National Institute for Health and Care Excellence

Final

Barrett's oesophagus and stage 1 oesophageal adenocarcinoma

[M] Evidence review for anti-reflux surgery to induce remission of disease or prevent recurrence

NICE guideline NG231

Evidence review underpinning recommendation 1.8.1 in the NICE guideline

February 2023

Final

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1.1 Review question

For adults with Barrett's oesophagus or stage 1 adenocarcinoma, what is the clinical and cost effectiveness of anti-reflux surgery to induce remission of disease or prevent recurrence?

1.1.1 Introduction

In adults with Barrett's oesophagus, anti-reflux surgery (laparoscopic fundoplication) can be used to try to induce remission of disease and prevent progression to cancer. This review aims to assess how clinically and cost effective anti-reflux surgery is to induce remission of disease and prevent recurrence.

1.1.2 Summary of the protocol

Table 1: PICO characteristics of review question

Population	Adults, 18 years and over, with Barrett's oesophagus with or without dysplasia (low-grade dysplasia, high-grade dysplasia, or stage 1 oesophageal adenocarcinoma).
Intervention	Anti-reflux surgery alone or in combination with endoscopic treatment: Any type of fundoplication
Comparison	No anti-reflux surgery
Outcomes	• Mortality (disease-specific mortality, treatment related mortality and all cause) • Health related quality of life • Progression of grade of dysplasia • Progression to cancer • Recurrence of Barrett's oesophagus/ dysplasia/cancer • Number of endoscopic treatments to achieve remission of Barrett's • Time duration of the endoscopic treatment • Adverse events (such as bleeding, pain)
Study design	• 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.

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.

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

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

One observational study was included in the review [2]. This is summarised in Table 2 below. The study aimed to assess the effects of Nissen fundoplication in patients who had complete eradication of metaplastic and dysplastic Barrett's oesophagus after Endoscopic radiofrequency ablation (RFA).

This was a prospective clinical study comparing daily PPI (esomeprazole 40 mg/day) with laparoscopic Nissen fundoplication (LNF) after or synchronous with RFA procedure. (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
Skrobic 2016 [2]	Patients were treated with daily PPI (esomeprazole 40 mg/day) (N=25) Vs Laparoscopic Nissen fundoplication (LNF) after or synchronous with RFA procedure (N=22)	Patients who had complete eradication of metaplastic and dysplastic Barrett's oesophagus after HALO endoscopic radiofrequency ablation (RFA) procedure (N=47) Mean age (SD): 47.3 (10.8) Serbia	Recurrence of Barrett's oesophagus 2-year follow-up	The post-RFA treatment modality was based on patients' preference Intestinal metaplasia: N=33 (70.2%) Low grade dysplasia: N=14 (29.7%)

See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Table 3: Clinical evidence summary: Anti reflux surgery with endoscopic treatment vs medical treatment

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No Anti reflux surgery	Risk difference with Anti reflux surgery with or without endoscopic treatment
Recurrence of Barrett's oesophagus	47 (1 observational study)	⨁◯◯◯ Very Low[a,b]	RR 0.45 (0.10 to 2.11)	200 per 1,000	110 fewer per 1,000 (180 fewer to 222 more)
Recurrence of Barrett's oesophagus C length > 4cm	13 (1 observational study)	⨁◯◯◯ Very Low[a,b]	RR 0.30 (0.10 to 0.89)	1,000 per 1,000	700 fewer per 1,000 (900 fewer to 110 fewer)

a. Downgraded by 2 increments due to very serious risk of bias.

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)

See Appendix F for full GRADE

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

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

Table 4: Unit costs

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	

*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, progression of dysplasia, progression to cancer, recurrence of Barrett's oesophagus/dysplasia/cancer, number of endoscopic treatments to achieve remission of Barrett's, time duration of the endoscopic treatment and adverse events (such as bleeding, pain). 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 outcome of recurrence of Barrett's oesophagus. No evidence for any other outcomes was identified.

1.1.12.2 The quality of the evidence

One observational study was identified comparing anti-reflux surgery with medical treatment (esomeprazole) as post radiofrequency ablation modality. The quality of the evidence was very low for both outcomes of recurrence of Barrett's oesophagus recurrence of Barrett's oesophagus in people with C length ≥ 4cm. The evidence was downgraded for imprecision in the effect estimates with the confidence intervals being very wide and very serious risk of bias due to potential selection bias as patients were divided into intervention groups on the basis of their preference after both interventions had been presented to them. No randomized controlled trials were identified relevant to the review protocol.

1.1.12.3 Benefits and harms

The evidence showed a clinically important benefit of anti-reflux surgery for recurrence of Barrett's oesophagus in the overall study population and in a sub-group of people with C length ≥ 4cm. However, the committee had low confidence in the quality of the evidence as it came from an observational study with very wide confidence intervals and a very small number of participants. The committee agreed, patients who fail to respond to radiofrequency

ablation can be referred for anti-reflux surgery. However, the committee also noted that very few patients are unresponsive to radiofrequency ablation, and in such cases other ablation therapies such as argon plasma coagulation (APC) could be considered instead of anti-reflux surgery as they are more likely to be beneficial. Due to the lack of sufficient evidence and because there was no consensus amongst the committee on the benefit of the intervention for this population they agreed to not make a recommendation for anti-reflux surgery to induce remission or prevent recurrence in people with stage 1 adenocarcinoma .The committee discussed making a research recommendation in people who do not achieve remission with RFA, but agreed that in current practice clinicians are more inclined towards other ablation modalities in patients who are unresponsive to RFA instead of anti-reflux surgery and anti-reflux surgery is not a priority area for further research.

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 unit cost of surgery was presented.

The clinical evidence showed a clinically important benefit with anti-reflux surgery versus no surgery in recurrence of Barrett's oesophagus of a length ≥4cm. The committee decided that the quality of the evidence was not sufficient to inform the cost effectiveness of surgery. Therefore, it abstained from making any recommendation.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendation 1.8.1.

1.1.14 References

1. 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

2. Skrobic O, Simic A, Radovanovic N, Ivanovic N, Micev M, Pesko P. Significance of Nissen fundoplication after endoscopic radiofrequency ablation of Barrett's esophagus. Surgical Endoscopy. 2016; 30(9):3802-3807

Appendices

Appendix A – Review protocols

Review protocol for anti-reflux surgery to induce remission of disease or prevent recurrence

ID	Field	Content
0.	PROSPERO registration number	CRD42022340835
1.	Review title	Anti-reflux surgery to induce remission of disease or prevent recurrence
2.	Review question	For adults with Barrett's oesophagus or stage 1 adenocarcinoma, what is the clinical and cost effectiveness of anti-reflux surgery to induce remission of disease or prevent recurrence?
3.	Objective	To assess the clinical and cost effectiveness of anti-reflux surgery, alone or in combination with ablative therapies, in adults with Barrett's oesophagus to improve the remission of the disease
4.	Searches	The following databases (from inception) will be searched: 1. Cochrane Central Register of Controlled Trials (CENTRAL) 2. Cochrane Database of Systematic Reviews (CDSR) 3. Embase 4. MEDLINE Searches will be restricted by: 5. English language studies 6. Human studies 7. Letters and comments are excluded

		Other searches: 8. Inclusion lists of systematic reviews will be checked by the reviewers The searches may 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 Barrett's Oesophagus with or without dysplasia (low-grade dysplasia, high-grade dysplasia, or stage 1 oesophageal adenocarcinoma). Exclusion: 1. patients with oesophageal adenocarcinoma stage higher than I
7.	Intervention	Anti-reflux surgery alone or in combination with endoscopic treatment: 2. Any type of fundoplication
8.	Comparator	3. No anti-reflux surgery
9.	Types of study to be included	9. RCT

		10. 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 to induce remission of disease and prevent progression to cancer. This review aims to assess how clinically and cost effective anti-reflux surgery is to induce remission of disease and prevent recurrence.
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: 11. Mortality (disease-specific mortality, treatment related mortality and all cause) 12. Health related quality of life 13. Progression of grade of dysplasia 14. Progression to cancer 15. Recurrence of Barrett's oesophagus/ dysplasia/cancer 16. Number of endoscopic treatments to achieve remission of Barrett's 17. Time duration of the endoscopic treatment 18. Adverse events (such as bleeding, pain) Time points: any time point available; no minimum follow-up

13.	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: 19. papers were included /excluded appropriately 20. a sample of the data extractions 21. correct methods are used to synthesise data 22. 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.
14.	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

15.	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.
16.	Analysis of sub-groups	Stratification: -no dysplasia -low-grade dysplasia -grade dysplasia/ stage 1 cancer Subgrouping:

		If serious or very serious heterogeneity (I2>50%) is present, sub-grouping will occur according to the following strategies: Length of Barrett's Patients requiring endoscopic resection in addition to radiofrequency ablation Low-grade dysplasia High-grade dysplasia T1a cancer Medical treatment (PPI vs no PPI) for people who do not receive ablative treatment.		
17.	Type and method of review		Intervention	
			Diagnostic	
			Prognostic	
			Qualitative	
			Epidemiologic	
			Service Delivery	
			Other (please specify)	
18.	Language	English		
19.	Country	England		
20.	Anticipated or actual start date			
21.	Anticipated completion date			
22.		Review stage	Started	Completed

	Stage of review at time of this submission	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		
23.	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		
24.	Review team members	From the National Guideline Centre: Norma O Flynn Gill Ritchie Amy Crisp		

		Lina Gulhane Vimal Bedia Muksitar Rahman Maheen Qureshi Melina Vasileiou
25.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
26.	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.
27.	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.
28.	Other registration details	
29.	Reference/URL for published protocol	
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: 23. notifying registered stakeholders of publication 24. publicising the guideline through NICE's newsletter and alerts

		25. 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.	
31.	Keywords	Barrett's Oesophagus	
32.	Details of existing review of same topic by same authors		
33.	Current review status		Ongoing
			Completed but not published
			Completed and published
			Completed, published and being updated
			Discontinued
34.	Additional information		
35.	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).[1] **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.[1]

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

Database	Dates searched	Search filters and limits applied
	Quality of Life 1946 – 29 April 2022	Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	Health Economics 1 January 2014 – 29 April 2022	Health economics studies Quality of life studies
	Quality of Life 1974 – 29 April 2022	Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
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

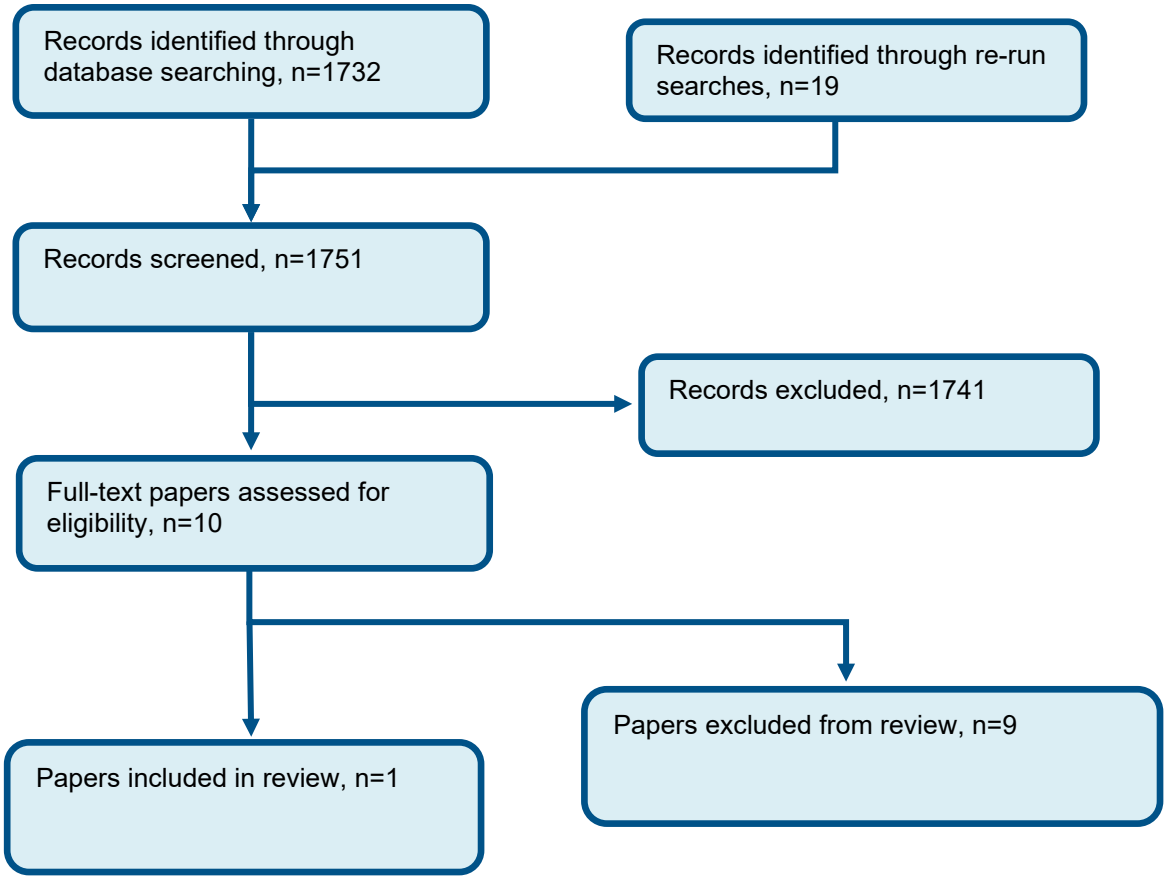
#1.	MeSH DESCRIPTOR Barrett Esophagus EXPLODE ALL TREES
#2.	(barrett*)
#3.	(speciali*) AND (epithel* or oesophag* or esophag* or mucos*)
#4.	(column*) AND (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)
#5.	#1 OR #2 OR #3 OR #4
#6.	MeSH DESCRIPTOR Precancerous Conditions 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 for remission



Appendix D – Effectiveness evidence

Skrobic, 2016

Bibliographic Reference	Skrobic, O.; Simic, A.; Radovanovic, N.; Ivanovic, N.; Micev, M.; Pesko, P.; Significance of Nissen fundoplication after endoscopic radiofrequency ablation of Barrett's esophagus; Surgical Endoscopy; 2016; vol. 30 (no. 9); 3802-7

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	Not applicable
Study type	Prospective cohort study
Study location	Serbia
Study setting	Department of Esophagogastric Surgery at: 1. First Surgical University Hospital

	2. Clinical Center of Serbia 3. School of Medicine 4. University of Belgrade
Study dates	Initiation in November 2009, patient selection in March 2013 and 2-year follow-up.
Sources of funding	None disclosed
Inclusion criteria	Patients treated with HALO RFA for histologically proven Barrett's oesophagus who had complete eradication of Barrett's oesophagus
Exclusion criteria	Patients with high grade dysplasia
Recruitment / selection of participants	Prospective
Intervention(s)	laparoscopic Nissen fundoplication (LNF) after or synchronous with RFA procedure. The post-RFA treatment modality was patient's preference.
Comparator	Patients was treated with daily PPI (esomeprazol 40 mg/day)
Number of participants	N=47
Duration of follow-up	2 years
Additional comments	

Study arms

HALO RFA + LNF (N = 22)
LNF= laparoscopic Nissen fundoplication

HALO RFA + PPI (N = 25)

Characteristics

Study-level characteristics

Characteristic	**Study (N = 47)**
Intestinal metaplasia (n (%)) Sample size	n = 33 ; % = 70.2
Low grade dysplasia (n (%)) Sample size	n = 14 ; % = 29.7

Arm-level characteristics

Characteristic	**HALO RFA + LNF (N = 22)**	**HALO RFA + PPI (N = 25)**
Age (years (mean)) Mean (SD)	45.4 (15.2)	48.1 (12.4)
Male	n = 15 ; % = 68.1	n = 17 ; % = 68

Characteristic	HALO RFA + LNF (N = 22)	HALO RFA + PPI (N = 25)
Sample size		
Female Sample size	n = 7 ; % = 31.8	n = 8 ; % = 32
Barrett's oesophagus C length (Mean (SD)) Mean (SD)	2.6 (1.3)	2.9 (1.1)

Outcomes

Study timepoints

- 2 year

Primary outcome

Outcome	HALO RFA + LNF, 2 year, N = 22	HALO RFA + PPI, 2 year, N = 25
Recurrence of Barrett's oesophagus (n (%)) No of events	n = 2 ; % = 9.1	n = 5 ; % = 20

Primary outcome

Outcome	HALO RFA + LNF, 2 year, N = 8	HALO RFA + PPI, 2 year, N = 5
Recurrence of BE with C length ≥ 4cm	n = 2 ; % = 25	n = 5 ; % = 100

Outcome	HALO RFA + LNF, 2 year, N = 8	HALO RFA + PPI, 2 year, N = 5
No of events		

Critical appraisal - ROBINS-I checklist

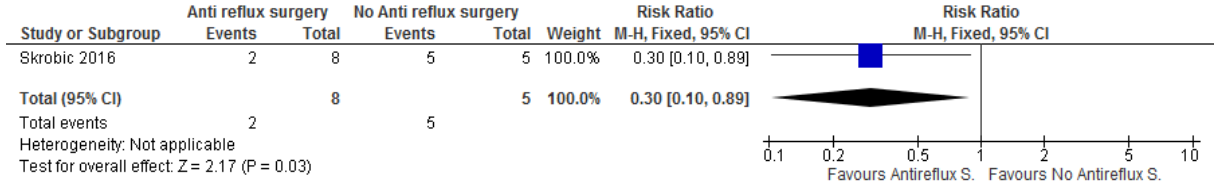
Primary outcome-Recurrence of Barrett's oesophagus -No Of Events-HALO RFA + LNF-HALO RFA + PPI-t2

Section	Question	Answer
Overall bias	Risk of bias judgement	Very serious *(Potential selection bias as patients were divided into groups on the basis of their preference after both interventions were presented to them; source of bias may have been introduced if presentation differed)*
Overall bias	Directness	Directly applicable

Appendix E – Forest plots

Figure 2: Recurrent of Barrett's oesophagus

Figure 3: Recurrent of Barrett's oesophagus length ≥ 4cm



Appendix F – GRADE

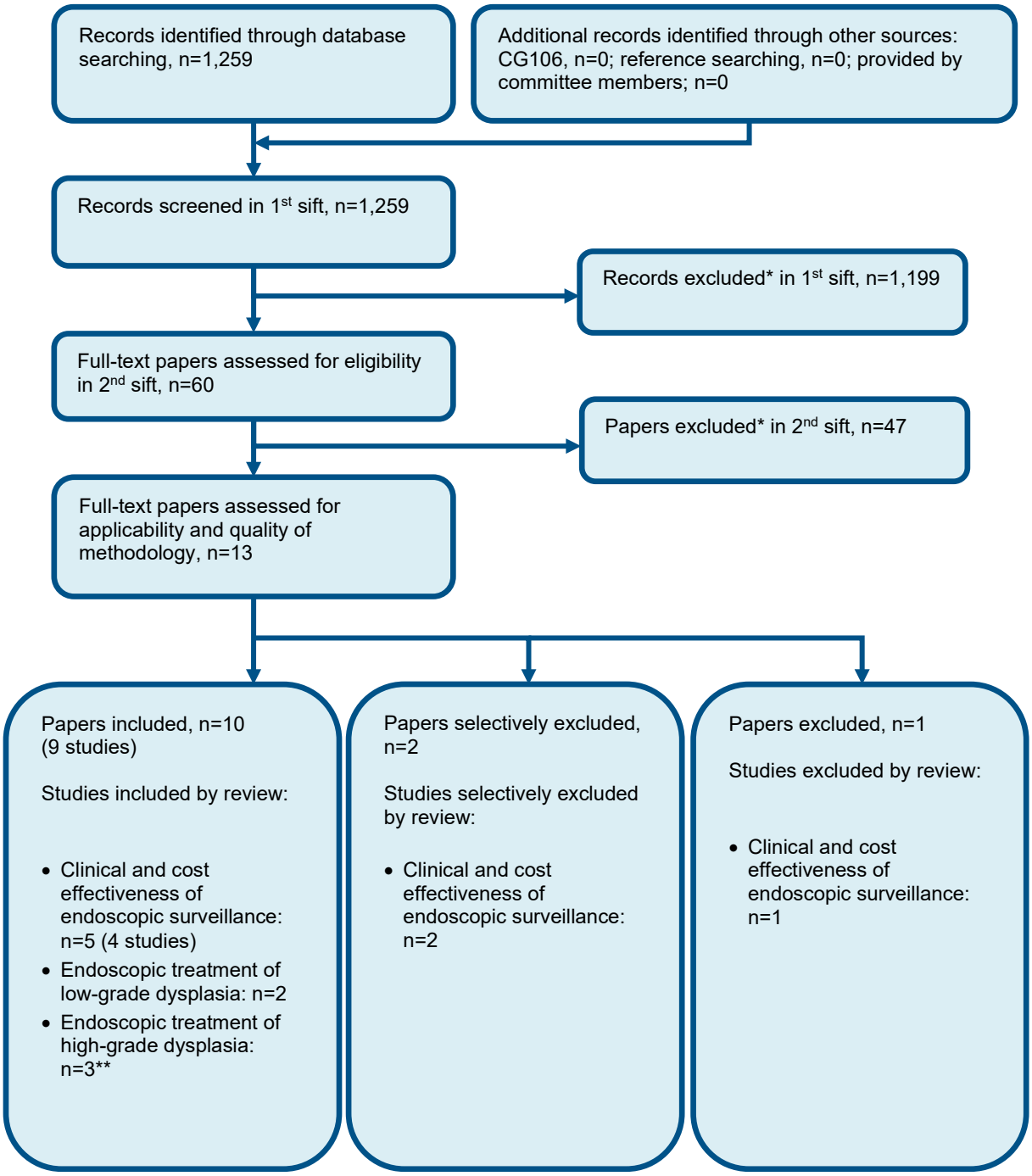
Table 7: Clinical evidence profile: Anti-reflux surgery with endoscopic treatment vs medical treatment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anti reflux surgery with or without endoscopic treatment	No Anti reflux surgery	Relative (95% CI)	Absolute (95% CI)		
Recurrence of Barrett's oesophagus												
1	observational studies	very serious	not serious	not serious	serious[a]	strong association	2/22 (9.1%)	5/25 (20.0%)	**RR 0.45** (0.10 to 2.11)	**110 fewer per 1,000** (from 180 fewer to 222 more)	⨁◯◯◯ Very low	CRITICAL
Recurrence of Barrett's oesophagus C length > 4cm												
1	observational studies	very serious	not serious	not serious	serious[a]	strong association	2/8 (25.0%)	5/5 (100.0%)	**RR 0.30** (0.10 to 0.89)	**700 fewer per 1,000** (from 900 fewer to 110 fewer)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by 2 increments due to very serious risk of bias.

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)

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
Ackroyd, R., Tam, W., Schoeman, M. et al. (2004) Prospective randomized controlled trial of argon plasma coagulation ablation vs. endoscopic surveillance of patients with Barrett's esophagus after antireflux surgery. Gastrointestinal Endoscopy 59(1): 1-7	- Study does not contain an intervention relevant to this review protocol Comparing APC ablation with endoscopic surveillance
Faybush, E. M. and Sampliner, R. E. (2005) Randomized trials in the treatment of Barrett's esophagus. Diseases of the Esophagus 18(5): 291-7	- Study does not contain an intervention relevant to this review protocol Systematic review comparing different treatment modalities not relevant to the review protocol
Hubbard, N. and Velanovich, V. (2007) Endoscopic endoluminal radiofrequency ablation of Barrett's esophagus in patients with fundoplications. Surgical Endoscopy 21(4): 625-8	- Outcome not relevant to this review protocol Assessing GERD related outcomes
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	- Study does not contain an intervention relevant to this review protocol Comparing different treatment modalities not relevant to this review
McCarthy, M. and Wilkinson, M. L. (1999) Treatment of Barrett's esophagus by endoscopic laser ablation and antireflux surgery. Gastrointestinal Endoscopy 49(1): 129-30	- Study design not relevant to this review protocol- Non-randomized study with no active comparator
O'Connell, K. and Velanovich, V. (2011) Effects of Nissen fundoplication on endoscopic endoluminal radiofrequency ablation of Barrett's esophagus. Surgical Endoscopy 25(3): 830-4	- Study design not relevant to this review protocol- Non-randomized study with no active comparator
Roorda, A. K.; Marcus, S. N.; Triadafilopoulos, G. (2007) Early experience with radiofrequency energy ablation therapy for Barrett's esophagus with and without dysplasia. Diseases of the Esophagus 20(6): 516-22	- Intervention not relevant to this review protocol Assessing safety and effectiveness of radiofrequency ablation combined with PPI therapy

Study	Reason for exclusion
Salo, J. A., Salminen, J. T., Kiviluoto, T. A. et al. (1998) Treatment of Barrett's esophagus by endoscopic laser ablation and antireflux surgery. Annals of Surgery 227(1): 40-4	- Outcomes not relevant to this review protocol Assessing regeneration of intestinal metaplasia by squamous epithelium
Tyselskyi, V., Poylin, V., Tkachuk, O. et al. (2021) Antireflux surgery is required after endoscopic treatment for Barrett's esophagus. Polski Przeglad Chirurgiczny 93(5): 1-5	- Intervention not relevant to this review protocol Comparing argon plasma coagulation with high frequency welding

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.