 2.65]**
Total events	1		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.09 (P = 0.27)



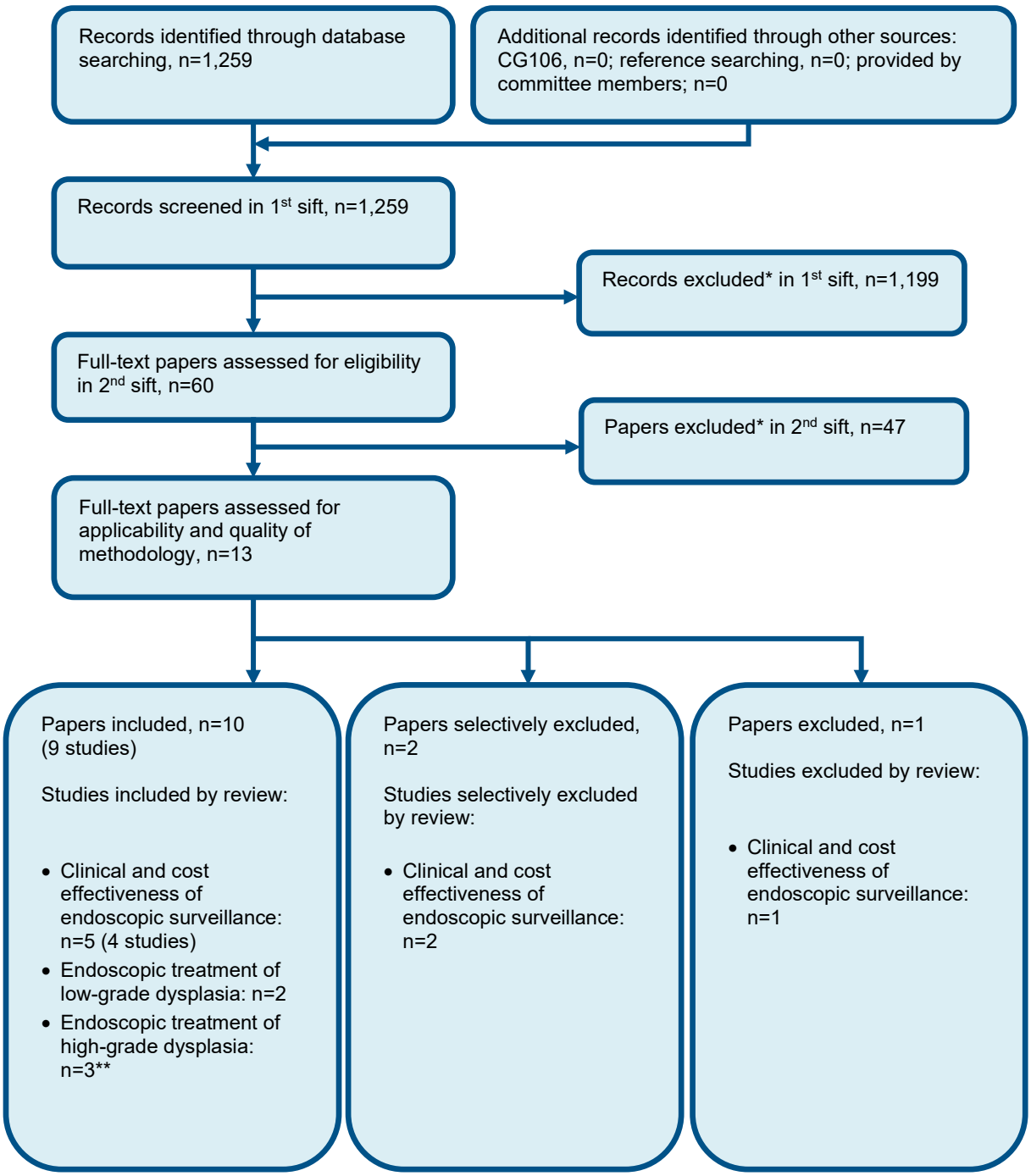
Appendix F – GRADE

Table 7: Clinical evidence profile: Anti reflux surgery vs medical treatment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anti reflux surgery	No treatment/Pharmacological treatment	Relative (95% CI)	Absolute (95% CI)		
Progression to High grade dysplasia												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	2/58 (3.4%)	2/43 (4.7%)	**RR 0.74** (0.11 to 5.06)	**12 fewer per 1,000** (from 41 fewer to 189 more)	⨁⨁◯◯ Low	CRITICAL
Dysplasia De novo												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	3/53 (5.7%)	8/40 (20.0%)	**RR 0.28** (0.08 to 1.00)	**144 fewer per 1,000** (from 184 fewer to 0 fewer)	⨁⨁◯◯ Low	CRITICAL
Complications												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	32/58 (55.2%)	0/43 (0.0%)	**OR 12.03** (5.14 to 28.18)	**530 more per 1,000** (from 400 more to 677 more)	⨁⨁⨁◯ Moderate	CRITICAL
Treatment failure												
1	randomised trials	not serious	not serious	not serious	very serious[b]	none	1/32 (3.1%)	3/28 (10.7%)	**RR 0.29** (0.03 to 2.65)	**76 fewer per 1,000** (from 104 fewer to 177 more)	⨁⨁◯◯ Low	CRITICAL

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs (default MIDs for dichotomous outcomes: 0.8 and 1.25)
b. Downgraded for indirectness as children are included in study participants
c. Calculated using the Risk difference: 0.53 (95% CI 0.40 to 0.67) due to zero events in the control group.

Appendix G – Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language
** One article identified was applicable to endoscopic treatment of low-grade dysplasia and endoscopic treatment for high-grade dysplasia, for the purposes of this diagram they have been included under endoscopic treatment of low-grade dysplasia only.

Appendix H – Excluded studies

Clinical studies

Table 8: Studies excluded from the clinical review

Study	Reason for exclusion
Abbas, A. E., Deschamps, C., Cassivi, S. D. et al. (2004) Barrett's esophagus: the role of laparoscopic fundoplication. Annals of Thoracic Surgery 77(2): 393-6	- Study does not contain an intervention relevant to this review protocol Observational study of patients who underwent anti-reflux surgery
Allaix, M. E. and Patti, M. G. (2015) Antireflux surgery for dysplastic Barrett. World Journal of Surgery 39(3): 588-94	- Systematic review not relevant to protocol Relevant study used in the systematic review added as primary study in the review
Attwood, S. E., Barlow, A. P., Norris, T. L. et al. (1992) Barrett's oesophagus: effect of antireflux surgery on symptom control and development of complications. British Journal of Surgery 79(10): 1050-3	- Study design not relevant to review protocol Non-randomized study and RCT evidence available
Baldaque-Silva, F., Vieth, M., Debel, M. et al. (2017) Impact of gastroesophageal reflux control through tailored proton pump inhibition therapy or fundoplication in patients with Barrett's esophagus. World Journal of Gastroenterology 23(17): 3174-3183	- Study design not relevant to review protocol Non-randomized study and RCT evidence available
Bammer, T., Hinder, R. A., Klaus, A. et al. (2001) Rationale for surgical therapy of Barrett esophagus. Mayo Clinic Proceedings 76(3): 335-42	- Study design not relevant to this review protocol Review article
Chang, E. Y., Morris, C. D., Seltman, A. K. et al. (2007) The effect of antireflux surgery on esophageal carcinogenesis in patients with barrett esophagus: a systematic review. Annals of Surgery 246(1): 11-21	- Systematic review not relevant to protocol Review of Non-randomized studies and RCT evidence available
Corey, K. E.; Schmitz, S. M.; Shaheen, N. J. (2003) Does a surgical antireflux procedure decrease the incidence of esophageal adenocarcinoma in Barrett's esophagus? A meta-analysis. American Journal of Gastroenterology 98(11): 2390-4	- Outcome not relevant to protocol Assessing cancer incidence rate

Study	Reason for exclusion
de Jonge, P. J., Spaander, M. C., Bruno, M. J. et al. (2015) Acid suppression and surgical therapy for Barrett's oesophagus. Best Practice & Research in Clinical Gastroenterology 29(1): 139-50	- Secondary publication of an included study that does not provide any additional relevant information
DeMeester, T. R. (2000) Antireflux surgery in the management of Barrett's esophagus. Journal of Gastrointestinal Surgery 4(2): 124-8	- Study design not relevant to review protocol Review article
Gatenby, P. and Soon, Y. (2014) Barrett's oesophagus: Evidence from the current meta-analyses. World Journal of Gastrointestinal Pathophysiology 5(3): 178-87	- Systematic review not relevant to protocol Includes studies assessing association of Barrett's oesophagus with gender, smoking habits, obesity, symptom association, presence of Helicobacter pylori (H. pylori), presence of hiatus hernia and pattern of proton pump inhibitor usage.
Gutschow, C. A., Schroder, W., Prenzel, K. et al. (2002) Impact of antireflux surgery on Barrett's esophagus. Langenbecks Archives of Surgery 387(34): 138-45	- Systematic review not relevant to protocol Includes Non-randomized studies and RCT evidence was available
Hunter, J. G., Trus, T. L., Branum, G. D. et al. (1996) A physiologic approach to laparoscopic fundoplication for gastroesophageal reflux disease. Annals of Surgery 223(6): 673-85; discussion 685	- Study does not contain an intervention relevant to this review protocol Observational study of patients with anti-reflux surgery and RCT evidence available
Isolauri, J., Luostarinen, M., Viljakka, M. et al. (1997) Long-term comparison of antireflux surgery versus conservative therapy for reflux esophagitis. Annals of Surgery 225(3): 295-9	- Population not relevant to review protocol GERD patients
Li, Y. M., Li, L., Yu, C. H. et al. (2008) A systematic review and meta-analysis of the treatment for Barrett's esophagus. Digestive Diseases & Sciences 53(11): 2837-46	- Systematic review not relevant to protocol Relevant study included as primary study in the review
Maret-Ouda, J., Konings, P., Lagergren, J. et al. (2016) Antireflux Surgery and Risk of Esophageal Adenocarcinoma: A Systematic Review and Meta-analysis. Annals of Surgery 263(2): 251-7	- Systematic review not relevant to protocol Review of Non-randomized studies, relevant RCT in the systematic review has been included as primary study in the review

Study	Reason for exclusion
Pagani, M., Granelli, P., Chella, B. et al. (2003) Barrett's esophagus: Combined treatment using argon plasma coagulation and laparoscopic antireflux surgery. Diseases of the Esophagus 16(4): 279-83	- Study does not contain an intervention relevant to this review protocol Study of patients undergoing endoscopic treatment with Argon Plasma Coagulation combined with surgery
Patti, M. G., Arcerito, M., Feo, C. V. et al. (1999) Barrett's esophagus: A surgical disease. Journal of Gastrointestinal Surgery 3(4): 397-403; discussion 403	- Study does not contain an intervention relevant to this review protocol Observational study with no active comparator
Rossi, M., Barreca, M., de Bortoli, N. et al. (2006) Efficacy of Nissen fundoplication versus medical therapy in the regression of low-grade dysplasia in patients with Barrett esophagus: a prospective study. Annals of Surgery 243(1): 58-63	- Study design not relevant to this review protocol Non-randomised study and RCT evidence available
Spechler, S. J. (1992) Comparison of medical and surgical therapy for complicated gastroesophageal reflux disease in veterans. The Department of Veterans Affairs Gastroesophageal Reflux Disease Study Group. New England Journal of Medicine 326(12): 786-92	- Population not relevant to this review protocol More than 50% population without Barrett's oesophagus
Spechler, S. J., Lee, E., Ahnen, D. et al. (2001) Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease: Follow-up of a randomized controlled trial. JAMA 285(18): 2331-8	- Population not relevant to this review protocol Patients with complicated GERD
Tolone, S., Limongelli, P., Romano, M. et al. (2015) The patterns of reflux can affect regression of non-dysplastic and low-grade dysplastic Barrett's esophagus after medical and surgical treatment: A prospective case-control study. Surgical Endoscopy 29(3): 648-57	- Outcomes not relevant to review protocol
Wetscher, G. J., Gadenstaetter, M., Klingler, P. J. et al. (2001) Efficacy of medical therapy and antireflux surgery to prevent Barrett's metaplasia in patients with gastroesophageal reflux disease. Annals of Surgery 234(5): 627-32	- Population not relevant to review protocol – Patients with GERD and esophagitis were included
Wilson, H., Mocanu, V., Sun, W. et al. (2021) Fundoplication is superior to medical therapy for Barrett's esophagus disease regression and	- Systematic review not relevant to protocol

Study	Reason for exclusion
progression: A systematic review and meta-analysis. Surgical Endoscopy 18: 18	Review of Non-randomized studies, relevant RCT in the systematic review has been included as primary study in the review
Zaninotto, G., Parente, P., Salvador, R. et al. (2012) Long-term follow-up of Barrett's epithelium: Medical versus antireflux surgical therapy. Journal of Gastrointestinal Surgery 16(1): 7-14; discussion 14	- Study design not relevant to this review protocol- observational study and RCT evidence available - Outcomes not relevant to review protocol

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2006 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

None.